DISSERTATION

ENANTIOSELECTIVE RHODIUM-CATALYZED [2 + 2 + 2] AND [4 + 2 + 2] CYCLOADDITION REACTIONS OF ALKENYL HETEROCUMULENES: APPLICATIONS TO ALKALOID SYNTHESIS

Submitted by

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In partial fulfillment of the requirements

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ROBERT TZU HSIANG YU ENTITLED ENANTIOSELECTIVE RHODIUM-CATALYZED [2 + 2 + 2] AND [4 + 2 + 2] CYCLOADDITION REACTIONS OF ALKENYL HETEROCUMULENES: APPLICATIONS TO ALKALOID SYNTHESIS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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Abstract of Dissertation

ENANTIOSELECTIVE RHODIUM-CATALYZED [2 + 2 + 2] AND [4 + 2 + 2] CYCLOADDITION REACTIONS OF ALKENYL HETEROCUMULENES: APPLICATIONS TO ALKALOID SYNTHESIS

An intermolecular rhodium-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and internal alkynes has been developed. In the presence of a catalytic amount of $[Rh(C_2H_4)_2Cl]_2$ and $P(4\text{-}MeO\text{-}C_6H_4)_3$, the cycloaddition produces substituted indolizinones and quinolizinones with newly formed sp^3-stereocenters. Depending on the alkynyl partners, a CO migration process can be involved during the cycloaddition to furnish cycloadducts possessing vinylogous amide functionality.

The use of TADDOL-based phosphoramidite ligands on rhodium allows for the incorporation of terminal alkynes in a highly enantioselective [2+2+2] cycloaddition with alkenyl isocyanates. Terminal alkyl alkynes provide bicyclic lactams, while the use of aryl alkynes provides complementary access to vinylogous amides through a CO migration process. Product selectivity seems to be governed by a combination of electronic and steric factors, with smaller and/or more electron-deficient substituents favoring lactam formation. The synthetic utility is demonstrated in an expedient asymmetric total synthesis of the alkaloid (+)-lasubine II.

A highly enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes and alkenyl carbodiimides has been realized. The cycloaddition with aryl alkynes provides complementary selectivity to the reaction previously described using isocyanates. In addition, this reaction demonstrates the feasibility of olefin insertion into

carbodiimide-derived metalacycles, and provides a new class of chiral bicyclic amidines as the major products.

A new catalyst system has been realized. The use of chiral biphenyl-based phosphoramidite ligands on rhodium provides an efficient cycloaddition between terminal alkyl alkynes and alkenyl isocyanates. The cycloaddition proceeds through a CO migration pathway, and generates various 5-alkyl indolizinone products with high enantiomeric excess. A four-step asymmetric synthesis of indolizidine (–)-209D has been achieved.

A highly enantioselective rhodium-catalyzed [4+2+2] cycloaddition of terminal alkynes and dienyl isocyanates has been developed. The cycloaddition provides a rapid entry to highly functionalized and enantioenriched bicyclic azocines. This reaction represents the first [4+2+2] cycloaddition strategy to construct nitrogen-containing eight-membered rings.

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Lastly, I would like to thank my loving family. Mom, Dad, Tony, and Chia-Ying, this Ph.D. work is dedicated to you. Without your support, I would not be here today. I love you guys. And Chia-Ying, what more can I say. You are the love of my life. Thank you for being here with me every second through this whole experience. It is not over yet as another adventure awaits us in Cambridge. Are you ready?

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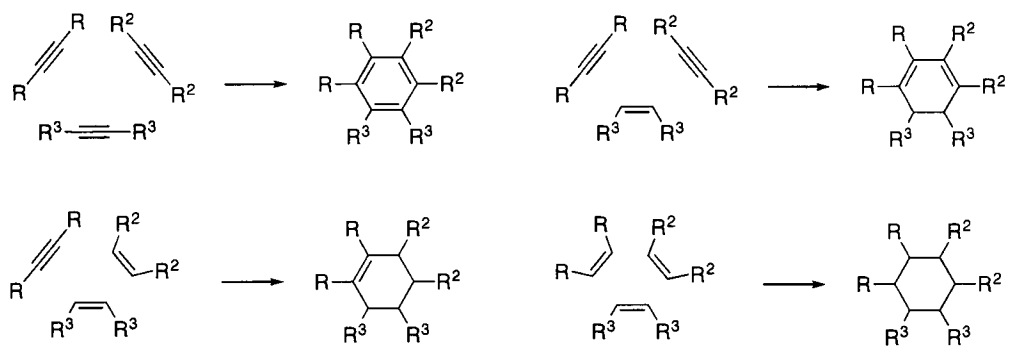
Chapter 1

The Development of a Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates

1.1. Introduction

The discovery of new carbon-carbon and carbon-heteroatom bond forming reactions, and the ability to effect them with high efficiency and selectivity are of paramount importance in organic synthesis. Transition-metal-catalyzed [*m*+*n*+*o*] cycloaddition reactions represent such powerful tools. The ability of cycloaddition reactions to form multiple bonds in a single operation allows for the rapid construction of polycyclic carbocycles and heterocycles.[1] Since many biologically active compounds contain such polycyclic motifs, developing new cycloaddition strategies is becoming increasingly popular and attracting keen interest of a wide range of organic chemists.[2] A simple analysis would reveal that strategies based on [2+2+2] cycloadditions are potentially more powerful than the Diels-Alder reaction for the formation of six-membered rings (Figure 1). Conceptually, three unsaturated moieties consisting of an equal number of carbons are brought together with the formation of three new bonds. Depending on the starting π systems, varying degrees of molecular complexity with up to six new chiral centers can be achieved.

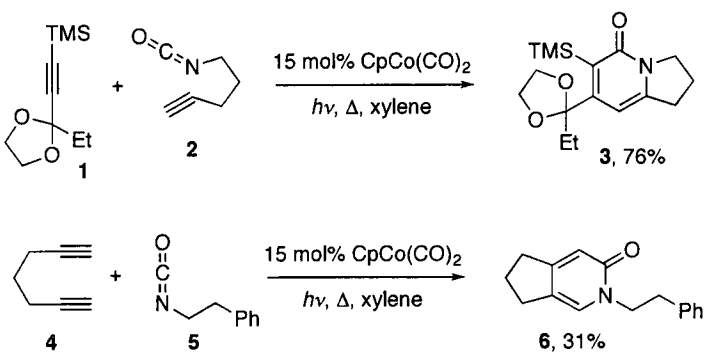
Figure 1.



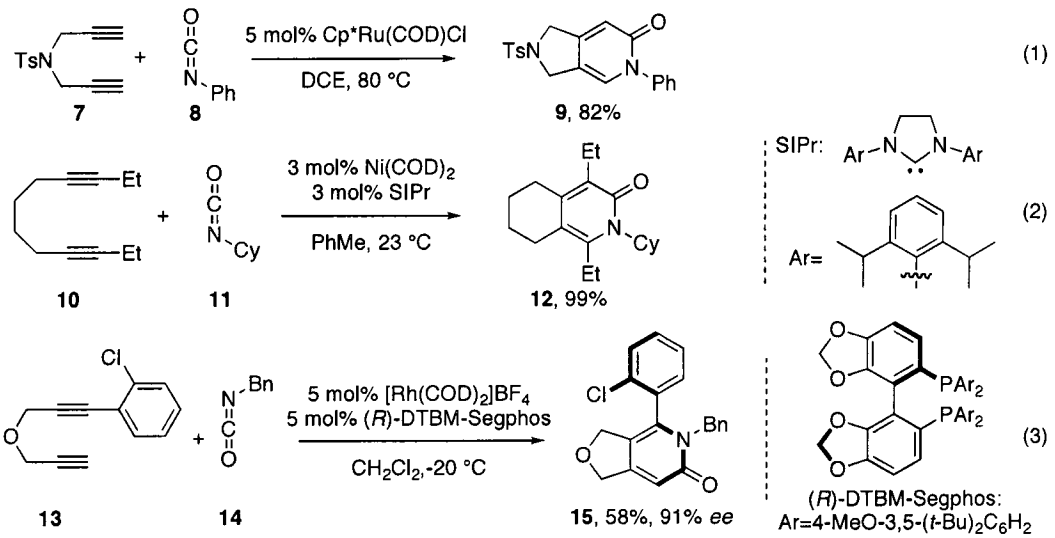
In addition to carbocycles, formation of nitrogen-containing heterocycles is especially worth our attention for reasons of their biological activities and their prominent presence in many natural products and drugs. [2+2+2] Cycloaddition reactions between two olefins and a nitrogen source would constitute a powerful and highly convergent strategy to six-membered *N*-heterocycles.

Isocyanates are particularly attractive building blocks for the construction of nitrogen-containing heterocycles, owing to their facile reactivity and embedded functionalities.[3] Vollhardt pioneered the cobalt-catalyzed [2+2+2] cycloaddition[4] and demonstrated that isocyanates are competent 2π components in reactions with two alkyne moieties to afford bicyclic pyridones (Scheme 1).[5] In the presence of $CpCo(CO)_2$, alkynyl isocyanate **2** was found to undergo cycloaddition with internal alkynes such as **1** to afford indolizinone **3**. The reaction scope is quite limited, as the trimethylsilyl group is required to obtain good regioselectivities. The same conditions can also be applied to the cycloaddition between heptadiyne **4** and isocyanate **5**, albeit in low yield. Maryanoff and coworkers have recently extended this reaction to include the synthesis of macrocycles by employing long-chain α,ω-diynes.[6]

Scheme 1.



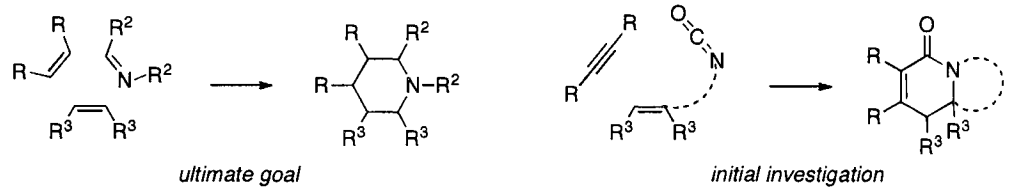
Since Vollhardt's reports, great progress has been made to improve the cycloaddition of diynes and isocyanates. Itoh and coworkers have shown that efficient cycloaddition of various diynes and isocyanates can be achieved by the use of a ruthenium(II) catalyst (eq 1),[7] while Louie and coworkers have realized that nickel-carbene complexes are also highly competent in this chemistry (eq 2).[8]



More recently, Tanaka and coworkers demonstrated that cationic rhodium(I) complexes also efficiently catalyze this reaction, and illustrated the potential of this chemistry to afford biaryls with control of axial chirality (eq 3).[9] With this single exception however, the body of literature in this area illustrates the formation of achiral aromatic products exclusively. The resulting bicyclic molecules lack sp^3-stereocenters and flexibility for further chemical transformations, and thus their applications toward complex molecule synthesis are inherently limited. It would be a clear benefit if alkenes could be demonstrated to participate since they enable the introduction of stereocenters in the products. Prior to our work, [2+2+2] cycloaddition strategies involving isocyanates were only limited to the use of alkynes. Herein, we describe our first encounter of

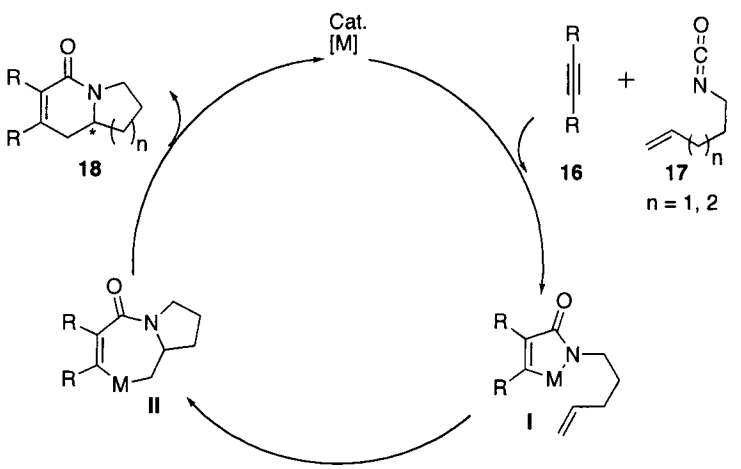
developing such cycloadditions involving an alkyne and an isocyanate with a tethered olefin (Figure 2).

Figure 2. [2+2+2] Cycloaddition Strategies to *N*-Heterocycles



At the outset of our investigation, we hypothesized that alkenes were reluctant to participate in these [2+2+2] cycloadditions due to the propensity of competitive insertion of an alkyne. Should the alkene be tethered to the isocyanate, the reaction may proceed via Hoberg's metalacycles[3] such as **I** with the tethered olefin in proximity, following an oxidative cyclization between alkyne **16** and isocyanate **17** (Scheme 2). The pendant alkene should compete more effectively with the exogenous alkyne to undergo the subsequent migratory insertion (**I** → **II**). Reductive elimination thus would provide indo- and quinolizinone-type products **18** with regeneration of the catalyst.

Scheme 2. Envisioned Reactivity



1.2. Synthesis of Alkenyl Isocyanates

For many people, the name "isocyanate" is a constant reminder of the tragic event referred to as the Bhopal disaster.[10] In the early hours of December 3 1984, a Union Carbide chemical plant in Bhopal in the state of Madhya Pradesh, India accidentally released more than 40 tons of methyl isocyanate gas, immediately killing more than 3,800 people and causing significant morbidity and premature death for many. It is important to note that methyl isocyanate is a highly toxic reagent with a low boiling point (39 °C), and today's isocyanate chemistry does not revolve around such reagents.

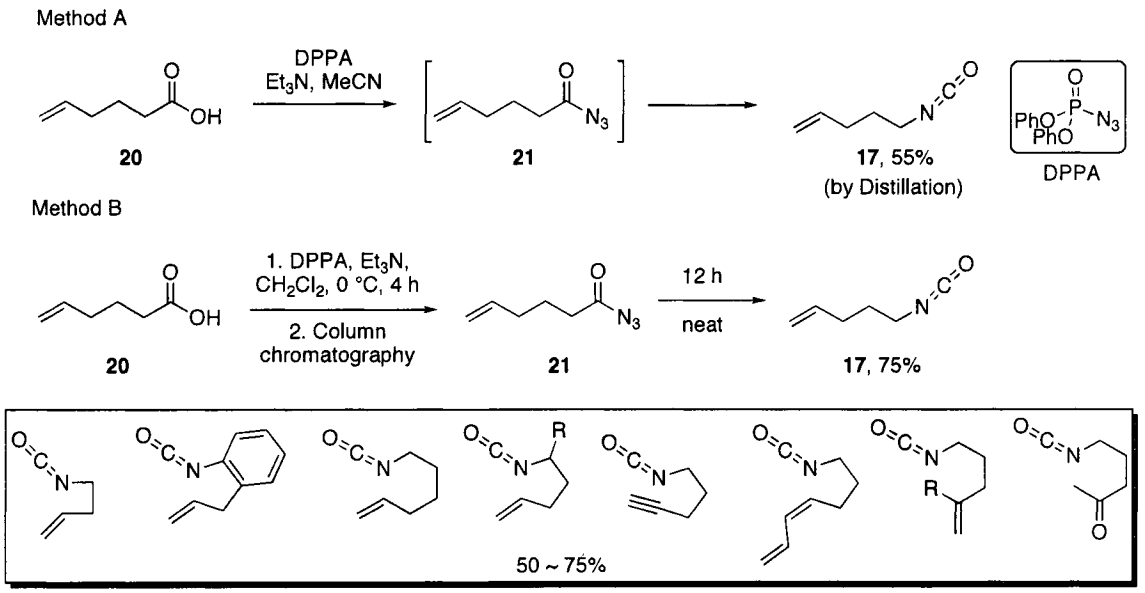
Organic isocyanates were first prepared and isolated by A. Wurtz in 1849 by the double decomposition reaction between alkyl sulfates and potassium cyanates (eq 4).[11] Today, there are more than 25 methods for their preparation in the literature and isocyanates have become powerful tools in organic synthesis.[12]

$$R_2SO_4 + KCNO \xrightarrow{A.\ Wurtz} O{=}C{=}N\text{-}R \qquad (4)$$

After extensive research, we have found that alkenyl isocyanates such as **17** are easily prepared via Curtius rearrangement employing one of the two following methods (Scheme 3). Treatment of carboxylic acid **20** with triethylamine followed by dropwise addition of diphenylphosphoryl azide (DPPA) at ambient temperature in acetonitrile triggers a very facile azide addition. Within 20 minutes, most of **20** is consumed as indicated by TLC analysis to afford presumably the acyl azide **21**. The process is accompanied with visible extrusion of N_2 from the solution (bubbling) indicating the rearrangement. Distillation under reduced pressure affords the target isocyanate **17** in good yield. Alternatively, we have determined that the Curtius rearrangement does not proceed measurably at 0 °C. The resulting acyl azide **20** may be purified and isolated by

flash chromatography using standard silica gel.[13] The acyl azide does not decompose or lose nitrogen during purification, but will undergo the rearrangement on sitting at ambient temperature in neat form, over a 16-24 h period. This technique allows the synthesis and isolation of non-volatile isocyanates. By applying one of the two methods, our group has successfully synthesized a variety of functionalized isocyanates (Scheme 3).

Scheme 3. Synthesis of Alkenyl Isocyanate **17**

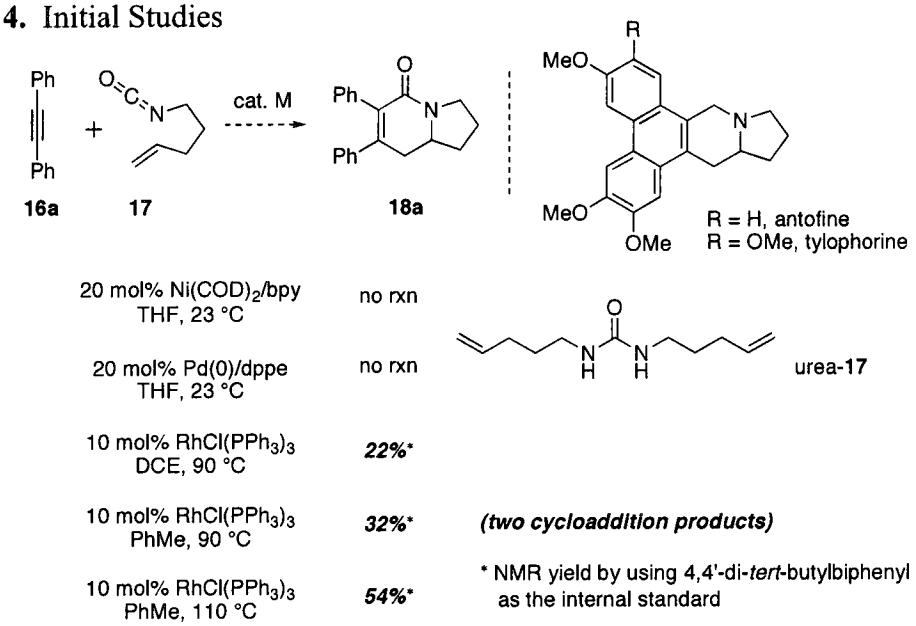


1.3. Reaction Development: Discovery of a CO Migration Process

With viable routes to alkenyl isocyanates, our study began by examining the cycloaddition of pentenyl isocyanate **17** and diphenylacetylene **16a** (Scheme 4). The choice of alkyne was based on a potential three-step synthesis to phenanthroindolizidine alkaloids, such as tylophorine.[14] Previous studies from our group have shown that both palladium(0) and nickel(0) are competent catalysts to access similar metalacycles by oxidative addition of cyclic anhydrides.[15] However, these conditions failed to provide the

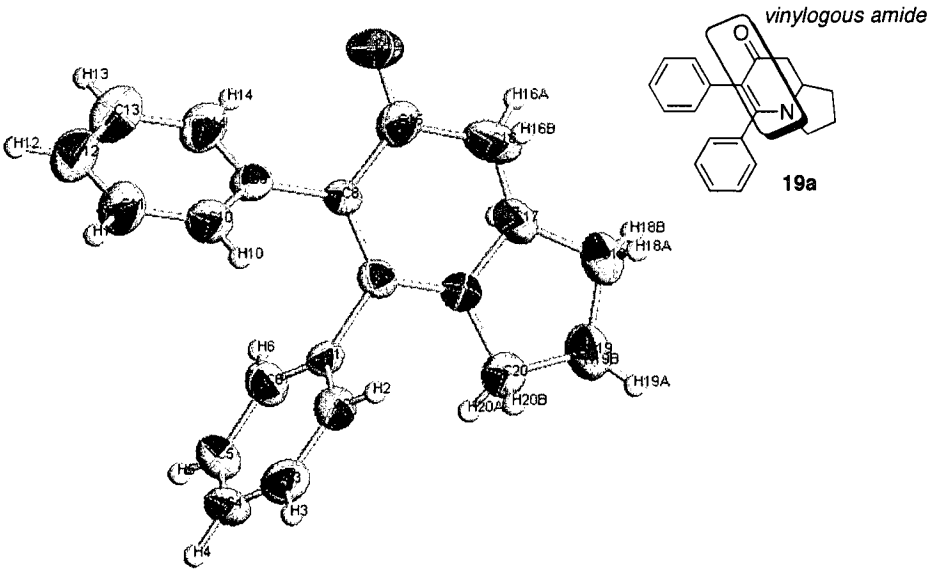
desired cycloadduct or any coupling products that incorporate both alkyne and isocyanate components. The only isolated product was the urea-**17**, whose formation can be rationalized by a metal-mediated dimerization process of the isocyanate.

Scheme 4. Initial Studies



The breakthrough came when we switched the choice of metal to rhodium(I). In the presence of 10 mol% of Wilkinson's catalyst at elevated temperature in dichloroethane (DCE), a cycloadduct having the same mass (by MS) as the expected bicyclic lactam **18a** was observed in 22% yield. Following this exciting result, we quickly identified toluene as the optimal solvent, and were able to increase the yield to 54% by conducting the reaction at 110 °C (Scheme 4). Interestingly, we detected a very small amount of secondary cycloaddition product (3~5%), whose spectral data was similar yet distinctive to the major cycloadduct. A closer examination of their respective ^{1}H and ^{13}C NMR spectra (*vide infra*) revealed that the minor product in fact matched perfectly with **18a**. An X-ray crystal structure of the major cycloadduct was ultimately obtained, and unambiguously assigned its structure to **19a** as shown in Figure 3. Instead

Figure 3.

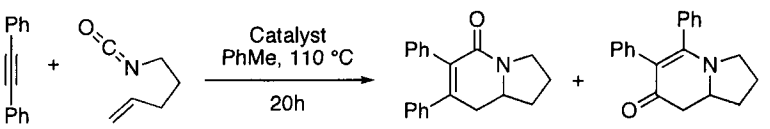


of formation of lactam **18a**, diphenylacetylene **16a** and pentenyl isocyanate **17** underwent a unique [2+2+2] cycloaddition to furnish the bicyclic product **19a**, possessing a vinylogous amide functionality. This remarkable Rh-catalyzed cycloaddition reaction consists of two C-C and one C-N bond-forming events and results in a rare CO migration process.

To further probe this reaction, we next examined the ligand effect on rhodium by using $[Rh(COD)Cl]_2$ as the precatalyst (Table 1). Employing bidentate phosphine ligands results in either no reaction or low yields (entries 3 – 5). In contrast, monodentate phosphine ligands generally exhibit much better reactivities toward the desired vinylogous amide **19a** (entries 6 – 11). The rhodium complex modified by either triphenyl phosphine or tricyclohexyl phosphine, with a 1:2 metal-to-ligand ratio, affords the cycloadduct in moderate yields (entries 6, 7). Employing electron-withdrawing or bulky phosphine ligands provides an inactive catalyst (entry 8, 9). The use of $[Rh(CO)_2Cl]_2$ does not promote the formation of **18a** by potentially supressing the CO

migration process responsible for the formation of **19a** (entry 10). The more electron-rich tris(4-methoxyphenyl) phosphine ligand provides the best yield (entry 11). The first key optimization came when we discovered that the metal-to-ligand ratio played a huge role in this reaction. Thus, the combination of $[Rh(COD)_2Cl]_2$ and 1 equiv of ligand per rhodium improves the reaction dramatically with a 61% isolated yield for **19a** (entry 12).

Table 1. Ligand Screen



16a **17** **18a** (<5%) **19a**

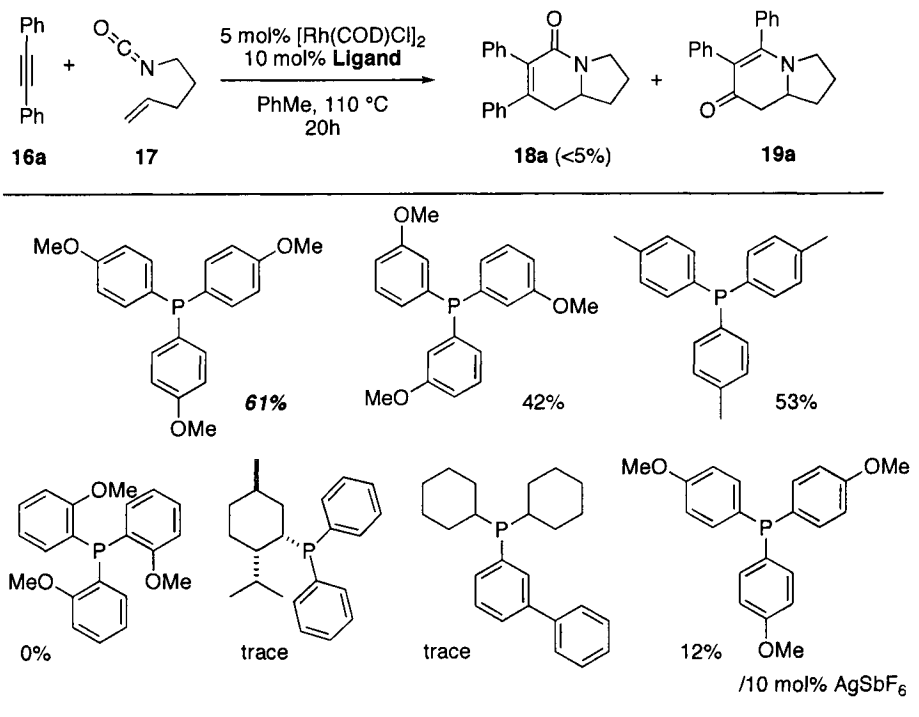
Entry	Catalyst	Yield (%) of **19a**[b]
1	10 mol% $RhCl(PPh_3)_3$	54
2	5 mol% $[Rh(COD)Cl]_2$	0
3	5 mol% $[Rh(COD)Cl]_2$, 10 mol% dppb	13
4	5 mol% $[Rh(COD)Cl]_2$, 10 mol% DIOP	12 [c]
5	5 mol% $[Rh(COD)Cl]_2$, 10 mol% BINAP	0
6	5 mol% $[Rh(COD)Cl]_2$, 20 mol% PPh_3	33
7	5 mol% $[Rh(COD)Cl]_2$, 20 mol% PCy_3	28
8	5 mol% $[Rh(COD)Cl]_2$, 20 mol% $P(t\text{-}Bu)_3$	0
9	5 mol% $[Rh(COD)Cl]_2$, 20 mol% $P(4\text{-}F\text{-}C_6H_4)_3$	trace
10	5 mol% $[Rh(CO)_2Cl]_2$	13
11	5 mol% $[Rh(COD)Cl]_2$, 20 mol% $P(4\text{-}MeO\text{-}C_6H_4)_3$	42 [c]
12	***5 mol% $[Rh(COD)Cl]_2$, 10 mol% $P(4\text{-}MeO\text{-}C_6H_4)_3$***	***61*** [c]

[a] Reaction conditions: **16a** (2 eq), **17**, indicated amount of Rh/L in refluxing PhMe under argon. [b] Determined by ^1H NMR of the unpurified reaction mixture using 4,4'-di-*tert*-butylbiphenyl as an internal standard. [c] Isolated yields.

With this new information in hand, we performed an additional catalyst screen with the aim to have a more complete reaction profile (Scheme 5). Both tris(*meta*-anisole) and tris(*para*-tolyl) phosphines are also competent ligands in this reaction, although not as efficient as $P(4\text{-}MeO\text{-}C_6H_4)_3$. Bulky ligands such as the *ortho*-anisole

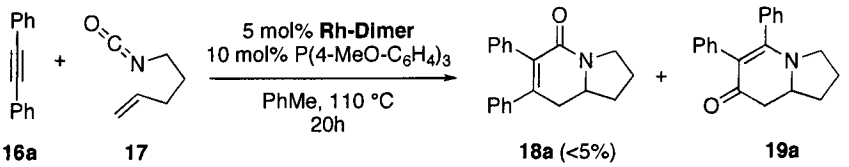
and menthol-derived phosphine ligands are largely inactive. Unlike many Rh(I)-catalyzed cycloaddition reactions in the literature, use of cationic rhodium complexes have detrimental effects to the reaction. For example, the cationic Rh(I)/P(4-MeO-$C_6H_4)_3$ complex, generated in situ by addition of $AgSbF_6$, promotes the reaction sluggishly with 12% isolated yield.

Scheme 5.



Unsatisfied with the current 61% chemical yield, we next screened various rhodium(I) precatalysts and found that the reaction can be further improved (Table 2). While the norbornadiene rhodium chloride dimer decreases the reactivity (entry 2), the bis-cyclooctene complex offers a similar reaction with slightly higher yields (entry 3). The bis-ethylene rhodium chloride dimer proves to be the optimal catalyst, affording the desired vinylogous amide in 74% isolated yield (entry 4).

Table 2. Rhodium Precatalyst Screen



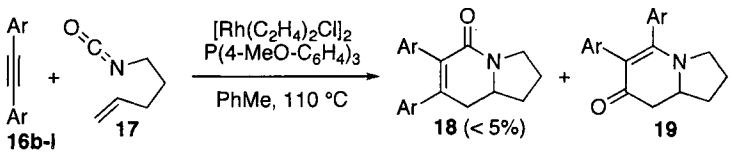
16a **17** **18a** (<5%) **19a**

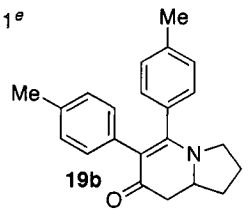
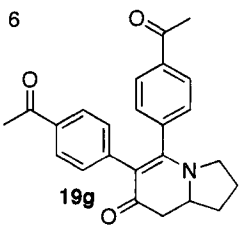
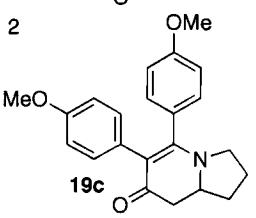
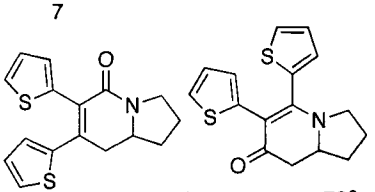
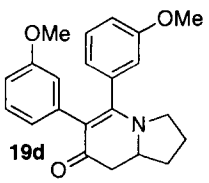
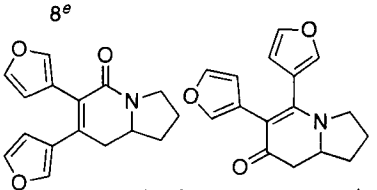
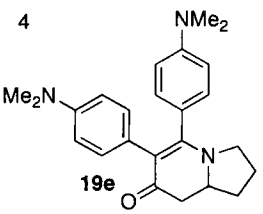
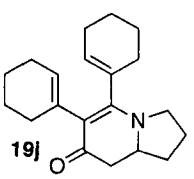
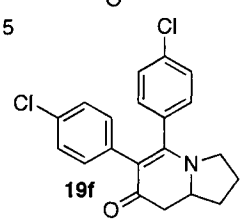
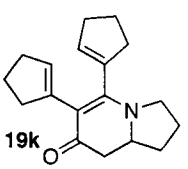
Entry	Rh-Dimer	Yield (%) of **19a**
1	$[Rh(COD)Cl]_2$	61
2	$[Rh(NBD)Cl]_2$	45
3	$[Rh(cyclooctene)_2Cl]_2$	66
4	***$[Rh(C_2H_4)_2Cl]_2$***	***74***

1.4. Reaction Scope

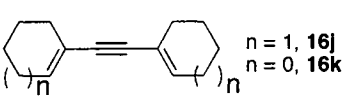
With optimal conditions in hand, we examined the substrate scope with a variety of symmetrical diaryl alkynes (tolanes **16b – 16i**). The newly developed [2+2+2] cycloaddition tailors well with a wide range of substituted tolanes, providing the desired bicyclic products in satisfactory chemical yields (**19b – 19g**, Table 3). Tolanes containing neutral or electron-rich substituents at either the *para-* or *meta-* positions readily participate in the cycloaddition (entries 1 – 3). Tolanes bearing amino and halogen functional groups (Me_2N, Cl) are also well tolerated (entry 4 and 5). Electron-withdrawing substituted tolanes appear to be less reactive,[16] with acetyl-substituted tolane affording the desired product in a modest yield (entry 6). Each of these tolanes furnishes the vinylogous amide-type products **19** selectively, resulting from a CO migration, while compounds **18** can only be observed in trace amounts (< 5%). The cycloadditions with the hetero-aryl tolanes (Ar = thiophene, furan) also proceed efficiently (entry 7 and 8). Interestingly, both the thiophene and furan tolanes generate both types of compounds in an approximately 1:1 ratio with good combined yields.

Table 3. Cycloaddition Scope[a]



Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1[e]	 **19b**	63	6	 **19g**	34
2	 **19c**	72	7	 **18h/19h** 1 : 1.3	72[c]
3	 **19d**	70	8[e]	 **18i/19i** 1 : 1.1	66[d]
4	 **19e**	61	9	 **19j**	75
5	 **19f**	60	10[f]	 **19k**	50

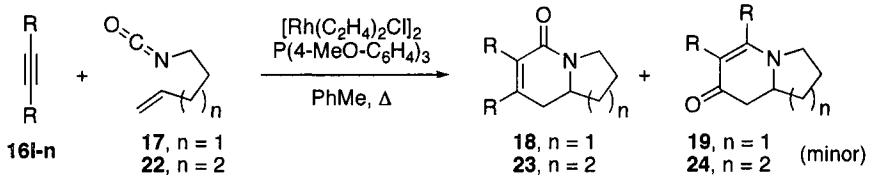
[a] Reaction conditions: **16** (2 eq), **17**, Rh cat. (5 mol%), **L** (10mol%) in PhMe at 110 °C. [b] Isolated yields. [c] Inseparable, combined yield. [d] Separable, combined yield. [e] 1.1 eq. alkyne employed. [f] 80 °C.

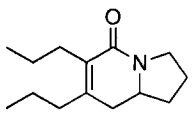
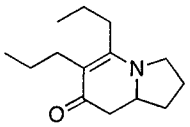
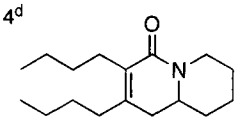
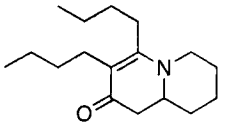
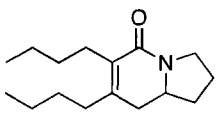
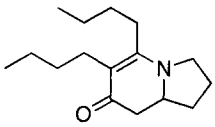
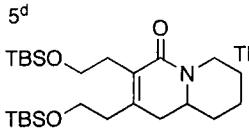
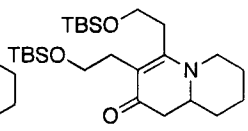
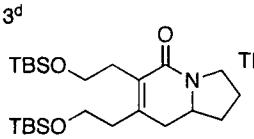
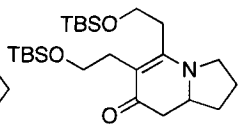


The substrate scope was further expanded to include the more sterically demanding cyclic dienynes. Cycloaddition between **16j** and **17** proceeds smoothly to afford exclusively indolizinone **19j** in 75% isolated yield (entry 9). Similarly, the bis(cyclopentene) substituted indolizinone **19k** can be obtained in a useful yield from enyne **16k** (entry 10), although lowering the temperature to 80 °C is necessary to prevent product decomposition.[17]

The steric environment of the substrates seems to dictate the reaction outcome. Bulky alkynes, such as dienyne **16j**, afford compounds **19** exclusively, while heteroaryl alkynes, such as **16h** and **16i**, possibly due to their lesser steric demand, might trigger an alternative mechanism and thus afford a mixture of both types. To test this hypothesis, the cycloaddition of primary dialkyl alkynes was examined with an anticipation of possibly changing the reaction course (Table 4). The cycloadditions proceed with almost complete inversion of selectivity, affording the direct cycloaddition products **18** with good isolated yields (entries 1-3). TBS-protected homopropargyl alcohol also participates in the reaction efficiently, providing **18n** in 56% yield (entry 3). The current protocol can also be employed for constructing the quinolizinone framework. Thus, by reacting an alkyl alkyne with the alkenyl isocyanate **17**, the resulting bicyclic compounds **23** may be obtained in good yields and selectivity (entries 4 and 5).

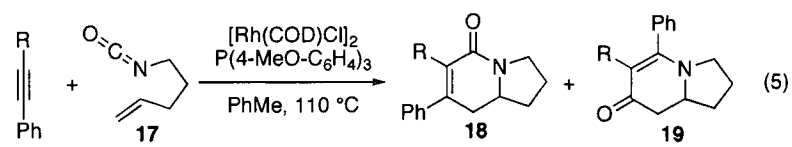
Table 4.



Entry	Yield (%) **18**[b]	Yield (%) **19**[b]	Entry	Yield (%) **23**[b]	Yield (%) **24**[b]
1[c]	 **18l**, 60%	 **19l**, trace	4[d]	 **23m**, 62%	 **24m**, 18%
2[c]	 **18m**, 70%	 **19m**, 12%	5[d]	 **23n**, 56%	 **24n**, trace
3[d]	 **18n**, 56%	 **19n**, trace			

[a] For reaction conditions, See Table 3. [b] Isolated yields. [c] At 80 °C. [d] At 110 °C.

The reaction of unsymmetrical alkyne **1o** generates both **18** and **19** with a slight preference for **18** (eq 5). The use of the homologous alkyne **1f** inverts this selectivity in favor of **19**, providing further support for the steric argument. It is noteworthy that in each case the bicyclic products were obtained in high regioselectivity (10:1; see Supporting Information).



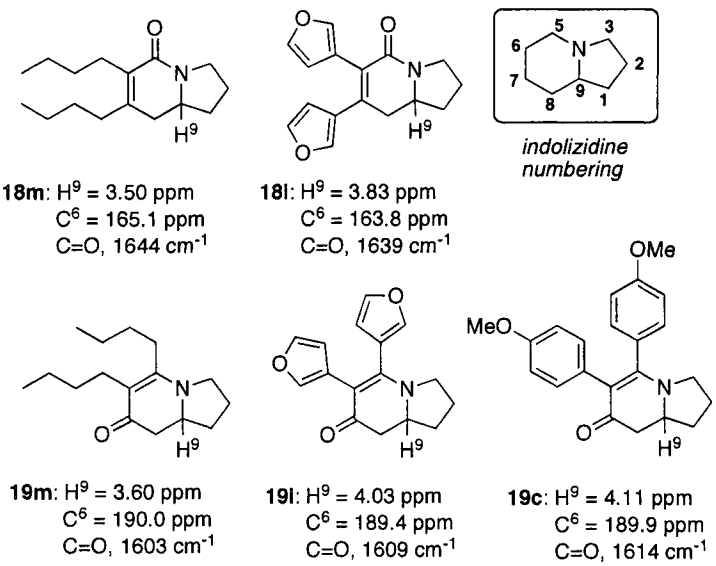
16o: R = Me
16p: R = Et

18o : **19o** (1.3 : 1), 60%
18p : **19p** (1 : 2.0), 63%

1.5. Lactam vs. Vinylogous Amide

In retrospect, the lactam and vinylogous amide cycloaddition products can easily be distinguished and assigned by using ^{1}H, ^{13}C NMR, as well as infrared spectroscopy (Figure 4). The methine hydrogen (H^9) at the ring junction is very diagnostic in differentiating between aryl-substituted lactam and vinylogous amide products. The chemical shifts of those hydrogens in **19** in the vinylogous amides are always more downfield and approximately at 4.00 ppm compared to lactams **18** (**19c**, **18l** *vs.* **19l**). They are, however, more difficult to identify in the cases of alkyl-substituted products (**18m** *vs.* **19m**). The ^{13}C data is the most useful tool to determine between the two types of cycloadducts. Regardless of the substitutions, all vinylogous amides **19** possess a ^{13}C signal approximately at 190 ppm, characteristic of a ketone carbonyl functionality. Similarly, all lactam-type products lack the signal at 190 ppm, and instead have a signal between 160 and 165 ppm, which is characteristic of an amide functionality. In many cases, IR spectra can also be useful by comparing the corresponding carbonyl stretches.

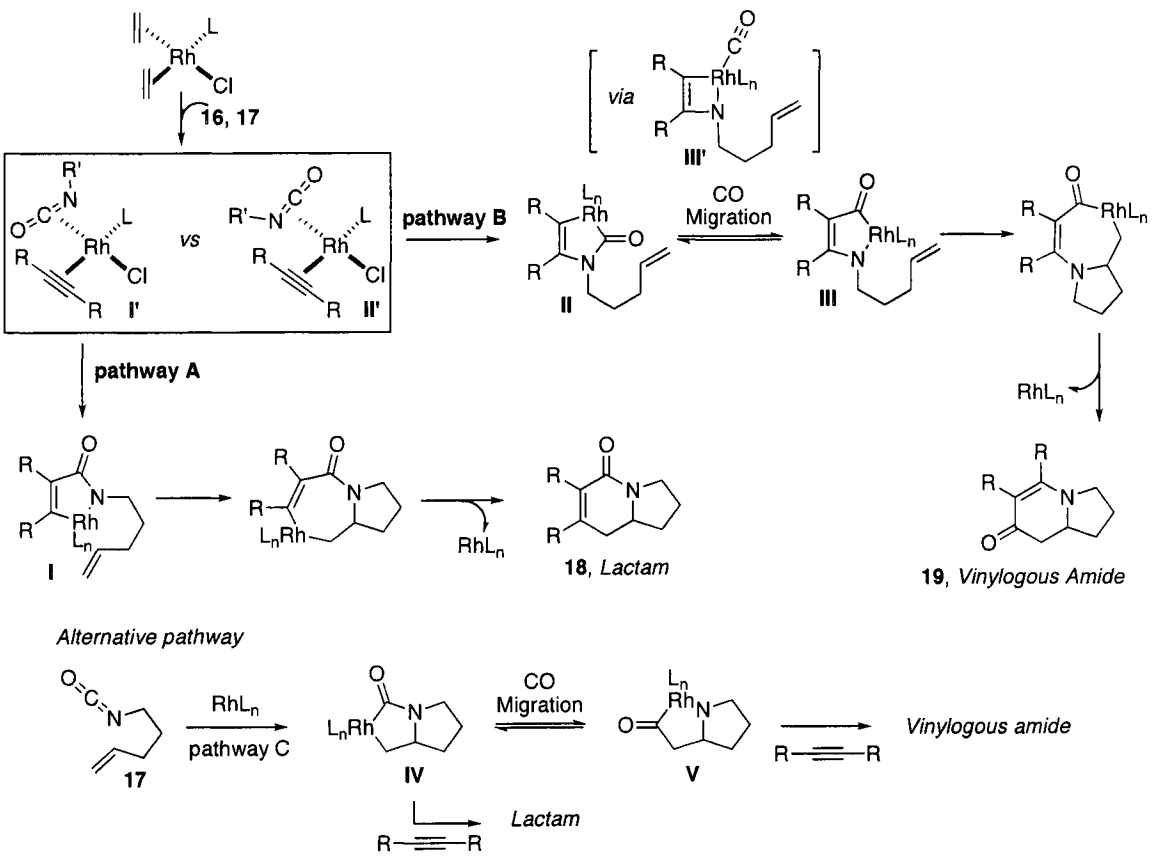
Figure 4.



1.6. Proposed Mechanism

A postulated mechanism is illustrated in Scheme 6. An oxidative cyclization between the isocyanate and alkyne in an orientation where a C-C bond is formed provides metalacycle **I** via rhodium complex **I'**. Subsequent olefin insertion and reductive elimination provides lactam products **18**. In a different orientation, complex **II'** gives rise to the formation of metalacycle **II**, where the construction of C-N bond takes place first. A CO migration[18] to **III** followed by olefin insertion and reductive elimination furnishes the vinylogous amides **19** (pathway B). Alternative routes, such as the intramolecular cyclization of alkenyl isocyanate **17** as the first step (pathway C), cannot be ruled out at this stage.

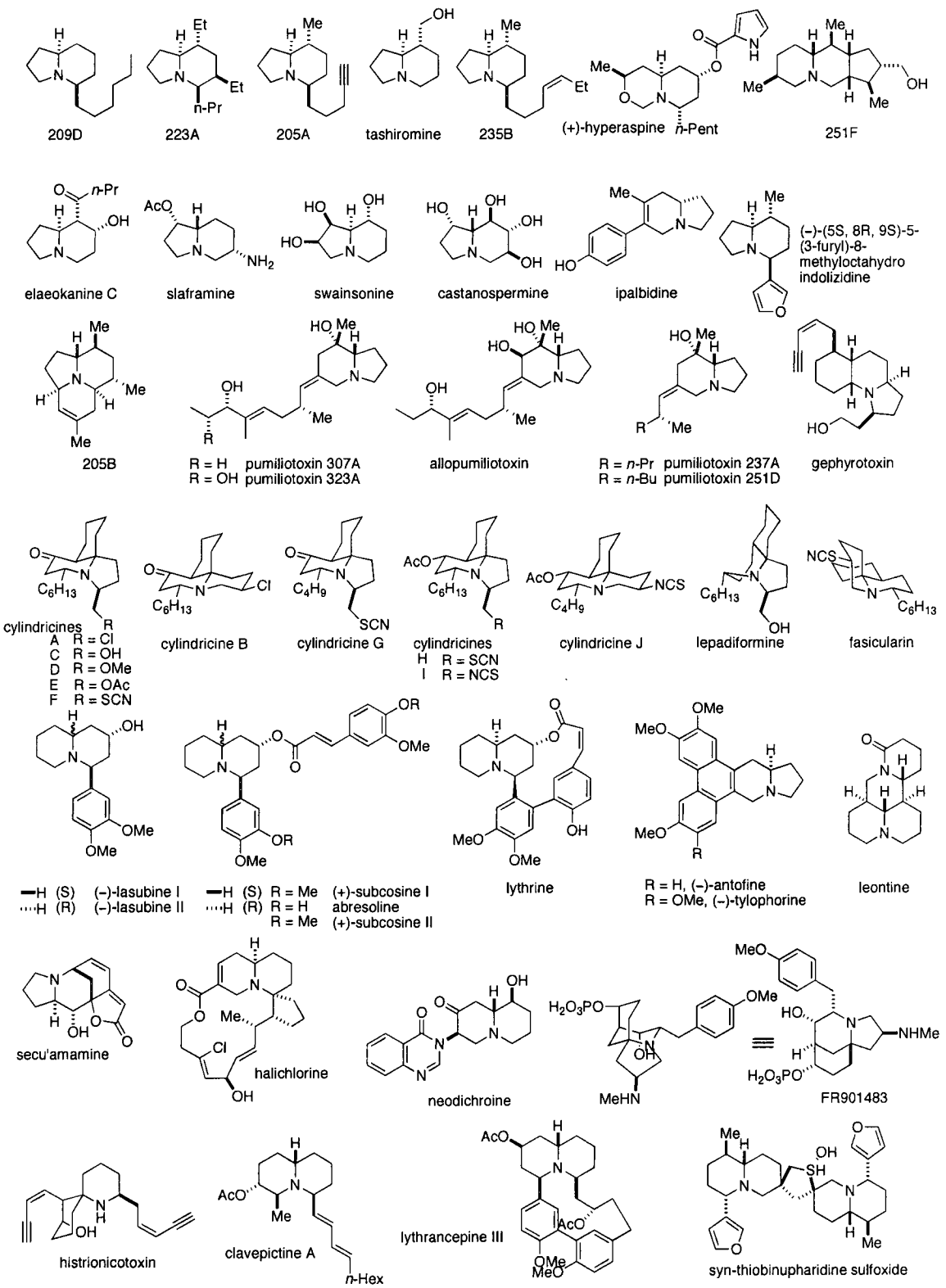
Scheme 6. Proposed Mechanism



1.7. Conclusion

In summary, we have discovered and developed a rhodium-catalyzed [2+2+2] cycloaddition involving alkynes and alkenyl isocyanates. Depending on the alkynyl substrates, two distinct indolizinone frameworks can be obtained selectively. The resulting products contain sp^3-stereogenic centers and functionalities, which should allow further manipulation for application to the synthesis of indo- and quinolizidine alkaloids (Scheme 7). Efforts focused on expanding the substrate scope and applying to natural product synthesis are currently underway.

Scheme 7. Selected Examples of Indo- and Quinolizidine Containing Alkaloids



1.8. References

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[2] For recent examples, see: (a) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005,** *127,* 12466. (b) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005,** *127,* 6530.

[3] Hoberg has extensively investigated the metal-mediated coupling of isocyanates and various π systems; see: (a) Hoberg, H.; Hernandez, E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 961. (b) Hoberg, H. *J. Organomet. Chem.* **1988**, *358*, 507. (c) Hoberg, H.; Bärhausen, D.; Mynott, R.; Schroth, G. *J. Organomet. Chem.* **1991**, *410*, 117.

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[7] (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001,** *3,* 2117. (b) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005,** *127,* 605.

[8] (a) Dong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004,** *126,* 11438. For the first Ni-catalyzed cycloaddition between alkynes and isocyanates, see: (b) Hoberg, H.; Oster, B. W. *Synthesis* **1982,** 324.

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[10] Broughton, E. *Environ. Health* **2005**, *4*, 6.

[11] Wurtz, A. *Justus Liebigs Ann. Chem.* **1849**, *71*, 326.

[12] For review on isocyanate chemistry, see: (a) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. (b) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389. (c) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927.

[13] Developed by Dr. Ernest E. Lee.

[14] For reviews on alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. For an example of their syntheses, see: (d) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997,** *62,* 7435. (e) Kim, S.; Lee, J.; Lee, T.; Park, H.-G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703.

[15] Our group has extensively explored the reactivity of such metalacycles, generated from the oxidative addition of cyclic anhydrides; see: (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002,** *124,* 174. (b) O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003,** *125,* 10498. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005,** *127,* 247.

[16] *p*-Nitro and *m*-nitrile substituted tolanes gave either no reaction or trace amount of product. Crude ^{1}H NMR showed no side products formed except partial consumption of the isocyanate to form a symmetrical urea.

[17] A complex mixture was obtained at 110 °C.

[18] (a) Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343. (b) Tanaka, K.; Fu, G. C. *Chem. Commun.* **2002**, 684.

Chapter 2

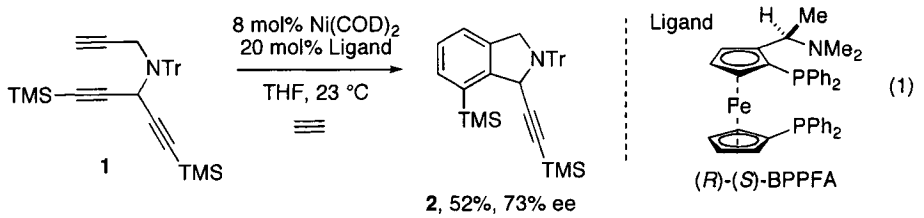
Enantioselective Rhodium-Catalyzed [2+2+2] Cycloadditions of Alkenyl Isocyanates and Terminal Alkynes: Application to the Total Synthesis of (+)-Lasubine II

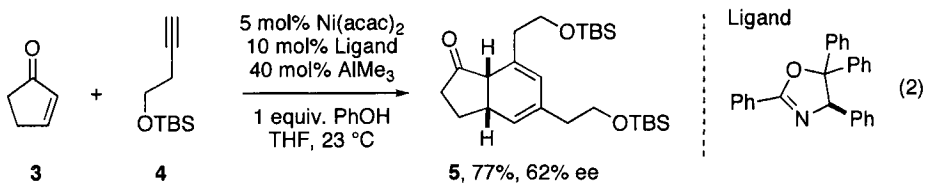
2.1. Introduction

In the past decades, intense research has focused on developing asymmetric reactions as a result of the growing need for efficient and practical syntheses of biologically active compounds. *Catalytic asymmetric reactions* are especially desirable due to their atom-economical way to induce asymmetry. It is a process that can be generally defined as the use of a small amount of chiral material to generate a large amount of chiral product. Over the years, many successful enantioselective processes such as asymmetric hydrogenations,[1] Sharpless asymmetric epoxidations and dihydroxylations of olefins,[2] palladium-catalyzed asymmetric allylic alkylations,[3] and asymmetric alkylations with organometallic reagents[4] have all gained wide acceptance, with some of them finding applications on industrial scale.

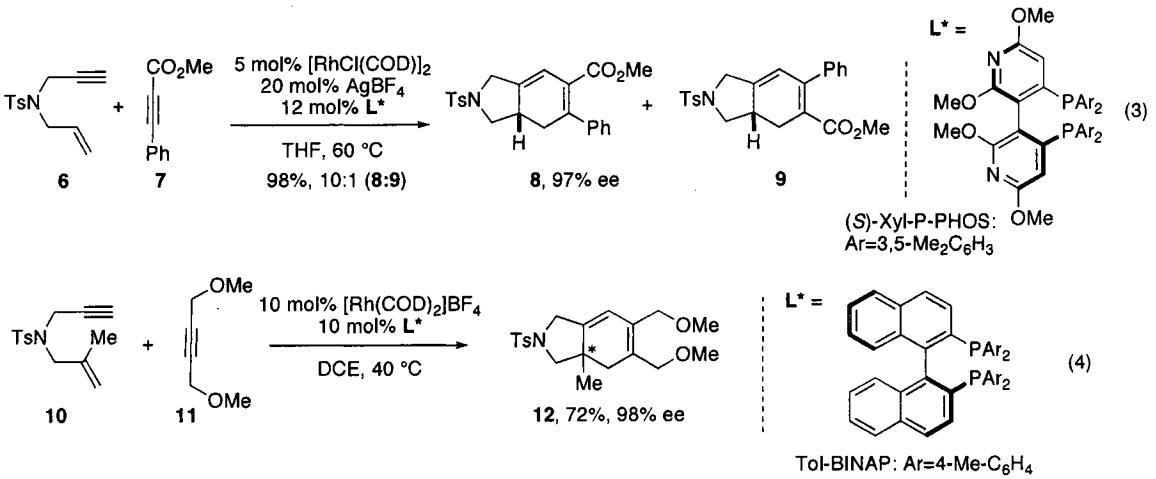
On the other hand, cycloaddition reactions of [*m*+*n*+*o*]-type catalyzed by transition metals are powerful methods to construct polycyclic carbocycles and heterocycles of structural and functional complexity.[5] In particular, [2+2+2] cycloaddition represents a general protocol for the synthesis of six-membered ring systems.[6] Thus, developing enantioselective [2+2+2] cycloaddition reactions to provide rapid entries to enantiopure ring systems will greatly advance the field of complex molecule synthesis.

Although cobalt-mediated asymmetric [2+2+2] cycloadditions of enediynes using chiral auxiliaries had been reported,[7] pioneering work of metal-catalyzed enantioselective [2+2+2] cycloaddition belongs to Mori and Ikeda's independent efforts employing chiral nickel catalysts (eq 1 and 2 respectively). Mori and coworkers described the use of chiral bidentate phosphine ligands to promote the cycloaddition of triyne **1** and acetylene.[8] Ikeda and coworkers reported an intermolecular reaction between two equivalents of an alkyne and enone **3** to provide cyclohexa-1,3-diene **5**, thus demonstrating the feasibility to incorporate an alkene.[9] Despite moderate enantiocontrol, these reactions represent the foundation of the growing field of enantioselective [2+2+2] cycloadditions.

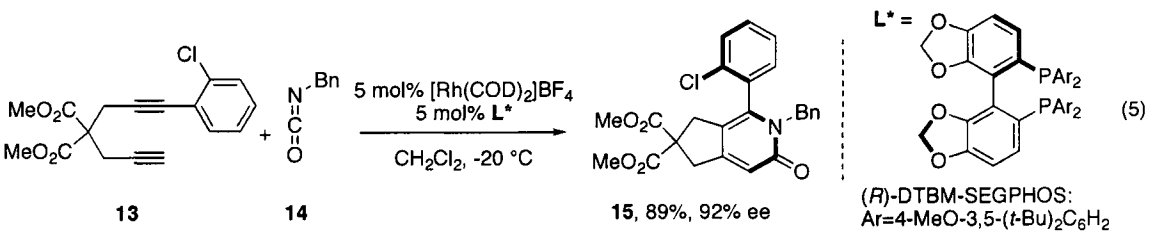




In 2005, Evans and coworkers successfully demonstrated a highly regio- and enantioselective rhodium-catalyzed [2+2+2] cycloaddition of 1,6-enynes and arylpropiolates (eq 3).[10] By employing cationic rhodium complexes modified with chiral bisphosphine ligands, a variety of bicyclohexadienes such as **8/9** can be accessed in high yields and enantioselectivities. Later on, Shibata and coworkers extended this reaction to incorporate enantioselective construction of quaternary carbon stereocenters (**12**) by using a similar catalyst (eq 4).[11]

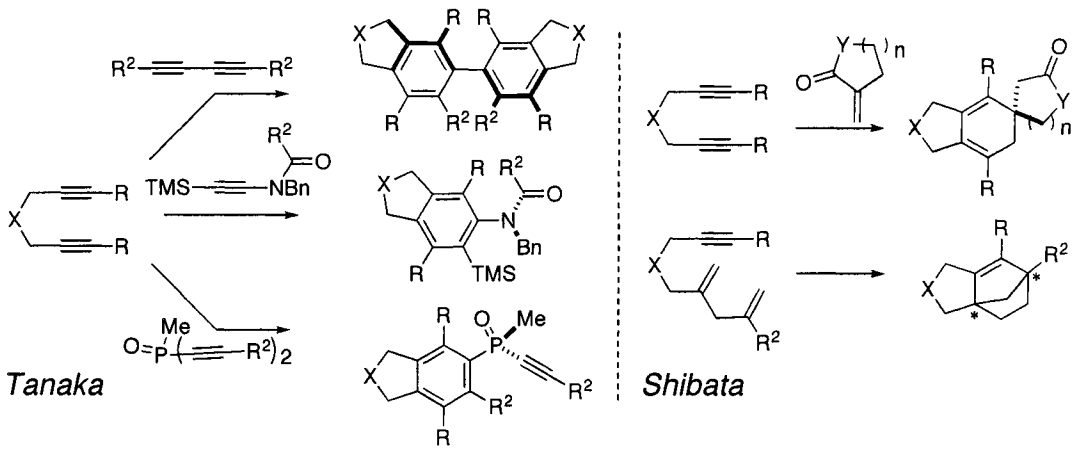


Shortly after, Tanaka and coworkers demonstrated the cycloaddition of sterically demanding diyne **13** and isocyanate **14** catalyzed by a similar rhodium complex to furnish axially chiral 2-pyridone **15** in excellent yield and enantioselectivity (eq 5).[12]



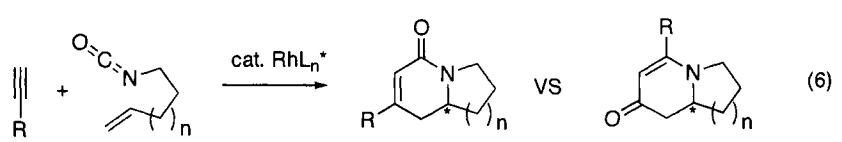
For the next three years, an epic battle between Shibata and Tanaka's research groups continued by examining various enantioselective [2+2+2] cycloadditions employing similar rhodium catalysts. Although some of their works overlapped, Tanaka and coworkers emphasized more on the construction of axially chiral molecules,[13] while Shibata's research continued to focus on the formation of quaternary carbon stereocenters (Scheme 1).[14]

Scheme 1.



Despite this tremendous body of work, most of the existing enantioselective [2+2+2] cycloaddition reactions focus on the construction of either strained compounds or compounds possessing only axial chirality. These restrictions preclude their use in further chemical transformations and make them unsuitable for synthetic applications.

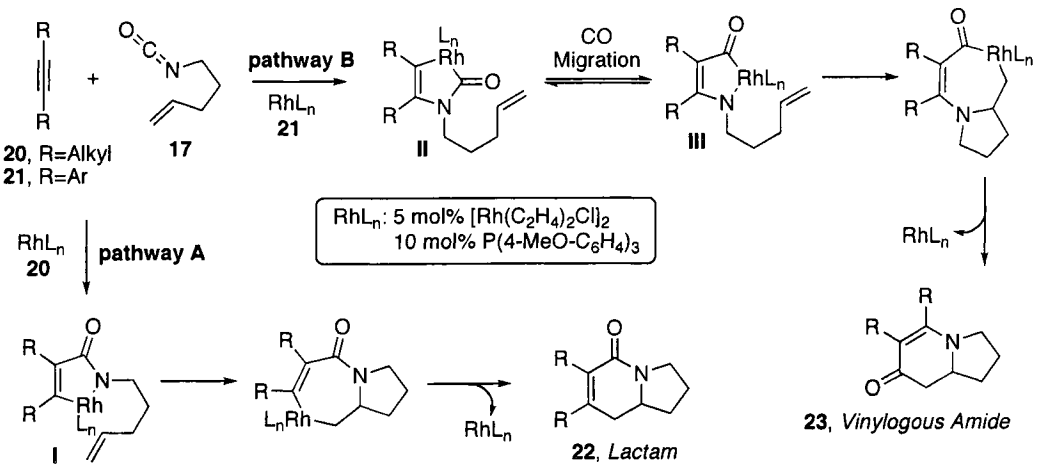
In light of potentially providing a general and efficient route to many indo- and quinolizidine alkaloid natural products, our group has focused on developing a catalyzed [2 + 2 + 2] cycloaddition of alkenyl isocyanates and alkynes.[15,16] Herein, we describe the regio- and enantioselective rhodium-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates with terminal alkynes to afford the corresponding bicyclic *lactams* and/or *vinylogous amides* using chiral phosphoramidites as ligands (eq 6). The synthetic utility is demonstrated in an expedient asymmetric total synthesis of (+)-lasubine II.



2.2. Expanding the Scope of Rhodium-catalyzed [2+2+2] Cycloadditions

Previously, we have developed a Rh(I)/tris(4-methoxyphenyl)phosphine catalyzed [2+2+2] cycloaddition between pentenyl isocyanate **17** and a variety of internal alkynes.[17] When the reaction is conducted in the presence of symmetrical alkyl alkynes **20**, the bicyclic lactam **22** can be formed in good yields via metalacycle **I** as the likely pathway (Scheme 2). Interestingly, when tolanes **21** are employed as the reacting partners, the cycloaddition diverts to a different pathway that includes a CO migration process (**II** → **III**) to afford the *vinylogous amides* **23** as the major products.

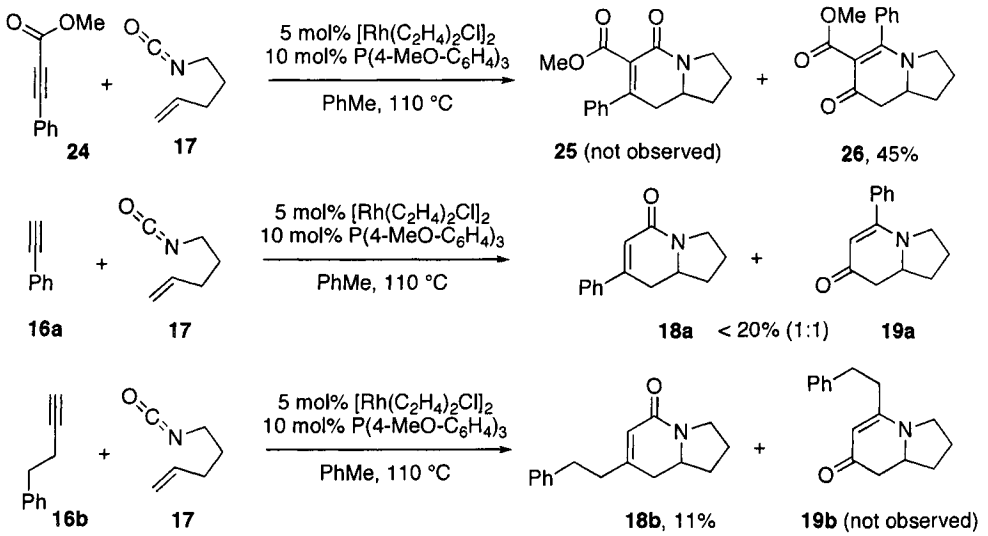
Scheme 2.



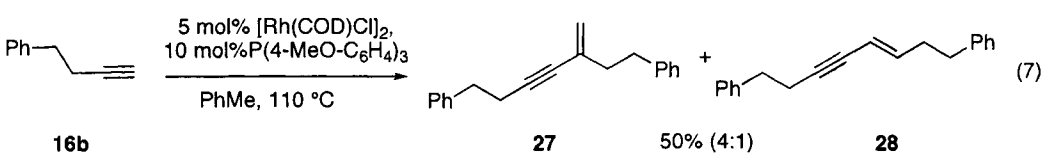
At the outset of our investigation, we aimed to expand the scope of this intriguing cycloaddition reaction beyond symmetrical alkyl alkynes and tolanes. Under the typical conditions, we examined the cycloaddition of alkenyl isocyanate **17** with methyl phenylpropiolate **24** and terminal alkynes **16** (Scheme 3). Cycloaddition with propiolate **24** provides exclusively the migration product **26** in a moderate 45% isolated yield at best. Conjugate addition of the electron-rich triarylphospine to the eletrophilic propiolate **24** can potentially trigger side reactions, leading to the unsatisfactory yields.

Cycloaddition with either aryl or alkyl terminal alkynes proceeded sluggishly. The crude ^{1}H NMR showed a complex mixture with at best an 18% combined yield, and a 1:1 ratio of **18a/19a** with phenyl acetylene **16a**. While the cycloaddition of alkyl terminal alkyne **16b** displayed great selectivity toward lactam **18b**, the reactivity was poor. The lack of

Scheme 3.

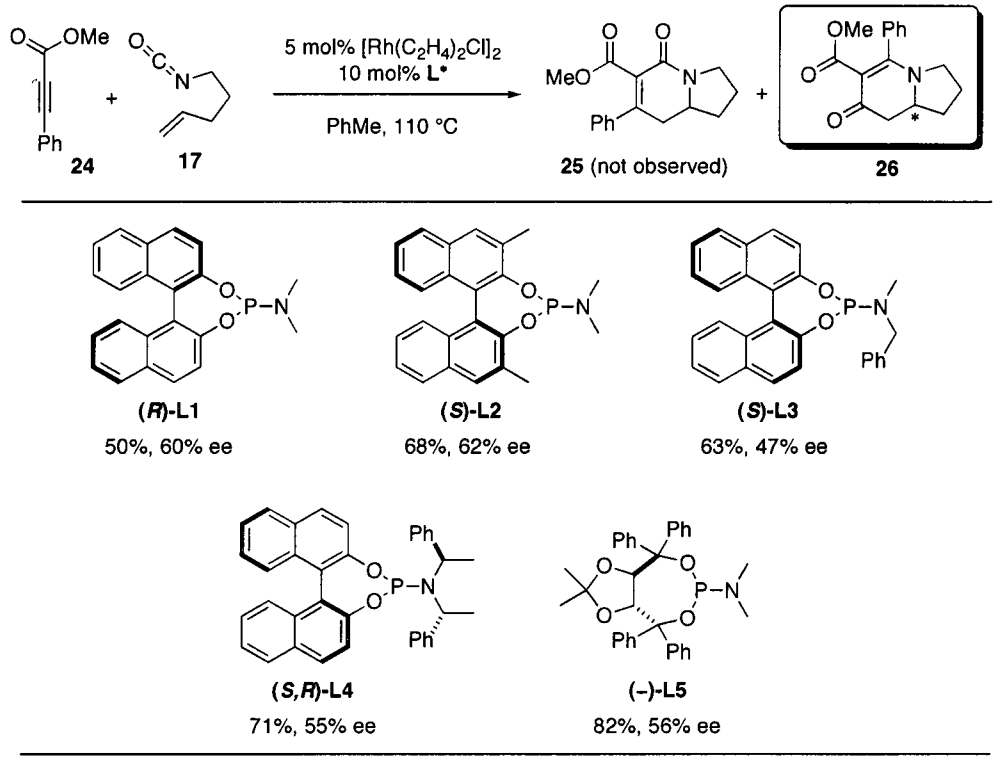


desired reactivity can be partly attributed to the competitive dimerization of terminal alkynes. Dimerizations of terminal alkynes catalyzed by neutral rhodium complexes such as Wilkinson's catalyst are well established in the literature.[18] In fact, when the terminal alkyne **16b** was subjected to the reaction conditions in the absence of isocyanate **17**, dimerized products **27/28** were obtained in a 50% combined yield with a 4:1 ratio favoring the head-to-tail **27** (eq 7).



After many failed attempts to improve the reaction, we identified neutral rhodium complexes modified with phosphoramidites[19] as more efficient catalysts for our [2+2+2] cycloaddition. By employing MONOPHOS (**L1**) as the ligand, the cycloaddition of isocyanate **17** and propiolate **24** proceeds cleanly to afford vinylogous amide **26** with a reproducible 50% yield (Scheme 4). The use of ligand **L2** with methyl groups substituted at the 3,3'-positions of the BINOL further improves the reaction to furnish cycloadduct **26** in 68% yield. Ligands **L3** and **L4**, which possess bulkier amino groups also increase the overall reactivity, although the enantioselectivity decreases. Cycloaddition promoted by the TADDOL-derived phosphoramidite **L5** proves to be optimal with the best chemical yield. Despite moderate enantioselectivities, these bulky chiral phosphoramidites are promising catalysts for further development.

Scheme 4.



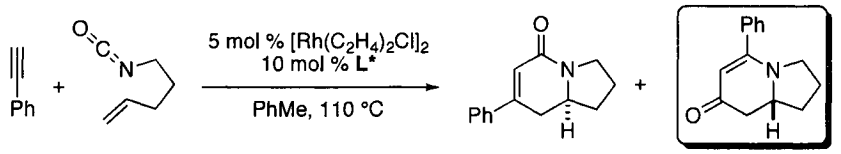
2.3. Enantioselective [2+2+2] Cycloadditions with Terminal Alkynes

As terminal alkynes are the most available alkynyl substrates, developing an efficient [2+2+2] cycloaddition between the alkenyl isocyanates and terminal alkynes is highly desirable. Rhodium catalysts modified by phosphoramidites provide a more efficient cycloaddition with terminal alkynes than the previously developed conditions (Table 1). Treatment of phenyl acetylene **16a** and isocyanate **17** with 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% BINOL-derived ligand **L1** (MONOPHOS) furnishes the cycloadducts **18a/19a** in 32% combined yield with a 1:2.2 product selectivity, favoring *vinylogous amide* **19a** with moderate enantiocontrol (entry 2). Although the bulkier ligand **L2** increases both the reactivity and *lactam-vinylogous amide* selectivity, the enantioselectivity of **19a** decreases significantly (entry 3). On the other hand, the bis[(*R*)-1-phenylethyl] amine substituted phosphoramidite **(*S,R*)-L4** provides a very selective cycloaddition toward the formation of *vinylogous amide* **19a** (entry 4). Although the cycloadduct can be obtained with a good 80% *ee*, the overall reactivity remains unsatisfying. The diastereomeric ligand **(*S,R*)-L4** affords **19a** with the optimal enantioselectivity of the two, but the chemical yield decreases dramatically (entry 5).

In contrast, TADDOL-derived phosphoramidites are found to be much superior ligands for the cycloaddition between phenyl acetylene **16a** and isocyanate **17**. The cycloaddition generally proceeds cleanly to furnish the cycloadducts in high yields and enantioselectivity (entries 6 – 8). The commercially available **L5** affords **19a** with very good *lactam-vinylogous amide* selectivity (entry 6). Replacing the dimethylamino group with the more rigid piperidyl as in **L6** increases the production of the *lactam* **18a** and decreases the enantiocontrol for the major cycloadduct **19a** (entry 7). The pyrrolidyl-

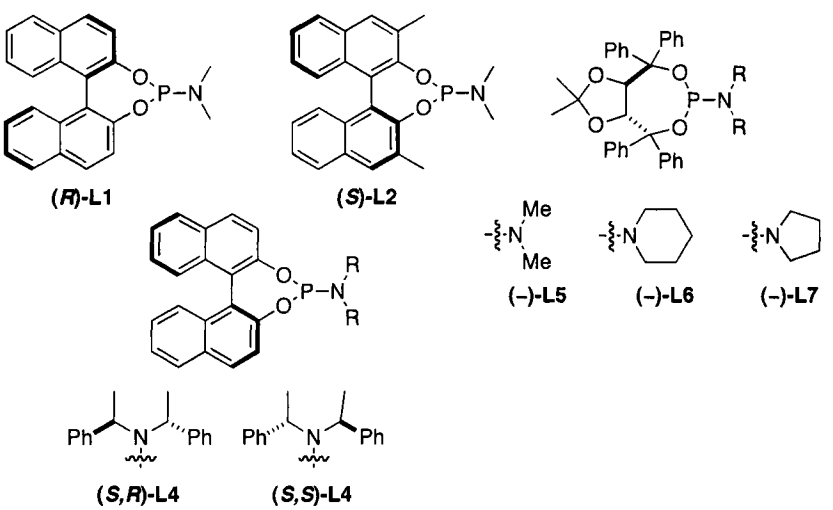
substituted ligand **L7** is the current standard, providing good product selectivity with excellent yield and enantioselectivity for the formation of vinylogous amide (entry 8).[20] It is noteworthy that the cycloaddition proceeds in a highly regioselective manner as both **(*S*)-18a** and **(*R*)-19a** are isolated as single regioisomers (> 20:1 by ^{1}H NMR).

Table 1. Ligand Screen[a]



entry	ligand	**18a : 19a**[b]	yield (%)[c]	ee (%) of **18a**[d]	ee (%) of **19a**[d]
1	$P(4\text{-MeO-}C_6H_4)_3$	1 : 1	< 20	-	-
2	**L1**	1 : 2.2	32	5	55[e]
3	**L2**	1 : 4.5	50	45[e]	8
4	**(*S,R*)-L4**	1 : 15	51	51	80
5	**(*S,S*)-L4**	1 : 15	29	82	85
6	**L5**	1 : 7.0	80	83	94
7	**L6**	1 : 3.3	76	90	81
8	***L7***	***1 : 7.3***	***87***	***89***	***94***

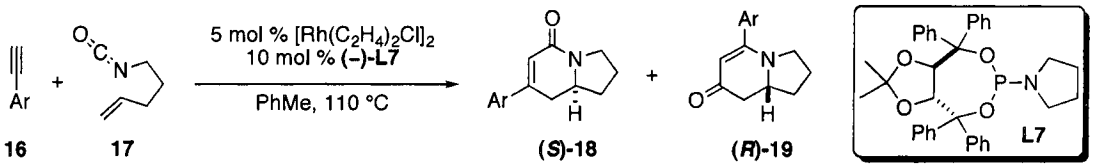
[a] Reaction conditions: **16a** (2 equiv),**17**, Rh cat. (5 mol%), **L** (10 mol%) in toluene at 110 °C, 16h. [b] Lactam-vinylogous amide product selectivity is determined by 1H NMR on the unpurified reaction mixture. [c] Combined isolated yield. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Opposite enantiomer.

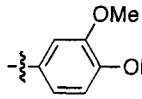
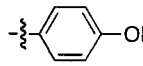
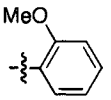
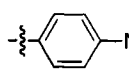
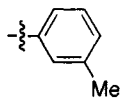
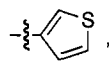
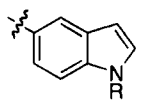
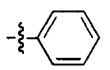
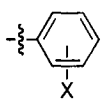
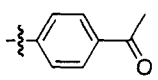
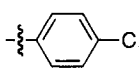
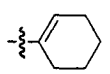


With the optimal conditions in hand, we next examined the scope of this newly developed enantioselective cycloaddition with a variety of aryl acetylenes (Table 2). We found strong dependence of electronics of alkynes on the *lactam-vinylogous amide* product selectivity, and Hammett $\sigma_{m/p}$ and σ_p^+ values have proven useful for correlation in this regard.[21] In general, cycloadditions with electron-rich substituents on the aryl alkynes provide the vinylogous amides **19** predominantly (entries 1—5) with excellent enantioselectivity (up to 94% *ee*). It is important to note that *ortho* substituents on the aromatic ring are well tolerated (entry 3). In addition, heteroaryl acetylenes including both free and protected indoles also undergo the cycloaddition smoothly to afford the corresponding cycloadducts **19** with good yields and excellent enantiocontrol (entries 6 – 8). Electron-withdrawing substituted aryl acetylenes also participate readily in the cycloaddition (up to 94% ee), with the product selectivity gradually shifting towards increased amounts of lactam **18** with increasing EWG strength (entries 10—14). In the most extreme case, where *para*-trifluoromethyl phenyl acetylene is employed as the reacting partner, the cycloaddition yields lactam **18o** as the major product with an excellent enantiomeric excess (entry 14). The reaction is not restricted to aryl acetylenes, as the cyclic enyne **16p** also participates to generate exclusively the corresponding *vinylogous amide* **19** in high efficiency (entry 15).

Absolute configurations of **18** and **19** were assigned by analogy to **(*S*)-18k** and **(*R*)-19k**, which were established unambiguously by X-ray analysis (see the experimental section).

Table 2. Scope of the Cycloaddition with Aryl Acetylenes[a]



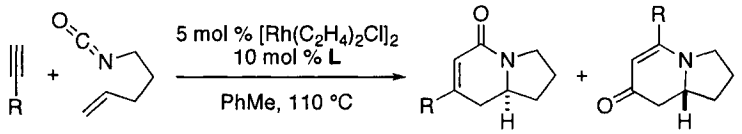
entry	Ar, **16**	$\sigma_{m/p}/\sigma_p^+$	**18** : **19**[b]	yield (%)[c]	ee (%) of **18**[d]	ee (%) of **19**[d]
1	 , **16c**	–	< 1 : 20	72	–	94
2	 , **16d**	-0.27/-0.78	< 1 : 20	70	–	90
3	 , **16e**	–	< 1 : 20	64	–	94
4[e]	 , **16f**	-0.83/-1.70	< 1 : 20	78	–	87
5	 , **16g**	-0.07	1 : 8.3	65	–	94
6[e]	 , **16h**	–	1 : 9.0	64	–	86
7	 R = H, **16i**	–	< 1 : 20	65	–	90
8	R = Boc, **16j**	–	< 1 : 20	85	–	91
9	 , **16a**	0	1 : 7.3	86	89	94
10	 R = *p*-Br, **16k**	0.23/0.15	1 : 3.2	72	90	89
11	R = *p*-Cl, **16l**	0.23/0.11	1 : 3.8	65	93	91
12	R = *m*-F, **16m**	0.34	1 : 1.8	68	94	94
13	 , **16n**	0.50	1 : 1.5	65	94	81
14	 , **16o**	0.54/0.61	2.5 : 1	50	94	–
15	 , **16p**	–	< 1 : 20	96	–	92

[a-d] See Table 1. [e] **L5** used as the ligand.

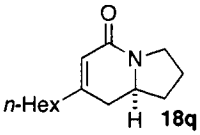
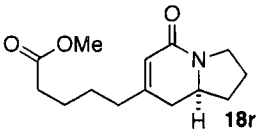
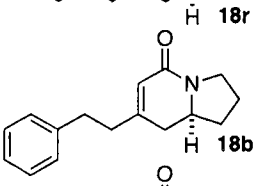
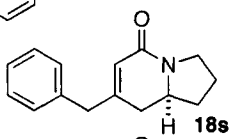
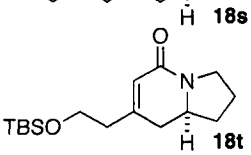
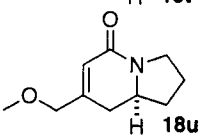
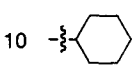
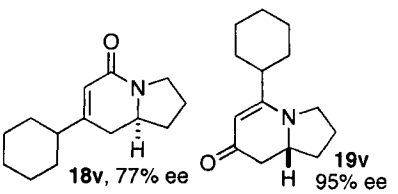
In contrast to the *vinylogous amide* selectivity observed for most aryl acetylenes, reactions with alkyl acetylenes provide primarily *lactam* products presumably due to the large electronic differences between the alkyl and aryl groups (Table 3). Treatment of **17** and 1-octyne **16q** with 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% (–)-TADDOL-P-NMe_2 phosphoramidite **L5** under identical conditions furnishes the desired cycloadducts in high yield (entry 1). The lactam-vinylogous amide product selectivity (3.2:1) illustrates that the catalyst can exert significant control in this reaction (entry 1 vs. 2). Analogous to the aryl acetylene series, the cycloaddition proceeds in a highly regioselective manner; both **18q** and **19q** are isolated as single regioisomers (> 20:1 by ^{1}H NMR). We were also pleased to find that the major product, lactam **18q**, is obtained in good enantiomeric excess (81% *ee*). The larger **L6**, bearing a piperidine ring on the phosphorus center, provides better selectivity in favor of the lactam. The ratio of **18q:19q** increases to 5.0:1 without degradation of both the reactivity and enantioselectivity (entry 3). While replacing the piperidine moiety with morpholine (not shown) gives virtually the same result (**18q:19q**, 4.8:1), the smaller pyrrolidine-containing ligand **L7** increases the production of the vinylogous amide (entry 4).

By employing **L6**, cycloadditions with various primary alkyl acetylenes proceed smoothly to afford *lactams* **3** with excellent product selectivity (up to > 20:1), good enantioselectivity (up to 87% *ee*) and in good combined yields (entries 5 – 9). The more sterically hindered cyclohexyl acetylene (entry 10) furnishes both types of products in an approximately 1:1 ratio with excellent enantioselectivity for **18v** (95% *ee*), suggesting that both sterics and electronics play a role in governing product selectivity.

Table 3. Cycloaddition with Alkyl Acetylenes[a]



16 17 (*S*)-18 (*R*)-19

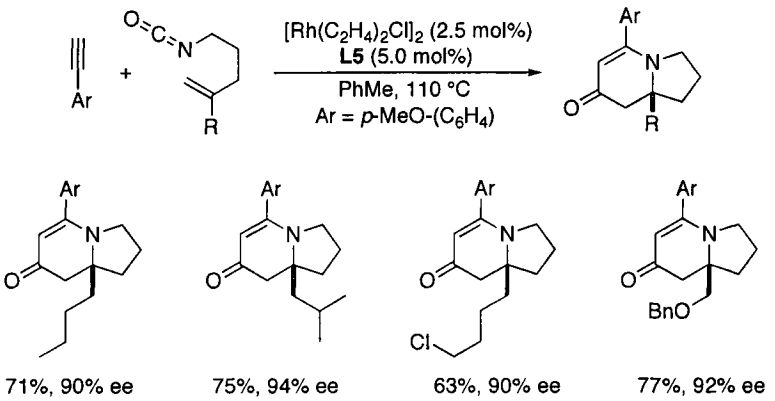
entry	R	L	18 : 19[b]	yield (%)[c]	Major Product	ee (%) of 18[d]
1	*n*-Hex, **16q**	**L5**	3.2 : 1	81	 **18q**	81
2	*n*-Hex, **16q**	P(4-MeO-C_6H_4)$_3$	1 : 0	11		–
3	*n*-Hex, **16q**	**L6**	5.0 : 1	78		80
4	*n*-Hex, **16q**	**L7**	2.4 : 1	80		83
5	$(CH_2)_4CO_2Me$, **16r**	**L6**	5.8 : 1	65	 **18r**	80
6	CH_2CH_2Ph, **16b**	**L6**	> 20 : 1	47	 **18b**	84
7	Bn, **16s**	**L6**	> 20 : 1	50	 **18s**	84
8	CH_2CH_2OTBS, **16t**	**L6**	> 20 : 1	65	 **18t**	87
9	CH_2OMe, **16u**	**L6**	> 20 : 1	46	 **18u**	76
10	 , **16v**	**L5**	1.2 : 1	82	 **18v**, 77% ee **19v** 95% ee	

[a-d] See Table 1.

My colleague, Dr. Ernest E. Lee, has successfully extended this methodology to include enantioselective construction of aza-quaternary stereocenters by demonstrating cycloaddition of various 1,1-disubstituted alkenyl isocyanates (Scheme 5).[22] Enantioselectivities and product ratios obtained are parallel with those obtained with

unsubstituted isocyanate **17**. These transformations are of particular interest as the aza quaternary stereocenters are functionalities traditionally difficult to prepare in an asymmetric fashion.

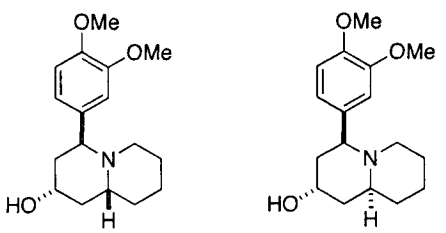
Scheme 5.



2.4. Total Synthesis of (+)-Lasubine II

Lasubine I and II (Figure 1) belong to a family of lythraceae alkaloids isolated by Fuji *et al.* from the leaves of *Lagerstroemia subcostata* Koehne, deciduous trees native to Japan, Taiwan, China, and the Philippines.[23] Since their isolation in 1978,[24] they have become very appealing structural motifs that have attracted significant interest from the synthetic community for the validation of new methodologies in alkaloid synthesis.

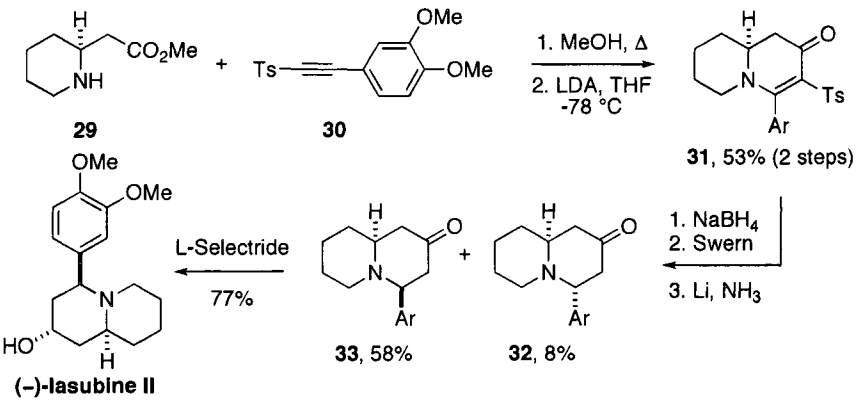
Figure 1.



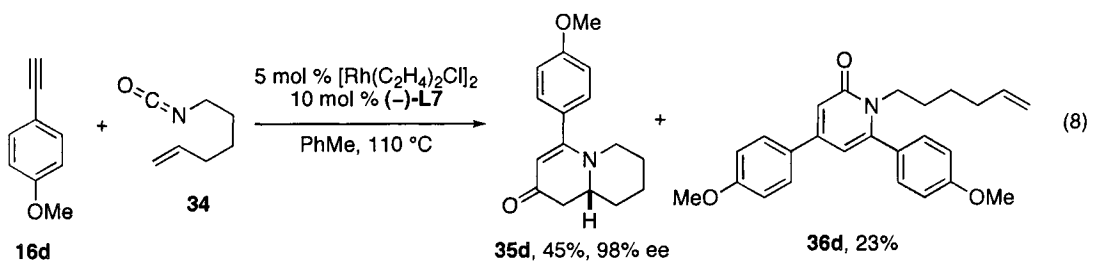
Although there are nine asymmetric syntheses of lasubine II known to date,[25,26] most of them are based on the application of either chiral auxiliary or chiral pool approaches.[27] In

Back and Hamilton's strategy, for example, the key intermediate **31** was built via a conjugate addition/LDA-promoted intramolecular acylation protocol from chiral amine **29** and acetylenic sulfone **30** (Scheme 6).[25g] The enantiopure **29** was in turn prepared by chiral auxiliary chemistry. From **31**, a four-step sequence involving desulfonylation and diastereoselective reduction provided the natural product.

Scheme 6.



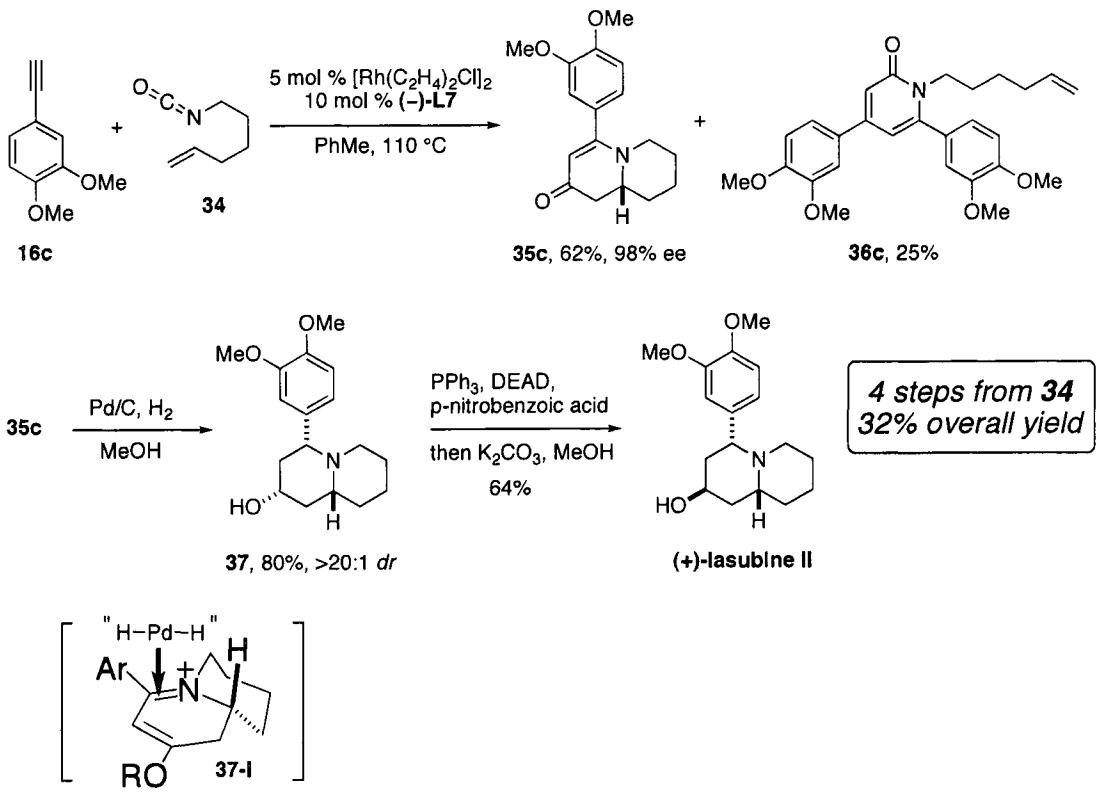
In order to achieve the synthesis of lasubine II, we extended our methodology to include the enantioselective synthesis of quinolizinone **35** by employing the homologous hexenyl isocyanate **34** (eq 8). Gratifyingly, cycloaddition of commercially available **16d** and isocyanate **34** yields the desired quinolizinone in 45% isolated yield and with a superb enantioselectivity. The reaction is accompanied by varying amounts of pyridone **36** as the major side product, suggesting that the olefin is the last 2π component to be incorporated (*vide infra*).



(8)

With the general reactivity established, our total synthesis commences with the enantioselective cycloaddition of isocyanate **34** and the requisite alkyne **16c** (Scheme 7), which is readily available by the Corey-Fuchs reaction.[28] To our delight, the cycloaddition proceeds with a great overall reactivity to afford the desired quinolizinone **35c** in 62% yield and 98% enantiomeric excess, albeit with the formation of 2-pyridone **36c**. Reduction of **35c** under typical hydrogenation conditions gives rise to the formation of enantiopure amino alcohol **37** as a single diastereomer. The reduction presumably involves the iminium species **37-I**, as the vinylogous amide **35c** is likely to tautomerize under the reaction conditions. The hydride source then adds from the less-hindered face (top) to deliver the observed diastereomer. Subjection of **37** to Mitsunobu conditions and the subsequent hydrolysis arrives at the target alkaloid, (+)-lasubine II, in four steps. Our approach represents the shortest synthesis known to date.

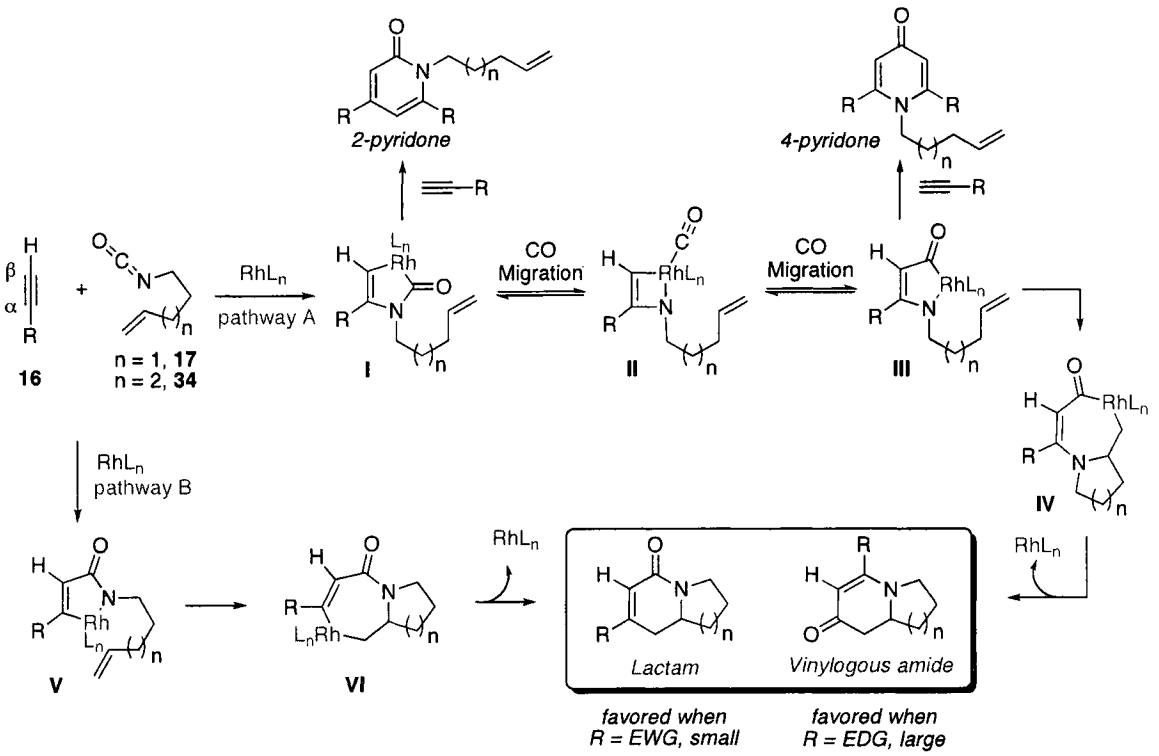
Scheme 7. Enantioselective Synthesis of (+)-Lasubine II



2.5. A Discussion on Mechanism: *Lactam vs Vinylogous Amide*

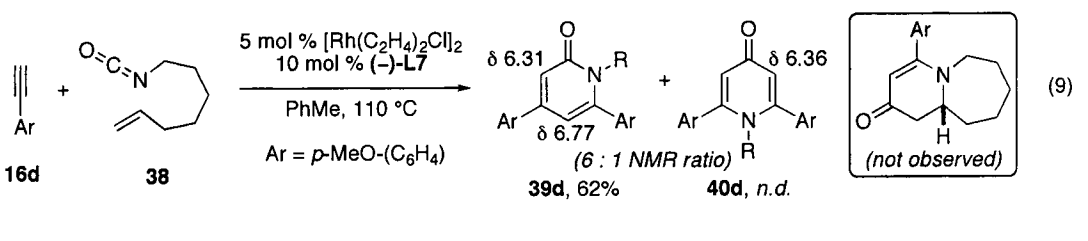
Our current mechanistic understanding is illustrated in Scheme 8. Our data suggests that product partitioning occurs at the cyclization of isocyanate and alkyne (pathway A and pathway B). While several metalacycles are possible, we believe that only two are productive intermediates, **I** and **V**. Oxidative cyclization to form **I** results in a species in which the olefin is incapable of inserting because of a prohibitively strained bridged geometry in the transition state (pathway A). CO extrusion to form **II** followed by re-insertion should lead to **III**, with the olefin now in a proximal relationship to the rhodium. Insertion and reductive elimination via **IV** affords the vinylogous amide product.

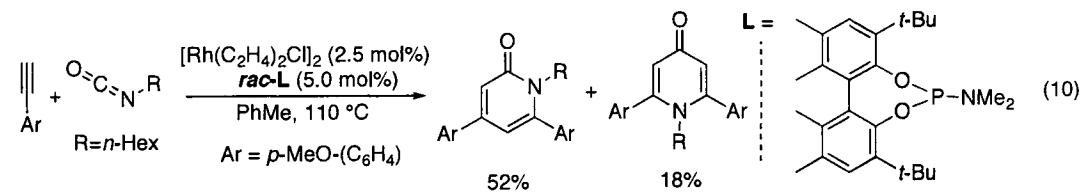
Scheme 8. Proposed Mechanism



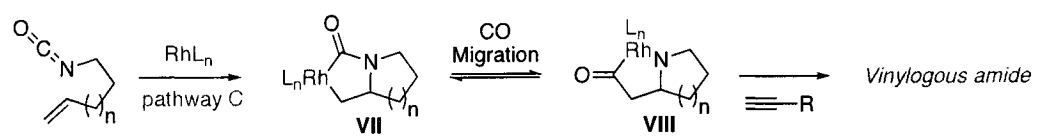
Conversely, the oxidative cyclization may occur with a different regioselectivity, where the C-C bond formation takes place first to afford **V** (pathway B). Subsequent olefin insertion and reductive elimination leads to the lactam product.

The observation that reactions involving longer olefin tethers or conducted in more concentrated solutions provide greater amounts of 2-pyridone products (2 alkynes plus isocyanate) indirectly suggests that metalacycles such as **I** and **III** are responsible for the formation of vinylogous amides. In fact, when we attempted the cycloaddition between alkyne **16d** and heptenyl isocyanate **38**, we were able to observe the formation of both 2-pyridone and 4-pyridone with a 6:1 ratio in the crude ^{1}H NMR (eq 9). Although we were not able to isolate the corresponding 4-pyridone at that time due to its high polarity and basicity, my colleagues Mark Oinen and Kevin Oberg later confirmed our suspicion by isolating 4-pyridones from various reactions (eq 10).[29] These new data strongly support the intermediacy of metalacycle **III** and the CO migration pathway A *en route to* vinylogous amide products. An alternative mechanism involving the intramolecular cyclization of isocyanate and the tethered alkene (pathway C) is less likely.

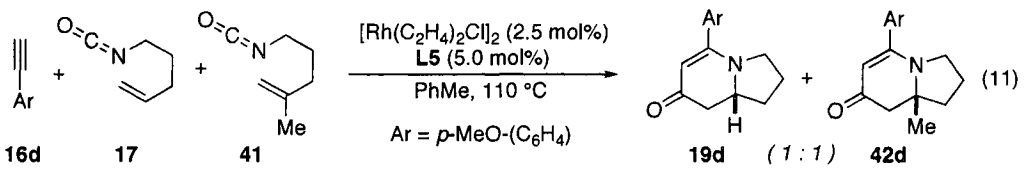




Alternative pathway



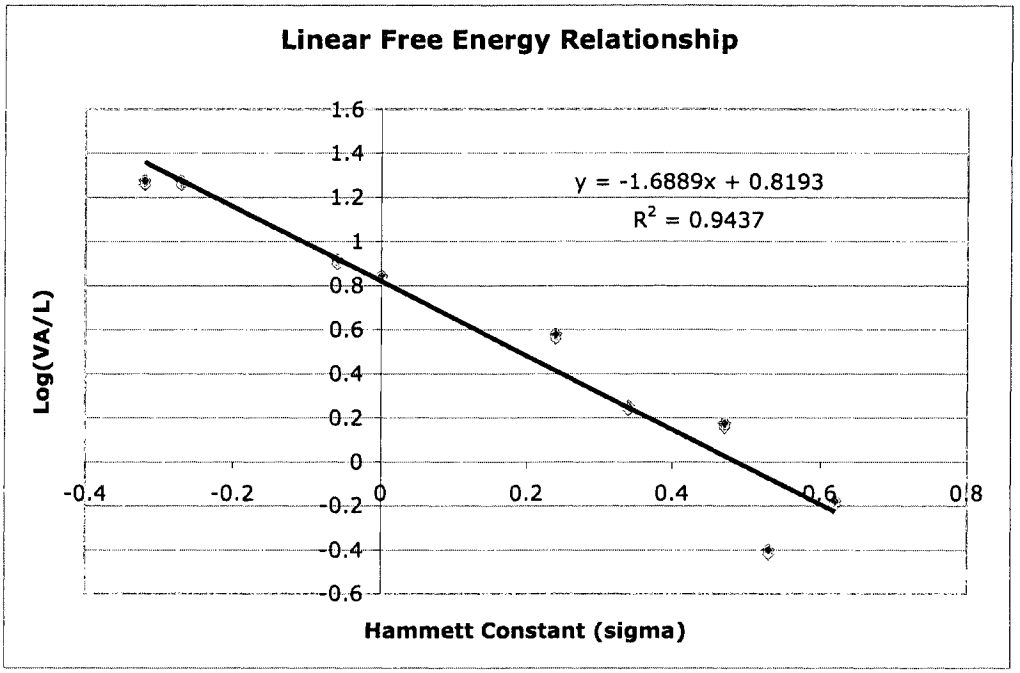
To gain more insight, my colleague, Dr. Ernest Lee, conducted a competition experiment between an isocyanate bearing a terminal alkene (**17**) and one bearing substituted alkenes with aryl acetylene **16d**, which results in product ratios of 1:1 (eq 11). Given that product selectivity does not vary significantly as a function of olefin substitution (which precludes a scenario involving olefin coordination to metal upon alkyne complexation) and that it is rather unlikely that terminal olefin and 1,1-disubstituted olefin insertion into the Rh-N bond would involve transition states of exactly equal energy, the first oxidative cyclization (paths **A** and **B** to metalacycles **I** and **V**) is most likely the first irreversible step.

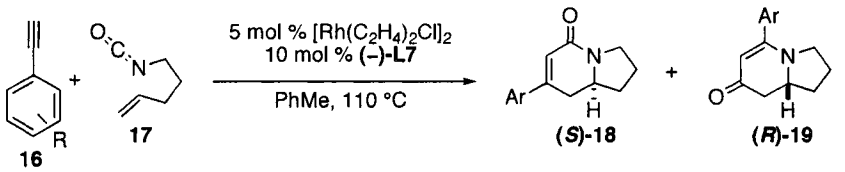


16d 17 41 19d 42d (11)

Although the observation of pyridone products has shed some light on the mechanism, a crucial question remains: what dictates the selectivity between the formation of metalacycles **I** and **V**. While there certainly is a steric component, our results in the aryl acetylene series (Table 2) also indicate a considerable and measurable electronic component. The data may be extrapolated to provide a quantitative measure of developing charge in the transition states leading to product partitioning between vinylogous amide and lactam (Figure 2). The significant ρ value (-1.7) indicates that there is a positive charge buildup at the alpha carbon of the alkyne in the transition state leading to vinylogous amide. Similar trends have been noted in the Rh-catalyzed asymmetric Pauson-Khand reaction[30] and the migratory aptitude of R groups onto a rhodium carbonyl ligand.[31]

Figure 2. LFER Diagram



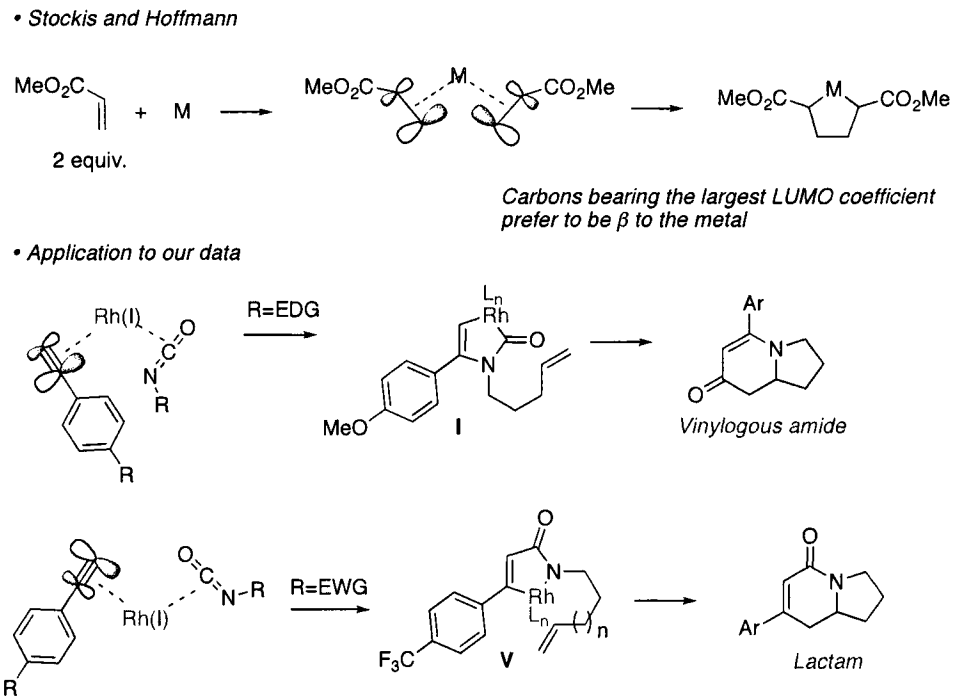


R	19 : 18	$\sigma_{m/p}$
p-OMe	95 : 5	–0.27
m-Me	89.2 : 10.8	–0.06
H	87.5 : 12.5	0
p-Cl	79.2 : 20.8	0.24
m-F	64.3 : 35.7	0.34
p-Ac	60 : 40	0.47
m-CN	40 : 60	0.62
p-CF_3	28.5 : 71.5	0.53

Qualitatively, our current mechanistic understanding involves the supposition that the regiochemistry of cyclization is dictated by electronic stabilization of each position; EDG or large substituents on the alkyne lead to vinylogous amides while EWG or small substituents provide lactams (Scheme 8). The observation on product selectivity between EDG and EWG is consistent with Stockis and Hoffmann's theoretical treatise of

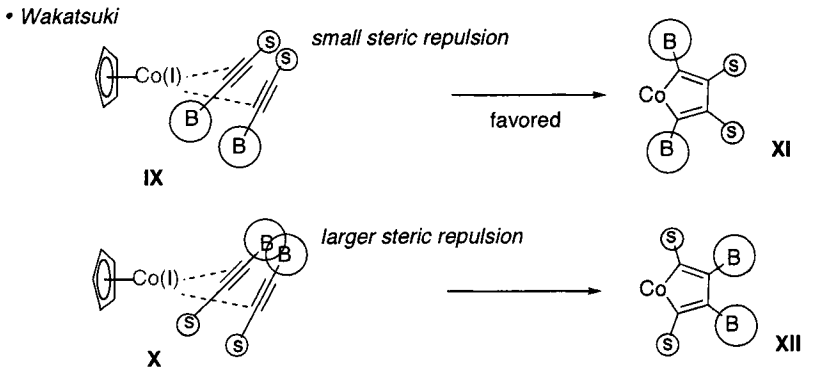
metalacycle formation.[32] They argue that the regioselectivity of metalacycle formation is determined by placement of the π systems with the largest coefficients in the LUMO β to the metal (Figure 3). This theoretical study agrees well with our cycloaddition trend, where the use of EWG aryl alkynes leads to increased amount of **V** and the resulting lactam products.

Figure 3. Electronic Factors

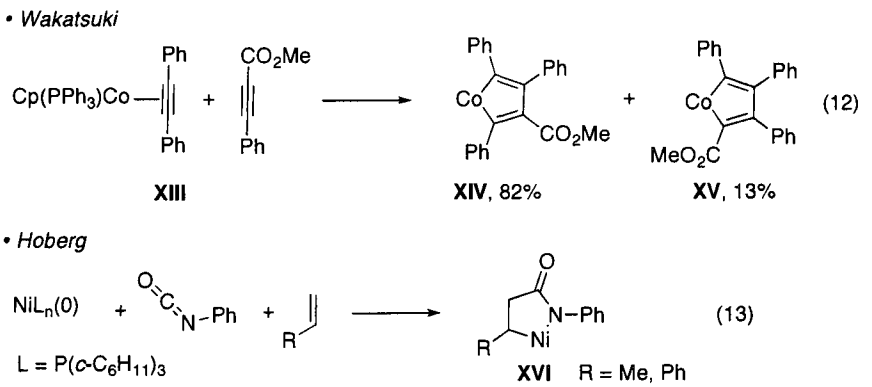


In contrast to aryl alkynes, cycloaddition with alkyl alkynes is most likely governed by steric factors. In Wakatsuki and coworker's theoretical study on the regioselectivity of cobaltacyclopentadiene formation, they argue that the bulkiest substituents on the alkyne will be placed α to the Co (Figure 4).[33] In their molecular orbital calculation, cobalt-acetylene complex **IX** is preferred, because the bulkier substituents, B, are directed to the least hindered sites. On the contrary, complex **X** is less favorable due to large steric repulsion between two bulky groups at the β-positions.

Figure 4. Wakatsuki's Steric Argument



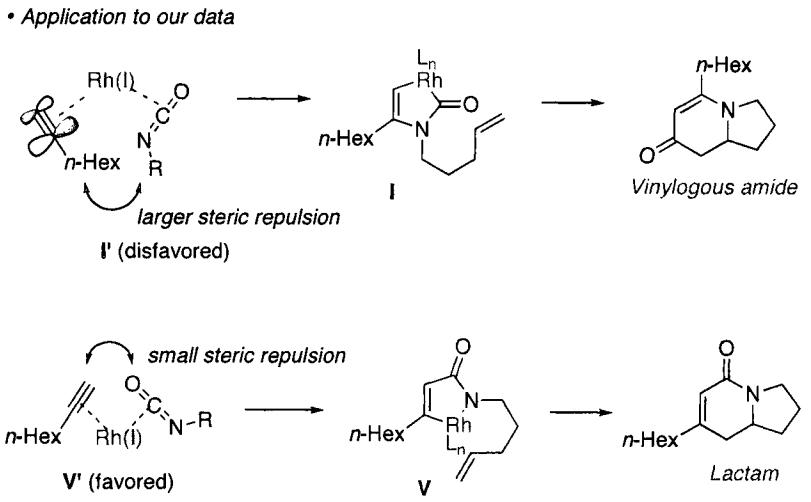
Wakatsuki has used this theorem to rationalize the selective formation of metalacycle **XIV**, which the electronic argument from Stockis and Hoffmann would fail to predict (eq 12). Likewise, the steric factor overrides the electronic effect in the exclusive formation of Hoberg's metalacycle **XVI** (eq 13).



Our experimental data on alkyl alkynes is in accord with Wakatsuki's steric argument (Figure 5). Rhodium complex **V'**, where the larger groups on the alkyne and the isocyanate are placed at the least hindered site, gives rise to the formation of metalacycle **V** as the major intermediate. On the other hand, complex **I'**, leading to vinylogous amide product, would be less favorable due to larger steric repulsion at the

distal positions. This agrees well with our cycloaddition trend, where the use of alkyl alkynes predominantly affords the lactam products.

Figure 5. Steric Factors



2.6. Conclusion

In summary, we have developed a highly regio- and enantioselective rhodium-catalyzed [2+2+2] cycloaddition involving alkenyl isocyanates and terminal alkynes, providing efficient access to indo- and quinolizinone cores. Depending on the substrates, product selectivity may be governed by a combination of electronics and sterics. The synthetic utility has been demonstrated by a concise total synthesis of (+)-lasubine II.

2.7. References

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Chapter 3

Asymmetric Synthesis of Bicyclic Amidines via Rhodium-Catalyzed [2+2+2] Cycloaddition of Carbodiimides

3.1. Introduction

In the previous study, we described an enantioselective cycloaddition between phenyl acetylene **1a** and isocyanate **2** (X=O, Scheme 1) catalyzed by Rh(I)/TADDOL-derived phosphoramidite complexes. It was discovered that the major pathway proceeds through the formation of metalacycles **I** and **II** involving a CO migration process to afford product **4** (X=O) in good yields and high enantioselectivities.[1] The secondary cycloadduct **3**, which is derived from metalacycle **III**, can only be formed as the minor component (**3**:**4** = 1:7, Ar=Ph). Despite numerous attempts to modify the catalysts, formation of **3** was never achieved at a proficient level. In an effort to selectively access products of type **3**, we envisioned that a cycloaddition employing carbodiimides **2** (X=NAr) should favor the formation of metalacycle **III** by placing the bulky imido moiety further away from the rhodium center (**I** vs. **III**, Figure 1). Herein, we report the successful application of this strategy, providing a complementary selectivity to the cycloaddition previously described using isocyanates.[2] In addition, this reaction offers a

Scheme 1.

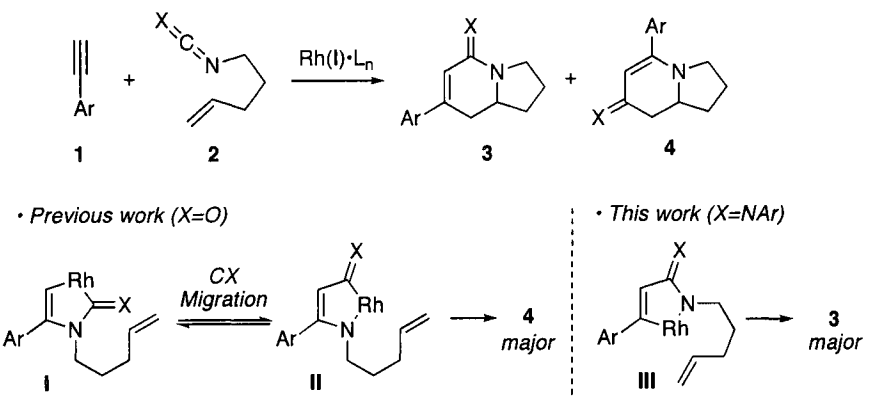
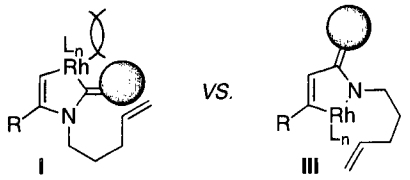
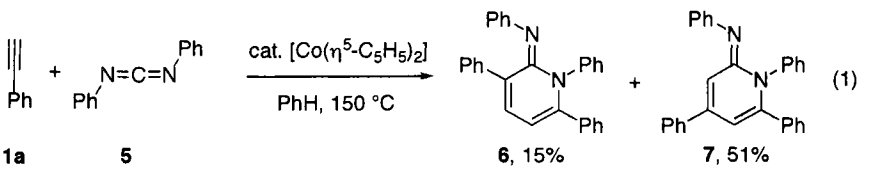


Figure 1.

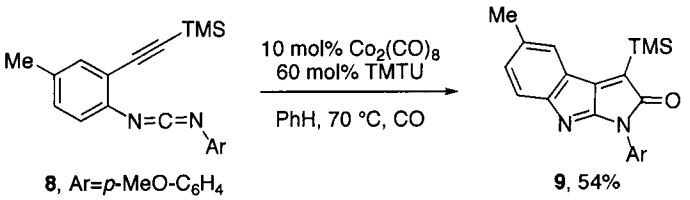


novel entry into the asymmetric synthesis of bicyclic amidines **3** (X=NAr).[3] Cyclic amidines are highly useful in medicinal chemistry, coordination chemistry, and material science.[4] They are also valuable building blocks in synthetic organic chemistry. Their nucleophilic character at the nitrogen centers has found broad utility in organic synthesis, including directed metalation, C—H activation, and catalysis as the non-metal-containing catalysts.

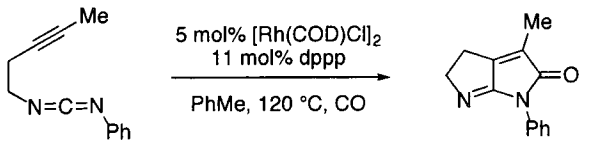
Recent advances in the field of transition metal-catalyzed cycloadditions have made them among the most efficient methods to assemble polycyclic carbocycles and heterocycles.[5] However, a brief survey of the literature reveals that cycloadditions employing carbodiimides are surprisingly scarce.[6] In 1977, Hong and Yamazaki reported an intermolecular cobalt-catalyzed cycloaddition between two equivalents of an alkyne such as **1a** and diphenylcarbodiimide **5** (eq. 1).[6a] The ratio of two isolated iminopyridines **6** and **7** varies depending on the alkyne substituent. The same reaction was also explored by Hoberg and coworkers employing a nickel catalyst,[6b] and later on by Diversi and coworkers focusing on the substrate scope.[6c]



Most recently, Mukai's and Saito's research laboratories have independently reported an intramolecular hetero-Pauson-Khand-type reaction, utilizing alkynyl carbodiimides such as **8** and **10** in the presence of a cobalt or rhodium catalyst, respectively (eq. 2 and 3).[7]

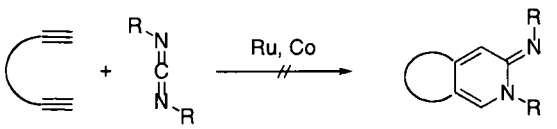


8, Ar=*p*-MeO-C_6H_4 **9**, 54% (2)



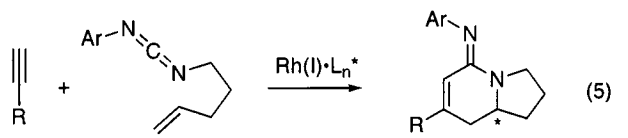
10 **11**, 43% (3)

Despite efforts from various research groups, transition metal-catalyzed [2+2+2] cycloadditions of diynes **12** and carbodiimides have been documented to provide mostly intractable product mixtures (eq. 4).[8,9]



12 **13** **14** (4)

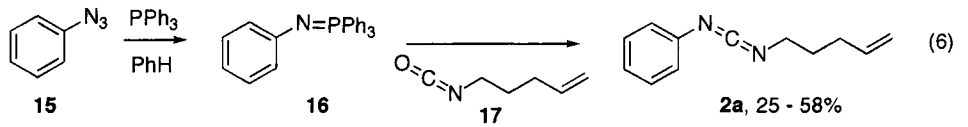
To the best of our knowledge, there have been no reports of successful enantioselective [*m*+*n*+*o*] type cycloadditions involving carbodiimides as a 2π component. In this chapter, we account the development of a highly enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes and alkenyl carbodiimides (eq. 5).



1 **2** **3** (5)

3.2. Reaction Development

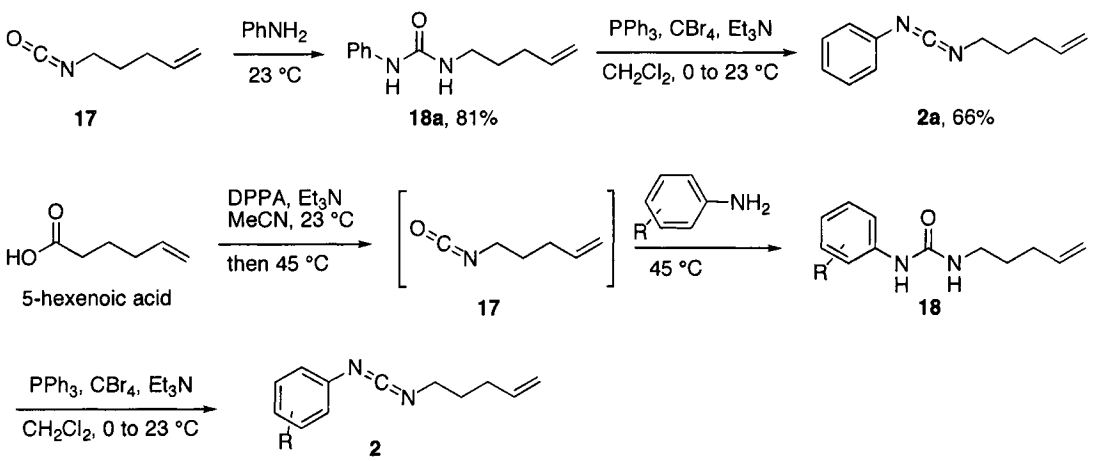
We began our investigation by developing an efficient strategy to the requisite alkenyl carbodiimides **2**. Initially, a two-step sequence, consisting of a Staudinger reaction to afford the iminophosphorane **16** and the subsequent aza-Wittig reaction with isocyanate **17** was used to prepare the phenyl-substituted carbodiimide **2a** (eq. 6).



15 **16** **17** **2a**, 25 - 58% (6)

However, the inconsistency in yields led us to an improved protocol as illustrated in Scheme 2. Treatment of the isocyanate **17**, prepared from the commercially available 5-hexenoic acid via Curtius rearrangement, with aniline furnishes the mixed urea **18a**. Dehydration by employing triphenylphosphine and carbon tetrabromide affords the alkenyl carbodiimide **2a** in a good overall yield. Alternatively, a one-pot procedure has been developed to access various mixed ureas **18** in good yields without the need to isolate isocyanate **17** (see the experimental section). Unlike isocyanates, these carbodiimides **2** are less moisture-sensitive and are stable to flash chromatography for purification purposes.

Scheme 2.



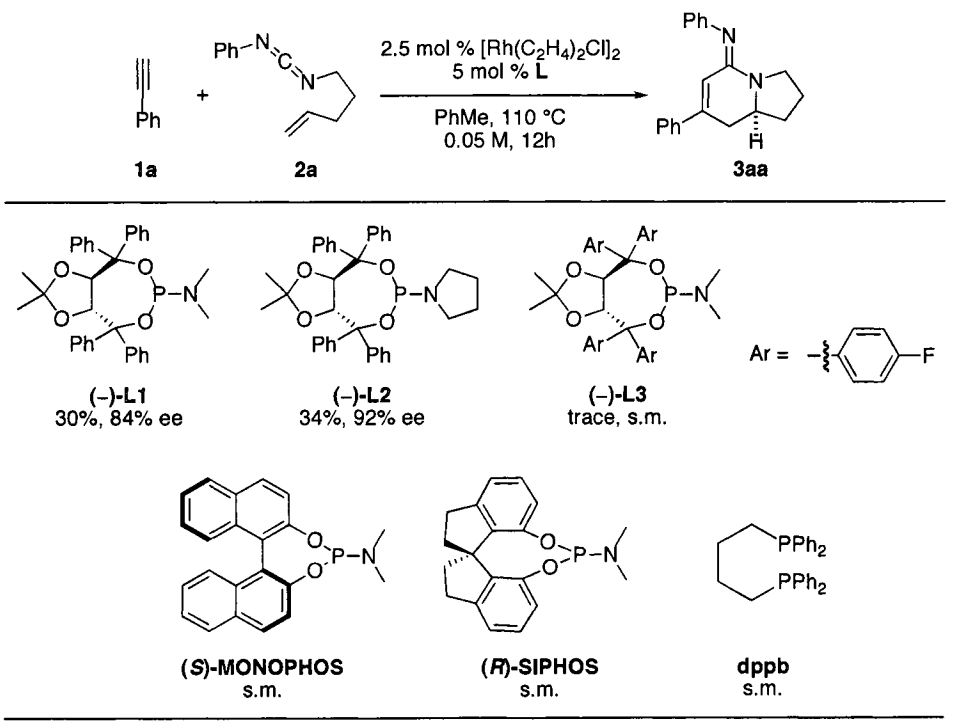
17 **18a**, 81% **2a**, 66%

17 **18**

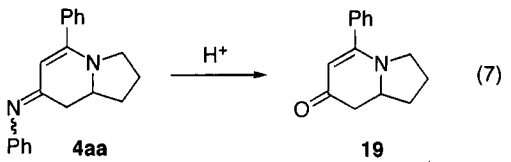
2

With an efficient approach to various alkenyl carbodiimides **2** in hand, we first evaluated the cycloaddition of phenyl acetylene **1a** and the phenyl-substituted pentenyl carbodiimide **2a** by conducting a brief ligand screen (Scheme 3). Gratifyingly, when we employed neutral Rh(I) complexes modified with either phosphoramidite **L1** or **L2**, catalysts developed previously for the isocyanate chemistry, these conditions indeed furnished the desired bicyclic amidine **3aa**. Despite the low yields, ligand **L2** afforded cycloadduct **3aa** with excellent enantioselectivity. The use of more electron-deficient phosphoramidite **L3** only provided a trace amount of cycloadduct. Other classes of phosphoramidites such as MONOPHOS and SIPHOS, and the bidentate dppb all yielded no desired product with the starting carbodiimide **2a** left unreacted.

Scheme 3. Initial Screen



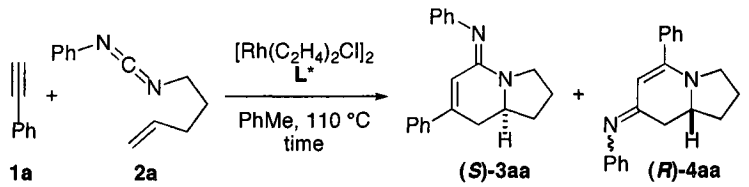
In the cases of ligands **L1** and **L2**, a secondary cycloaddition product was isolated in 10 to 12% yield (the structure was first inferred based on the mass obtained from HRMS). After converting to the known vinylogous amide **19** under acidic conditions, the mysterious cycloadduct was unambiguously proven to be the type **4** product resulting from a rare isocyanide (CNR) migration[10] (eq. 7). Vinylogous amidine **4aa** was isolated as a 3:1 mixture of imine isomers (determined by ^{1}H NMR).



(7)

Treatment of **1a** and carbodiimide **2a** with 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L2** furnishes both cycloadducts **3aa**/**4aa** in a 2.8:1 product selectivity, favoring the desired amidine **3aa** with a moderate yield and excellent enantioselectivity (Table 1, entry 2). Although increasing catalyst loading slightly improves the chemical yields of **3aa** (entries 1, 2), the overall reactivity remains unsatisfying. To further optimize the desired [2+2+2] cycloaddition, we turned our attention to new catalysts by fine-tuning the phosphoramidites. The *p*-tol-TADDOL derived ligand **L4** provides a very efficient reaction with half the catalyst loading and shorter reaction times (entry 3). Further optimization led to the identification of *m*-xylyl-TADDOL derivative **L5** as the best ligand, affording the bicyclic amidine with good chemical yield and excellent enantioselectivity (entry 4). The amino group on the ligand proves to have a significant effect on the reaction: replacing the pyrrolidinyl moiety with the piperidinyl (**L6**) can further improve the product selectivity for **3aa**, although the enantioselectivity decreases dramatically (entry 5).

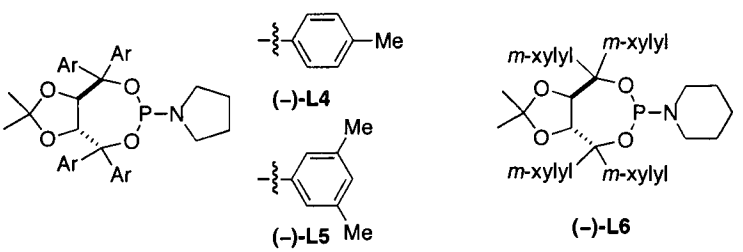
Table 1. Ligand Screen[a]



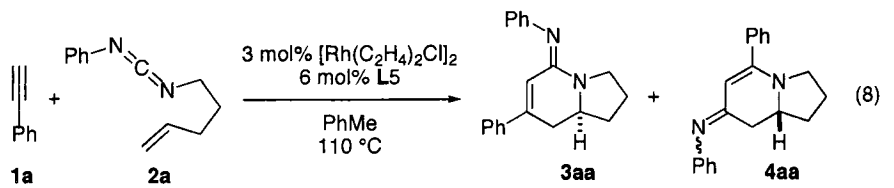
1a 2a (*S*)-3aa (*R*)-4aa

entry	$[Rh(C_2H_4)_2Cl_2]$	L* (mol %)	time (h)	3 : 4[b]	yield (%) of 3aa[c]	*ee* (%) of 3aa[d]
1	5%	**L1** (10)	12	2.4 : 1	40	84
2	5%	**L2** (10)	12	2.8 : 1	57	94
3	3%	**L4** (6)	3	3.4 : 1	64	95
4	***3%***	***L5 (6)***	***3***	***3.4 : 1***	***70***	***97***
5	3%	**L6** (6)	3	4.8 : 1	78	89

[a] Conditions: **1** (2 equiv), **2** (0.16 mmol), Rh catalyst, **L** in PhMe at 110 °C. [b] Product selectivity (**3 : 4**) is determined by ^1H NMR of the unpurified reaction mixture. [c] Isolated yield. [d] Determined by HPLC analysis using a chiral stationary phase.



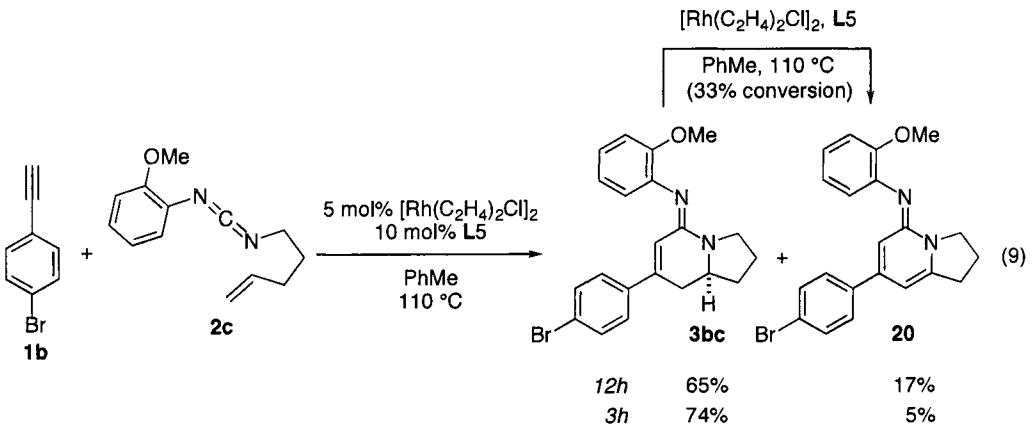
The short reaction time (*ca.* 3 hours) turns out to be quite crucial as both cycloadducts **3** and **4** can slowly decompose under the new conditions (**L4** – **L6**). For example, the cycloaddition of **1a** and **2a** promoted by the ligand **L5** yields 18% of cycloadduct **4aa** after 3 hours, but only gives less than 9% yield when the reaction time is extended to 12 hours (eq 8). The significance of decomposition of cycloadduct **3** varies



1a 2a 3aa 4aa (8)

	3aa	4aa
12h	70%	9%
3h	70%	18%

depending on the electronics of products. During the investigation, we discovered that when the reaction between *para*-bromo phenyl acetylene **1b** and carbodiimide **2c** was conducted for an extended time period, a significant amount of iminopyridine **20** was isolated (eq 9). The formation of iminopyridine **20** can be rationalized by the oxidation of amidine **3bc**. Simple air oxidation is not likely since refluxing the amidine in toluene for 12 hours gives only a trace amount of iminopyridine **20**. In contrast, resubjecting amidine **3bc** to the reaction conditions affords the oxidized product with up to 33% conversion, suggesting that this is a metal-mediated process.

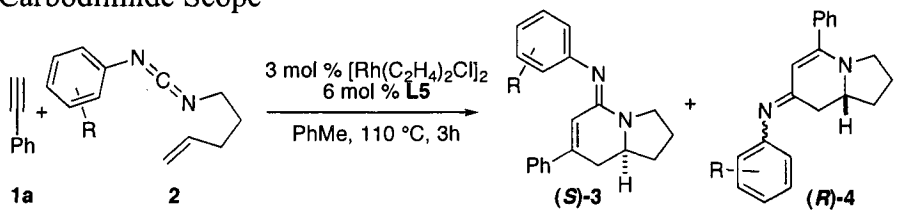


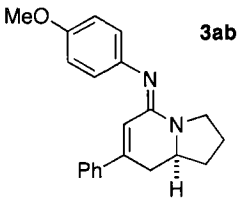
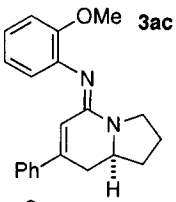
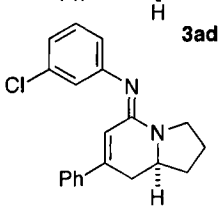
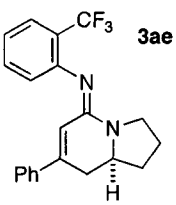
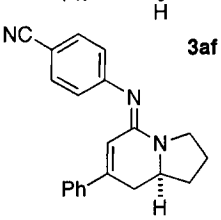
3.3. Substrate Scope

Table 2 summarizes the scope of the enantioselective [2+2+2] cycloaddition of phenyl acetylene **1a** and a variety of aryl-substituted carbodiimides. An electron-rich methoxy group at either *para* (**2b**) or *ortho* (**2c**) position of the aromatic ring is well tolerated and furnishes the corresponding bicyclic amidines in good yields and excellent enantioselectivities (entries 1, 2). We employed the *ortho*-anisole-substituted carbodiimide **2c** in larger scale cycloaddition to further test the method. For larger scale reactions, the catalyst loading may be reduced to 1 mol% $[Rh(C_2H_4)_2Cl]_2$ with virtually identical yield and enantioselectivity (entry 2). Cycloaddition with the carbodiimide **2d**,

bearing chlorine at the *meta* position, proceeds smoothly to provide amidine **3ad** in 67% isolated yield and 97% ee (entry 3). Delightfully, aryl carbodiimides with strong electron-withdrawing groups such as trifluoromethane and nitrile provide much greater product selectivity toward the desired amidine **3**, while maintaining the high enantioselectivities (entries 4, 5).

Table 2. Carbodiimide Scope

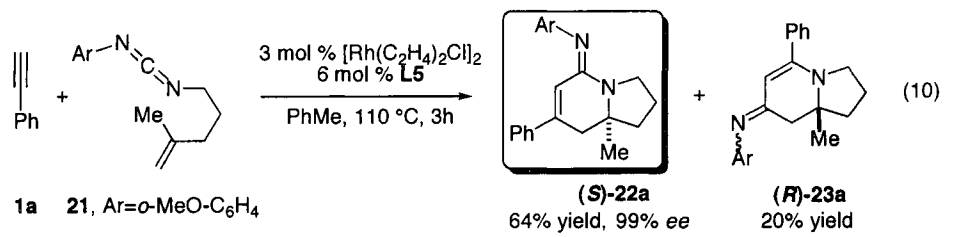


entry	R	Cycloadduct 3	3 : 4[b]	yield (%) of 3[c]	*ee* (%) of 3[d]
1	*p*-OMe, **2b**	**3ab** 	3.6 : 1	70	94
2	*o*-OMe, **2c**	**3ac** 	3.8 : 1	68 (62)[e]	98 (96)[e]
3	*m*-Cl, **2d**	**3ad** 	3.4 : 1	67	97
4	*o*-CF_3, **2e**	**3ae** 	9.4 : 1	82	97
5[f]	*p*-CN, **2f**	**3af** 	9.5 : 1	55	92

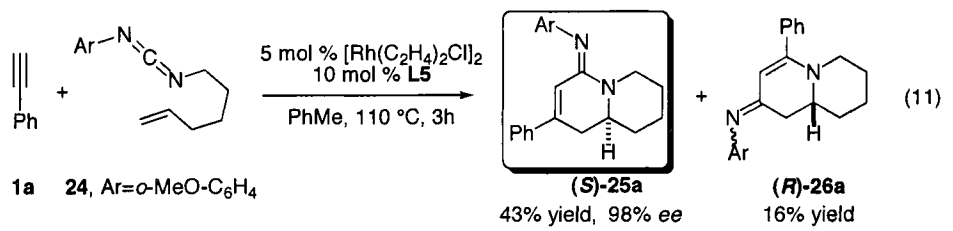
[a-d] See Table 1. [e] 0.8 mmol scale of **2c**, 1 mol% Rh catalyst and 2 mol% **L5**.
[f] 5 mol % Rh catalyst and 10 mol % **L5**.

For further substrate development, we chose the *o*-anisidine derived carbodiimide as the standard cycloaddition partner. This selection was based on the optimal enantioselectivity obtained and its potential role as an oxidatively cleavable protecting group of the resulting cycloadducts.[11]

The asymmetric synthesis of amidine **22a** possessing a nitrogen-substituted quaternary center can be achieved in high efficiency from the corresponding disubstituted alkenyl carbodiimide (eq. 10).[1c] Although a much more sluggish reaction, cycloaddition of carbodiimide **24** to construct the desired [4.4.0] bicyclic amidine **25a** proceeds in a moderate yield with excellent enantiocontrol (eq. 11).

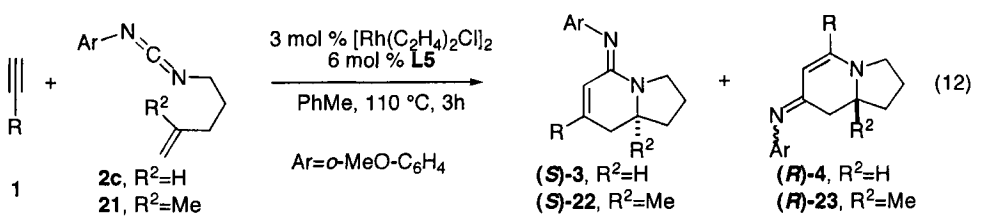


(10)



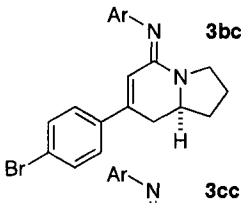
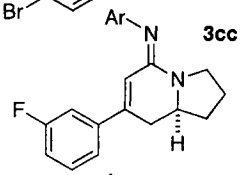
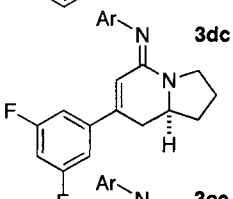
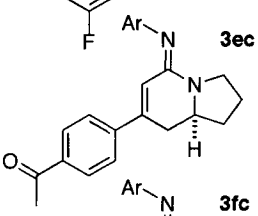
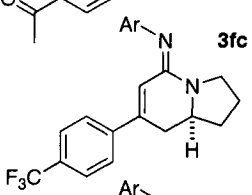
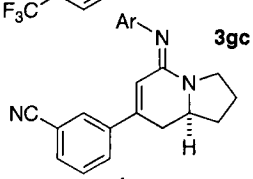
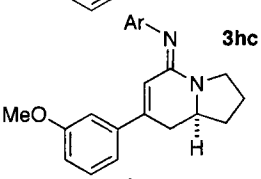
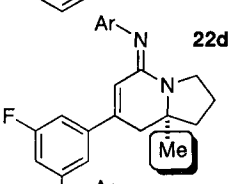
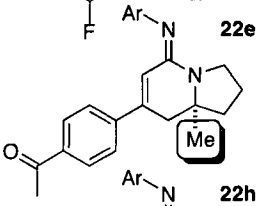
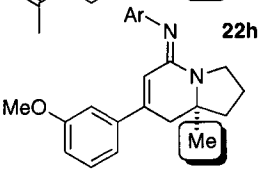
(11)

The cycloadditions of a variety of terminal aryl alkynes and carbodiimides **2c** and **21** were examined (eq. 12, Table 3). The electronic and steric effects of alkynyl partners play an important role in the reaction outcome. Aryl acetylenes substituted with various



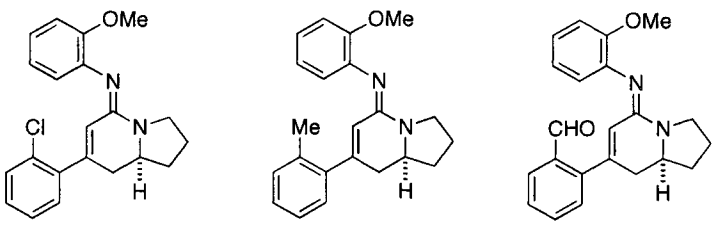
(12)

Table 3.
Alkyne Scope

entry	R	Cycloadduct **3** or **22**	**3** : **4** or **22** : **23**	yield (%) of **3** or **22**	*ee* (%) of **3** or **22**
1	*p*-Br-C_6H_4, **1b**	 **3bc**	16 : 1	75	98
2	*m*-F-C_6H_4, **1c**	 **3cc**	> 19 : 1	77	99
3	3,5-F-C_6H_3, **1d**	 **3dc**	> 19 : 1	66	99
4	*p*-Ac-C_6H_4, **1e**	 **3ec**	> 19 : 1	78	99
5	*p*-CF_3-C_6H_4, **1f**	 **3fc**	> 19 : 1	68	96
6	*m*-CN-C_6H_4, **1g**	 **3gc**	> 19 : 1	62	94
7	*m*-OMe-C_6H_4, **1h**	 **3hc**	6.3 : 1	69	99
8	3,5-F-C_6H_3, **1d**	 **22d**	> 19 : 1	79	98
9	*p*-Ac-C_6H_4, **1e**	 **22e**	16 : 1	74	99
10	*m*-OMe-C_6H_4, **1h**	 **22h**	4.5 : 1	66	96

electron-poor groups participate in the cycloaddition readily to furnish almost exclusively the bicyclic amidine **3** or **22** with good yields and exceptional enantioselectivity (entries 1 – 6, 8, 9). The reactions of alkyne **1h**, which possesses a moderate σ-withdrawing group, proceed with the same efficiency to afford the desired amidines in good product ratio (entries 7, 10). Overall, the optimized cycloaddition shows good compatibility with halogens, cyano, acetyl, and trifluoromethyl groups substituted at either *para* or *meta* positions of the aryl alkynes. *ortho*-Substituted aryl alkynes are not tolerated under current conditions. Cycloaddition with 1-chloro-2-ethynyl benzene **1i** gives product **3** in only 35% yield and 31% *ee* while reactions with either 2-ethynyltoluene **1j** or 2-ethynylbenzaldehyde **1k** provide no cycloadducts (Scheme 3).

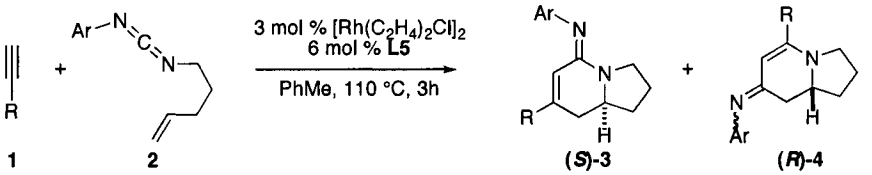
Scheme 3.



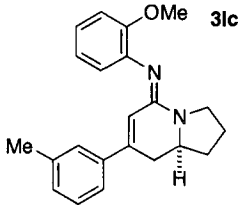
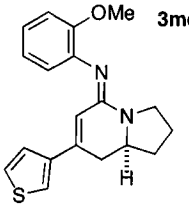
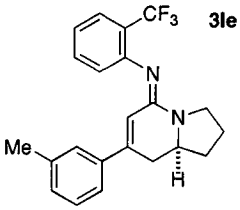
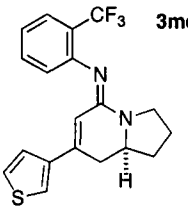
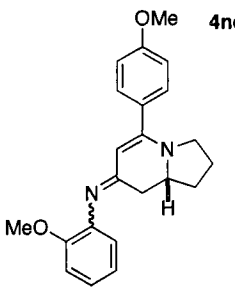
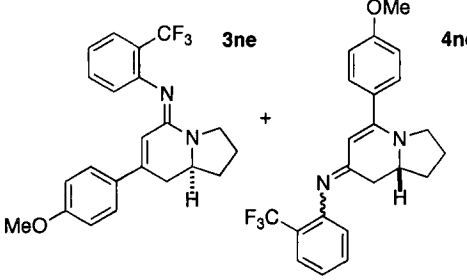
3ic, 35%, 31% ee **3jc**, no reaction **3kc**, no reaction

m-Tolyl acetylene **1l**, which is slightly more electron-rich than phenyl acetylene **1a**, undergoes the cycloaddition to provide the corresponding amidine in high enantiomeric excess with a product ratio similar to those obtained with **1a** (entry 1, Table 4). The heterocycle ethynyl thiophene **1m** is also tolerated, to afford the thiophene-containing amidine **3mc** in a similar efficiency (entry 2). The moderate product ratio with carbodiimide **2c** can be greatly improved while maintaining the excellent enantiocontrol by using the *o*-CF_3-phenyl carbodiimide **2e** (entries 3, 4).

Table 4.



1 2 (*S*)-3 (*R*)-4

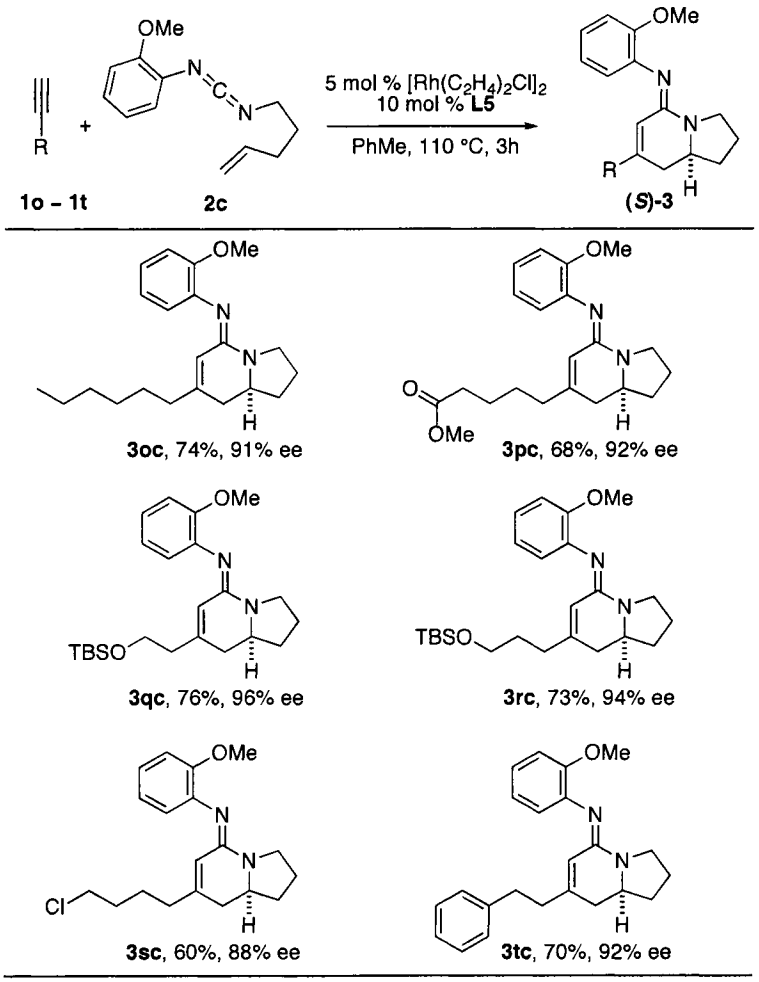
entry	R	carbodiimide	Major Cycloadduct	3 : 4	yield (%) of 3	*ee* (%) of 3
1	*m*-Me-C_6H_4, **1l**	**2c**	 **3lc**	3.4 : 1	61	98
2	 , **1m**	**2c**	 **3mc**	3.2 : 1	58	98
3	*m*-Me-C_6H_4, **1l**	**2e**	 **3le**	8.3 : 1	74	98
4	 , **1m**	**2e**	 **3me**	7.2 : 1	79	97
5	*p*-OMe-C_6H_4, **1n**	**2c**	 **4nc**, 52%	1 : 2.8	20	99
6	*p*-OMe-C_6H_4, **1n**	**2e**	 **3ne** + **4ne**, 36%	1 : 1	37	96

On the other hand, the reaction of electron-rich aryl acetylene **1n** proceeds with an opposite product selectivity, a trend that is consistent with our previous study.[1b] Thus, the combination of alkyne **1n** and carbodiimide **2c** furnishes the cycloadducts with a 2.8:1 selectivity favoring the isocyanide migration product **4** (entry 5). The reaction provides good overall yield and excellent enantioselectivity for **3**. By employing carbodiimide **2e**, our best candidate for selective amidine formation, the desired amidine **3** can be isolated in 37% yield and 97% ee with an overall 1:1 product selectivity (entry 6).

The absolute configuration of cycloadducts **3** were assigned by analogy to **(*S*)-3bc**, which was established by X-ray analysis (see supporting information).

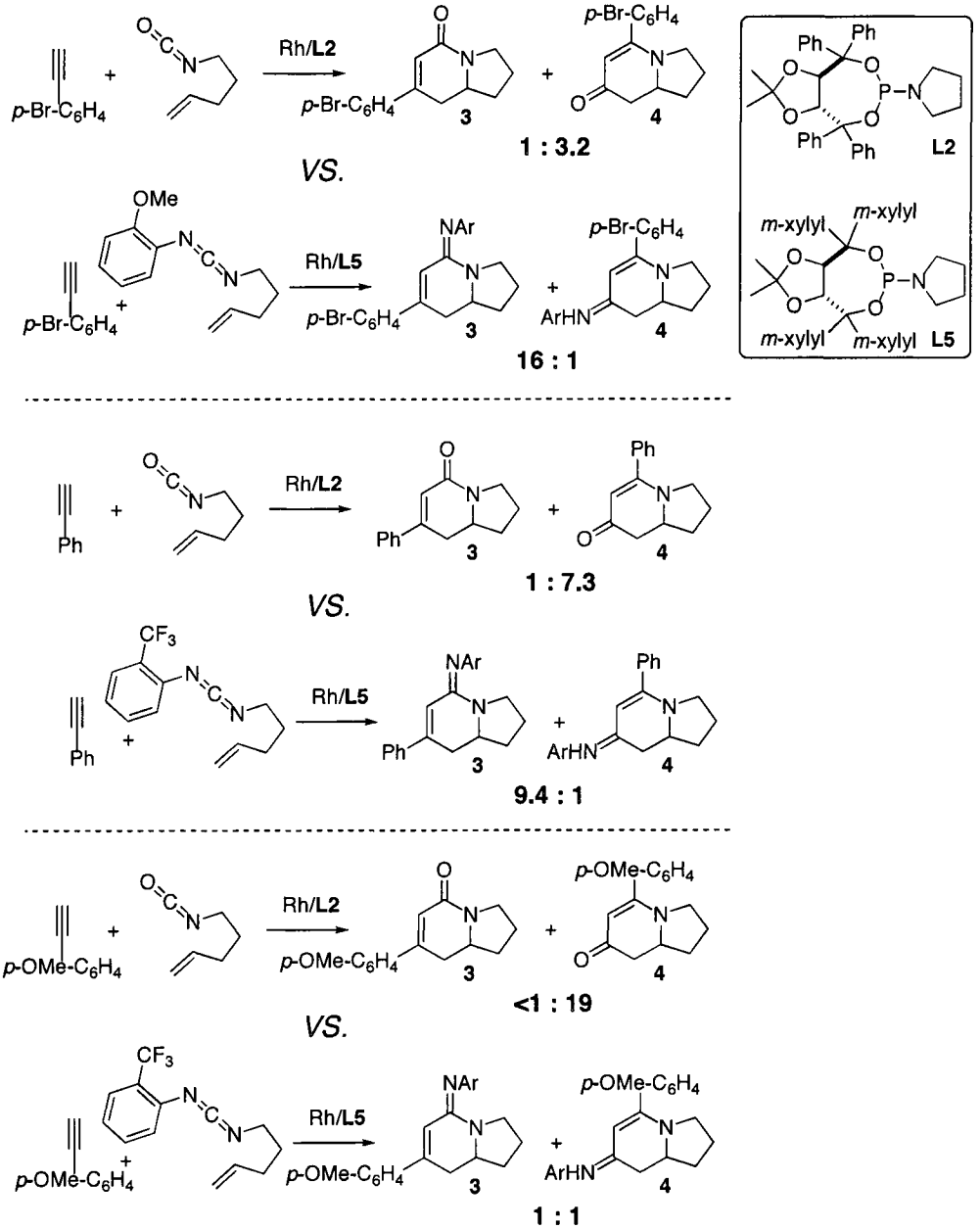
This newly developed cycloaddition using carbodiimides can be extended to include alkyl acetylenes (Scheme 4). Although the reactions require slightly higher catalyst loading to ensure complete conversion, many functional groups such as an ester, a silyl ether, and a chloride are well tolerated. In all cases, the cycloaddition generates exclusively the bicyclic amidines **3** with high efficiency. The enantioselectivities are uniformly high, although slightly lower than those obtained with aryl acetylenes (88 - 96% ee).

Scheme 4.



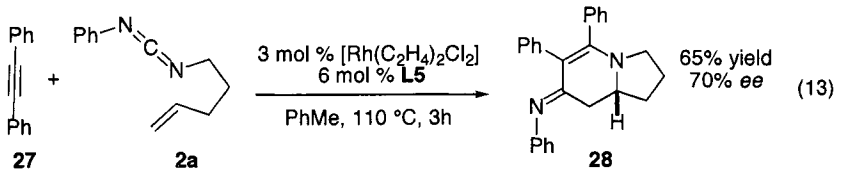
Overall, cycloaddition reactions employing carbodiimides provide complementary results to the isocyanate chemistry. To recall, reactions of isocyanates and aryl alkynes typically afford the CO-migration products **4** as the major components. And within the terminal aryl alkyne series, the more electron-donating the alkyne is, the more selective the reaction becomes toward **4**. We have just witnessed that by replacing the isocyanate moiety with aryl carbodiimides, we are able to reverse the product selectivity quite well (Scheme 5).

Scheme 5. Isocyanate versus Carbodiimide



Diaryl acetylenes represent the most extreme class of alkynes, which provide exclusively the migration cycloadduct **4** in all cases. Unlike terminal aryl alkynes, this trend does not change even with the use of carbodiimides. For example, cycloaddition of diphenyl acetylene **27** and carbodiimide **2a** furnishes exclusively the vinylogous amidine

28 in 65% isolated yield and with a decent 70% ee (eq. 13). Unlike monosubstituted cycloadduct **4**, the cycloaddition yields **28** as a single imine isomer.

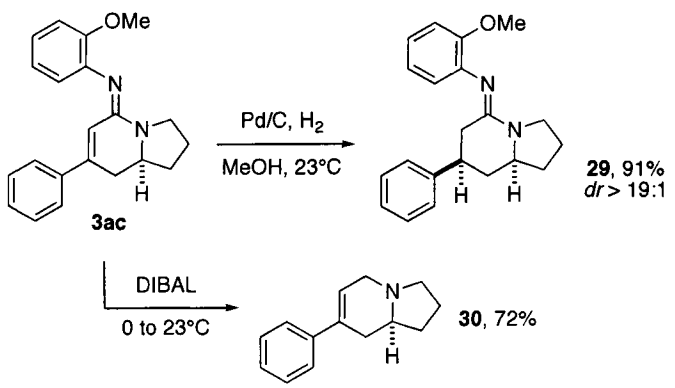


27 2a 28

3.4. Synthetic utilities

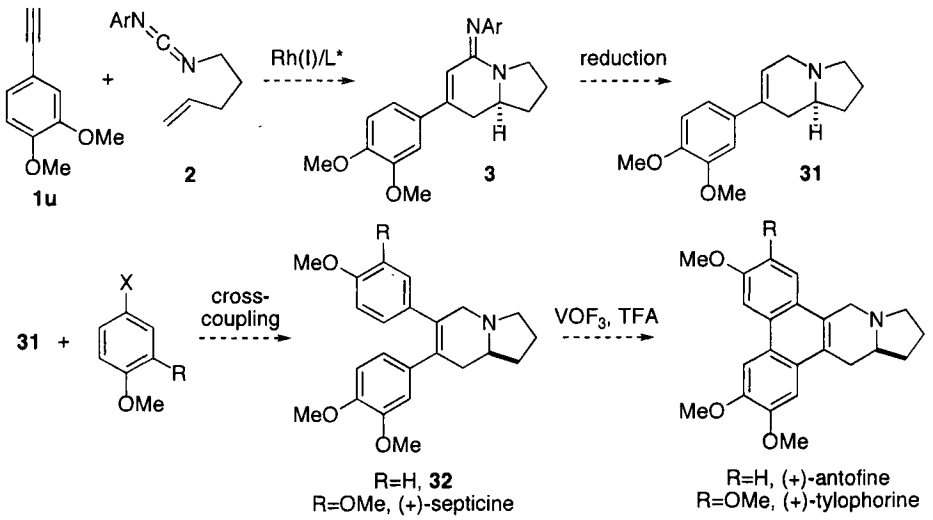
The resulting bicyclic amidines **3** are potentially useful chiral building blocks. Under appropriate conditions, the olefin and the amidine moiety can each be selectively reduced while leaving the other functionality untouched for further transformation (Scheme 6). For example, amidine **3ac** smoothly transforms into the saturated amidine **29** as a single diastereomer under typical hydrogenation conditions. On the other hand, treatment with DIBAL from 0 °C to ambient temperature reduces the amidine cleanly to provide the resulting indolizidine **30**.

Scheme 6.



As part of a program directed toward synthesis of indolizidine alkaloids, we envision that the present methodology could provide a viable route to the phenanthroindolizidine alkaloids such as tylophorine and antofine.[12] Both tylophorine and antofine exhibit a wide range of biological properties including antitumor activity, and have been the subjects of intense investigation.[13] As illustrated in Scheme 7, our synthetic plan calls for the preparation of enantiopure indolizidine **31**, which will come from the [2+2+2] cycloaddition protocol employing alkyne **1u**. An intermolecular Heck

Scheme 7.

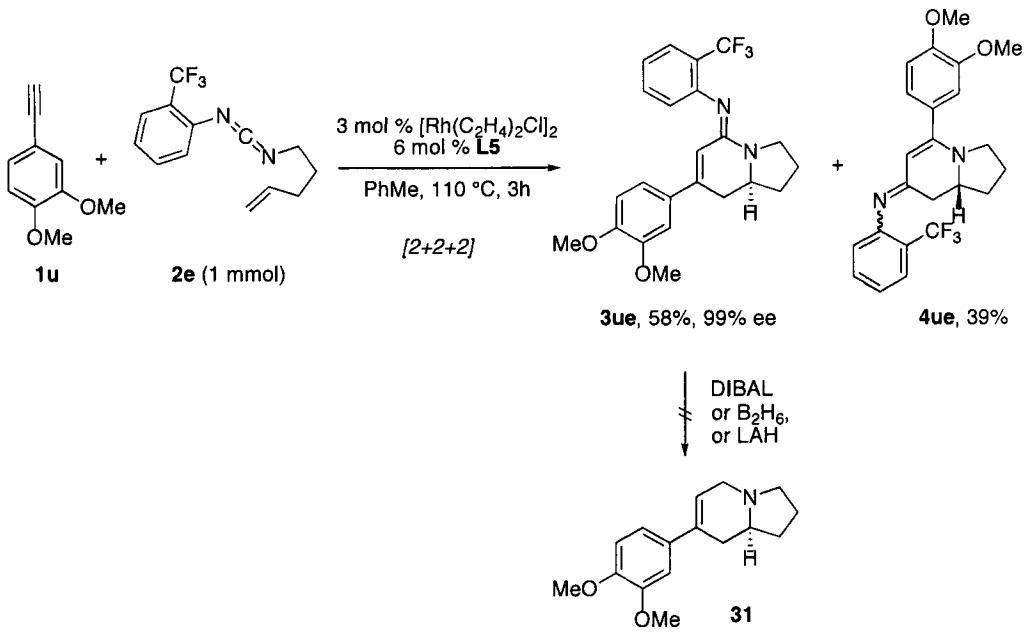


reaction or a Heck-type reaction[14] with appropriate aryl halides should give rise to the formation of **32** (R=H) and the naturally occurring septicine (R=OMe). Vanadium(V)-mediated oxidative couplings of **32** and septicine, demonstrated by Comins,[15] will provide antofine and tylophorine respectively.

From our substrate scope, the *o*-CF_3-phenyl carbodiimide **2e** is the best candidate to achieve the desired cycloaddition with the electron-rich alkyne **1u**. Indeed, the cycloaddition proceeds smoothly under standard conditions to furnish the desired amidine

3ue as the major product with excellent enantiocontrol. This reaction is highly efficient and can be performed at 1 mmol scale (Scheme 8). Unfortunately, treatment of amidine **3ue** with DIBAL resulted in no reaction. Reductions with a variety of nucleophilic reagents such as LAH and $NaBH_4$ all failed to provide any desired indolizidine **31**. Further investigation to solve this reduction problem is ongoing.

Scheme 8.



3.5. Conclusion

In conclusion, a highly enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes and alkenyl carbodiimides has been developed. This reaction demonstrates the feasibility of olefin insertion into carbodiimide-derived metalacycles, and provides a new class of chiral bicyclic amidines as the major products. An isonitrile migration process responsible for the formation of the minor cycloadduct can be observed, and is highly sensitive to the electronics of alkynyl substrates. Studies to explore the synthetic utility of bicyclic amidines **3** are underway.

3.6. References

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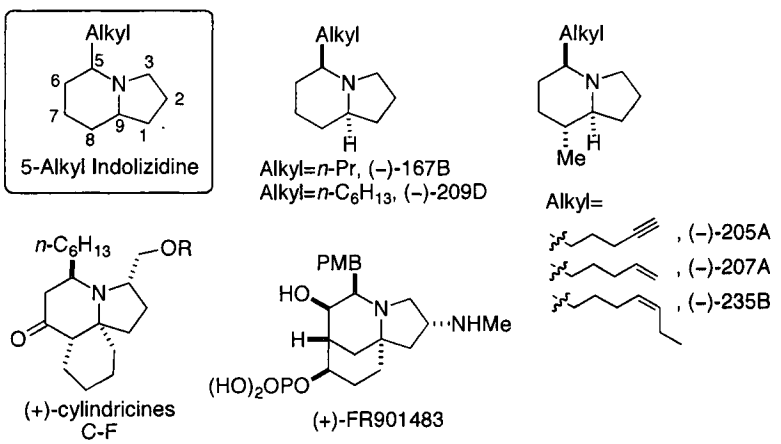
Chapter 4

The Missing Piece: A Catalyst-Controlled Cycloaddition of Alkenyl Isocyanates and Terminal Alkyl Alkynes for the Construction of 5-Alkyl Indolizinones, and Application to the Synthesis of Indolizidine (–)-209D

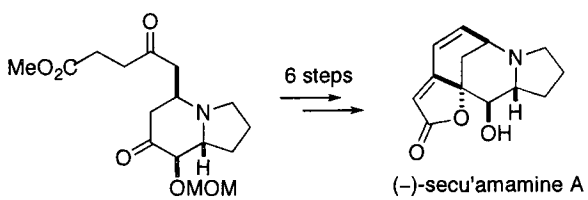
4.1. Introduction

Indolizidine frameworks possessing an alkyl group substituted at the 5-position (indolizidine numbering) represent a huge class of naturally occurring compounds.[1] Alkaloids ranging from structurally simple indolizidines 167B and 209D to more complex marine alkaloids such as cylindricines[2], and the immunosuppressant FR901483[3] (Scheme 1) all contain such ring systems.

Scheme 1.



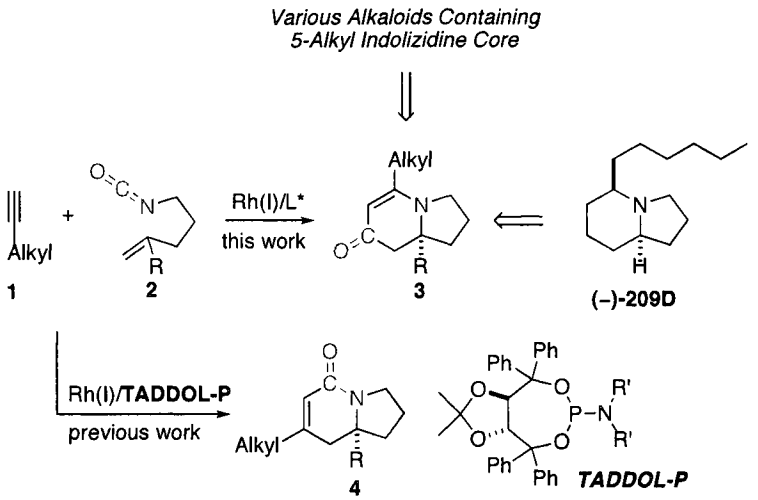
Recently, Weinreb and coworkers described the first total synthesis of secu'amamine A, a novel tetracyclic alkaloid, via a 5-alkyl indolizinone as a late-stage intermediate (eq 1).[4] In this chapter, we detail the development of an enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkyl alkynes **1** and alkenyl



(1)

isocyanates **2** to generate various 5-alkyl indolizinones **3** (Scheme 2). As part of a program directed toward developing a universal strategy to indolizidine alkaloids, the synthetic utility here is demonstrated by an expedient synthesis of (–)-209D.

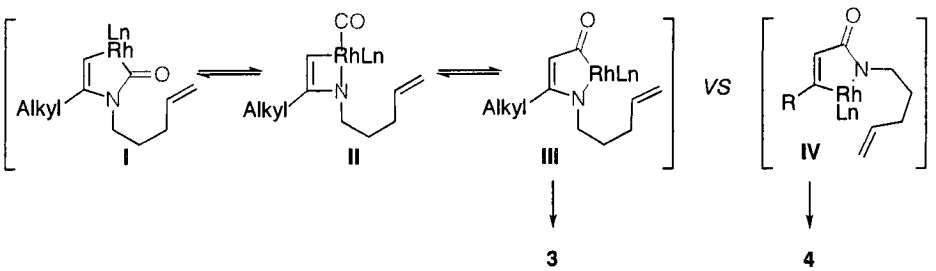
Scheme 2.



We have been exploring the use of neutral rhodium(I)/TADDOL-derived phosphoramidite complexes as enantioselective catalysts for various [2+2+2] cycloadditions, including reactions of terminal alkynes with isocyanates[5] or with carbodiimides.[6] In previous studies, the [2+2+2] cycloadditions of aryl alkynes and alkenyl isocyanates were shown to provide cycloadducts of type **3** (aryl groups substituted) selectively. In contrast, the use of terminal alkyl alkynes with these catalysts provides efficient cycloadditions to afford various bicyclic lactams **4** (Scheme 2) in good yields and enantioselectivities, while the 5-alkyl indolizinone cycloadducts **3**, resulting from a CO migration process, can only be observed as minor components. Herein, a new catalyst system to achieve a catalyst-controlled cycloaddition *en route* to 5-alkyl indolizinones **3** has been realized.

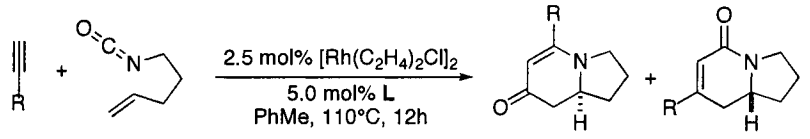
4.2. Initial Studies

To tune product selectivity through catalyst design, we began our study by examining the cycloaddition of 1-octyne **1a** and alkenyl isocyanate **2** with various phosphoramidite ligands[7] (Table 1). Switching from TADDOL-derived ligands such as **L1** to BINOL-derived **L2** led to a complete inversion of product selectivity (entry 1 vs. 2) favoring the indolizinone **3a**. Formation of **3** is thought to proceed through the initial metalacycle **I** followed by a CO migration process via **II** to arrive at **III**. Migratory

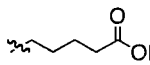
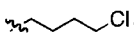


insertion of the pendant alkene into Rh-N bond followed by reductive elimination gives rise to cycloadducts **3**. Selectivity for the formation of two initial metalacycles (**I** vs. **IV**) can be reflected with the product selectivity of **3** and **4**. Despite the low yield and poor enantioselectivity, the fundamental difference in product selectivity prompted further investigation into BINOL-derived phosphoramidites. Ligands possessing substitutions at the 3,3'-positions of the BINOL backbone improve the reaction efficiency greatly toward the desired indolizinone **3a**. Both phenyl- (**L3**) and methyl-substituted (**L4**) ligands give an increased product selectivity of 3:1 favoring **3a** with encouraging yields (entries 3 – 4). Since the phosphoramidite **L4** affords a much higher enantioselectivity between the two, we next turned our attention to ligands equipped with sp^3-carbon substitutions at the 3,3'-positions. Further exploration led to the discovery of GUIPHOS.[8] This TMS-substituted phosphoramidite **L5** provides a much better reaction with product selectivity

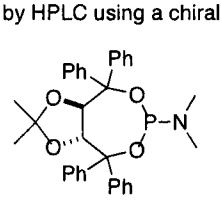
Table 1. Initial Ligand Screen.[a]

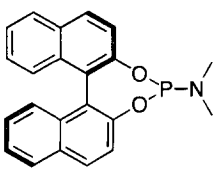


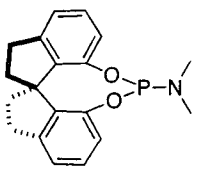
1 2 (*S*)-3 (*R*)-4

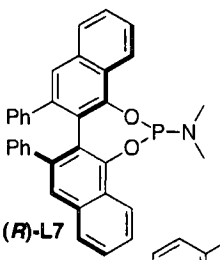
entry	R	L	3 : 4[b]	yield (%) of 3[c]	*ee* (%) of 3[d]
1	*n*-C_6H_{13}, **1a**	**L1**	1 : 3.2	20	73[e]
2	*n*-C_6H_{13}, **1a**	**L2**	2.2 : 1	22	72
3	*n*-C_6H_{13}, **1a**	**L3**	3.0 : 1	43	30
4	*n*-C_6H_{13}, **1a**	**L4**	3.3 : 1	40	62[e]
5	***n*-C_6H_{13}, *1a***	***L5***	***3.8 : 1***	***60***	***96***
6	*n*-C_6H_{13}, **1a**	**L6**	3.6 : 1	41	50
7	 **1b**	**L5**	3.2 : 1	51	96
8	 **1c**	**L5**	3.3 : 1	45	94

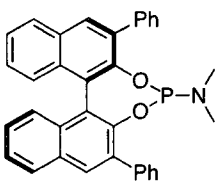
[a] Conditions: **1** (2 equiv), **2** (0.27 mmol), Rh/**L** in PhMe (0.07 M) at 110 C. [b] Product selectivity determined by 1H NMR of the unpurified mixture. [c] Isolated yield. [d] Determined by HPLC using a chiral stationary phase. [e] Other enantiomer.

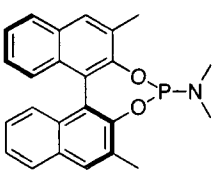

(–)-L1

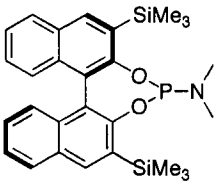

(*R*)-L2 (MONOPHOS)

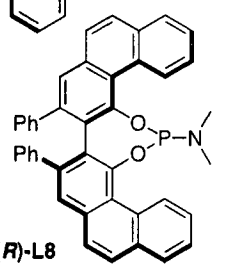

(*R*)-L6 (SIPHOS)


(*R*)-L7


(*R*)-L3


(*S*)-L4


(*R*)-L5 (GUIPHOS)


(*R*)-L8

just below 4:1, a good chemical yield, and most importantly an excellent 96% enantioselectivity for **3a** (entry 5). The enantioselectivities of the minor products **4a** are typically between 30 ~ 50% ee with the BINOL-based ligands. A brief survey on alkyne scope reveals that while GUIPHOS represents a general solution for obtaining excellent enantiocontrol, its impact on product selectivity and reactivity remains suboptimal (entries 7 – 8). A brief solvent screen was conducted at 110 °C. While the reaction

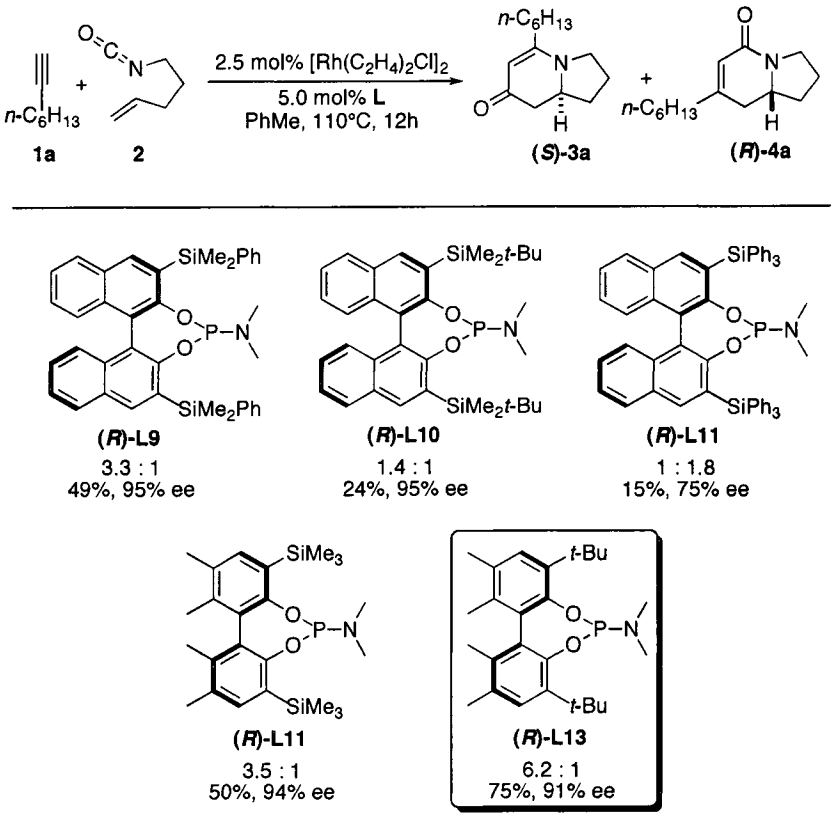
proceeds quite smoothly in THF, dichloroethane, or nitromethane, the product selectivities remained relatively unchanged (approx. 3:1). Solvents such as acetonitrile, dioxane, DMF, and DMSO all had deleterious effects on the reaction, providing a complex mixture with only trace amounts of cycloadducts detected by ^{1}H NMR. Other phosphoramidite ligands with different backbones have also been explored. The spiro-phosphoramidite **L6**[9] provided a quite efficient reaction with product selectivity comparable to GUIPHOS, although the level of enantiocontrol was only moderate (entry 6). Cycloaddition with either the VANOL or VAPOL-derived phosphoramidites (**L7** and **L8**) gave a very sluggish reaction.

4.3. Ligand Fine-tuning

A second round of ligand screening was initially focused on the variants of GUIPHOS (Chart 1). The dimethylphenyl silylated phosphoramidite **L9** gives enantioselectivity similar to those obtained with GUIPHOS, but no improvement in product selectivity. Interestingly, the bulkier TBDMS **L10** provides an unselective cycloaddition with a product ratio of 1.4:1 while maintaining the excellent enantiocontrol for **3a**. The triphenyl silylated ligand **L11**, being most sterically hindered of the three, favored the formation of lactam product **4a** with a selectivity 1:1.8. This series of ligand studies suggests that, although a bulky group such as TMS is required for high enantioselectivity, the product selectivity toward **3** decreases once the steric environment becomes too congested. We then turned our attention to another class of ligands. Although the TMS-substituted biphenol-derived phosphoramidite **L12** proved to behave no differently than GUIPHOS, the corresponding ligand possessing *tert*-butyl groups at the 3,3'-positions (**L13**)[10] turned out to be superior. Precatalyst $[Rh(C_2H_4)_2Cl]_2$ modified

with **L13** provides a clean reaction to furnish the desired indolizinone **3a** with a good product ratio (6.2:1) in excellent yield (75%) and enantioselectivity (91%). We have tentatively attributed the increase in product selectivity to a steric argument, with the *tert*-butyl groups at the 3,3'-positions acting as smaller groups than TMS. It is important to note that while the *tert*-butyl group has a much higher *A* value, carbon-silicon bonds (1.85 Å) are much longer than carbon-carbon bonds (1.54 Å). As a result, the *tert*-butyl groups are more compact at the 3,3'-positions at the BINOL, and provide less steric crowding around the reacting center (the rhodium).

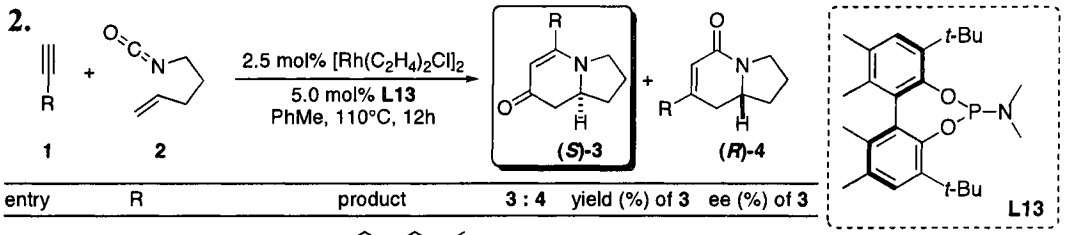
Chart 1. Ligand Fine-Tuning

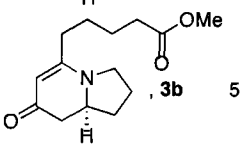
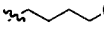
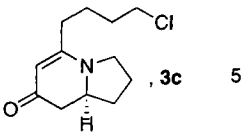
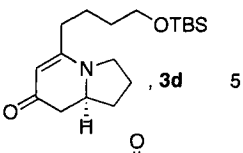
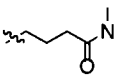
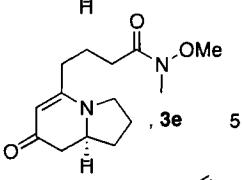
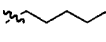
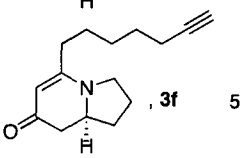
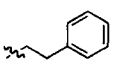
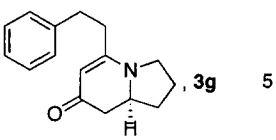
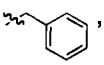
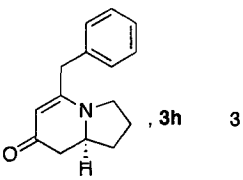
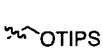
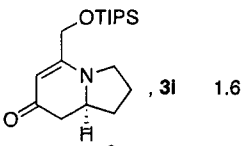
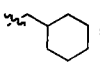
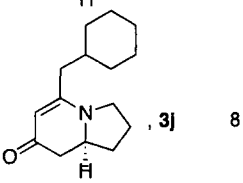


4.4. Reaction Scope

The newly developed Rh/phosphoramidite **L13** catalyst promotes the enantioselective synthesis of various 5-alkyl indolizinones very efficiently (Table 2). Alkyl alkynes bearing an array of functional groups including ester, chloride, silyl ether, Weinreb amide, unprotected terminal alkyne, and phenyl ring all react smoothly to afford cycloadducts in good product ratios and excellent enantioselectivities (entries 2 – 7). The cycloaddition is highly sensitive to both electronic and steric components of the alkynyl partners. The product selectivity shifts more toward the formation of lactams **4** with electron-withdrawing substituents closer to the alkynyl center. For example, cycloaddition of 3-phenyl-1-propyne **1h** gave a product ratio of 3:1 favoring the benzyl-substituted indolizinone **3h**, instead of the ratio of 5:1 obtained with **1g** (entry 7 vs. entry 8). In a more extreme case, cycloaddition of TIPS-protected propargyl alcohol **1i** furnishes a 1.6:1 product mixture that slightly favors the formation of indolizinone **3i** (entry 9). On the other hand, reaction with the more sterically hindered alkyne **1j** improved the product selectivity to provide the desired cycloadduct **3j** in a high yield and excellent enantioselectivity (entry 10). Both the electronic and steric effects observed here are consistent with our previous reports.[5,6]

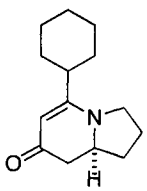
Table 2.



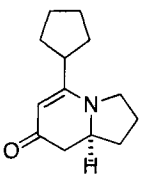
entry	R	product	3 : 4	yield (%) of 3	ee (%) of 3
1	n-C_6H_{13}, **1a**	, **3a**	6 : 1	75	91
2	 , **1b**	 , **3b**	5 : 1	66	90
3	 , **1c**	 , **3c**	5 : 1	57	94
4	 , **1d**	 , **3d**	5 : 1	62	90
5	 , **1e**	 , **3e**	5 : 1	54	90
6	 , **1f**	 , **3f**	5 : 1	55	91
7	 , **1g**	 , **3g**	5 : 1	56	91
8	 , **1h**	 , **3h**	3 : 1	52	90
9	 , **1i**	 , **3i**	1.6 : 1	44	87
10	 , **1j**	 , **3j**	8 : 1	72	91

In fact, bulky alkynes such as cyclohexyl and cyclopentyl acetylenes are among the best cycloaddition partners. The corresponding indolizinone products **3k** and **3l** can be obtained in high yields and enantioselectivities with excellent 14:1 product selectivities (Chart 2). Even more impressively, the rhodium catalyst modified by ligand **L13** promotes the cycloaddition of tertiary alkyl-substituted alkynes (**1m**, **1n**) to gain access to highly congested 5-alkyl indolizinones. For example, the MOM-protected cyclopentanol-substituted cycloadduct **3m** can be produced in 60% yield with a slightly diminished 81% enantioselectivity as the only product. In general, cycloaddition with the *tert*-butyl substituted phosphoramidite **L13** produces the best product selectivity and high overall reactivity, while the use of GUIPHOS usually gives the best level of enantiocontrol. Although GUIPHOS displays low reactivity toward most sterically hindered alkynes (**3k**: 44% yield, 95% ee; **3m**: 23% yield, 80% ee), it does provide an efficient cycloaddition for the formation of *tert*-butyl substituted indolizinone **3n** in a good chemical yield and enantioselectivity.

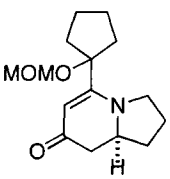
Chart 2. Synthesis of Sterically Hindered 5-Alkyl Indolizinones



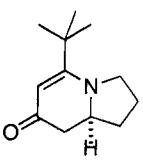
(*S*)-3k



(*S*)-3l



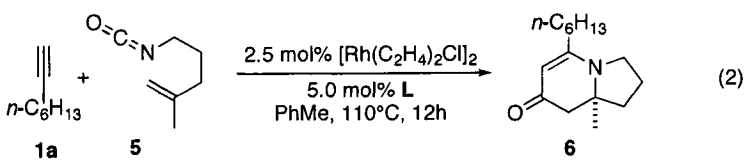
(*S*)-3m

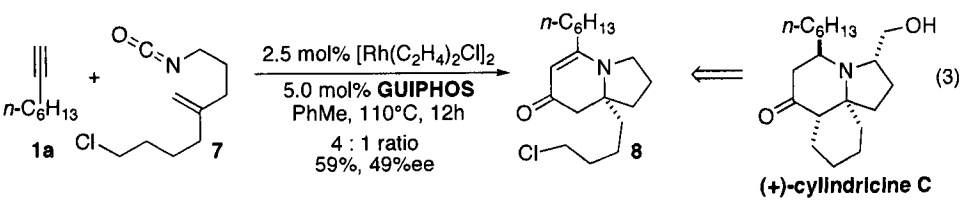


(*S*)-3n

	(*S*)-3k	(*S*)-3l	(*S*)-3m	(*S*)-3n
w/ L13	14 : 1 ratio 86%, 91%ee	14 : 1 ratio 87%, 89%ee	>20 : 1 ratio 60%, 81%ee	10 : 1 ratio 67%, 79%ee
w/ GUIPHOS	12 : 1 ratio 44%, 95%ee	N/A	6 : 1 ratio 23%, 80%ee	6 : 1 ratio 66%, 88%ee

This newly developed protocol can also be applied to the synthesis of 5,9-dialkyl indolizinones (eq. 2 and 3). 1,1-Disubstituted alkenyl isocyanates such as **5** and **7** participate in the cycloadditions with 1-octyne **1a** quite efficiently to provide the corresponding cycloadducts **6** and **8** in good product ratios and isolated yields.[11] Interestingly, while the product selectivities stay relatively unchanged, as with those obtained with the unsubstituted alkenyl isocyanate **2**, a profound effect on the enantioselectivity is observed and worth further investigation. In the case of isocyanate **5**, the use of GUIPHOS provides a partial solution, and improves the enantioselectivity significantly. Despite the lack of enantioselectivity, the cycloaddition protocol permits the large scale synthesis of indolizinone **8** quite efficiently. With just 2 mol% of $[Rh(C_2H_4)_2Cl]_2$ and 4 mol% of GUIPHOS (added in two portions with a ten-hour interval), the desired cycloadduct **8** can be prepared on a gram-scale. This highly functionalized cycloadduct is being evaluated for use in the total synthesis of cylindricines.

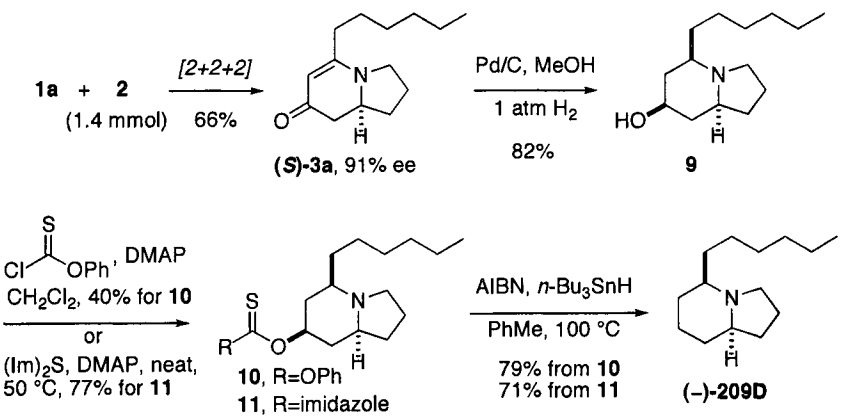




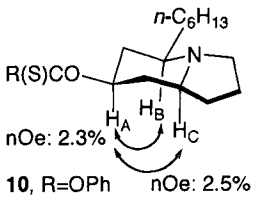
4.5. Enantioselective Synthesis of Indolizidine (–)-209D

Indolizidine 209D belongs to a family of 22 natural products, commonly referred to as gephyrotoxins, isolated from the skin secretions of neotropical frogs.[12] Along with indolizidine 167B (Scheme 1), these two structurally simpler alkaloids have only been isolated in minute quantities from unidentified dendrobatid frogs found in a single population. Over the years, they have attracted much interest from the synthetic community to prepare them in greater quantities, as well as a tool to validate new methodologies.[13] In our own effort, the key intermediate 5-hexyl indolizinone **3a** can be prepared conveniently by the cycloaddition protocol in one step and is suitable for scale-up. The resulting vinylogous amide functionality readily undergoes a diastereoselective hydrogenation to afford enantioenriched amino alcohol **9** as a single diastereomer (Scheme 3). With the Barton-McCombie deoxygenation reaction in mind, phenylthionocarbonyl formate **10** was synthesized from the secondary alcohol **9** under standard conditions. Despite several attempts, the acylation suffered from low

Scheme 3. Synthesis of Indolizidine (–)-209D.



conversions even after 23 h of heating, and gave 40% isolated yields at best. Synthesis of the radical precursor can be greatly improved by employing a solid-state reaction with thiocarbonyldiimidazole, developed by Hagiwara and coworkers,[14] to afford the thiocarbonylimidazolide **11** in 77% yield. Nuclear Overhauser effect (nOe) experiments were conducted on **10** and show an all *syn* environment between protons H_A, H_B, and H_C, thus confirming the stereochemistry of **9**. Radical cleavage of either the thioxoester **10** or



11 completes the four-step enantioselective synthesis of (–)-209D, which also confirms the absolute configuration of **3a**: $[\alpha]^{22}_D$ = -66.5° (c 1.0, CH_2Cl_2); lit.[13a] $[\alpha]^{26}_D$ = -80.4° (c 1.0, CH_2Cl_2). Considering that alkenyl isocyanate **2** can be prepared in one step from the commercially available 5-hexenoic acid, this constitutes the shortest synthesis of indolizidine (–)-209D to date.

4.6. Conclusion

In conclusion, we have developed an efficient catalyst system that promotes a cycloaddition between terminal alkyl alkynes and alkenyl isocyanates involving a CO migration. This previously unattainable process allows access to various 5-alkyl indolizinones including an enantioselective synthesis of indolizidine (–)-209D. Further studies on the reaction scope as well as applications to the synthesis of alkaloids are ongoing.

4.7. References

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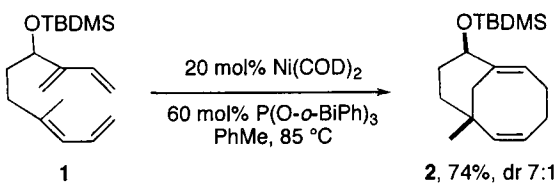
Chapter 5

Highyl Enantioselective Rhodium-Catalyzed [4+2+2] Cycloaddition Utilizing Dienyl Isocyanates: A New Method for the Synthesis of Nitrogen-Containing Eight-Membered Rings

5.1. Introduction

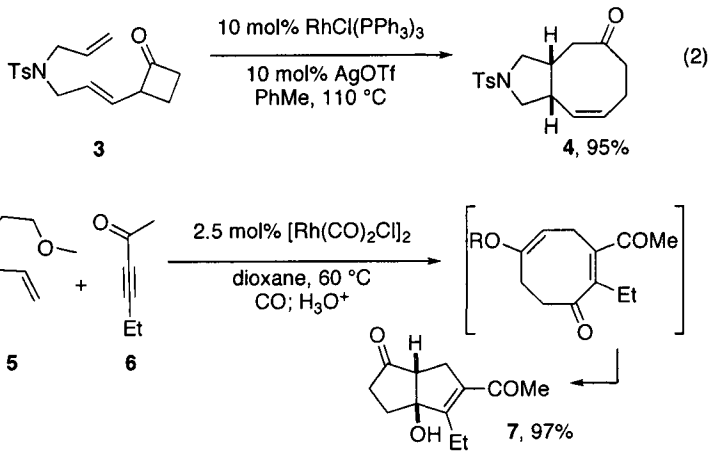
Formation of medium-sized rings has become increasingly important in organic synthesis due to their occurrence in a large number of biologically important natural products.[1] The discovery of taxol in 1971 has sparked a global investigation and inspired numerous methods for the construction of eight-membered carbocycles (B ring of taxol).[2] Despite intense efforts, a relatively small number of methods were successful. Many of them, consisting mostly of either Diels-Alder or ring-expansion reactions, suffered from low yields. Unlike the formation of common-sized rings, preparation of eight-membered rings has proven to be notoriously difficult, due to entropic factors and high transannular strain. Transition metal-catalyzed cycloadditions take advantage of entropic factors by adjoining the substrates through coordination to the metal center prior to reaction. In 1986, Paul Wender and coworkers demonstrated such a concept through an efficient nickel-catalyzed [4+4] cycloaddition of bis-dienes to afford various eight-membered carbocycles, including a system (**2**) resembling the AB rings of taxol (eq 1).[3]



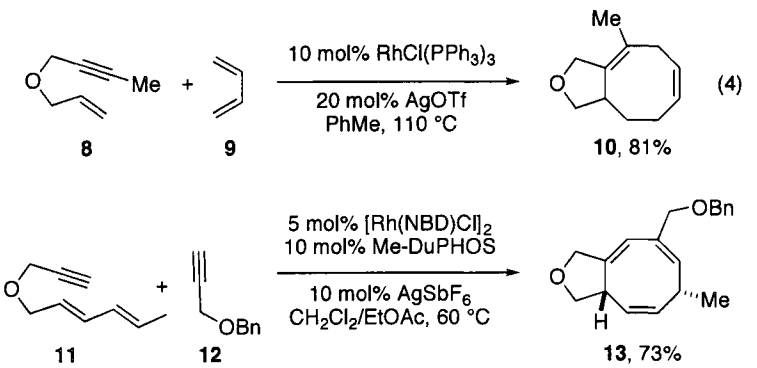
1 **2**, 74%, dr 7:1 (1)

Over the last decade transition metal-catalyzed cycloadditions, especially with rhodium catalysts, have proven among the most attractive methods to construct medium-sized ring

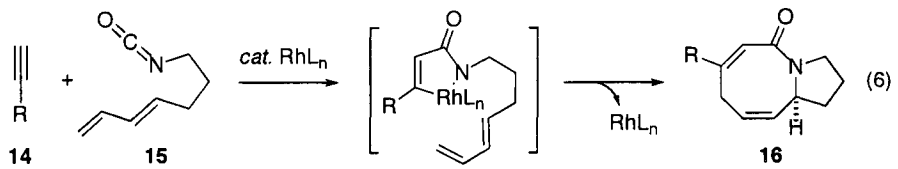
systems.[4] In 2000, Wender and coworkers disclosed an intramolecular Rh-catalyzed [6+2] cycloaddition.[5] Various vinylcyclobutanones, such as **3**, undergo cycloadditions via a cyclobutanone ring-opening mechanism to afford the desired fused eight-membered rings **4** in high yields (eq 2). Further studies from the same research group led to an intermolecular [5+2+1] cycloaddition involving a vinylcyclopropane **5**, an activated alkyne **6**, and a molecule of carbon monoxide (eq 3).[6]



Following Wender's reports, Evans' and Gilbertson's research groups have independently described the first rhodium-catalyzed [4+2+2] cycloadditions. They utilize different dienyl substrates (**9** and **11**) as templates to synthesize bicyclic eight-membered rings such as **10** and **13** (eq 4 and eq 5 respectively) in good yields.[7]



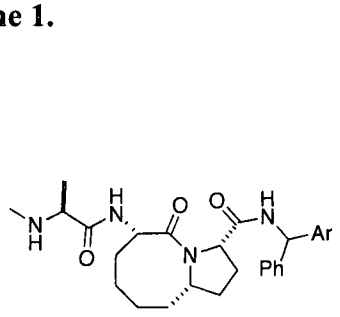
Although strategies such as [4+4], [6+2], [5+2+1], and [4+2+2] cycloadditions have all been elegantly demonstrated for the synthesis of various eight-membered carbocycles, the formation of eight-membered nitrogen-containing rings (azocine) has not been explored. In addition, there is no reported example of successful enantioselective cycloaddition to construct eight-membered rings.[8] We have recently demonstrated that Rh(I) catalysts are capable of effecting enantioselective [2+2+2] cycloadditions between terminal alkynes and alkenyl isocyanates.[9] Herein we describe a highly enantioselective rhodium-catalyzed [4+2+2] cycloaddition of terminal alkynes and dienyl isocyanates to afford bicyclo[6.3.0] azocine derivatives (eq. 6).



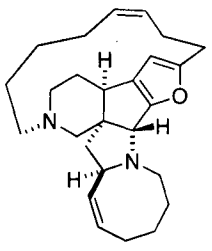
5.2. The Vision

The bicyclo[6.3.0] azocine ring system is a unique architecture that has found applications in biologically active compounds. Wang and coworkers have recently designed a potent XIAP antagonist, a small molecule consisting of the bicyclic azocine as the basic template (Scheme 1).[10] Many manzamine alkaloids such as nakadomarin A and manzamine A, which exhibit potent antimalarial and antituberculosis activity, are

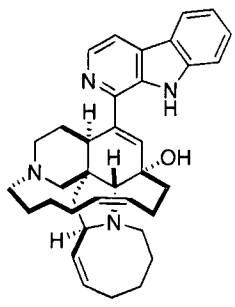
Scheme 1.



Antagonist of XIAP



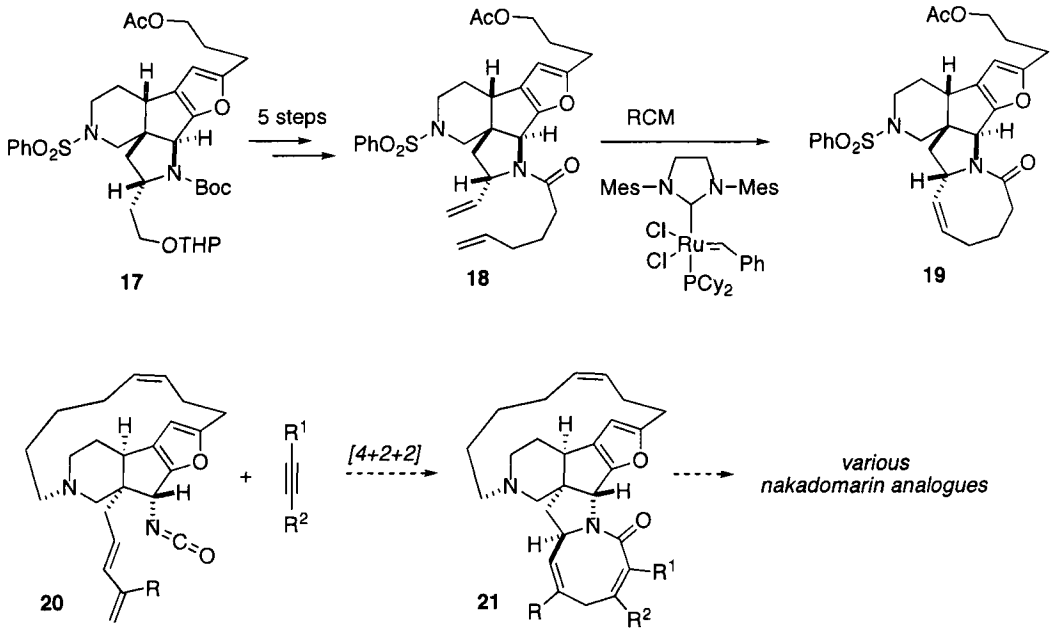
Nakadomarin A



Manzamine A

equipped with such ring systems.[11] Traditionally, the bicyclo[6.3.0] rings are built in a stepwise fashion, including a ring-closing metathesis (RCM), to afford the eight-membered ring.[12] In Nishida and coworkers' first total synthesis of (+)-nakadomarin A, the tetracyclic intermediate **17** was converted to the RCM precursor **18** through a five-step sequence (Scheme 2).[11c] Although the subsequent RCM reaction afforded the target azocine **19**, the lengthy sequence and limitations of RCM make the synthesis of any potential manzamine analogues with derivatization on the azocine ring impractical. The [4+2+2] cycloaddition strategy allows a new route to functionalized bicyclic azocine ring systems in one chemical step. An ultimate goal, for instance, will involve a dienyl isocyanate possessing a manzamine backbone, such as **20**, to undergo the cycloaddition with various alkynes. Such successful application will yield an array of analogues with modifications on the azocine ring system, and should provide valuable structure-activity relationship information.

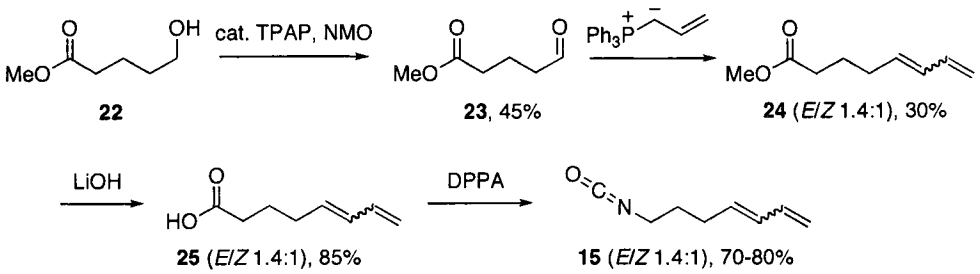
Scheme 2.



5.3. Optimization Studies

Our initial efforts to effect the [4+2+2] cycloaddition focused on the dienyl isocyanate **15** as a mixture of *E/Z* isomers, which can be prepared from the known alcohol **22** (Scheme 3). A Ley oxidation followed by Wittig olefination quickly arrives at ester **24** as a 1.4:1 mixture of *E/Z* isomers. Saponification to acid **25** and subsequent treatment with DPPA to trigger the Curtius rearrangement gives the requisite isocyanate **15**. Disappointingly, when the **(*E/Z*)-15** was reacted with phenyl acetylene **14a** in the

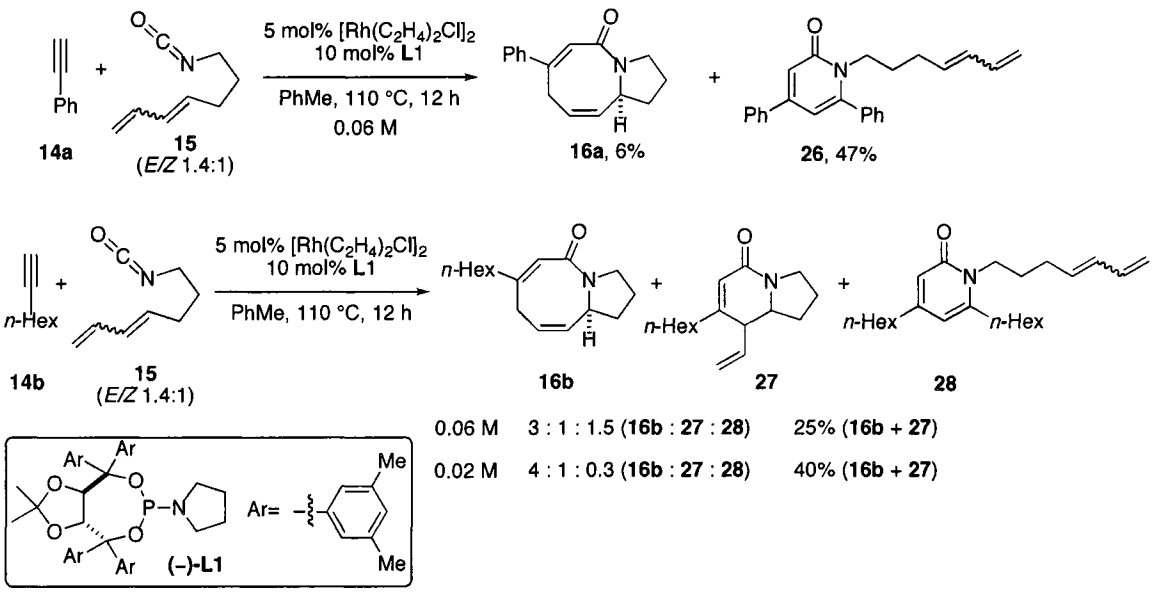
Scheme 3. Synthesis of the **(*E/Z*)-15**



presence of $[Rh(C_2H_4)_2Cl]_2$ modified with phosphoramidite **L1**, a standard catalyst employed in our [2+2+2] cycloadditions,[9] pyridone **26** was isolated as the major product while the desired [4+2+2] cycloadduct **16a** was observed as a very minor component (Scheme 4). Encouragingly, when we conducted the experiment with 1-octyne **14b**, the cycloaddition furnished both the [4+2+2] cycloadduct **16b** and the [2+2+2] cycloadduct **27** as substantial products. The formation of pyridone **28** could be suppressed by employing more dilute conditions, thus leading to an improved 40% combined yield of both **16b** and **27** as an inseparable 4:1 mixture. At this point, the [4+2+2] cycloaddition faced two major obstacles: [2+2+2] cycloaddition as the competing pathway, and low

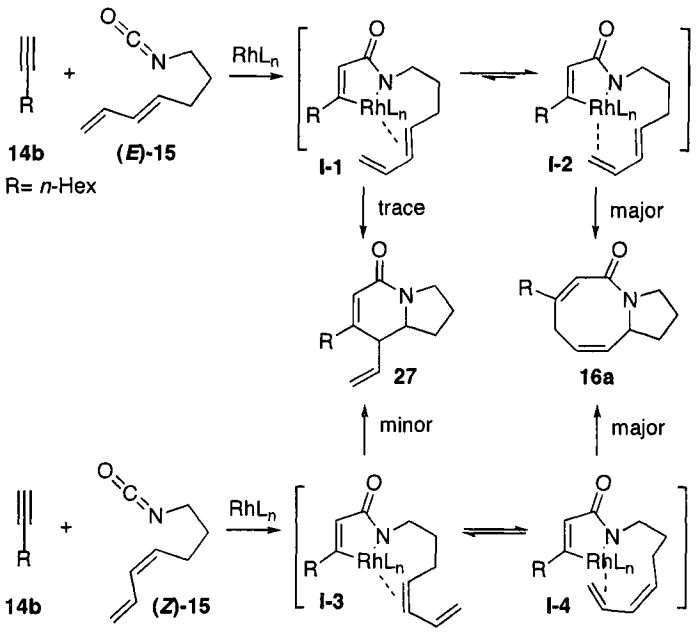
conversions. To address the first problem, we hypothesized that when a molecule of **(*E*)-15** enters the catalytic cycle, the formation of metalacycle **I-1**, where the rhodium is

Scheme 4. Early Results



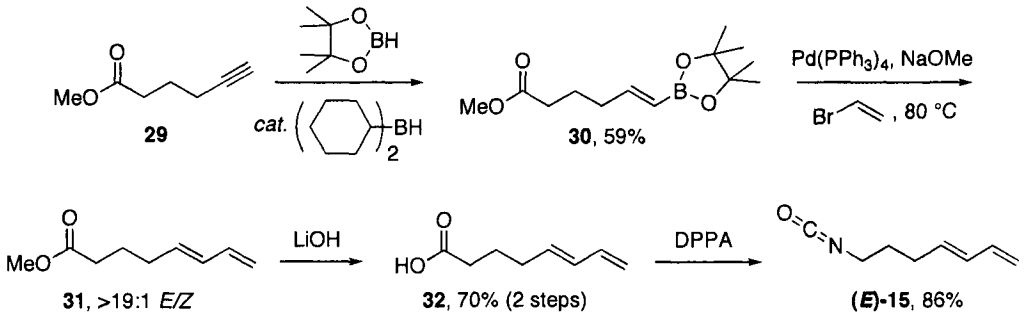
coordinated to the *trans*-alkene, and the formation of metalacycle **I-2**, in which the rhodium is coordinated to the terminal olefin, will take place. The equilibrium should lie favorably toward **I-2** with a more stable alkene/rhodium complex, thus triggering the diene insertion as the major pathway to afford **16b** (Scheme 5). In fact, studies have shown that a 1-butene/Rh(I) complex is 46 times more stable than a *trans*-2-butene/Rh(I) complex.[13] On the other hand, the *cis*-alkene/Rh(I) complex **I-3**, resulting from the **(*Z*)-15**, is probably much more stable than **I-1**, and makes the ensuing [2+2+2] process more competitive. Based on these arguments, use of the isomerically pure diene **(*E*)-15** should achieve the [4+2+2] cycloaddition selectively.

Scheme 5.



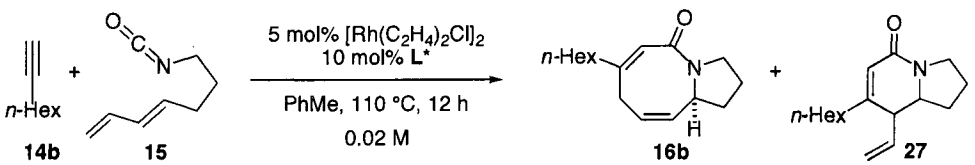
After extensive research, a four-step sequence has been developed to prepare the requisite dienyl isocyanate **(*E*)-15** in gram-scale (Scheme 6). Starting from the commercially available alkyne **29**, hydroboration under Hoshi's conditions[14] gives the (*E*)-alkenylboronic acid pinacol ester **30** selectively without reducing the methyl ester functionality. A standard Suzuki-Miyaura cross-coupling with vinyl bromide provides access to the (*E*)-diene **31** with a >19:1 *E*/*Z* selectivity. Saponification followed by DPPA treatment gives rise to the formation of dienyl isocyanate **(*E*)-15** with a decent overall yield (36% from **29**).

Scheme 6. Synthesis of the **(*E*)-15**



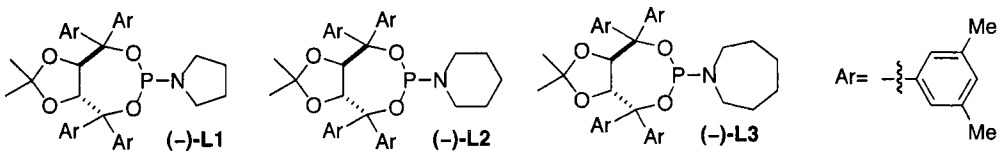
Gratifyingly, when the isomerically-pure dienyl isocyanate **(*E*)-15** was treated under the same conditions in the presence of 1-octyne, the desired [4+2+2] cycloaddition took place to afford **16b** selectively (Table 1, entry 1 vs 2).[15] Despite a significant amount of unreacted isocyanate **15**, the desired bicyclic azocine **16b** was obtained with

Table 1. Ligand Screen[a]



entry	*E/Z* ratio of **15**	L*	**16b** : **27**[b]	**16b** : **15**[b]	yield (%) of **16b**[c]	*ee* (%) of **16b**[d]
1	1.4 : 1	**L1**	4 : 1	1 : 2.5	40[e]	n.d.
2	≥19 : 1	**L1**	≥19 : 1	1 : 2.5	47	99
3	***≥19 : 1***	***L2***	***≥19 : 1***	***1 : 10***	***74***	***99***
4	≥19 : 1	**L3**	≥19 : 1	1 : 10	67	99

[a] Conditions: **14** (1.5 equiv), **15** (0.18 mmol), Rh catalyst, **L** in PhMe at 110 °C. [b] The ratio of **16b:27** and **16b:15** are determined by ^{1}H NMR of the unpurified reaction mixture. [c] Isolated yield. [d] Determined by HPLC using a chiral stationary phase. [e] Combined yield of **16b** and **27**.



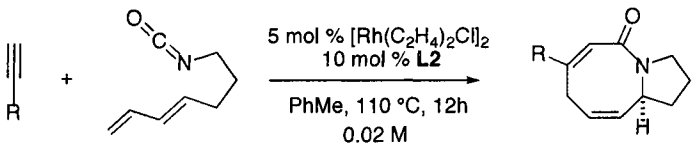
an exceptional enantioselectivity (99% ee). With the optimal substrate in hand, various conditions including temperature and solvent studies were investigated in an attempt to improve the reaction efficiency. In the end, we found that by simply replacing the pyrrolidinyl group on phosphoramidite ligand with either the piperidine (**L2**) or azepine (**L3**), the reactivity would dramatically increase toward azocine ring formation, while maintaining the high level of enantiocontrol (entries 3 – 4). The structure of **16b** was

unambiguously assigned by NMR spectroscopy including ^{1}H, ^{13}C, and HSQC (see supporting information).

5.4. Substrate Scope

With optimal conditions in hand, a variety of substituted bicyclic azocines can be synthesized in good yields and excellent enantioselectivities (Table 2). Alkyl alkynes bearing a chloride, a methyl ester, or an unprotected terminal alkyne (**14c – 14e**) all react smoothly to provide the corresponding cycloadducts (**16c – 16e**). Moreover, alkynes possessing functionalities such as silyl ether, phthalimide, phenyl, and Boc-protected indole at the propargylic positions (**14f – 14i**) are well tolerated to furnish the [4+2+2] cycloadducts (**16f – 16i**) in good yields and excellent enantioselectivities. Cycloaddition of isocyanates possessing substitution at the diene portion is also feasible. For example, when 2-methyl dienyl isocyanate (***E*)-33** is reacted under the standard conditions, [4+2+2] cycloadditions with various alkynes all proceed efficiently to deliver the corresponding disubstituted azocines in decent yields and excellent enantioselectivities (Table 3). The requisite isocyanate **33** can be easily prepared by the same synthetic sequence illustrated in Scheme 6, with 2-bromopropene as the cross-coupling partner.

Table 2. Substrate Scope



14b-14i **(*E*)-15** **16**

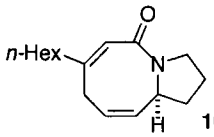
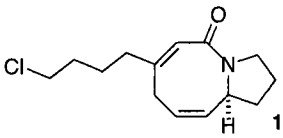
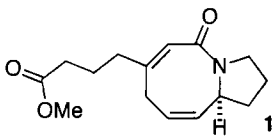
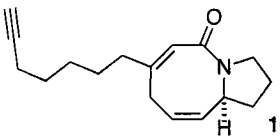
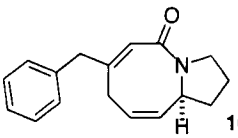
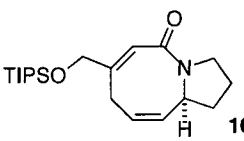
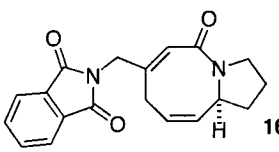
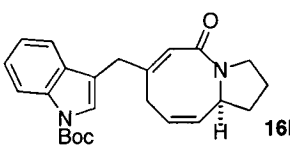
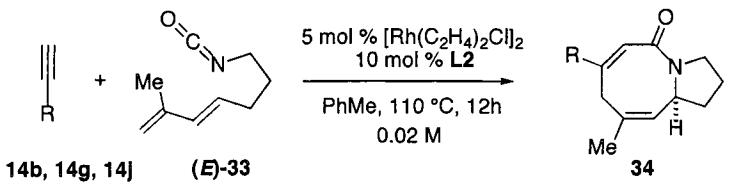
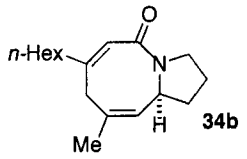
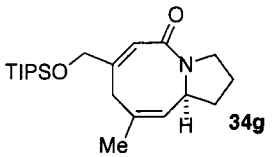
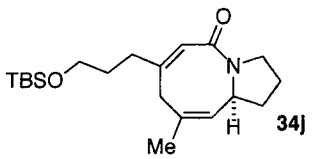
entry	Product	yield (%)	ee (%)
1	 **16b**	74	99
2	 **16c**	69	99
3	 **16d**	70	99
4	 **16e**	55	99
5	 **16f**	68	99
6	 **16g**	82	99
7	 **16h**	65	97
8	 **16i**	57	97

Table 3. Synthesis of Disubstituted Bicyclo[6.3.0] Azocines

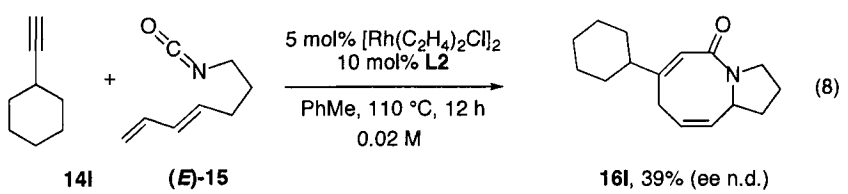


14b, 14g, 14j **(*E*)-33** **34**

entry	Product	yield (%)	ee (%)
1	 **34b**	62	99
2	 **34g**	51	99
3	 **34j**	54	99

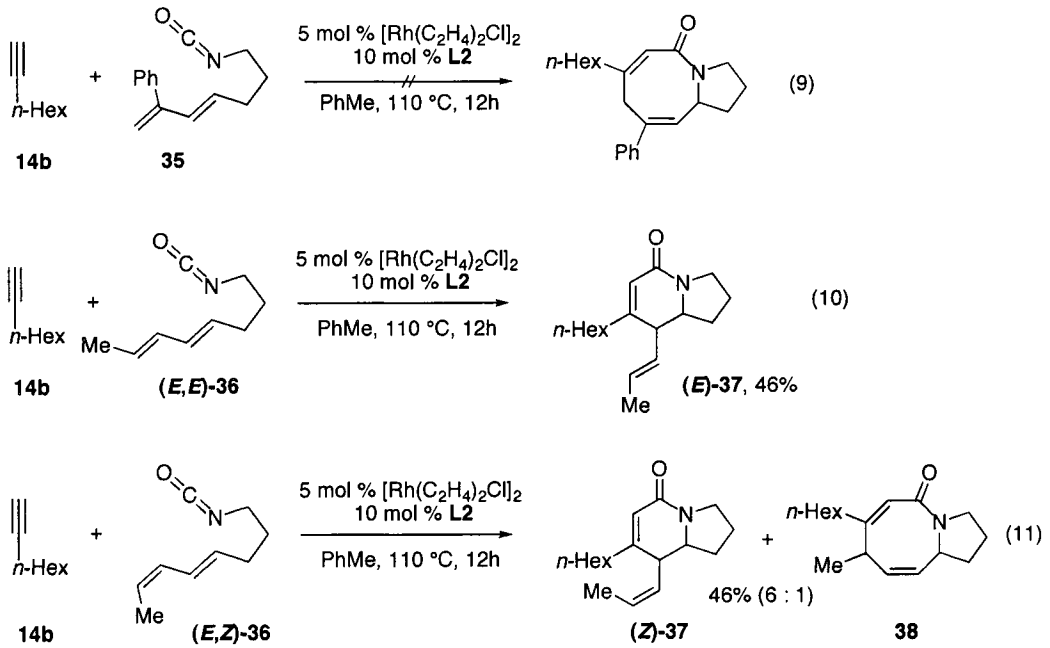
Reactions with aryl alkynes, however, proceeded only in moderate conversions. With 1-bromo-4-ethynylbenzene (**14k**), cycloadduct **16k** can only be obtained in 35% isolated yield, although with the same high enantioselectivity (eq 7). Similarly, cycloaddition with a sterically hindered alkyl alkyne such as **14l** afforded the desired azocine in only 39% yield with a significant amount of starting isocyanate remaining in solution (eq 8).

14k **(*E*)-15** **16k**, 35%, 99% ee (7)



14l **(*E*)-15** **16l**, 39% (ee n.d.) (8)

Attempts to cyclize the styrenyl isocyanate **35** failed. The crude ^{1}H NMR spectrum consists mostly of starting material **35** along with a small amount of pyridone (eq. 9). Cycloadditions of isocyanates with a terminal substitution at the diene portion, however, do not lead to [4+2+2] cycloadducts. When the ***(E,E)*-36** was treated under the standard conditions, the corresponding [2+2+2] cycloadduct was formed exclusively in 46% yield (eq. 10). In the case of ***(E,Z)*-36**, both [2+2+2] and [4+2+2] cycloadducts were isolated as a 6:1 mixture heavily favoring the [2+2+2] cycloaddition (eq. 11). The significant preference for [2+2+2] cycloaddition is most likely a kinetic argument, in which the migratory insertion with the more proximal alkene is expected to be much faster.

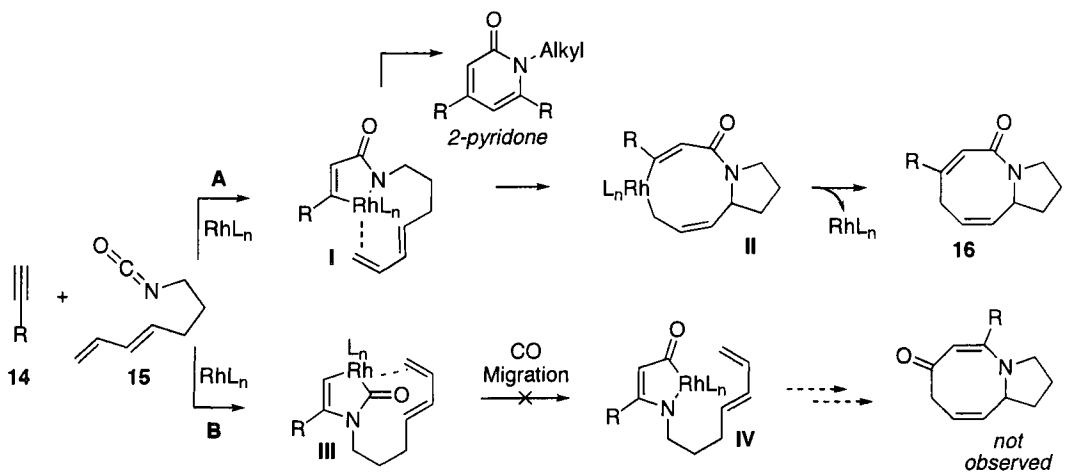


5.5. Proposed Mechanism

The current mechanistic hypothesis is outlined in Scheme 7. Terminal alkyne **14** and the isocyanate moiety of **15** should coordinate to the rhodium leading to the formation of metalacycle **I**. Coordination of the diene should precede migratory insertion

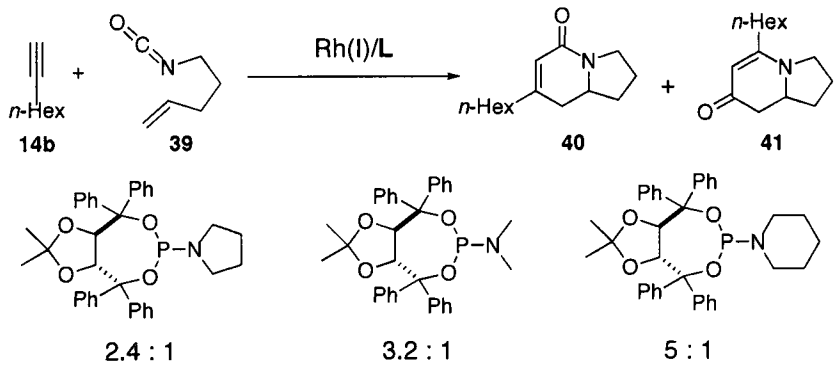
(**I** → **II**), followed by reductive elimination to afford the [4+2+2] cycloadduct **16**. This proposed pathway **A** is in accordance with the isolation of 2-pyridones (a migratory insertion of **I** with a second equivalence of alkyne **14**) as side products when reactions are performed under more concentrated conditions. The low conversions with aryl alkynes and sterically hindered alkyl alkynes can be rationalized by the formation of metalacycle **III** as the major intermediate (pathway **B**). Instead of undergoing CO migration to **IV**, the rhodacycle **III** may be tied up by coordinating to the tethered diene, preventing any productive processes. This hypothesis is in accord to our previous findings in [2+2+2] cycloaddition, for which the CO migration process (pathway **B**) dominates with aryl alkynes. Unlike the [2+2+2] cycloaddition, the CO migration cycloadducts were not detected in any of the [4+2+2] cycloadditions. Attempts to effect the CO migration during the [4+2+2] cycloaddition by employing previously developed conditions (chapter 4) were also not successful. These observations further reinforce the hypothesis stated above.

Scheme 7. Proposed Mechanism



In our previous studies on [2+2+2] cycloaddition with 1-octyne **14b** and alkenyl isocyanate **39**, it was determined that the product selectivity between lactam **40** and CO migration product **41** could be tuned by modifying nitrogen groups on the ligand (Scheme 8). The piperidine-substituted ligand provides the optimal selectivity for formation of **40**. The increase of product selectivity for **40** observed in this study can be correlated directly to the ligand effect study shown in Table 1, in which the piperidine-substituted ligand **L2** promotes formation of azocine **16** with an increased conversion over the pyrrolidinyl ligand **L1** (entry 2 vs. entry 3). In other words, ligand **L2** is more efficient toward [4+2+2] cycloaddition because it is more selective toward the productive pathway **A** (Scheme 7).

Scheme 8.

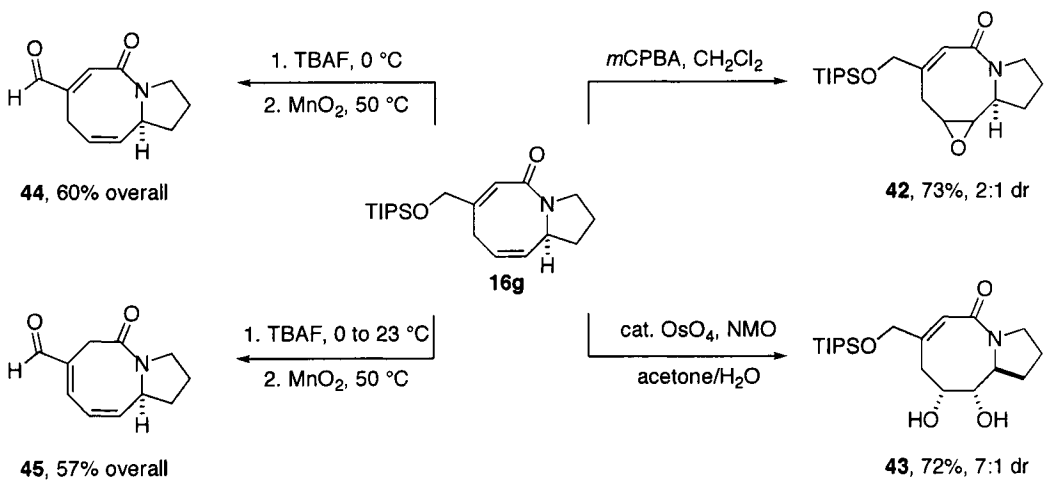


5.6. Synthesis of Highly Functionalized Azocines

The Rh-catalyzed cycloaddition protocol allows access to synthetically useful bicyclic azocines. As illustrated in Scheme 9, treatment of azocine **16g** with *m*CPBA leads to the corresponding epoxide **42** in good yields. The resulting 2:1 diastereomeric ratio indicates that the bicyclic azocine framework equipped with four degrees of

unsaturation (2 rings, 2 double bonds) is quite flat. Bulkier reagents should exert more bias on the system and lead to more selective reactions. Indeed, dihydroxylation in the presence of a catalytic amount of OsO_4 and 1 equiv of NMO gives rise to the formation of diol **43** in 72% yield for the major diastereomer with a good 7:1 *dr*. The bicyclic azocines embedded with a α,β-unsaturated aldehyde functionality can be readily unmasked in two simple steps from **16g**. Treatment with excess TBAF (5 equiv.) at 0 °C for two hours followed by oxidation in the presence of manganese dioxide provides the desired aldehyde **44** in a good overall yield. On the other hand, exposure to TBAF for an extended period of time results in a complete double bond isomerization and leads to aldehyde **45**, possessing a conjugated diene.

Scheme 9. Derivatization



5.7. Conclusion

In conclusion, we have developed the first enantioselective rhodium-catalyzed [4+2+2] cycloaddition of terminal alkynes and dienyl isocyanates. The process provides access to highly functionalized bicyclo[6.3.0] azocine ring systems with exceptional

enantioselectivities. Further studies on the full scope of this new process and applications to complex molecule synthesis are in progress.

5.8. References

[1] Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551; **1986**, *3*, 1; **1987**, *4*, 539; **1989**, *5*, 613.

[2] For recent reviews, see: (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (b) Nicolaou, K. C.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2079.

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[15] Further studies on [2+2+2] cycloadditions with various 1,2-disubstituted alkenyl isocyanates are ongoing.

Chapter 1 Experimental

The Development of a Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Acetonitrile (certified ACS grade) and triethylamine (peptide synthesis grade) were purchased from Fisher Scientific and used without further purification. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and $KMnO_4$ followed by heating.

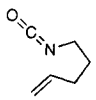
Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

Alkynes **16a**, **16l**, **16m,** and **16o, 16p** were all purchased from Aldrich Chemicals Co. and used without further purification. Alkynes **16b – 16k** were prepared according to

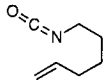
the literature method.[1] Alkyne **16n** was prepared by a typical TBS-protection of the corresponding diol, which was prepared by the literature method.[2] Alkenyl isocyanates **17** and **22** are known compounds and can be synthesized by the procedure described within. 5-hexenoic acid, 6-heptenoic acid, and diphenyl phosphoryl azide were purchased from Aldrich Chemicals Co. $RhCl(PPh_3)_3$, $[Rh(COD)Cl]_2$, and $[Rh(CH_2Cl_2)_2Cl]_2$ were purchased from Strem Chemical, Inc. and used without further purification. Tris(4-methoxyphenyl) phosphine was purchased from Aldrich Chemicals Co. and used without further purification.

General procedure for synthesis of alkenyl isocyanates:

Method A:



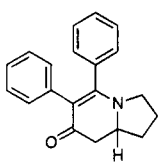
5-isocyanatopent-1-ene (17). To a solution of 2.23 g of 5-hexenoic acid (19.54 mmol) in 20 ml of MeCN (ca. 1 M) was added 2.9 ml of Et_3N (20.71 mmol) slowly, followed by 4.5 ml of diphenyl phosphoryl azide (20.71 mmol) dropwise at ambient temperature. The reaction mixture was stirred at ambient temperature for another 20 minutes. The reaction mixture directly underwent distillation under reduced pressure. MeCN and Et_3N were first collected at *ca.* 150 mmHg. The isocyanate was collected at 30 mmHg as a colorless oil (1.135 g, 52%): bp 60 °C (30 mmHg); ^1H NMR (400 MHz, $CDCl_3$) d 5.75 (ddt, 1H, J = 6.8, 10.2, 17.1 Hz), 5.05 (dm, 1H, J = 17.1 Hz), 5.00 (dm, 1H, J = 10.2 Hz), 3.29 (t, 2H, J = 6.6 Hz), 2.14 (dt, 2H, J = 7.0, 7.0 Hz), 1.69 (tt, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 137.0, 116.1, 42.4, 30.7, 30.4; IR (NaCl, $CHCl_3$) 2955, 2279, 1644, 1516, 1434, 1358 cm^{-1}.



6-isocyanatohex-1-ene (22) To a solution of 706 mg of 6-heptenoic acid (5.508 mmol) in 6 ml of MeCN (*ca.* 1 M) was added 0.82 ml of Et_3N (5.840 mmol) slowly, followed by 1.3 ml of diphenyl phosphoryl azide (5.840 mmol) dropwise at ambient temperature. The reaction mixture was stirred at ambient temperature for another 20 minutes. The reaction mixture directly underwent distillation under reduced pressure. MeCN and Et_3N were first collected at *ca.* 150 mmHg. The isocyanate was collected at 30 mmHg as a colorless oil (497 mg, 72%): bp 70 – 75 °C (30 mmHg); ^1H NMR (300 MHz, $CDCl_3$) d 5.79 (ddt, 1H, J = 6.6, 10.3, 16.9 Hz), 5.02 (dm, 1H, J = 16.9 Hz), 4.98 (dm, 1H, J = 9.9 Hz), 3.31 (t, 2H, J = 6.4 Hz), 2.08 (dt, 2H, J = 7.0, 7.0 Hz), 1.63 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) d 138.2, 115.2, 43.2, 33.3, 31.0, 26.1; IR (NaCl, $CHCl_3$) 2940, 2274, 1634, 1527, 1440, 1363 cm^{-1}.

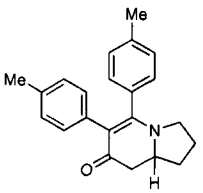
Method B: In a flame-dried round bottom flask under Ar atmosphere, triethylamine (23.22 mmol, 1.06 eq) was added to a stirring solution of carboxylic acid (21.90 mmol) in dichloromethane (23.0 mL) at 0 °C. Diphenylphosphoryl azide (23.22 mmol, 1.06 eq) was then slowly added. After 4 hours, the reaction was concentrated under vacuum and rapidly purified by flash chromatography (20:1 Hex:EtOAc, solvent removal was carried out with the rotovap bath temperature less than 23 °C). The resulting acyl azide was slowly converted to the desired isocyanate by sitting in neat at ambient temperature for 24 hours followed by gently heating at 35 °C for 3-6 hours (75% for **17**, 70% for **22** on 8 mmol scale).

General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and alkynes: A flame-dried round bottom flask was charged with $[Rh(CH_2Cl_2)_2Cl]_2$ (0.05 eq) and tris(4-methoxyphenyl) phosphine (0.1 eq), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml toluene was added via syringe and the resulting orange solution was stirred at ambient temperature under argon flow for 15 minutes. To this solution was added a solution of alkyne **16** (2.0 eq) and isocyanate **17** or **22** (0.270 mmol) in 2 ml of toluene via syringe or cannula. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 14 h. The reaction mixture was cooled to ambient temperature and a small amount of silica gel was added. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (gradient elution typically 3:7 ethyl acetate/hexane). Evaporation of solvent afforded the analytically pure product.[3]

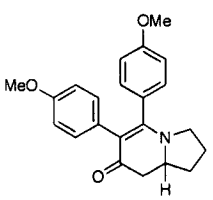


5,6-diphenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19a). According to the general procedure, in the presence of 5.5 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.8 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 96.2 mg (0.540 mmol) of **16a** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 58.1 mg (74%) of the desired product was isolated as a waxy yellow solid: R_f = 0.13 (1:1 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.04 – 7.30 (m, 5H), 7.00 (m, 2H), 6.88 – 6.94 (m, 3H), 4.14 (dddd, 1H, J = 6.8, 6.8, 6.8, 13.6 Hz), 3.40 (ddd, 1H, J = 4.0, 7.5, 11.5 Hz), 3.11 (ddd, 1H, J = 7.5,

7.5, 10.9 Hz), 2.67 (dd, 1H, J = 15.6, 15.6 Hz), 2.59 (dd, 1H, J = 5.3, 16.0 Hz), 2.35 (m, 1H), 1.94 – 2.03 (m, 1H), 1.73 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.9, 161.1, 136.7, 135.9, 132.2, 128.9, 128.2, 127.4, 125.3, 112.4, 57.8, 50.1, 42.1, 32.5, 24.4; IR (NaCl, $CDCl_3$) 1617, 1528, 1450, 1383, 1304, 1091 cm^{-1}; HRMS $[C_{20}H_{20}NO]^+$ calcd 290.1545. Found 290.1545 (FAB+). X-ray data is attached at the end of this manuscript.

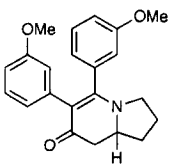


5,6-di*p*-tolyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19b). According to the general procedure, in the presence of 5.4 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.8 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 61.3 mg (0.297 mmol) of **16b** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 54.3 mg (63%) of the desired product was isolated as a yellow oil, which becomes a waxy solid upon standing: R_f = 0.34 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 6.80 – 7.20 (m, 8H), 4.10 (dddd, 1H, J = 7.1, 7.1, 7.1, 12.2 Hz), 3.38 (ddd, 1H, J = 4.5, 7.2, 11.7 Hz), 3.08 (ddd, 1H, J = 7.5, 7.5, 11.1 Hz), 2.64 (dd, 1H, J = 15.8, 15.8 Hz), 2.54 (dd, 1H, J = 4.9, 15.8 Hz), 2.32 (m, 1H), 2.24 (s, 3H), 2.15 (s, 3H), 1.92 – 2.01 (m, 1H), 1.71 – 1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.1, 161.1, 138.7, 134.5, 133.8, 133.1, 132.0, 129.0, 128.2, 112.2, 57.7, 50.1, 42.2, 32.5, 24.4, 21.5, 21.3; IR (NaCl, $CHCl_3$) 1609, 1527, 1445, 1301, 1040 cm^{-1}; HRMS $[C_{22}H_{24}NO]^+$ calcd 318.1858. Found 318.1845 (FAB+).

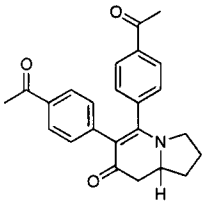


5,6-bis(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19c). According to the general procedure, in the presence of 5.7 mg (0.015 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.7 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 129.0 mg (0.540 mmol) of

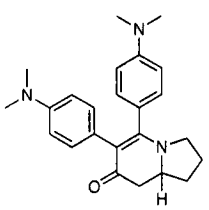
16c were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 68.0 mg (72%) of the desired product was isolated as a yellow oil: R_f = 0.21 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 6.54 – 7.20 (m, 8H), 4.11 (dddd, 1H, *J* = 6.5, 6.5, 6.5, 12.9 Hz), 3.71 (s, 3H), 3.65 (s, 3H), 3.43 (m, 1H), 3.10 (m, 1H), 2.64 (dd, 1H, *J* = 15.8, 15.8 Hz), 2.55 (dd, 1H, *J* = 4.5, 15.8 Hz), 2.31 (m, 1H), 1.91 – 2.01 (m, 1H), 1.71 – 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.9, 161.0, 159.8, 157.1, 133.0, 130.6, 129.3, 128.2, 113.6, 113.1, 111.8, 57.5, 55.3, 55.2, 50.3, 42.0, 32.3, 24.5; IR (NaCl, $CHCl_3$) 1614, 1521, 1440, 1301, 1030 cm^{-1}; HRMS $[C_{22}H_{24}NO_3]^+$ calcd 350.1756. Found 350.1761 (FAB+).



5,6-bis(3-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19d). According to the general procedure, in the presence of 5.6 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.9 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 129.0 mg (0.540 mmol) of **16d** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 66.1 mg (70%) of the desired product was isolated as a yellow oil: R_f = 0.21 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 6.46 – 7.18 (m, 8H), 4.12 (dddd, 1H, *J* = 6.8, 6.8, 6.8, 13.6 Hz), 3.50 – 3.76 (m, 6H), 3.43 (m, 1H), 3.14 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.65 (dd, 1H, *J* = 15.7, 15.7 Hz), 2.57 (dd, 1H, *J* = 5.3, 15.9 Hz), 2.34 (m, 1H), 1.94 – 2.03 (m, 1H), 1.73 – 1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.9, 160.7, 159.4, 158.9, 138.2, 137.1, 129.4, 128.3, 124.8, 121.4, 117.2, 114.6, 111.8, 57.9, 55.4, 55.2, 50.1, 42.1, 32.5, 24.4; IR (NaCl, $CHCl_3$) 1614, 1521, 1460, 1419, 1312, 1045 cm^{-1}; HRMS $[C_{22}H_{23}NO_3]^+$ calcd 349.1678. Found 349.1667 (EI+).

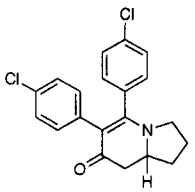


1,1'-(4,4'-(7-oxo-1,2,3,7,8,8a-hexahydroindolizine-5,6-diyl)bis(4,1-phenylene))diethanone (19g). According to the general procedure, in the presence of 5.6 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 10.1 mg (0.029 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 142.0 mg (0.540 mmol) of **16g** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 34.6 mg (34%) of the desired product was isolated as a yellow oil: R_f = 0.13 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.89 (broad d, 1H, *J* = 7.0), 7.67 (broad d, 1H, *J* = 7.2), 7.59 (d, 2H, *J* = 8.3), 7.39 (broad d, 1H, *J* = 6.8), 7.03 (broad d, 1H, *J* = 7.5), 6.98 (d, 2H, *J* = 8.3), 4.17 (dddd, 1H, *J* = 7.0, 7.0, 7.0, 14.1 Hz), 3.40 (ddd, 1H, *J* = 4.3, 7.5, 11.6 Hz), 3.08 (ddd, 1H, *J* = 7.5, 7.5, 11.1 Hz), 2.67 (dd, 1H, *J* = 15.3, 15.3 Hz), 2.61 (dd, 1H, *J* = 6.1, 15.8 Hz), 2.52 (s, 3H), 2.44 (s, 3H), 2.38 (dddd, 1H, *J* = 4.3, 6.6, 6.6, 6.6 Hz), 2.01 (m, 1H), 1.75 – 1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 198.3, 197.4, 189.6, 159.9, 142.0, 140.0, 137.5, 134.1, 132.1, 129.6, 129.4, 128.8, 128.3, 127.7, 111.7, 58.1, 50.3, 41.8, 32.4, 26.8, 26.7, 24.5; IR (NaCl, $CHCl_3$) 1680, 1619, 1521, 1429, 1301, 1040 cm^{-1}; HRMS $[C_{24}H_{24}NO_3]^+$ calcd 374.1756. Found 374.1739 (FAB+).

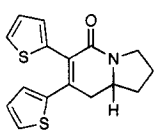


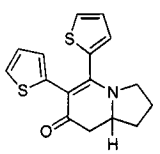
5,6-bis(4-(dimethylamino)phenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19e). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.6 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 143.0 mg (0.540 mmol) of **16e** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 61.0 mg (61%) of the desired product was isolated as a yellow oil, which becomes an orange-yellow waxy solid upon standing: R_f = 0.15 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 6.42 – 7.02 (m, 8H), 4.12 (m, 1H), 3.49 (m, 1H), 3.13 (m, 1H), 2.87 –

2.93 (m, 6H), 2.79 (s, 6H), 2.64 (dd, 1H, J = 15.9, 15.9 Hz), 2.46 (dd, 1H, J = 4.4, 15.7 Hz), 2.28 (m, 1H), 1.94 (m, 1H), 1.70 – 1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.3, 161.4, 150.3, 132.6, 130.8, 123.7, 112.8, 111.8, 111.2, 57.1, 50.7, 42.3, 41.2, 40.3, 32.0, 24.6; IR (NaCl, $CHCl_3$) 1603, 1516, 1470, 1434, 1358, 1306, 1045 cm^{-1}; HRMS $[C_{24}H_{30}N_3O]^+$ calcd 376.2389. Found 376.2379 (FAB+).



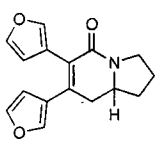
5,6-bis(4-chlorophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19f). According to the general procedure, in the presence of 5.4 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 10.0 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 133.5 mg (0.540 mmol) of **16f** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 58.2 mg (60%) of the desired product was isolated as a yellow oil, which becomes a yellow waxy solid upon standing: R_f = 0.25 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 6.76 – 7.32 (m, 8H), 4.12 (dddd, 1H, J = 7.2, 7.2, 7.2, 14.4 Hz), 3.39 (ddd, 1H, J = 4.3, 7.5, 11.5 Hz), 3.09 (ddd, 1H, J = 7.5, 7.5, 11.1 Hz), 2.63 (dd, 1H, J = 16.0, 16.0 Hz), 2.61 (dd, 1H, J = 6.6, 16.0 Hz), 2.35 (dddd, 1H, J = 4.3, 6.7, 6.7, 6.7 Hz), 1.95 – 2.04 (m, 1H), 1.73 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.5, 160.0, 135.3, 134.9, 133.9, 133.3, 131.2, 130.6, 130.3, 128.8, 127.8, 111.4, 57.9, 50.3, 41.7, 32.4, 24.4; IR (NaCl, $CHCl_3$) 1614, 1516, 1440, 1301, 1086 cm^{-1}; HRMS $[C_{20}H_{18}Cl_2NO]^+$ calcd 358.0765. Found 358.0755 (FAB+).



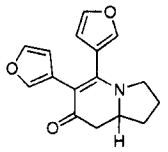


6,7-di(thiophen-2-yl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18h) & 5,6-di(thiophen-2-yl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19h). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.7 mg (0.028 mmol) of tris(4-

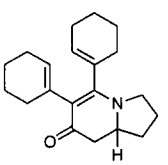
methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 103.0 mg (0.540 mmol) of **16h** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 59.1 mg (72%) of the desired products (**18h** and **19h**) were isolated as an inseparable mixture as a yellow oil, which becomes a yellow waxy solid upon standing: R_f = 0.50 (EtOAc); See ref 4[4] for its ^{1}H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.2, 172.8, 163.3, 154.2, 141.4, 139.8, 138.3, 136.2, 136.1, 130.4, 129.7, 129.6, 129.3, 129.2, 128.8, 128.0, 127.1, 127.1, 127.0, 126.7, 126.4, 125.9, 124.5, 124.3, 106.8, 57.3, 55.5, 50.9, 45.1, 42.0, 37.3, 33.8, 31.9, 24.5, 23.4; IR (NaCl, $CHCl_3$) 1629, 1521, 1496, 1429, 1281, 1040 cm^{-1}; HRMS $[C_{16}H_{16}S_2NO]^+$ calcd 302.0673. Found 302.0662 (FAB+).



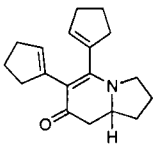
6,7-di(furan-3-yl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18i). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 45.0 mg (0.284 mmol) of **16i** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 22.7 mg (31%) of **18i** was isolated as a yellow oil: R_f = 0.44 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.60 (m, 1H), 7.41 (m, 1H), 7.35 (dd, 1H, *J* = 1.6, 2.9 Hz), 7.26 (dd, 1H, *J* = 1.5, 3.0 Hz), 6.24 (m, 1H), 6.11 (m, 1H), 3.83 (dddd, 1H, *J* = 5.1, 5.1, 9.9, 14.4 Hz), 3.64 (ddd, 1H, *J* = 2.1, 8.7, 11.5 Hz), 3.54 (ddd, 1H, *J* = 7.5, 9.8, 12.0 Hz), 2.76 (dd, 1H, *J* = 4.5, 16.8 Hz), 2.47 (dd, 1H, *J* = 13.7, 16.8 Hz), 2.27 (ddd, 1H, *J* = 6.0, 6.0, 6.0 Hz), 2.04 (m, 1H), 1.83 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 163.8, 143.1, 142.7, 142.4, 142.0, 135.9, 124.9, 123.4, 119.4, 112.6, 110.6, 55.6, 45.0, 36.6, 33.8, 23.4; IR (NaCl, $CHCl_3$) 1639, 1614, 1516, 1434, 1035 cm^{-1}; HRMS $[C_{16}H_{16}NO_3]^+$ calcd 270.1130. Found 270.1129 (FAB+).



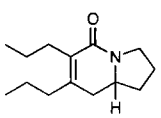
5,6-di(furan-3-yl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19i). From the same reaction, 25.3 mg (35%) of **19i** was also isolated as a yellow oil: R_f = 0.38 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.39 (m, 2H), 7.32 (m, 1H), 7.15 (m, 1H), 6.30 (m, 1H), 5.90 (m, 1H), 4.03 (dddd, 1H, *J* = 6.7, 6.7, 6.7, 13.7 Hz), 3.57 (ddd, 1H, *J* = 5.1, 7.5, 11.7 Hz), 3.30 (ddd, 1H, *J* = 7.5, 7.5, 11.3 Hz), 2.56 (dd, 1H, *J* = 15.4, 15.4 Hz), 2.50 (dd, 1H, *J* = 6.0, 16.0 Hz), 2.31 (dddd, 1H, *J* = 6.7, 6.7, 6.7, 6.7 Hz), 2.01 (m, 1H), 1.91 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.4, 152.6, 143.3, 143.1, 141.4, 141.0, 120.6, 119.7, 112.1, 111.3, 103.6, 57.3, 50.3, 42.1, 32.1, 24.4; IR (NaCl, $CHCl_3$) 1609, 1588, 1516, 1491, 1434, 1311, 1045 cm^{-1}; HRMS $[C_{16}H_{16}NO_3]^+$ calcd 270.1130. Found 270.1133 (FAB+).



5,6-dicyclohexenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19j). According to the general procedure, in the presence of 5.4 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.7 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 101.0 mg (0.540 mmol) of **16j** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 60.1 mg (75%) of the desired product was isolated as a waxy pale yellow solid: R_f = 0.29 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 5.58 (m, 1H), 5.32 (m, 1H), 3.73 (dddd, 1H, *J* = 9.6, 9.6, 9.6, 16.9 Hz), 3.24 – 3.52 (m, 2H), 2.28 – 2.36 (m, 2H), 2.21 (dddd, 2H, *J* = 2.9, 6.5, 6.5, 12.7 Hz), 1.92 – 2.08 (m, 7H), 1.79 (m, 2H), 1.44 – 1.66 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.2, 162.5, 134.3, 126.8, 57.6, 48.4, 42.3, 32.7, 30.2, 28.6, 26.0, 25.1, 24.3, 23.5, 22.6, 22.6, 22.1; IR (NaCl, $CHCl_3$) 1598, 1511, 1475, 1440, 1296, 1040 cm^{-1}; HRMS $[C_{20}H_{28}NO]^+$ calcd 298.2171. Found 298.2175 (FAB+).

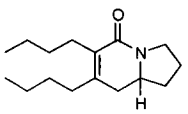


5,6-dicyclopentenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19k). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 85.4 mg (0.540 mmol) of **16k** were reacted in 4 ml of toluene at 80 °C for 23 hours. Upon purification 36.5 mg (50%) of the desired product was isolated as a yellow oil: R_f = 0.24 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 5.71 (m, 1H), 5.38 (m, 1H), 3.80 (dddd, 1H, *J* = 7.9, 7.9, 7.9, 15.1 Hz), 3.45 (ddd, 1H, *J* = 4.0, 8.1, 11.3 Hz), 3.29 (ddd, 1H, *J* = 8.1, 8.1, 10.8 Hz), 2.61 (dddddd, 1H, *J* = 2.4, 2.4, 2.4, 6.5, 6.5, 13.5 Hz), 2.32 – 2.42 (m, 6H), 2.18 – 2.31 (m, 3H), 2.09 (m, 1H), 1.97 (m, 1H), 1.75 – 1.90 (m, 5H), 1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.9, 158.3, 139.6, 139.2, 132.8, 129.2, 107.8, 57.5, 49.0, 42.2, 36.2, 35.8, 33.3, 32.9, 32.5, 24.2, 24.2, 23.9; IR (NaCl, $CHCl_3$) 1603, 1511, 1475, 1419, 1040 cm^{-1}; HRMS $[C_{18}H_{24}NO]^+$ calcd 270.1858. Found 270.1848 (FAB+).

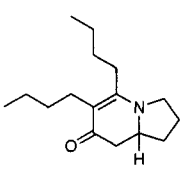


6,7-dipropyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18l). According to the general procedure, in the presence of 5.4 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.8 mg (0.028 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 60.0 mg (0.540 mmol) of **16l** were reacted in 4 ml of toluene at 80 °C for 23 hours. Upon purification 35.9 mg (60%) of the desired product was isolated as a yellow oil: R_f = 0.30 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 3.59 (dm, 1H, *J* = 2.1 Hz), 3.52 (m, 1H), 3.45 (ddd, 1H, *J* = 7.5, 9.8, 11.9 Hz), 2.42 (m, 1H), 2.26 (dd, 1H, *J* = 4.4, 16.0 Hz), 2.05 – 2.20 (m, 5H), 1.96 (m, 1H), 1.74 (ddddd, 1H, *J* = 6.6, 9.5, 9.5, 12.3, 12.3 Hz), 1.54 (dddd, 1H, *J* = 7.1, 10.4, 11.7, 11.7 Hz), 1.42 (m, 2H), 1.39 (m,

2H), 0.91 (t, 3H, J = 7.4 Hz), 0.89 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.1, 144.9, 130.8, 55.6, 44.7, 35.9, 35.2, 33.9, 28.4, 23.4, 23.3, 21.2, 14.4, 14.3; IR (NaCl, $CHCl_3$) 1655, 1603, 1521, 1419, 1045 cm^{-1}; HRMS $[C_{14}H_{24}NO]^+$ calcd 222.1858. Found 222.1865 (FAB+).

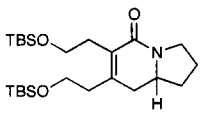


6,7-dibutyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18m). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 75.0 mg (0.540 mmol) of **16m** were reacted in 4 ml of toluene at 80 °C for 23 hours. Upon purification 47.4 mg (70%) of the desired product was isolated as a yellow oil: R_f = 0.64 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 3.58 (dm, 1H, J = 2.1 Hz), 3.51 (m, 1H), 3.45 (ddd, 1H, J = 7.7, 10.0, 11.9 Hz), 2.41 (m, 1H), 2.25 (dd, 1H, J = 4.7, 16.2 Hz), 2.05 – 2.20 (m, 5H), 1.95 (m, 1H), 1.74 (ddddd, 1H, J = 6.6, 9.5, 9.5, 12.3, 12.3 Hz), 1.53 (dddd, 1H, J = 7.1, 10.0, 11.7, 11.7 Hz), 1.27 – 1.38 (m, 8H), 0.89 (t, 3H, J = 7.0 Hz), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.1, 144.8, 130.8, 55.6, 44.6, 35.3, 33.9, 33.6, 32.5, 30.2, 26.2, 23.3, 23.1, 22.9, 14.2; IR (NaCl, $CHCl_3$) 1644, 1598, 1521, 1440, 1045 cm^{-1}; HRMS $[C_{16}H_{28}NO]^+$ calcd 250.2171. Found 250.2163 (FAB+).

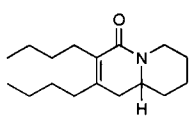


5,6-dibutyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19m). From the same reaction, 8.2 mg (12%) of **19m** was also isolated as an oil: R_f = 0.35 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 3.60 (m, 1H), 3.54 (dm, 1H, J = 2.3 Hz), 3.45 (ddd, 1H, J = 7.5, 9.8, 9.8 Hz), 2.39 (dd, 1H, J = 4.5, 15.8 Hz), 2.26 – 2.33 (m, 2H), 2.18 (m, 3H), 2.03 (m, 1H), 1.81 (ddddd, 1H, J = 6.9, 9.2, 9.2, 12.2, 12.2 Hz), 1.61 (dddd, 1H, J = 7.2, 10.3, 11.8, 11.8 Hz), 1.41 (m, 4H), 1.29 (m, 4H), 0.93 (t,

3H, J = 7.0 Hz), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.0, 161.8, 108.5, 58.2, 47.5, 42.1, 33.5, 32.8, 30.6, 30.3, 25.0, 23.8, 23.2, 23.1, 14.3, 14.0; IR (NaCl, $CHCl_3$) 1532, 1475, 1424, 1045 cm^{-1}; HRMS $[C_{16}H_{28}NO]^+$ calcd 250.2171. Found 250.2159 (FAB+).

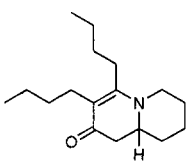


6,7-bis(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18n). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 185.0 mg (0.540 mmol) of **16n** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 68.4 mg (56%) of the desired product was isolated as a yellow oil: R_f = 0.36 (3:7 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) d 3.67 (m, 4H), 3.56 (m, 1H), 3.52 (m, 1H), 3.44 (ddd, 1H, J = 7.7, 9.8, 11.7 Hz), 2.66 (m, 1H), 2.54 (dt, 1H, J = 6.5, 13.0 Hz), 2.48 (dt, 1H, J = 7.2, 13.6 Hz), 2.39 (dd, 1H, J = 4.3, 15.8 Hz), 2.38 (dd, 1H, J = 13.2, 13.2 Hz), 2.13 (m, 2H), 1.95 (m, 1H), 1.73 (ddddd, 1H, J = 6.6, 9.4, 9.4, 11.9, 11.9 Hz), 1.53 (dddd, 1H, J = 7.1, 10.0, 11.8, 11.8 Hz), 0.85 (dm, 18H, J = 1.9 Hz), 0.01 (dm, 12H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.6, 144.4, 128.5, 62.9, 61.9, 55.6, 44.6, 37.5, 36.2, 33.9, 30.4, 26.2, 26.1, 23.2, 18.5, 18.4, -5.1, -5.2; IR (NaCl, $CHCl_3$) 1650, 1609, 1527, 1419, 1086 cm^{-1}; HRMS $[C_{24}H_{48}Si_2NO_3]^+$ calcd 454.3173. Found 454.3167 (FAB+).

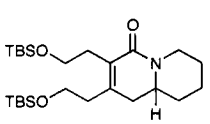


2,3-dibutyl-7,8,9,9a-tetrahydro-1*H*-quinolizin-4(6*H*)-one (23m). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **22** and 74.7 mg (0.540 mmol) of **16m** were reacted

in 4 ml of toluene at 110 °C for 23 hours. Upon purification 44.1 mg (62%) of the desired product was isolated as a yellow oil: R_f = 0.64 (3:7 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) d 4.44 (dm, 1H, *J* = 13.6 Hz), 3.23 (dddd, 1H, *J* = 3.3, 5.6, 10.3, 10.3 Hz), 2.47 (ddd, 1H, *J* = 3.0, 13.0, 13.0 Hz), 2.19 (dd, 1H, *J* = 5.8, 17.3 Hz), 2.28 (m, 2H), 2.07 – 2.15 (m, 3H), 1.76 (m, 1H), 1.70 (m, 1H), 1.68 (m, 1H), 1.26 – 1.43 (m, 11H), 0.89 (t, 3H, *J* = 7.1 Hz), 0.87 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.5, 145.5, 129.3, 54.1, 43.4, 35.5, 33.6, 33.4, 32.6, 30.1, 26.6, 25.0, 23.9, 23.2, 23.0, 14.2, 14.2; IR (NaCl, $CHCl_3$) 1660, 1609, 1521, 1429, 1332, 1045 cm^{-1}; HRMS $[C_{17}H_{30}NO]^+$ calcd 264.2327. Found 264.2326 (FAB+).

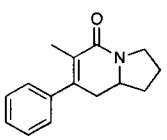


3,4-dibutyl-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (23m). From the same reaction, 13.2 mg (18%) of **23m** was also isolated as a yellow oil: R_f = 0.24 (3:7 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) d 3.74 (dm, 1H, *J* = 13.0 Hz), 3.15 (dddd, 1H, *J* = 3.6, 5.1, 11.1, 11.1 Hz), 2.69 (ddd, 1H, *J* = 2.6, 12.6, 12.6 Hz), 2.44 (dd, 1H, *J* = 5.4, 16.1 Hz) 2.21 – 2.38 (m, 4H), 2.13 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.48 – 1.60 (m, 3H), 1.41 (m, 5H), 1.27 (m, 4H), 0.93 (t, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.3, 163.6, 112.4, 58.2, 49.0, 43.3, 33.2, 31.7, 30.9, 29.4, 26.4, 25.4, 24.0, 23.2, 23.1, 14.3, 14.0; IR (NaCl, $CHCl_3$) 1603, 1527, 1419, 1040 cm^{-1}; HRMS $[C_{17}H_{30}NO]^+$ calcd 264.2327. Found 264.2331 (FAB+).



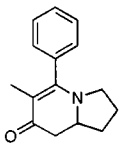
2,3-bis(2-(*tert*-butyldimethylsilyloxy)ethyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-4(6*H*)-one (23n). According to the general procedure, in the presence of 5.3 mg (0.014 mmol) of $[Rh(CH_2Cl_2)_2Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **22** and 185.0 mg (0.540

mmol) of **16n** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 71.1 mg (56%) of the desired product was isolated as an oil: R_f = 0.74 (3:7 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) d 4.43 (dm, 1H, *J* = 13.4 Hz), 3.69 (m, 2H), 3.63 (m, 2H), 3.23 (dddd, 1H, *J* = 3.2, 5.6, 10.5, 10.5 Hz), 2.36 – 2.61 (m, 6H), 2.18 (dd, 1H, *J* = 10.9, 17.3 Hz), 1.76 (m, 1H), 1.71 (m, 1H), 1.68 (m, 1H), 1.30 – 1.46 (m, 3H), 0.85 (dm, 18H, *J* = 3.2 Hz), 0.08 (dm, 12H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.1, 145.2, 127.0, 62.9, 61.7, 54.0, 43.3, 37.5, 36.5, 33.4, 30.7, 26.2, 26.1, 25.0, 23.8, 18.5, 18.4, -5.1, -5.2; IR (NaCl, $CHCl_3$) 1660, 1609, 1521, 1475, 1424, 1086, 1045 cm^{-1}; HRMS $[C_{25}H_{50}Si_2NO_3]^+$ calcd 468.3329. Found 468.3324 (FAB+).



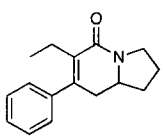
6-methyl-7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18o). According to the general procedure, in the presence of 6.7 mg (0.0135 mmol) of $[Rh(COD)Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 63.0 mg (0.540 mmol) of **16o** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 21.2 mg (34%) of **18o** was isolated as a yellow oil: R_f = 0.30 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.34 (br t, 2H, *J* = 7.5 Hz), 7.27 (m, 1H), 7.17 (m, 2H), 3.77 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 14.9 Hz), 3.64 (ddd, 1H, *J* = 2.1, 9.2, 11.4 Hz), 3.52 (ddd, 1H, *J* = 7.6, 10.0, 11.8 Hz), 2.60 (dd, 1H, *J* = 4.7, 16.2 Hz), 2.49 (ddq, 1H, *J* = 2.1, 4.8, 16.4 Hz), 2.19 (m, 1H), 2.02 (m, 1H), 1.85 (d, 3H, *J* = 2.1), 1.79 (m, 1H), 1.60 (dddd, 1H, *J* = 7.0, 9.8, 11.7, 11.7); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.3, 143.6, 141.0, 130.5, 128.5, 127.9, 127.7, 127.1, 56.0, 44.8, 37.5, 33.9, 23.3, 14.0; IR (NaCl, $CHCl_3$) 1644, 1608, 1445, 1378, 1091 cm^{-1}; HRMS $[C_{15}H_{18}NO]^+$ calcd 228.1388. Found 228.1400 (FAB+).

Regiochemistry: Isolated as a single regioisomer. Assigned based on the observation of the homoallylic proton coupling between the Methyl group and the hydrogen at 2.49 ppm, and the 2D-NOSEY.



6-methyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19o). From the same reaction, 15.7 mg (26%) of **19o** was also isolated as a waxy yellow solid: R_f = 0.16 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.39 (m, 3H), 7.18 (dm, 2H, *J* = 6.4 Hz), 3.88 (dddd, 1H, *J* = 6.6, 6.6, 6.6, 14.9 Hz), 3.17 (ddd, 1H, *J* = 3.4, 7.7, 10.9 Hz), 3.03 (ddd, 1H, *J* = 7.9, 7.9, 10.7 Hz), 2.51 (dd, 1H, *J* = 6.2, 16.0 Hz), 2.46 (dd, 1H, *J* = 16.0, 16.0 Hz), 2.27 (m, 1H), 1.90 (m, 1H), 1.64 – 1.81 (m, 2H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.5, 160.4, 136.1, 129.0, 128.9, 127.8, 125.9, 104.2, 58.0, 49.5, 41.9, 32.8, 24.2, 11.9; IR (NaCl, $CHCl_3$) 1615, 1535, 1469, 1375, 1295, 1098 cm^{-1}; HRMS $[C_{15}H_{18}NO]^+$ calcd 228.1388. Found 228.1387 (FAB+).

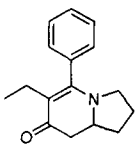
Regiochemistry: Regiochemistry > 95:5 indicated by 'H NMR and GC-MS. Assigned based on 2D-NOSEY.



6-ethyl-7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18p). According to the general procedure, in the presence of 6.7 mg (0.0135 mmol) of $[Rh(COD)Cl]_2$ and 9.5 mg (0.027 mmol) of tris(4-methoxyphenyl) phosphine, 30.0 mg (0.270 mmol) of **17** and 70.3 mg (0.540 mmol) of **16p** were reacted in 4 ml of toluene at 110 °C for 23 hours. Upon purification 13.7 mg (21%) of **18p** was isolated as a yellow oil: R_f = 0.45 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.35 (tm, 2H, *J* = 7.3 Hz), 7.27 (m, 1H), 7.16 (m, 2H), 3.78 (dddd, 1H, *J* = 5.8, 7.9, 10.5, 10.5 Hz), 3.67 (ddd, 1H, *J* = 2.2, 9.0, 11.7 Hz), 3.53 (ddd, 1H, *J* = 7.5, 10.0, 11.9 Hz), 2.52 (m, 2H), 2.44 (m, 1H), 2.10 – 2.22 (m, 2H), 2.02 (ddddd, 1H, *J* = 2.1, 2.1, 7.5, 7.5, 14.7 Hz), 1.80 (ddddd, 1H, *J*

= 6.6, 9.8, 9.8, 11.9, 11.9 Hz), 1.60 (dddd, 1H, J = 7.0, 10.0, 11.7, 11.7) 0.97 (t, 3H, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.6, 143.6, 141.2, 134.3, 128.6, 127.6, 127.4, 55.8, 44.8, 37.9, 33.9, 23.3, 20.9, 14.9; IR (NaCl, $CHCl_3$) 1644, 1609, 1521, 1450, 1045 cm^{-1}; HRMS $[C_{16}H_{20}NO]^+$ calcd 242.1545. Found 242.1544 (FAB+).

Regiochemistry: Assigned based on **18o**.



6-ethyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19p). From the same reaction, 27.5 mg (42%) of **19p** was also isolated as a waxy yellow solid: R_f = 0.30 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.39 (m, 3H), 7.19 (m, 2H), 3.85 (dddd, 1H, J = 6.0, 6.0, 9.0, 12.2 Hz), 3.09 (ddd, 1H, J = 3.0, 7.9, 11.1 Hz), 3.00 (m, 1H), 2.51 (dd, 1H, J = 6.0, 16.0 Hz), 2.46 (dd, 1H, J = 15.8, 15.8 Hz), 2.26 (m, 1H), 1.81 – 2.00 (m, 3H), 1.72 (m, 1H), 0.77 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.0, 160.6, 136.0, 129.0, 128.9, 128.8, 127.5, 126.1, 111.1, 58.1, 49.3, 42.2, 33.0, 24.0, 19.4, 15.6; IR (NaCl, $CHCl_3$) 1614, 1527, 1455, 1414, 1265, 1158 cm^{-1}; HRMS $[C_{16}H_{20}NO]^+$ calcd 242.1545. Found 242.1543 (FAB+).

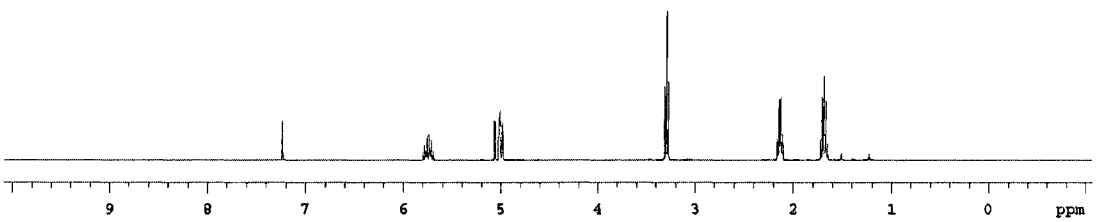
Regiochemistry: Assigned based on **18o**.

Regioselectivity of both **18p** and **19p** ~ 10 :1. Two minor isomers isolated with the **19p** batch. According to GC-MS and proton NMR, ratio of **18p** : **19p** : minor isomer 1 : minor isomer 2 = 8.9 : 15 : 1.5 : 1.

17

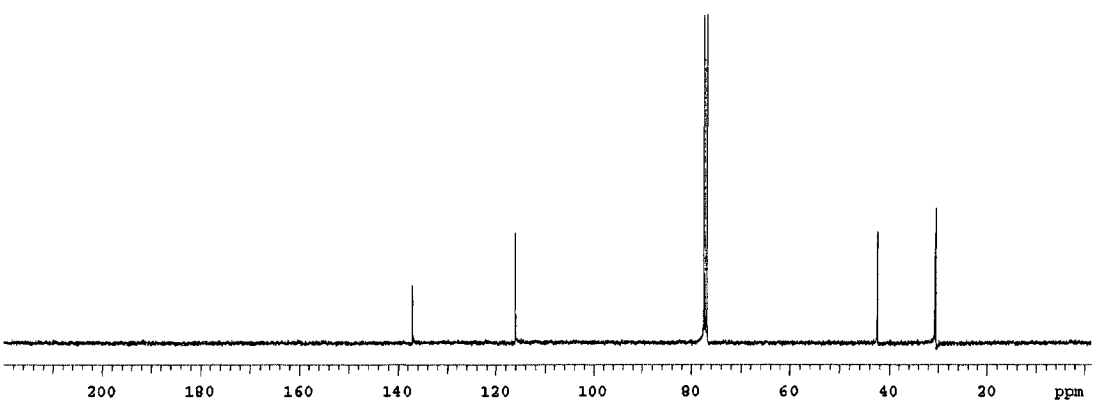
STANDARD 1H OBSERVE

yu1-280



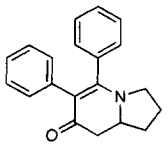
13C OBSERVE

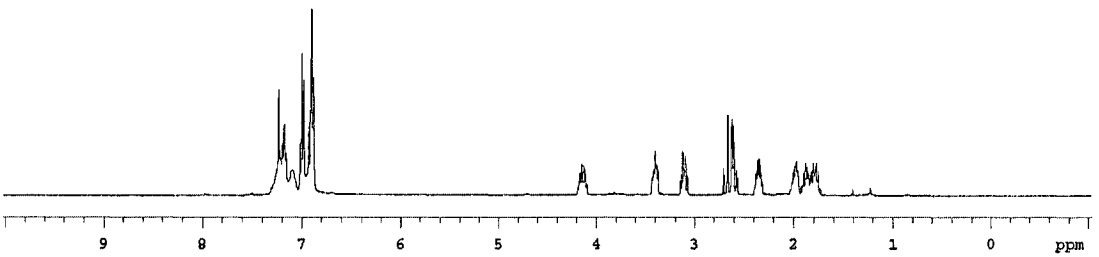
yu1-280

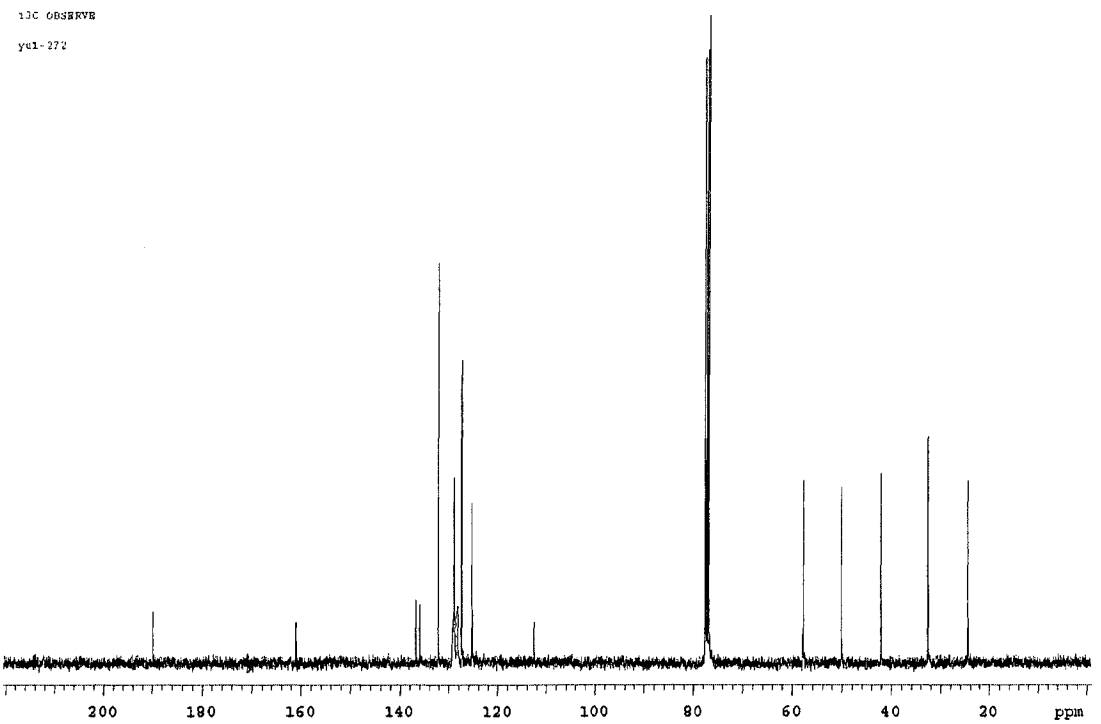


19a

yu1-272-cosy_07Dec2004
yu1-272



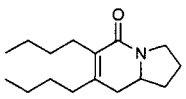


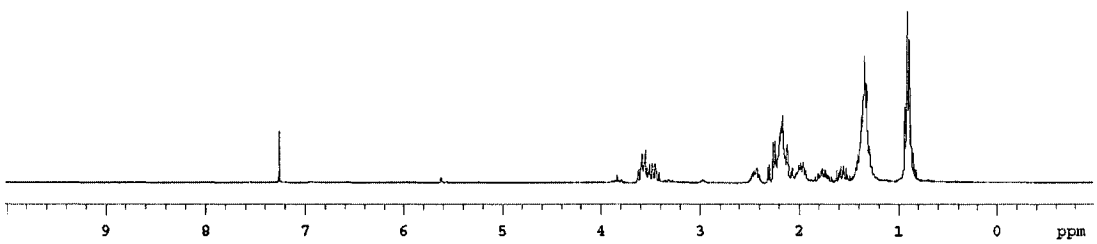


18m

STANDARD 1H OBSERVE

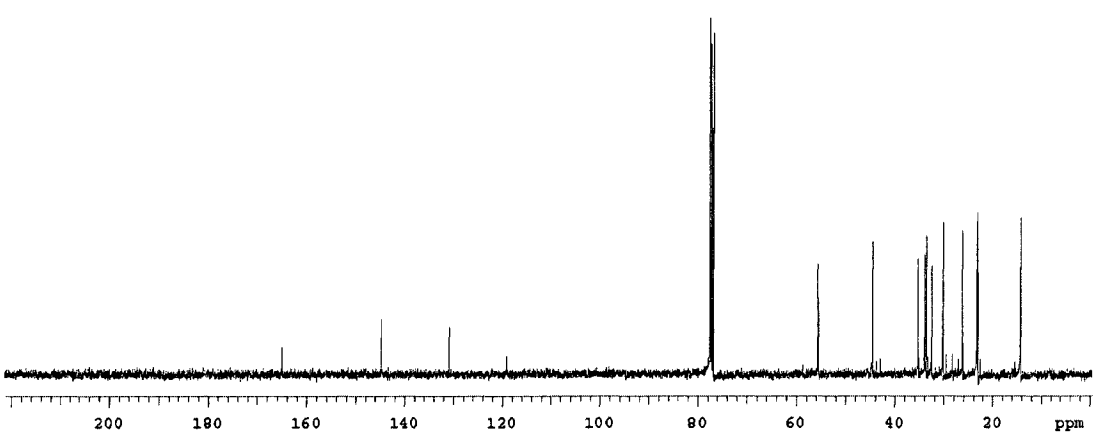
yu1-425



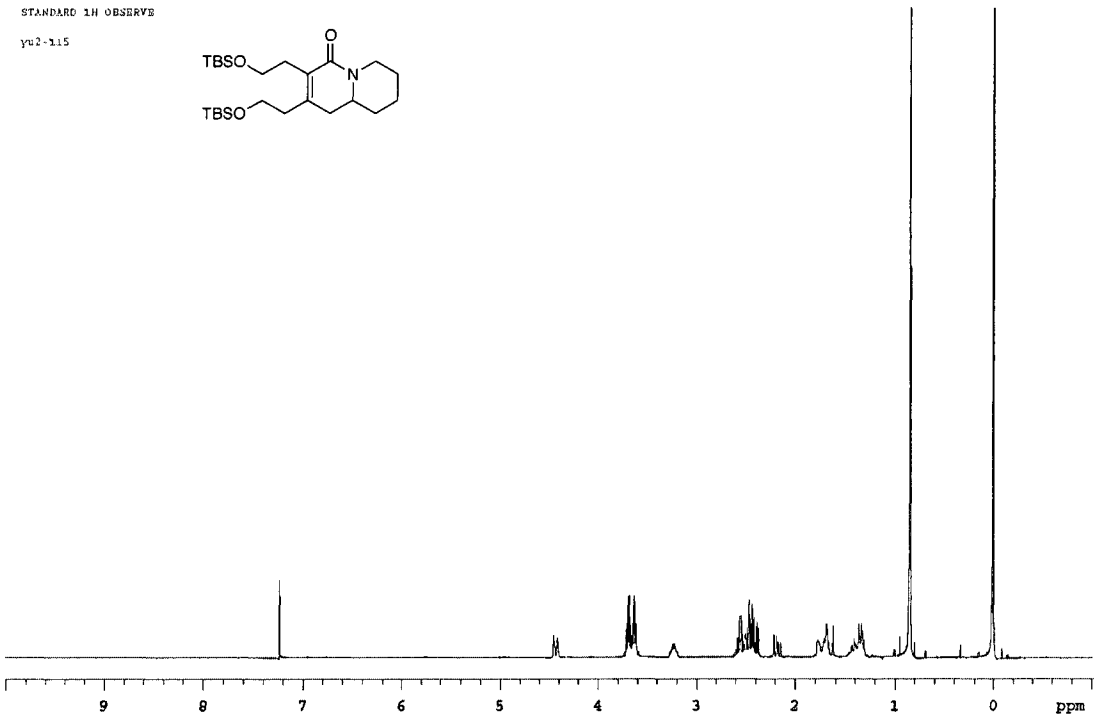


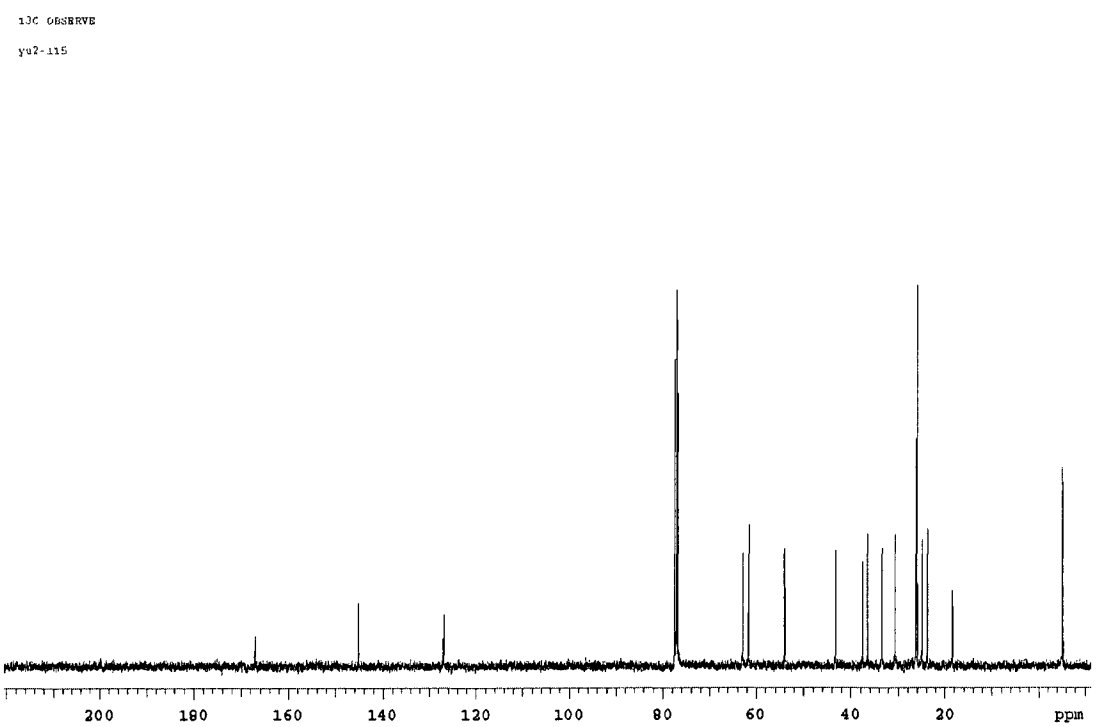
13C OBSERVE

yu1-425



23n





Crystal Structure Data for 19a

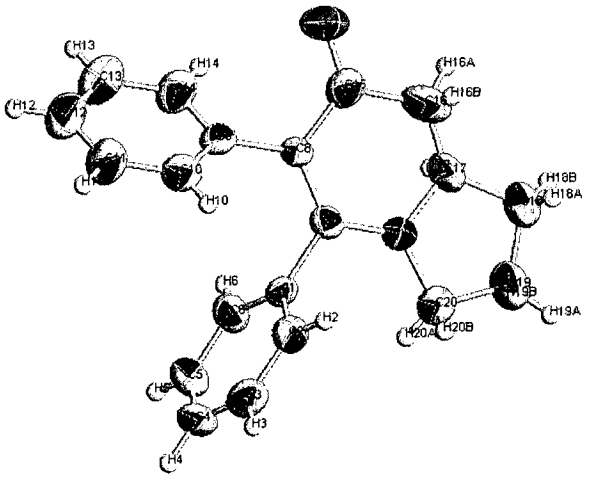


Table 1. Crystal data and structure refinement for rovis11m.

Identification code	rovis11m	
Empirical formula	C20 H19 N O	
Formula weight	289.36	
Temperature	298(2) K	
Wavelength	0.71073 ≈	
Crystal system	monoclinic	
Space group	P2(1)/C	
Unit cell dimensions	a = 9.656(2) ≈	□= 90∞.
	b = 10.634(2) ≈	□= 103.175(5)∞.
	c = 15.602(4) ≈	□ = 90∞.
Volume	1559.9(6) ≈^{3}	
Z	4	
Density (calculated)	1.232 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	616	
Crystal size	0.08 x 0.20 x 0.40 mm^3	
Theta range for data collection	2.17 to 17.99∞.	
Index ranges	-8<=h<=8, -9<=k<=9, -13<=l<=13	

Reflections collected	5581
Independent reflections	1077 [R(int) = 0.0845]
Completeness to theta = 17.99∞	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1077 / 0 / 200
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0504, wR2 = 0.1195
R indices (all data)	R1 = 0.0869, wR2 = 0.1404
Extinction coefficient	0.0008(13)
Largest diff. peak and hole	0.174 and -0.158 e.$\approx^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for rovis11m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2611(5)	1843(5)	-469(3)	87(2)
N(1)	3157(5)	4609(5)	1339(4)	54(2)
C(1)	2597(8)	6282(7)	290(3)	38(2)
C(2)	3763(7)	7055(8)	391(3)	54(2)
C(3)	3573(9)	8326(8)	206(4)	66(2)
C(4)	2248(12)	8832(7)	-65(4)	70(2)
C(5)	1102(8)	8062(8)	-156(4)	65(2)
C(6)	1270(8)	6792(7)	14(4)	54(2)
C(7)	2770(6)	4908(7)	477(6)	40(2)
C(8)	2514(6)	4012(7)	-178(4)	41(2)
C(9)	2065(8)	4333(7)	-1114(5)	47(2)
C(10)	2741(7)	5229(7)	-1522(5)	60(2)
C(11)	2251(10)	5533(6)	-2396(6)	76(2)
C(12)	1075(11)	4954(8)	-2893(5)	79(2)
C(13)	393(7)	4043(8)	-2515(6)	76(2)
C(14)	881(8)	3736(6)	-1639(6)	62(2)
C(15)	2753(7)	2708(8)	65(4)	59(2)
C(16)	3316(9)	2434(7)	1018(6)	103(3)
C(17)	3123(9)	3309(8)	1622(5)	99(3)

C(18)	3677(7)	3332(6)	2583(4)	70(2)
C(19)	3399(8)	4625(7)	2871(4)	100(3)
C(20)	3353(7)	5465(6)	2092(4)	66(2)

Table 3. Bond lengths [≈] and angles [∞] for rovis11m.

O(1)-C(15)	1.228(7)
N(1)-C(7)	1.349(6)
N(1)-C(17)	1.453(7)
N(1)-C(20)	1.465(7)
C(1)-C(6)	1.367(7)
C(1)-C(2)	1.374(7)
C(1)-C(7)	1.492(8)
C(2)-C(3)	1.386(8)
C(3)-C(4)	1.363(8)
C(4)-C(5)	1.358(8)
C(5)-C(6)	1.379(8)
C(7)-C(8)	1.377(7)
C(8)-C(15)	1.442(8)
C(8)-C(9)	1.466(8)
C(9)-C(10)	1.389(7)
C(9)-C(14)	1.399(7)
C(10)-C(11)	1.376(8)
C(11)-C(12)	1.367(8)
C(12)-C(13)	1.378(8)
C(13)-C(14)	1.379(8)
C(15)-C(16)	1.492(9)
C(16)-C(17)	1.367(8)
C(17)-C(18)	1.472(8)
C(18)-C(19)	1.490(7)
C(19)-C(20)	1.501(7)
C(7)-N(1)-C(17)	120.5(5)
C(7)-N(1)-C(20)	127.5(6)
C(17)-N(1)-C(20)	110.8(6)
C(6)-C(1)-C(2)	118.9(6)
C(6)-C(1)-C(7)	120.3(7)
C(2)-C(1)-C(7)	120.7(7)
C(1)-C(2)-C(3)	119.5(6)
C(4)-C(3)-C(2)	121.4(7)
C(5)-C(4)-C(3)	118.6(7)
C(4)-C(5)-C(6)	120.9(7)
C(1)-C(6)-C(5)	120.6(6)
N(1)-C(7)-C(8)	122.6(6)
N(1)-C(7)-C(1)	114.8(6)
C(8)-C(7)-C(1)	122.6(7)
C(7)-C(8)-C(15)	118.7(6)
C(7)-C(8)-C(9)	122.7(7)
C(15)-C(8)-C(9)	118.6(6)
C(10)-C(9)-C(14)	116.7(6)
C(10)-C(9)-C(8)	123.6(7)
C(14)-C(9)-C(8)	119.7(7)
C(11)-C(10)-C(9)	121.7(6)
C(12)-C(11)-C(10)	120.6(7)
C(11)-C(12)-C(13)	119.4(7)
C(12)-C(13)-C(14)	120.1(7)
C(13)-C(14)-C(9)	121.5(6)
O(1)-C(15)-C(8)	123.8(6)
O(1)-C(15)-C(16)	119.2(7)
C(8)-C(15)-C(16)	116.7(6)
C(17)-C(16)-C(15)	118.6(6)
C(16)-C(17)-N(1)	115.0(6)
C(16)-C(17)-C(18)	129.6(8)
N(1)-C(17)-C(18)	105.4(6)
C(17)-C(18)-C(19)	105.9(5)
C(18)-C(19)-C(20)	106.1(5)
N(1)-C(20)-C(19)	104.8(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for rovis11m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	150(5)	44(3)	69(4)	-10(3)	28(3)	-6(3)
N(1)	74(4)	37(5)	46(5)	0(4)	3(3)	-3(3)
C(1)	44(6)	33(6)	34(4)	-4(3)	5(4)	-9(5)
C(2)	62(6)	48(6)	50(5)	2(4)	7(4)	-5(5)
C(3)	84(8)	52(7)	58(5)	-4(4)	7(5)	-22(5)
C(4)	116(8)	31(5)	59(5)	2(4)	12(5)	-3(6)
C(5)	80(7)	46(6)	65(5)	5(4)	7(4)	12(5)
C(6)	57(6)	47(6)	57(5)	8(4)	10(4)	0(5)
C(7)	38(4)	34(6)	47(6)	4(5)	8(4)	-7(4)
C(8)	49(4)	30(6)	41(6)	0(5)	7(4)	-4(3)
C(9)	51(5)	42(5)	45(6)	-8(5)	7(5)	1(4)
C(10)	75(5)	50(5)	55(6)	-1(4)	17(5)	-5(4)
C(11)	110(7)	73(5)	46(6)	8(5)	23(5)	-9(6)
C(12)	94(7)	89(7)	50(5)	-7(5)	8(6)	8(5)
C(13)	64(6)	100(7)	61(7)	-11(5)	12(5)	-8(5)
C(14)	68(6)	76(5)	46(6)	-5(5)	23(4)	4(5)
C(15)	85(6)	56(7)	40(6)	3(5)	23(4)	-12(5)
C(16)	189(9)	41(5)	81(7)	5(6)	36(6)	6(5)
C(17)	188(9)	46(7)	54(7)	14(5)	9(5)	19(5)
C(18)	91(6)	62(6)	55(6)	17(4)	14(4)	2(4)
C(19)	166(8)	76(6)	54(5)	17(5)	18(5)	26(6)
C(20)	90(6)	54(5)	50(5)	1(5)	7(4)	-3(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\approx^2$x 10^3) for rovis11m.

	x	y	z	U(eq)
H(2)	4674	6727	582	65
H(3)	4365	8844	267	80
H(4)	2131	9687	-186	84
H(5)	191	8396	-334	78
H(6)	473	6277	-61	65
H(10)	3544	5633	-1197	72
H(11)	2725	6139	-2651	91
H(12)	739	5173	-3481	95
H(13)	-398	3634	-2851	91
H(14)	412	3117	-1393	74
H(16A)	2886	1654	1151	123
H(16B)	4329	2283	1109	123
H(17)	2104	3207	1590	118
H(18A)	4688	3152	2730	83
H(18B)	3194	2712	2865	83
H(19A)	4151	4887	3364	120
H(19B)	2501	4654	3050	120
H(20A)	2568	6054	2021	79
H(20B)	4233	5933	2159	79

References:

[1] Mio, M. J.; Kopel, L. C.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G., Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002,** *4,* 3199.

[2] Malacria, M.; Vollhardt, K. P. C. *J. Org. Chem.* **1984,** *49,* 5010.

[3] Many vinylogous amide bicyclic products exist as rotamers, especially in the aromatic region. Therefore proton-coupling constants are not resolved in some cases.

[4] Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006,** *128,* 2782.

Chapter 2 Experimental

Enantioselective Rhodium-Catalyzed [2+2+2] Cycloadditions of Alkenyl Isocyanates and Terminal Alkynes: Application to the Total Synthesis of (+)-Lasubine II

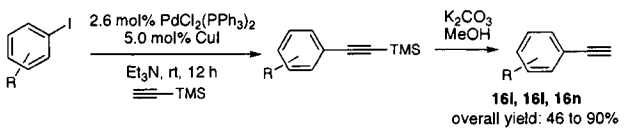
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine (peptide synthesis grade) was purchased from Fisher Scientific and used without further purification. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and $KMnO_4$ followed by heating.

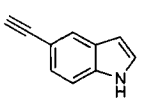
Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

Alkynes **16a – 16b, 16d – 16h, 16k, 16m, 16o – 16s, 16u,** and **16v** were all purchased from Aldrich Chemicals Co. and used without further purification. Alkyne

16c[1] was prepared according to the literature methods. Alkyne **16t** was prepared by a typical TBS-protection of the corresponding alcohol, which was purchased from Aldrich Chemicals Co. Alkynes **16i**, **16j**, **16l** and ligands **L6** and **L7** are known compounds and can be synthesized by the procedure described within. Phosphorus trichloride and tris(4-methoxyphenyl) phosphine were purchased from Aldrich Chemicals Co. $[Rh(ethylene)_2Cl]_2$, $PdCl_2(PPh_3)_2$, ligands **L1** – **L5**, and trimethylsilylacetylene were purchased from Strem Chemical, Inc. and used without further purification. All racemate products are obtained via the same cycloaddition using the *rac*-**L5** as the ligand.

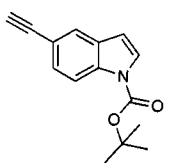
General procedure for synthesis of terminal aryl alkynes (16i as the example**):**





5-ethynyl-1*H*-indole (16i). To a solution of 2.02 g of Boc-protected 5-iodoindole (5.886 mmol) and 0.84 ml of trimethylsilylacetylene (5.886 mmol) in 50 ml of Et_3N (ca. 0.12 M) at 0 °C was added 107 mg of $PdCl_2(PPh_3)_2$ (0.153 mmol) and 56 mg of CuI (0.294 mmol). The reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was then filtered and concentrated in vacuo. The resulting slurry was dissolved in 20 ml of MeOH (ca. 0.3 M), and treated with 1.62 g of K_2CO_3 (11.772 mmol). After stirring at ambient temperature for 2 h, the mixture was diluted with Et_2O, partitioned with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by flash column chromatography (1:10 EtOAc/Hexane) to give the free indole **16i** (400 mg, 48% overall yield): R_f = 0.13 (1:10 EtOAc/hex); ^1H

NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.82 (s, 1H), 7.30 – 7.34 (m, 2H), 7.21 (dd, 1H, J = 2.6, 3.2 Hz), 6.52 (dd, 1H, J = 2.1, 3.0 Hz), 2.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 127.8, 126.2, 125.5, 125.3, 113.4, 111.3, 103.1, 85.5, 74.8; IR (NaCl, $CDCl_3$) 3421, 3283, 1614, 1465, 1413, 1337, 1306 cm^{-1}; HRMS $[C_{10}H_7N]^+$ calcd 141.0578. Found 141.0583 (FAB+).



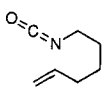
***tert*-butyl 5-ethynyl-1*H*-indole-1-carboxylate (16j).** To a solution of 270 mg of **16i** (1.91 mmol) and 7.0 mg of DMAP (0.057 mmol) in 2 ml of dry acetonitrile (ca. 0.96 M) was added 0.48 ml of $(Boc)_2O$ (2.10 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 20 h. The reaction mixture was concentrated in vacuo, partitioned with EtOAc/H_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by flash column chromatography (1:10 EtOAc/Hexane) to give **16j** as a yellow oil (409 mg, 89% yield): R_f = 0.64 (1:10 EtOAc/hex); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 8.3 Hz), 7.69 (s, 1H), 7.58 (br s, 1H), 7.41 (d, 1H, J = 8.7 Hz), 6.51 (m, 1H), 3.03 (s, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 135.2, 130.6, 128.3, 127.1, 125.3, 116.3, 115.3, 107.2, 84.5, 84.3, 76.0, 28.4; IR (NaCl, $CDCl_3$) 3294, 2979, 1736, 1462, 1369, 1339, 1252, 1159, 1024 cm^{-1}; HRMS $[C_{15}H_{16}NO_2]^+$ calcd 242.1181. Found 242.1183 (FAB+).

General procedure for synthesis of alkenyl isocyanates:

In a flame-dried round bottom flask under Ar atmosphere, triethylamine (23.22 mmol, 1.06 eq) was added to a stirring solution of carboxylic acid (21.90 mmol) in dichloromethane (23.0 mL) at 0 °C. Diphenylphosphoryl azide (23.22 mmol, 1.06 eq) was then slowly added. After 4 hours, the reaction was concentrated under vacuum and

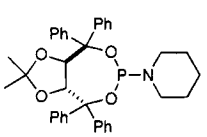
rapidly purified by flash chromatography (20:1 Hex:EtOAc, solvent removal was carried out with the rotovap bath temperature less than 23 °C). The resulting acyl azide was slowly converted to the desired isocyanate by sitting in neat at ambient temperature for 24 hours followed by gently heating at 35 °C for 3-6 hours.

5-isocyanatopent-1-ene (17). Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (76%); ^{1}H NMR (400 MHz, $CDCl_3$) d 5.75 (ddt, 1H, *J* = 6.8, 10.2, 17.1 Hz), 5.05 (dm, 1H, *J* = 17.1 Hz), 5.00 (dm, 1H, *J* = 10.2 Hz), 3.29 (t, 2H, *J* = 6.6 Hz), 2.14 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.69 (tt, 2H, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 137.0, 116.1, 42.4, 30.7, 30.4; IR (NaCl, $CHCl_3$) 2955, 2279, 1644, 1516, 1434, 1358 cm^{-1}.



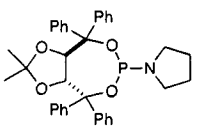
6-isocyanatohex-1-ene (34) Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (70% on 8.0 mmol scale); ^{1}H NMR (300 MHz, $CDCl_3$) d 5.79 (ddt, 1H, *J* = 6.6, 10.3, 16.9 Hz), 5.02 (dm, 1H, *J* = 16.9 Hz), 4.98 (dm, 1H, *J* = 9.9 Hz), 3.31 (t, 2H, *J* = 6.4 Hz), 2.08 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.63 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) d 138.2, 115.2, 43.2, 33.3, 31.0, 26.1; IR (NaCl, $CHCl_3$) 2940, 2274, 1634, 1527, 1440, 1363 cm^{-1}.

Ligand Synthesis:



1-((3a*R*,8a*R*)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl)piperidine (L6). To a flame-dried round bottom flask charged with a magnetic stir bar was added 4 Å molecular sieves, followed by 500 mg of (–)-TADDOL[2] (1.072 mmol) and 4.6 ml of THF. To the reaction mixture was added 0.51 ml of Et_3N (3.644 mmol) and 0.112 ml of

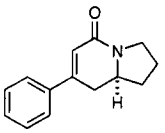
phosphorus trichloride (1.286 mmol) dropwise at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 40 minutes. A solution of piperidine (10.72 mmol) in 5.4 ml of THF was added slowly at 0 °C. The reaction was allowed to stir overnight at ambient temperature before it was diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo and the resulting crude material was purified by flash column chromatography (4:96 EtOAc/Hexane) to afford the desired phosphoramidite (400 mg, 65% yield): R_f = 0.58 (1:10 EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) d 7.78 (d, 2H, *J* = 7.3 Hz), 7.63 (d, 2H, *J* = 7.0 Hz), 7.48 (d, 2H, *J* = 7.3 Hz), 7.42 (d, 2H, *J* = 7.3 Hz), 7.14 – 7.36 (m, 12H), 5.16 (m, 1H), 4.76 (d, 1H, *J* = 8.4 Hz), 3.02 –3.38 (m, 4H), 1.50 – 1.68 (m, 6H), 1.33 (s, 3H), 0.29 (s, 3H); ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.48.



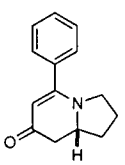
1-((3a*R*,8a*R*)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl)pyrrolidine (L7). To a flame-dried round bottom flask charged with a magnetic stir bar was added 4 Å molecular sieves, followed by 1.20 g of (–)-TADDOL (2.572 mmol) and 11 ml of THF. To the reaction mixture was added 1.23 ml of Et_3N (8.745 mmol) and 0.27 ml of phosphorus trichloride (3.086 mmol) dropwise at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 40 minutes. A solution of piperidine (25.72 mmol) in 13 ml of THF was added slowly at 0 °C. The reaction was allowed to stir overnight at ambient temperature before it was diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo and the resulting crude material was purified by flash column chromatography (4:96 EtOAc/Hexane) to afford the desired phosphoramidite (610 mg, 42% yield): R_f = 0.50 (1:10 EtOAc/hex); $[\alpha]_D^{20}$ = -123.6 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.72 (d, 2H, *J* = 7.0 Hz), 7.56 (d, 2H, *J* = 7.3 Hz), 7.46 (d, 2H, *J* = 7.3

Hz), 7.39 (d, 2H, J = 7.3 Hz), 7.16 – 7.29 (m, 12H), 5.18 (dd, 1H, J = 2.9, 8.4 Hz), 4.80 (d, 1H, J = 8.4 Hz), 3.10 –3.38 (m, 4H), 1.66 – 1.82 (m, 4H), 1.25 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.7, 142.5, 142.2, 129.2, 129.0, 128.3, 127.9, 127.7, 127.6, 127.4, 127.3, 127.3, 127.2, 111.9, 82.8, 82.6, 82.4, 82.0, 81.4, 81.3, 45.3, 45.1, 27.7, 26.2, 26.2, 25.5; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.20; IR (Thin Film) 2967, 2866, 1492, 1447, 1214, 1164, 1035, 1003 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 565.2382, found 565.23828.

General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and terminal alkynes: A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.05 eq) and the phosphoramidite ligand **L** (0.1 eq), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml toluene was added via syringe and the resulting yellow solution was stirred at ambient temperature under argon flow for 15 minutes. To this solution was added a solution of alkyne **16** (2.0 eq) and isocyanate **17** or **34** (0.270 mmol) in 2 ml of toluene via syringe or cannula. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

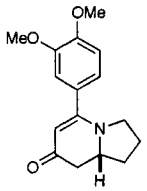


(*S*)-7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18a). According to the general procedure with ligand **L7**, alkyne **16a**, and isocyanate **17**. Upon purification 4.6 mg (8%) of the desired product was isolated: R_f = 0.21 (EtOAc); $[\alpha]_D^{20}$ = +166.9 (c = 0.16, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 24.4 minutes, Minor: 19.6 minutes, 254 nm detection light, *ee* = 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.49 (m, 2H), 7.33 – 7.40 (m, 3H), 6.29 (d, 1H, *J* = 2.8 Hz), 3.81 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 14.9 Hz), 3.67 (ddd, 1H, *J* = 2.1, 9.0, 11.7 Hz), 3.51 (ddd, 1H, *J* = 7.7, 9.4, 11.5 Hz), 2.90 (dd, 1H, *J* = 4.7, 16.6 Hz), 2.51 (ddd, 1H, *J* = 2.8, 14.1, 16.6 Hz), 2.27 (ddd, 1H, *J* = 5.3, 5.3, 12.1 Hz), 2.06 (m, 1H), 1.84 (ddddd, 1H, *J* = 6.6, 9.6, 9.6, 12.2, 12.2 Hz), 1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 148.7, 138.1, 129.5, 129.0, 126.1, 121.0, 56.8, 44.2, 33.7, 33.4, 23.3; IR (NaCl, CH_2Cl_2) 1644, 1593, 1450, 1352, 1327 cm^{-1}; HRMS $[C_{14}H_{16}NO]^+$ calcd 214.1232. Found 214.1233 (FAB+).

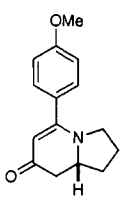


(*R*)-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19a). According to the general procedure with ligand **L7**, alkyne **16a**, and isocyanate **17**. From the same reaction as above, upon purification 44 mg (79%) of the desired product was isolated: R_f = 0.15 (EtOAc); $[\alpha]_D^{20}$ = +640.0 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 0.3 ml/min, Major: 49.9 minutes, Minor: 48.9 minutes, 330 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.40 (m, 5H), 5.05 (s, 1H), 4.00 (dddd, 1H, *J* = 7.2, 7.2, 7.2, 14.3 Hz), 3.46 (ddd, 1H, *J* = 4.5, 7.7, 11.5 Hz), 3.23 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.45 (dd, 1H, *J* = 16.0, 16.0 Hz), 2.40 (dd, 1H, *J* = 6.7, 16.2 Hz), 2.29 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 163.1, 136.4, 130.0, 128.7, 127.8, 100.2,

59.1, 49.5, 41.7, 32.2, 24.7; IR (NaCl, CH_2Cl_2) 1624, 1532, 1460, 1332, 1260, 1235 cm^{-1}; HRMS $[C_{14}H_{16}NO]^+$ calcd 214.1232. Found 214.1231 (FAB+).

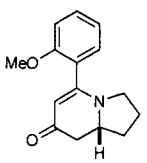


(*R*)-5-(3,4-dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19c). According to the general procedure with ligand **L7**, alkyne **16c**, and isocyanate **17**. Upon purification 53.2 mg (72%) of the desired product was isolated: R_f = 0.05 (EtOAc); $[\alpha]_D^{20}$ = +452.4 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 24.2 minutes, Minor: 21.8 minutes, 330 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, 1H, *J* = 1.7, 8.3 Hz), 6.88 (br s, 1H), 6.85 (d, 1H, *J* = 8.3 Hz), 5.19 (s, 1H), 4.04 (dddd, 1H, *J* = 7.0, 7.0, 7.0, 13.4 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.54 (ddd, 1H, *J* = 6.6, 6.6, 11.7 Hz), 3.27 (ddd, 1H, *J* = 7.0, 7.0, 10.9 Hz), 2.46 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.38 (dd, 1H, *J* = 5.8, 16.2 Hz), 2.28 (dddd, 1H, *J* = 6.4, 6.4, 6.4, 12.8 Hz), 1.99 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 163.1, 150.6, 149.0, 128.9, 121.0, 111.1, 110.9, 100.0, 58.9, 56.2, 56.2, 50.0, 41.6, 31.9, 24.9; IR (NaCl, $CDCl_3$) 1619, 1511, 1475, 1332, 1260, 1137, 922 cm^{-1}; HRMS $[C_{16}H_{20}NO_3]^+$ calcd 274.1443. Found 274.1450 (FAB+).

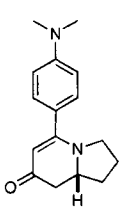


(*R*)-5-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19d). According to the general procedure with ligand **L7**, alkyne **16d**, and isocyanate **17**. Upon purification 45.8 mg (70%) of the desired product was isolated: R_f = 0.05 (EtOAc); $[\alpha]_D^{20}$ = +462.4 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 10.6 minutes, Minor: 12.1 minutes, 210 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dm, 2H, *J* = 8.7 Hz), 6.88 (dm, 2H, *J* = 8.9 Hz), 5.06 (s, 1H), 4.02 (dddd, 1H, *J* = 6.7, 6.7, 6.7,

13.5 Hz), 3.80 (s, 3H), 3.53 (ddd, 1H, J = 5.5, 7.3, 11.8 Hz), 3.25 (ddd, 1H, J = 7.0, 7.0, 10.7 Hz), 2.44 (dd, 1H, J = 16.2, 16.2 Hz), 2.37 (dd, 1H, J = 5.6, 16.2 Hz), 2.27 (m, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 163.0, 161.1, 129.5, 128.8, 114.0, 100.0, 58.9, 55.6, 49.8, 41.7, 31.9, 24.8; IR (NaCl, $CDCl_3$) 1624, 1603, 1511, 1465, 1245, 1173, 1030 cm^{-1}; HRMS $[C_{15}H_{18}NO_2]^+$ calcd 244.1338. Found 244.1337 (FAB+).

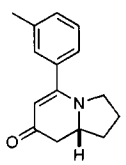


(*R*)-5-(2-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19e). According to the general procedure with ligand **L7**, alkyne **16e**, and isocyanate **17**. Upon purification 42 mg (64%) of the desired product was isolated: R_f = 0.11 (EtOAc); $[\alpha]_D^{20}$ = +464.8 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 14.5 minutes, Minor: 13.9 minutes, 330 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (ddd, 1H, J = 1.5, 8.5, 8.5 Hz), 7.18 (m, 1H), 6.96 (dd, 1H, J = 7.5, 7.5 Hz), 6.90 (d, 1H, J = 8.3 Hz), 4.95 (s, 1H), 3.95 (m, 1H), 3.81 (s, 3H), 3.10 – 3.35 (m, 2H), 2.39 – 2.48 (m, 2H), 2.28 (dddd, 1H, J = 2.8, 6.4, 6.4, 8.7 Hz), 1.96 (m, 1H), 1.68 – 1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 160.8, 155.9, 131.2, 129.5, 125.4, 121.0, 111.2, 99.4, 59.2, 55.9, 48.1, 41.7, 32.8, 24.2; IR (NaCl, $CDCl_3$) 1619, 1527, 1475, 1332, 1240, 1132, 1015 cm^{-1}; HRMS $[C_{15}H_{18}NO_2]^+$ calcd 244.1338. Found 244.1336 (FAB+).



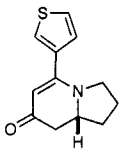
(*R*)-5-(4-(dimethylamino)phenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19f). According to the general procedure with ligand **L5**, alkyne **16f**, and isocyanate **17**. Upon purification 52.5 mg (78%) of the desired product was isolated: R_f = 0.05 (EtOAc); $[\alpha]_D^{20}$ = +70.3 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 21.2 minutes, Minor: 24.4

minutes, 330 nm detection light, *ee* = 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H, *J* = 9.0 Hz), 6.65 (d, 2H, *J* = 9.0 Hz), 5.11 (s, 1H), 4.04 (dddd, 1H, *J* = 6.4, 6.4, 6.4, 12.4 Hz), 3.60 (ddd, 1H, *J* = 6.6, 6.6, 10.9 Hz), 3.31 (ddd, 1H, *J* = 6.6, 6.6, 11.1 Hz), 2.98 (s, 6H), 2.45 (dd, 1H, *J* = 16.0, 16.0 Hz), 2.34 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.25 (dddd, 1H, *J* = 6.8, 6.8, 6.8, 13.4 Hz), 1.96 (m, 1H), 1.86 (m, 1H), 1.73 (dddd, 1H, *J* = 6.9, 6.9, 6.9, 13.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 163.8, 151.7, 129.5, 123.4, 111.5, 99.3, 58.7, 50.3, 41.7, 40.4, 31.6, 25.0; IR (NaCl, $CDCl_3$) 1603, 1557, 1496, 1358, 1240, 1189, 1132 cm^{-1}; HRMS $[C_{16}H_{21}N_2O]^+$ calcd 257.1654. Found 257.1643 (FAB+).



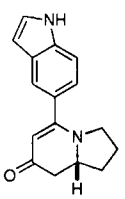
(*R*)-5-*m*-tolyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19g). According to the general procedure with ligand **L7**, alkyne **16g**, and isocyanate **17**. Upon purification 36.1 mg (59%) of the desired product was isolated: R_f = 0.14 (EtOAc); $[\alpha]_D^{20}$ = +609.2 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 22.1 minutes, Minor: 21.9 minutes, 330 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.20 (d, 1H, *J* = 7.6 Hz), 7.17 (s, 1H), 7.14 (d, 1H, *J* = 7.5 Hz), 5.04 (s, 1H), 3.99 (dddd, 1H, *J* = 7.5, 7.5, 7.5, 14.7 Hz), 3.47 (ddd, 1H, *J* = 4.5, 7.7, 11.5 Hz), 3.23 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.44 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.39 (dd, 1H, *J* = 7.0, 16.2 Hz), 2.28 (dddd, 1H, *J* = 4.1, 6.4, 6.4, 10.9 Hz), 1.98 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 163.3, 138.5, 136.4, 130.7, 128.6, 128.4, 124.8, 100.1, 59.1, 49.5, 41.6, 32.2, 24.7, 21.6; IR (NaCl, $CDCl_3$) 1624, 1527, 1470, 1337, 1260, 1235, 1127 cm^{-1}; HRMS $[C_{15}H_{18}NO]^+$ calcd 228.1388. Found 228.1384 (FAB+).

From the same reaction mixture, 4 mg (6%) of **18g** was also isolated but not fully characterized due to its small quantity.



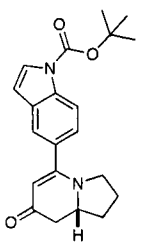
(R)-5-(thiophen-3-yl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (19h). According to the general procedure with ligand **L5**, alkyne **16h**, and isocyanate **17**. Upon purification 34.2 mg (58%) of the desired product was isolated: R_f = 0.10 (EtOAc); $[\alpha]_D^{20}$ = +455.0 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 10.6 minutes, Minor: 10.1 minutes, 330 nm detection light, *ee* = 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, 1H, *J* = 1.1, 3.0 Hz), 7.33 (dd, 1H, *J* = 3.0, 5.1 Hz), 7.13 (dd, 1H, *J* = 1.3, 5.1 Hz), 5.15 (s, 1H), 3.99 (dddd, 1H, *J* = 7.5, 7.5, 7.5, 14.5 Hz), 3.59 (ddd, 1H, *J* = 5.1, 7.7, 11.1 Hz), 3.39 (ddd, 1H, *J* = 7.2, 7.2, 10.9 Hz), 2.43 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.39 (dd, 1H, *J* = 7.0, 16.2 Hz), 2.28 (dddd, 1H, *J* = 6.6, 6.6, 6.6, 11.9 Hz), 2.02 (m, 1H), 1.89 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 157.6, 137.1, 127.3, 126.5, 126.5, 99.8, 59.1, 49.8, 41.6, 31.9, 24.8; IR (NaCl, $CDCl_3$) 1619, 1521, 1470, 1332, 1265, 1240, 1127 cm^{-1}; HRMS $[C_{12}H_{14}NOS]^+$ calcd 220.0796. Found 220.0797 (FAB+).

From the same reaction mixture, 3.8 mg (6%) of **18h** was also isolated but not fully characterized due to its small quantity.

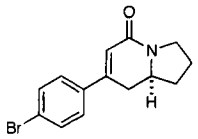


(*R*)-5-(1*H*-indol-5-yl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19i). According to the general procedure with ligand **L7**, alkyne **16i**, and isocyanate **17**. Upon purification 44.3 mg (65%) of the desired product was isolated: R_f = 0.05 (EtOAc); $[\alpha]_D^{20}$ = +290.2 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.9 minutes, Minor: 15.5 minutes, 254 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 7.67 (s, 1H), 7.40 (d, 1H, *J* = 8.3 Hz), 7.26 (dd, 1H, *J* = 2.7, 2.7 Hz), 7.16 (d, 1H, *J* = 8.3

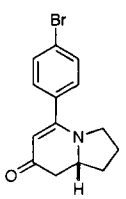
Hz), 6.55 (m, 1H), 5.19 (s, 1H), 4.08 (dddd, 1H, J = 6.8, 6.8, 6.8, 13.0 Hz), 3.61 (ddd, 1H, J = 6.4, 6.4, 11.7 Hz), 3.29 (ddd, 1H, J = 7.0, 7.0, 11.1 Hz), 2.51 (dd, 1H, J = 16.0, 16.0 Hz), 2.42 (dd, 1H, J = 5.5, 16.2 Hz), 2.30 (dddd, 1H, J = 6.2, 6.2, 6.2, 12.2 Hz), 1.97 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 165.3, 136.8, 127.8, 127.7, 125.9, 121.8, 120.8, 111.4, 103.2, 100.1, 59.0, 50.1, 41.5, 31.9, 24.8; IR (NaCl, $CDCl_3$) 1598, 1506, 1455, 1334, 1271, 1237, 1128 cm^{-1}; HRMS $[C_{16}H_{17}N_2O]^+$ calcd 253.1341. Found 253.1344 (FAB+).



(*R*)-*tert*-butyl 5-(7-oxo-1,2,3,7,8,8a-hexahydroindolizin-5-yl)-1*H*-indole-1-carboxylate (19j). According to the general procedure with ligand **L7**, alkyne **16j**, and isocyanate **17**. Upon purification 80.6 mg (85%) of the desired product was isolated: R_f = 0.12 (EtOAc); $[\alpha]_D^{20}$ = +320.4 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 24.9 minutes, Minor: 22.4 minutes, 230 nm detection light, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 8.3 Hz), 7.62 (d, 1H, J = 3.6 Hz), 7.58 (s, 1H), 7.30 (d, 1H, J = 8.5 Hz), 6.55 (d, 1H, J = 3.6), 5.15 (s, 1H), 4.05 (dddd, 1H, J = 6.8, 6.8, 6.8, 13.9 Hz), 3.54 (ddd, 1H, J = 5.1, 7.5, 11.7 Hz), 3.25 (ddd, 1H, J = 7.3, 7.3, 11.1 Hz), 2.48 (dd, 1H, J = 16.0, 16.0 Hz), 2.42 (dd, 1H, J = 6.1, 16.2 Hz), 2.30 (dddd, 1H, J = 6.4, 6.4, 6.4, 11.5 Hz), 1.99 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 163.8, 149.7, 136.0, 130.9, 130.6, 127.3, 124.0, 120.7, 115.3, 107.5, 100.4, 84.4, 59.1, 49.7, 41.7, 32.1, 28.3, 24.8; IR (NaCl, $CDCl_3$) 1736, 1615, 1524, 1449, 1369, 1329, 1271, 1151, 1025 cm^{-1}; HRMS $[C_{21}H_{25}N_2O_3]^+$ calcd 353.1865. Found 353.1852 (FAB+).

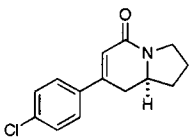


(*S*)-7-(4-bromophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18k). According to the general procedure with ligand **L7**, alkyne **16k**, and isocyanate **17**. Upon purification 13.5 mg (17%) of the desired product was isolated: R_f = 0.19 (EtOAc); $[\alpha]_D^{20}$ = +102.0 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 23.6 minutes, Minor: 25.0 minutes, 254 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, *J* = 8.7 Hz), 7.33 (d, 2H, *J* = 8.7 Hz), 6.27 (d, 1H, *J* = 2.6 Hz), 3.80 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 14.9 Hz), 3.67 (m, 1H), 3.50 (m, 1H), 2.84 (dd, 1H, *J* = 4.7, 16.4 Hz), 2.50 (ddd, 1H, *J* = 2.6, 14.1, 16.6 Hz), 2.27 (ddd, 1H, *J* = 5.8, 5.8, 11.9 Hz), 2.06 (m, 1H), 1.84 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 147.6, 136.9, 132.1, 127.6, 123.7, 121.4, 56.7, 44.2, 33.7, 33.3, 23.2; IR (NaCl, $CDCl_3$) 1650, 1539, 1486, 1445, 1347, 1004, 835, 815 cm^{-1}; HRMS $[C_{14}H_{15}NOBr]^+$ calcd 292.0337. Found 292.0333 (FAB+). X-ray data of this compound is attached at the end of this manuscript.

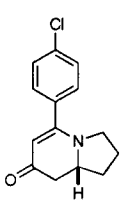


(*R*)-5-(4-bromophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19k). According to the general procedure with ligand **L7**, alkyne **16k**, and isocyanate **17**. From the same reaction as above, upon purification 43.4 mg (55%) of the desired product was isolated: R_f = 0.13 (EtOAc); $[\alpha]_D^{20}$ = +469.0 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 21.3 minutes, Minor: 19.7 minutes, 254 nm detection light, *ee* = 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J* = 8.3 Hz), 7.24 (d, 2H, *J* = 8.3 Hz), 5.01 (s, 1H), 4.00 (dddd, 1H, *J* = 7.9, 7.9, 7.9, 15.3 Hz), 3.44 (ddd, 1H, *J* = 4.5, 7.3, 11.3 Hz), 3.22 (ddd, 1H, *J* = 7.7, 7.7, 10.7 Hz), 2.44 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.42 (dd, 1H, *J* = 7.8, 16.2 Hz), 2.29 (m, 1H), 1.99 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 192.2, 161.8, 135.3, 132.0, 129.4, 124.4, 100.4, 59.2, 49.5, 41.6, 32.1, 24.7; IR (NaCl, $CDCl_3$) 1619, 1568, 1527, 1465, 1260, 1235, 1127, 1004 cm^{-1}; HRMS $[C_{14}H_{15}NOBr]^+$ calcd 292.0337. Found 292.0330 (FAB+). X-ray of this compound is attached at the end of this manuscript.

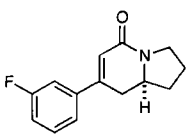


(*S*)-7-(4-chlorophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18l). According to the general procedure with ligand **L7**, alkyne **16l**, and isocyanate **17**. Upon purification 9.4 mg (14%) of the desired product was isolated: R_f = 0.13 (EtOAc); $[\alpha]_D^{20}$ = +93.5 (c = 0.52, $CHCl_3$); HPLC analysis – Chiracel OD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 19.5 minutes, Minor: 18.1 minutes, 254 nm detection light, *ee* = 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.5 Hz), 6.27 (d, 1H, *J* = 2.8 Hz), 3.81 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 14.7 Hz), 3.67 (ddd, 1H, *J* = 2.1, 9.2, 11.7 Hz), 3.50 (ddd, 1H, *J* = 7.7, 9.6, 11.5 Hz), 2.85 (dd, 1H, *J* = 4.7, 16.4 Hz), 2.50 (ddd, 1H, *J* = 2.6, 13.9, 16.4 Hz), 2.27 (ddd, 1H, *J* = 5.0, 5.0, 11.3 Hz), 2.06 (m, 1H), 1.84 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 147.5, 136.5, 135.5, 129.2, 127.3, 121.3, 56.7, 44.2, 33.7, 33.3, 23.2; IR (NaCl, $CDCl_3$) 1650, 1598, 1489, 1443, 1345, 1087, 829 cm^{-1}; HRMS $[C_{14}H_{15}NOCl]^+$ calcd 248.0842. Found 248.0853 (FAB+).

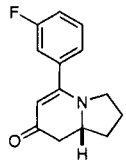


(*R*)-5-(4-chlorophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19l). According to the general procedure with ligand **L7**, alkyne **16l**, and isocyanate **17**. From the same reaction as above, upon purification 34.1 mg (51%) of the desired product was isolated: R_f = 0.08 (EtOAc); $[\alpha]_D^{20}$ = +383.9 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 23.3 minutes, Minor: 22.3 minutes, 330 nm detection light, *ee* = 90%; ^1H NMR (400

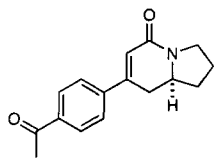
MHz, $CDCl_3$) δ 7.37 (d, 2H, *J* = 8.3 Hz), 7.31 (d, 2H, *J* = 8.3 Hz), 5.03 (s, 1H), 4.01 (dddd, 1H, *J* = 7.9, 7.9, 7.9, 15.1 Hz), 3.45 (ddd, 1H, *J* = 4.5, 7.5, 11.7 Hz), 3.23 (ddd, 1H, *J* = 7.7, 7.7, 10.9 Hz), 2.45 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.42 (dd, 1H, *J* = 8.0, 16.2 Hz), 2.29 (m, 1H), 1.99 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 161.8, 136.1, 134.8, 129.2, 129.1, 100.4, 59.2, 49.5, 41.6, 32.1, 24.7; IR (NaCl, $CDCl_3$) 1624, 1572, 1527, 1470, 1265, 1240, 1086, 1004 cm^{-1}; HRMS $[C_{14}H_{15}NOCl]^+$ calcd 248.0842. Found 248.0843 (FAB+).



(*S*)-7-(3-fluorophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18m). According to the general procedure with ligand **L7**, alkyne **16m**, and isocyanate **17**. Upon purification 15.5 mg (25%) of the desired product was isolated: R_f = 0.21 (EtOAc); $[\alpha]_D^{20}$ = +88.3 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 17.1 minutes, Minor: 12.9 minutes, 254 nm detection light, *ee* = 94%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (ddd, 1H, *J* = 6.0, 8.1, 8.1 Hz), 7.25 (m, 1H), 7.15 (ddd, 1H, *J* = 2.1, 2.1, 10.2 Hz), 7.04 (m, 1H), 6.29 (d, 1H, *J* = 2.8 Hz), 3.81 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 14.9 Hz), 3.67 (ddd, 1H, *J* = 1.7, 8.7, 11.5 Hz), 3.50 (ddd, 1H, *J* = 7.7, 9.4, 11.9 Hz), 2.85 (dd, 1H, *J* = 4.7, 16.6 Hz), 2.51 (ddd, 1H, *J* = 2.8, 14.1, 16.6 Hz), 2.27 (ddd, 1H, *J* = 5.5, 5.5, 11.9 Hz), 2.07 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.8, 161.9, 147.4, 130.5, 130.4, 121.9, 121.7, 116.4, 116.2, 113.1, 112.9, 56.7, 44.2, 33.7, 33.4, 23.2; IR (NaCl, $CDCl_3$) 1650, 1598, 1434, 1327, 1265, 1173, 1158, 876 cm^{-1}; HRMS $[C_{14}H_{15}NOF]^+$ calcd 232.1138. Found 232.1141 (FAB+).

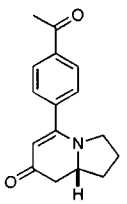


(*R*)-5-(3-fluorophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19m). According to the general procedure with ligand **L7**, alkyne **16m**, and isocyanate **17**. From the same reaction as above, upon purification 27.0 mg (43%) of the desired product was isolated: R_f = 0.15 (EtOAc); $[\alpha]_D^{20}$ = +366.7 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97:3 hexane:iPrOH, 1.0 ml/min, Major: 25.6 minutes, Minor: 24.8 minutes, 330 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (ddd, 1H, *J* = 5.8, 7.9, 7.9 Hz), 7.05 – 7.16 (m, 3H), 5.05 (s, 1H), 4.00 (dddd, 1H, *J* = 8.8, 8.1, 8.1, 12.2 Hz), 3.45 (ddd, 1H, *J* = 4.5, 7.7, 11.3 Hz), 3.24 (ddd, 1H, *J* = 7.5, 7.5, 10.7 Hz), 2.46 (dd, 1H, *J* = 16.2, 16.2 Hz), 2.42 (dd, 1H, *J* = 7.5, 16.2 Hz), 2.30 (dddd, 1H, *J* = 4.1, 6.4, 6.4, 10.9 Hz), 2.01 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 163.9, 161.6, 161.4, 138.4, 130.6, 130.5, 123.5, 117.1, 116.9, 115.1, 114.9, 100.4, 59.2, 49.5, 41.6, 32.2, 24.7; IR (NaCl, $CDCl_3$) 1629, 1527, 1470, 1260, 1239, 1122, 933 cm^{-1}; HRMS $[C_{14}H_{15}NOF]^+$ calcd 232.1138. Found 232.1139 (FAB+).

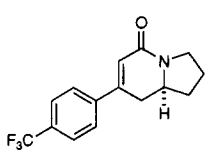


(*S*)-7-(4-acetylphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18n). According to the general procedure with ligand **L7**, alkyne **16n**, and isocyanate **17**. Upon purification 17.8 mg (26%) of the desired product was isolated: R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = +82.6 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 23.0 minutes, Minor: 21.1 minutes, 254 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 2H, *J* = 8.3 Hz), 7.55 (d, 2H, *J* = 8.3 Hz), 6.36 (d, 1H, *J* = 2.8 Hz), 3.83 (dddd, 1H, *J* = 5.1, 5.1, 10.0, 14.7 Hz), 3.68 (ddd, 1H, *J* = 2.3, 9.4, 11.7 Hz), 3.51 (ddd, 1H, *J* = 8.1, 9.6, 11.8 Hz), 2.90 (dd, 1H, *J* = 4.7, 16.6 Hz), 2.59 (s, 3H), 2.57 (m, 1H), 2.29 (m, 1H), 2.07

(m, 1H), 1.84 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 163.6, 147.5, 142.6, 137.5, 129.0, 126.2, 122.8, 56.7, 44.2, 33.7, 33.3, 26.9, 23.2; IR (NaCl, $CDCl_3$) 1672, 1649, 1598, 1445, 1360, 1269, 843 cm^{-1}; HRMS $[C_{16}H_{18}NO_2]^+$ calcd 256.1338. Found 256.1327 (FAB+).

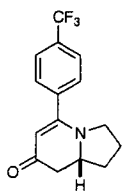


(*R*)-5-(4-acetylphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19n). According to the general procedure with ligand **L7**, alkyne **16n**, and isocyanate **17**. From the same reaction as above, upon purification 26.8 mg (39%) of the desired product was isolated: R_f = 0.04 (EtOAc); $[\alpha]_D^{20}$ = +347.3 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 21.3 minutes, Minor: 23.1 minutes, 254 nm detection light, *ca. ee* = 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2H, *J* = 8.3 Hz), 7.46 (d, 2H, *J* = 8.1 Hz), 5.02 (s, 1H), 4.01 (m, 1H), 3.42 (ddd, 1H, *J* = 4.3, 7.7, 11.3 Hz), 3.23 (ddd, 1H, *J* = 7.7, 7.7, 10.9 Hz), 2.60 (s, 3H), 2.42 – 2.51 (m, 2H), 2.31 (m, 1H), 2.01 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 192.1, 161.7, 140.7, 138.1, 128.7, 128.1, 100.6, 59.3, 49.4, 41.5, 32.2, 26.9, 24.7; IR (NaCl, $CDCl_3$) 1683, 1621, 1530, 1507, 1468, 1257, 1127 cm^{-1}; HRMS $[C_{16}H_{18}NO_2]^+$ calcd 256.1338. Found 256.1336 (FAB+).

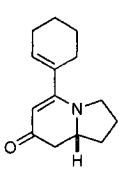


(*S*)-7-(4-(trifluoromethyl)phenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18o). According to the general procedure with ligand **L7**, alkyne **16o**, and isocyanate **17**. Upon purification 27.2 mg (36%) of the desired product was isolated: R_f = 0.20 (EtOAc); $[\alpha]_D^{20}$ = +104.5 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 17.0 minutes, Minor: 15.8 minutes, 254 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 8.3 Hz), 7.56 (d, 2H, *J* = 8.5 Hz), 6.34 (d, 1H, *J* = 2.6 Hz), 3.83 (dddd, 1H, *J* =

5.1, 5.1, 10.2, 14.7 Hz), 3.69 (ddd, 1H, J = 2.1, 9.2, 11.7 Hz), 3.52 (ddd, 1H, J = 7.7, 9.6, 11.7 Hz), 2.88 (dd, 1H, J = 4.7, 16.4 Hz), 2.55 (ddd, 1H, J = 2.6, 14.1, 16.6 Hz), 2.29 (m, 1H), 2.08 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 147.3, 141.6, 126.4, 125.9, 125.9, 122.8, 56.7, 44.2, 33.7, 33.4, 23.2; IR (NaCl, $CDCl_3$) 1654, 1601, 1450, 1410, 1328, 1152, 1124, 1071, 849 cm^{-1}; HRMS $[C_{15}H_{15}NOF_3]^+$ calcd 282.1106. Found 282.1094 (FAB+).

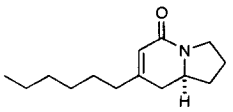


(*R*)-5-(4-(trifluoromethyl)phenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19o). According to the general procedure with ligand **L7**, alkyne **16o**, and isocyanate **17**. From the same reaction as above, upon purification 10.6 mg (14%) of the desired product was isolated: R_f = 0.14 (EtOAc); $[\alpha]_D^{20}$ = +318.9 (c = 1.0, $CHCl_3$); *ee* is not determined; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8.1 Hz), 7.49 (d, 2H, J = 8.1 Hz), 5.08 (s, 1H), 4.02 (dddd, 1H, J = 9.2, 9.2, 9.2, 9.2 Hz), 3.42 (ddd, 1H, J = 4.1, 7.9, 11.3 Hz), 3.23 (ddd, 1H, J = 7.5, 7.5, 10.4 Hz), 2.42 – 2.52 (m, 2H), 2.32 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 161.5, 150.8, 139.8, 128.2, 125.8, 100.6, 59.3, 49.4, 41.4, 32.2, 24.7; IR (NaCl, $CDCl_3$) 1625, 1538, 1514, 1461, 1322, 1164, 1124, 1065 cm^{-1}; HRMS $[C_{15}H_{15}NOF_3]^+$ calcd 282.1106. Found 282.1115 (FAB+).



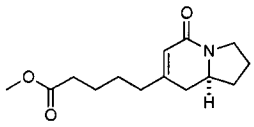
(*R*)-5-cyclohexenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19p). According to the general procedure with ligand **L7**, alkyne **16p**, and isocyanate **17**. Upon purification 56.3 mg (96%) of the desired product was isolated: R_f = 0.12 (EtOAc); $[\alpha]_D^{20}$ = +477.5 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 10.9 minutes, Minor: 10.3 minutes, 330 nm detection light, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H),

4.88 (s, 1H), 3.80 (m, 1H), 3.46 (ddd, 1H, J = 4.5, 8.1, 11.3 Hz), 3.34 (ddd, 1H, J = 7.7, 7.7, 10.9 Hz), 2.27 – 2.35 (m, 2H), 2.21 (dddd, 1H, J = 4.1, 6.6, 6.6, 12.6 Hz), 2.05 – 2.11 (m, 4H), 2.00 (m, 1H), 1.84 (m, 1H), 1.54 – 1.72 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 165.5, 134.7, 129.7, 97.8, 58.9, 48.6, 41.5, 32.1, 27.4, 25.2, 24.6, 22.5, 21.9; IR (NaCl, $CDCl_3$) 1621, 1512, 1466, 1329, 1260, 1231, 1122, 922 cm^{-1}; HRMS $[C_{14}H_{20}NO]^+$ calcd 218.1545. Found 218.1541 (FAB+).



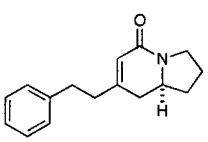
(*S*)-7-hexyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18q). According to the general procedure with ligand **L6**, alkyne **16q**, and isocyanate **17**. Upon purification 38.3 mg (64%) of the desired product was isolated: R_f = 0.39 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ = +95.3 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 97:3 hexane:iPrOH, 1.0 ml/min, Major: 20.2 minutes, Minor: 21.9 minutes, 230 nm detection light, *ee* = 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (m, 1H), 3.62 (dddd, 1H, J = 5.1, 5.1, 10.2, 15.1 Hz), 3.58 (ddd, 1H, J = 2.1, 9.4, 11.7 Hz), 3.42 (ddd, 1H, J = 7.9, 9.8, 11.7 Hz), 2.27 (dd, 1H, J = 4.9, 16.6 Hz), 2.06 – 2.19 (m, 4H), 1.98 (m, 1H), 1.75 (ddddd, 1H, J = 6.6, 9.6, 9.6, 12.2, 12.2 Hz), 1.56 (m, 1H), 1.38 – 1.46 (m, 2H), 1.21 – 1.31 (m, 6H), 0.84 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 153.6, 120.4, 56.7, 44.0, 36.7, 34.8, 33.7, 31.8, 29.0, 26.9, 23.2, 22.7, 14.3; IR (NaCl, CH_2Cl_2) 1660, 1609, 1445, 1342, 1265 cm^{-1}; HRMS $[C_{14}H_{24}NO]^+$ calcd 222.1858. Found 222.1853 (FAB+).

From the same reaction mixture, the minor product **19q** (8.5 mg, 14%) was also isolated, For its characterization, please refer to Chapter 4 experimental, compound **3a**.



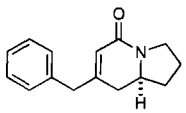
(*S*)-methyl 5-(5-oxo-1,2,3,5,8,8a-hexahydroindolizin-7-yl)pentanoate (18r). According to the general procedure with ligand **L6**, alkyne **16r**, and isocyanate **17**. Upon purification 37.8 mg (56%) of the desired product was isolated: R_f = 0.12 (EtOAc); $[\alpha]_D^{20}$ = +71.6 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 16.3 minutes, Minor: 14.4 minutes, 254 nm detection light, *ee* = 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 3.64 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.3 Hz), 3.63 (s, 3H), 3.58 (ddd, 1H, *J* = 2.3, 9.4, 11.7 Hz), 3.41 (ddd, 1H, *J* = 7.9, 9.8, 11.7 Hz), 2.29 (t, 2H, *J* = 7.3 Hz), 2.26 (dd, 1H, *J* = 4.9, 16.6 Hz), 2.06 – 2.20 (m, 4H), 1.98 (m, 1H), 1.76 (ddddd, 1H, *J* = 6.6, 9.4, 9.4, 12.2, 12.2 Hz), 1.53 – 1.64 (m, 3H), 1.43 – 1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 164.2, 152.9, 120.6, 56.6, 51.8, 44.0, 36.3, 34.7, 33.9, 33.6, 26.3, 24.6, 23.2; IR (NaCl, $CDCl_3$) 1734, 1661, 1615, 1439, 1354, 1326, 1195, 1161, 866 cm^{-1}; HRMS $[C_{14}H_{22}NO_3]^+$ calcd 252.1600. Found 252.1588 (FAB+).

From the same reaction mixture, the minor product **19r** (6.0 mg, 9%) was also isolated but not fully characterized due to its small quantity.

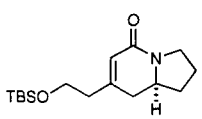


(*S*)-7-phenethyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18b). According to the general procedure with ligand **L6**, alkyne **16b**, and isocyanate **17**. Upon purification 32.6 mg (50%) of the desired product was isolated: R_f = 0.38 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ = +101.9 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 15.0 minutes, Minor: 13.7 minutes, 210 nm detection light, *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 7.0 Hz), 7.25 (d, 1H, *J* = 7.7 Hz), 7.13 – 7.19 (m, 3H), 5.74 (m, 1H), 3.63 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.4 Hz), 3.59 (m, 1H), 3.42 (ddd, 1H, *J* = 7.9, 9.8, 11.7

Hz), 2.77 (dd, 1H, J = 7.2, 7.2 Hz), 2.77 (dd, 1H, J = 8.5, 8.5 Hz), 2.46 (dd, 1H, J = 8.5, 8.5 Hz), 2.46 (dd, 1H, J = 7.4, 7.4 Hz), 2.28 (dd, 1H, J = 4.9, 16.6 Hz), 2.08 – 2.20 (m, 2H), 1.99 (m, 1H), 1.76 (ddddd, 1H, J = 6.6, 9.6, 9.6, 12.2, 12.2 Hz), 1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 152.5, 141.0, 128.7, 128.5, 126.4, 120.9, 56.6, 44.0, 38.4, 35.0, 33.6, 33.5, 23.2; IR (NaCl, $CDCl_3$) 1655, 1609, 1445, 1347, 1327, 1240, 856 cm^{-1}; HRMS $[C_{16}H_{20}NO]^+$ calcd 245.1545. Found 245.1547 (FAB+).

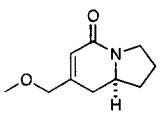


(*S*)-7-benzyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18s). According to the general procedure with ligand **L6**, alkyne **16s**, and isocyanate **17**. Upon purification 28.6 mg (47%) of the desired product was isolated: R_f = 0.13 (EtOAc); $[\alpha]_D^{20}$ = +81.5 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 30.3 minutes, Minor: 29.2 minutes, 210 nm detection light, *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.32 (m, 5H), 5.75 (m, 1H), 3.55 – 3.66 (m, 2H), 3.37 – 3.50 (m, 3H), 2.25 (dd, 1H, J = 4.9, 16.6 Hz), 2.02 – 2.15 (m, 2H), 1.97 (m, 1H), 1.74 (ddddd, 1H, J = 6.8, 9.6, 9.6, 12.2, 12.2 Hz), 1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 152.0, 137.4, 129.3, 128.9, 127.0, 122.1, 56.8, 44.0, 43.2, 34.2, 33.6, 23.2; IR (NaCl, CH_2Cl_2) 1664, 1605, 1445, 1347, 1320 cm^{-1}; HRMS $[C_{15}H_{18}NO]^+$ calcd 228.1388. Found 228.1383 (FAB+).

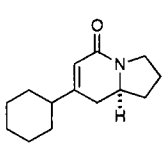


(*S*)-7-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18t). According to the general procedure with ligand **L6**, alkyne **16t**, and isocyanate **17**. Upon purification 51.9 mg (65%) of the desired product was isolated: R_f = 0.13 (EtOAc); $[\alpha]_D^{20}$ = +75.4 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexane:iPrOH, 1.0 ml/min, Major: 18.2 minutes, Minor: 16.1 minutes, 210 nm detection light, *ee* = 87%; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 5.71 (m, 1H), 3.72 (t, 2H, *J* = 6.6 Hz), 3.64 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.1 Hz), 3.59 (ddd, 1H, *J* = 2.1, 9.2, 11.5 Hz), 3.42 (ddd, 1H, *J* = 7.7, 9.8, 11.7 Hz), 2.38 (dd, 1H, *J* = 4.7, 16.6 Hz), 2.32 – 2.36 (m, 2H), 2.08 – 2.19 (m, 2H), 1.98 (m, 1H), 1.76 (ddddd, 1H, *J* = 6.6, 9.4, 9.4, 11.9, 11.9 Hz), 1.56 (m, 1H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 151.0, 121.9, 61.6, 56.6, 44.0, 39.8, 35.2, 33.6, 26.1, 23.2, 18.4, -5.2; IR (NaCl, $CDCl_3$) 1660, 1598, 1455, 1352, 1327, 1245, 1091, 1050, 835 cm^{-1}; HRMS $[C_{16}H_{30}NO_2Si]^+$ calcd 296.2046. Found 296.2057 (FAB+).

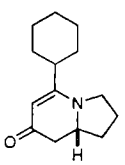


(*S*)-7-(methoxymethyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18u). According to the general procedure with ligand **L6**, alkyne **16u**, and isocyanate **17** (seal tube). Upon purification 22.6 mg (46%) of the desired product was isolated: R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = +66.9 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 9.1 minutes, Minor: 10.2 minutes, 210 nm detection light, *ee* = 77%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (m, 1H), 3.98 (d, 1H, *J* = 13.9 Hz), 3.92 (d, 1H, *J* = 13.9 Hz), 3.67 (dddd, 1H, *J* = 5.1, 5.1, 10.4, 15.1 Hz), 3.61 (ddd, 1H, *J* = 2.1, 9.2, 11.5 Hz), 3.44 (m, 1H), 3.31 (s, 3H), 2.42 (dd, 1H, *J* = 4.7, 16.6 Hz), 2.19 (ddd, 1H, *J* = 6.2, 6.2, 11.7 Hz), 1.96 – 2.11 (m, 2H), 1.77 (ddddd, 1H, *J* = 6.8, 9.8, 9.8, 12.4, 12.4 Hz), 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 148.9, 121.4, 74.0, 58.6, 56.7, 44.1, 33.6, 31.5, 23.2; IR (NaCl, $CDCl_3$) 1667, 1610, 1449, 1340, 1191, 1105 cm^{-1}; HRMS $[C_{10}H_{16}NO_2]^+$ calcd 182.1181. Found 182.1181 (FAB+).

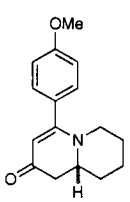


(*S*)-7-cyclohexyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (18v). According to the general procedure with ligand **L5**, alkyne **16v**, and isocyanate **17**. Upon purification 26.2 mg (44%) of the desired product was isolated: R_f =

0.17 (EtOAc); $[\alpha]_D^{20}$ = +68.9 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 39.3 minutes, Minor: 29.3 minutes, 210 nm detection light, *ee* = 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (m, 1H), 3.54 – 3.64 (m, 2H), 3.42 (ddd, 1H, *J* = 7.7, 9.6, 11.7 Hz), 2.32 (dd, 1H, *J* = 4.7, 16.4 Hz), 2.16 (ddd, 1H, *J* = 5.5, 5.5, 11.9 Hz), 2.09 (ddd, 1H, *J* = 2.6, 14.5, 16.6 Hz), 1.93 – 2.02 (m, 2H), 1.63 – 1.81 (m, 6H), 1.57 (m, 1H), 1.07 – 1.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 158.2, 118.6, 56.8, 44.8, 44.0, 33.7, 33.5, 31.3, 30.9, 26.5, 26.4, 26.3, 23.2; IR (NaCl, CH_2Cl_2) 1655, 1603, 1445, 1332, 1163, 851 cm^{-1}; HRMS $[C_{14}H_{22}NO]^+$ calcd 220.1701. Found 220.1712 (FAB+).

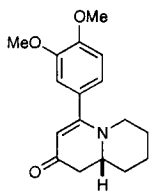


(*R*)-5-cyclohexyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19v). From the same reaction as above, upon purification 22.4 mg (38%) of the desired product was isolated: R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = +432.3 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 16.5 minutes, Minor: 15.7 minutes, 330 nm detection light, *ee* = 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 3.68 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.8 Hz), 3.59 (m, 1H), 3.42 (m, 1H), 2.35 (dd, 1H, *J* = 4.7, 15.8 Hz), 2.13 – 2.27 (m, 3H), 2.07 (m, 1H), 1.58 – 1.91 (m, 7H), 1.14 – 1.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 169.0, 94.9, 59.4, 46.5, 41.9, 41.5, 32.6, 31.4, 31.3, 26.6, 26.4, 26.0, 24.0; IR (NaCl, $CDCl_3$) 1624, 1537, 1481, 1342, 1260, 1245, 1128 cm^{-1}; HRMS $[C_{14}H_{22}NO]^+$ calcd 220.1701. Found 220.1699 (FAB+).

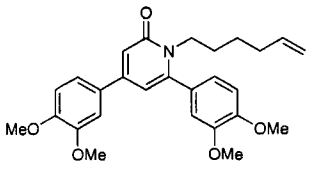


(*R*)-4-(4-methoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (35d). According to the general procedure with ligand **L7**, alkyne **16d**, and isocyanate **34**. Upon purification 31.3 mg (45%) of the desired product was

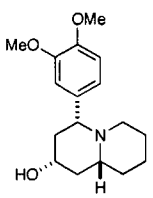
isolated: R_f = 0.22 (EtOAc); $[\alpha]_D^{20}$ = +52 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 13.3 minutes, Minor: 15.8 minutes, 330 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (br d, 2H, *J* = 8.7 Hz), 6.89 (br d, 2H, *J* = 8.5 Hz), 5.02 (s, 1H), 3.80 (s, 3H), 3.60 (m, 1H), 3.44 (dddd, 1H, *J* = 6.0, 6.0, 11.3, 11.3 Hz), 2.57 (dd, 1H, *J* = 5.8, 16.4 Hz), 2.56 (m, 1H), 2.40 (dd, 1H, *J* = 11.3, 16.4 Hz), 1.83 (m, 1H), 1.69 – 1.75 (m, 2H), 1.38 – 1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 166.1, 160.3, 129.2, 128.7, 114.2, 103.6, 58.8, 55.5, 50.6, 42.8, 31.6, 26.2, 24.1; IR (NaCl, $CDCl_3$) 1639, 1603, 1547, 1511, 1434, 1245, 1178, 1132 cm^{-1}; HRMS $[C_{16}H_{20}NO_2]^+$ calcd 258.1494. Found 258.1484 (FAB+).



(*R*)-4-(3,4-dimethoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (35c). According to the general procedure with ligand **L7**, alkyne **16c**, and isocyanate **34**. Upon purification 47.9 mg (62%) of the desired product was isolated: R_f = 0.15 (EtOAc); $[\alpha]_D^{20}$ = +54.5 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 20.6 minutes, Minor: 22.4 minutes, 330 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, 1H, *J* = 8.1 Hz), 6.82 (dd, 1H, *J* = 1.7, 8.1 Hz), 6.76 (d, 1H, *J* = 1.7 Hz), 5.07 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.63 (m, 1H), 3.44 (dddd, 1H, *J* = 6.0, 6.0, 11.3, 11.3 Hz), 2.58 (m, 1H), 2.57 (dd, 1H, *J* = 5.8, 16.2 Hz), 2.40 (dd, 1H, *J* = 11.1, 16.2 Hz), 1.84 (m, 1H), 1.69 – 1.76 (m, 2H), 1.38 – 1.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 166.1, 149.7, 149.1, 129.4, 119.9, 111.2, 110.4, 103.5, 58.9, 56.2, 56.1, 50.7, 42.7, 31.6, 26.2, 24.1; IR (NaCl, $CDCl_3$) 1634, 1547, 1511, 1440, 1342, 1250, 1137, 1025 cm^{-1}; HRMS $[C_{17}H_{22}NO_3]^+$ calcd 288.1600. Found 288.1591 (FAB+).

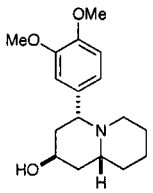


4,6-bis(3,4-dimethoxyphenyl)-1-(hex-5-enyl)pyridin-2(1*H*)-one (36c). From the same reaction as above, the pyridone side product (*ca.* 27 mg, 22%) was isolated and characterized: R_f = 0.41 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, 1H, *J* = 2.1, 8.5 Hz), 7.08 (d, 1H, *J* = 2.1 Hz), 6.92 – 6.94 (m, 2H), 6.88 (d, 1H, *J* = 8.5 Hz), 6.85 (s, 1H), 6.74 (d, 1H, *J* = 2.1 Hz), 6.30 (d, 1H, *J* = 2.1 Hz), 5.66 (dddd, 1H, *J* = 6.6, 6.6, 10.5, 16.8 Hz), 4.84 – 4.92 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 – 3.89 (m, 2H), 1.90 (q, 2H, *J* = 7.0 Hz), 1.60 (m, 2H), 1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.4, 150.0, 149.8, 149.5, 149.4, 148.9, 138.5, 130.3, 128.5, 121.5, 119.7, 114.9, 114.8, 111.9, 111.4, 111.0, 109.8, 107.6, 56.3, 56.2, 45.8, 33.4, 28.7, 26.2; IR (NaCl, $CDCl_3$) 1650, 1603, 1583, 1506, 1455, 1265, 1137, 1025 cm^{-1}; HRMS $[C_{27}H_{32}NO_5]^+$ calcd 450.2280. Found 450.2276 (FAB+).

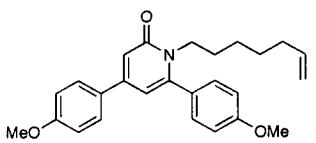


(2*S*,4*R*,9a*R*)-4-(3,4-dimethoxyphenyl)octahydro-1*H*-quinolizin-2-ol (37). A mixture of **35c** (66 mg, 0.23 mmol) and 34 mg of 10% Pd/C in 9 ml of MeOH was stirred at ambient temperature under hydrogen atmosphere (1 atm) for 30 hours. The reaction mixture was filtered through celite and concentrated in vacuo. Upon purification by column chromatography 53.5 mg (80%) of the desired product **37** was isolated: R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = +53.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 – 7.10 (m, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.75 (m, 1H), 2.93 (br d, 1H, *J* = 10.8 Hz), 2.70 (br d, 1H, *J* = 10.9 Hz), 1.88 – 2.08 (m, 3H), 1.33 – 1.80 (m, 9H), 1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 122.4, 110.8, 68.6, 68.5, 56.2, 56.1, 53.2, 45.4, 43.0, 33.8, 26.3, 24.8; IR (NaCl, $CDCl_3$) 2934, 1592, 1506, 1455, 1363, 1260, 1225, 1128, 1025, 910, 727 cm^{-1}; HRMS $[C_{17}H_{26}NO_3]^+$ calcd 292.1913. Found

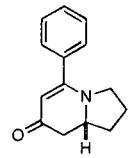
292.1914 (FAB+). Spectral properties were in agreement with literature values reported for the opposite enantiomer.[3]



(+)-Lasubine II. According to the literature procedure,[3] a Mitsunobu reaction on **37** followed by hydrolysis (42.0 mg, 0.144 mmol) provided 27.0 mg (64%) of the desired product: R_f = 0.24 (8:1 EtOAc/MeOH); $[\alpha]_D^{20}$ = +43.4 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 – 6.91 (m, 3H), 4.12 (br s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.29 (br d, 1H, *J* = 10.2 Hz), 2.66 (br d, 1H, *J* = 10.6 Hz), 2.36 (m, 1H), 1.20 – 1.92 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.0, 137.4, 119.9, 111.0, 107.0, 65.3, 63.6, 56.7, 56.2, 56.0, 53.4, 43.0, 40.5, 33.8, 26.3, 25.1; IR (NaCl, $CDCl_3$) 2930, 1588, 1516, 1460, 1414, 1260, 1132, 1025 cm^{-1}; HRMS $[C_{17}H_{26}NO_3]^+$ calcd 292.1913. Found 292.1916 (FAB+). Spectral properties were in agreement with literature values reported for the (–)-lasubine II.[4]



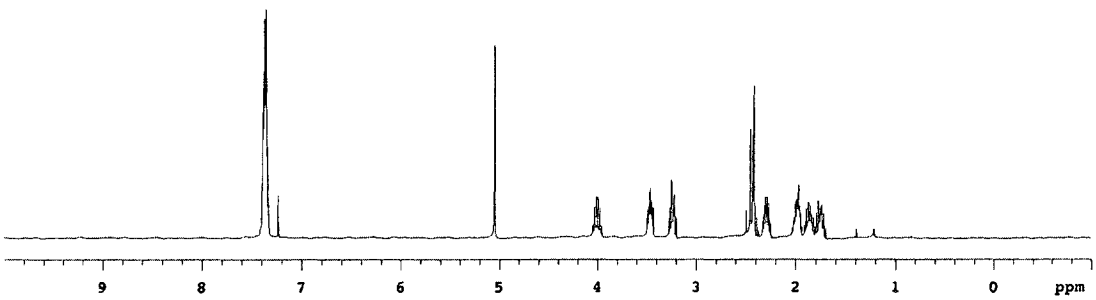
1-(hept-6-enyl)-4,6-bis(4-methoxyphenyl)pyridin-2(1*H*)-one (39d). R_f = 0.54 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J* = 9.2 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 6.97 – 6.91 (m, 4H), 6.73 (d, 1H, *J* = 2.0 Hz), 6.28 (d, 1H, *J* = 2.0 Hz), 5.69 (dddd, 1H, *J* = 6.6, 6.6, 10.5, 16.8 Hz), 4.92 – 4.85 (m, 2H), 3.87 (t, 2H, *J* = 8.0 Hz), 3.85 (s, 3H), 3.81 (s, 3H), 1.90 (q, 2H, *J* = 7.2 Hz), 1.56 (m, 2H), 1.23 – 1.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.9, 160.3, 149.8, 149.5, 139.0, 130.2, 130.0, 128.4, 128.2, 114.5, 114.1, 107.8, 55.6, 45.6, 33.6, 28.7, 28.4, 26.4; IR (NaCl, $CDCl_3$) 1652, 1609, 1586, 1508, 1463, 1251, 1179, 1030 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 403.21474, found 403.21447.



19a

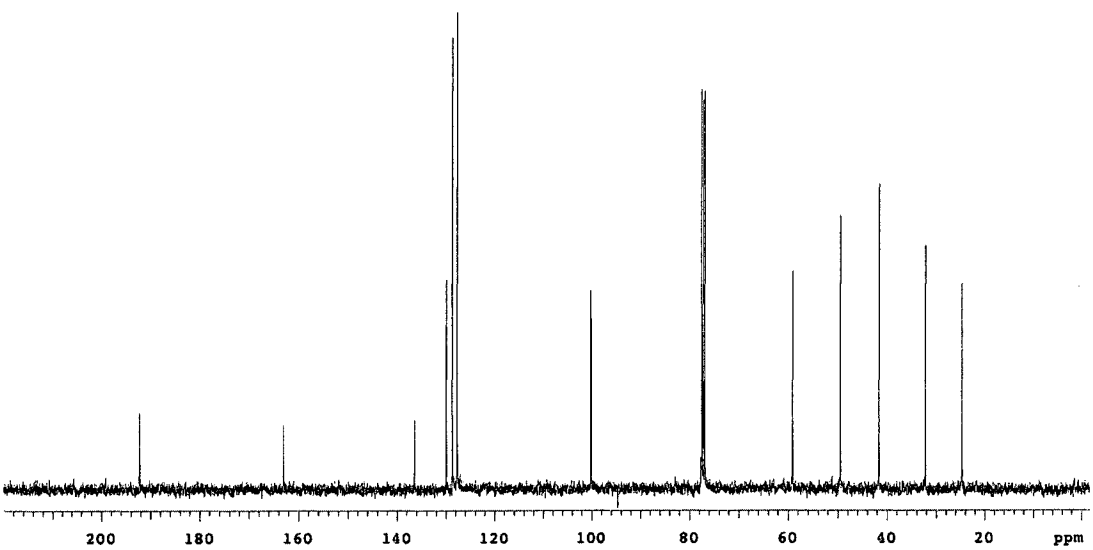
STANDARD 1H OBSERVE

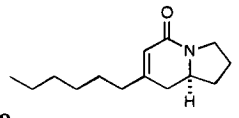
yu2-209-2



13C OBSERVE

yu2-209-2

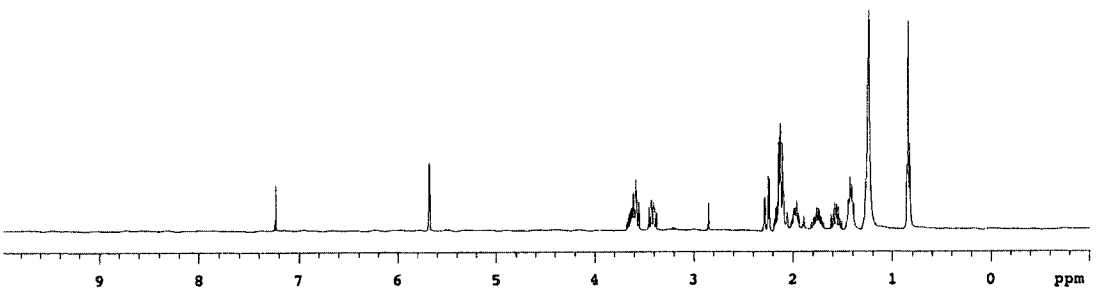




18q

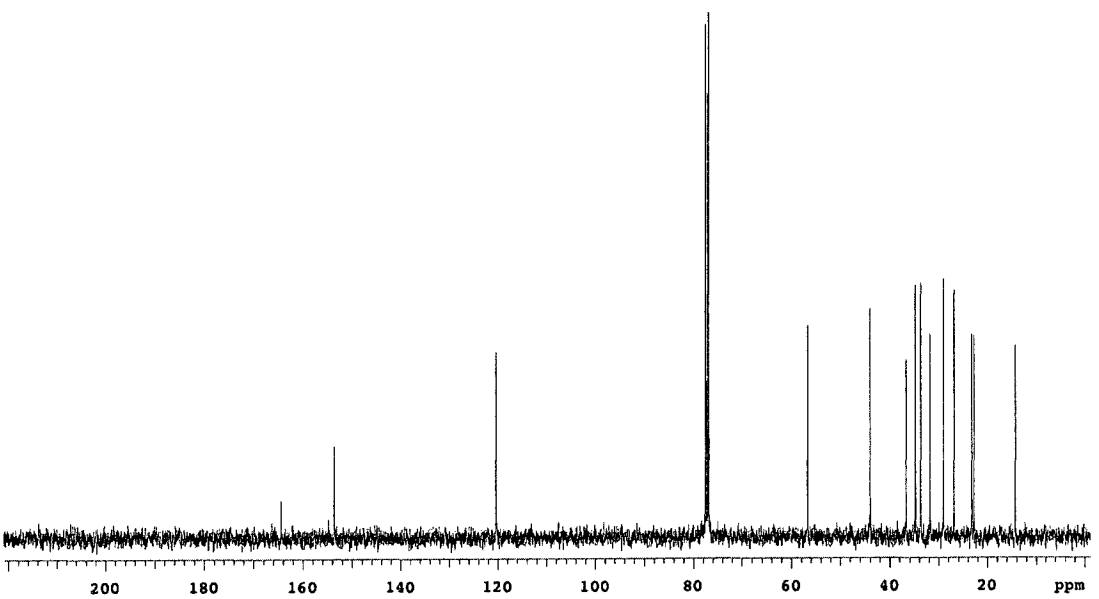
STANDARD 1H OBSERVE

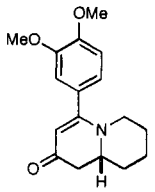
yu2-208-1



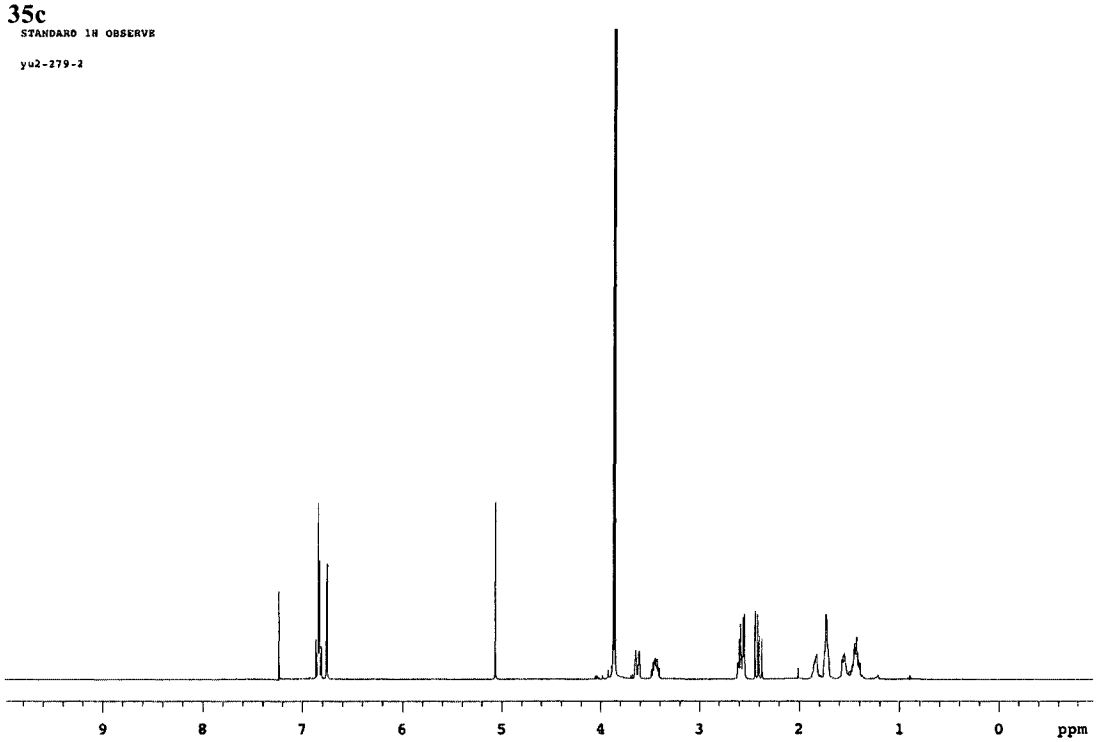
13C OBSERVE

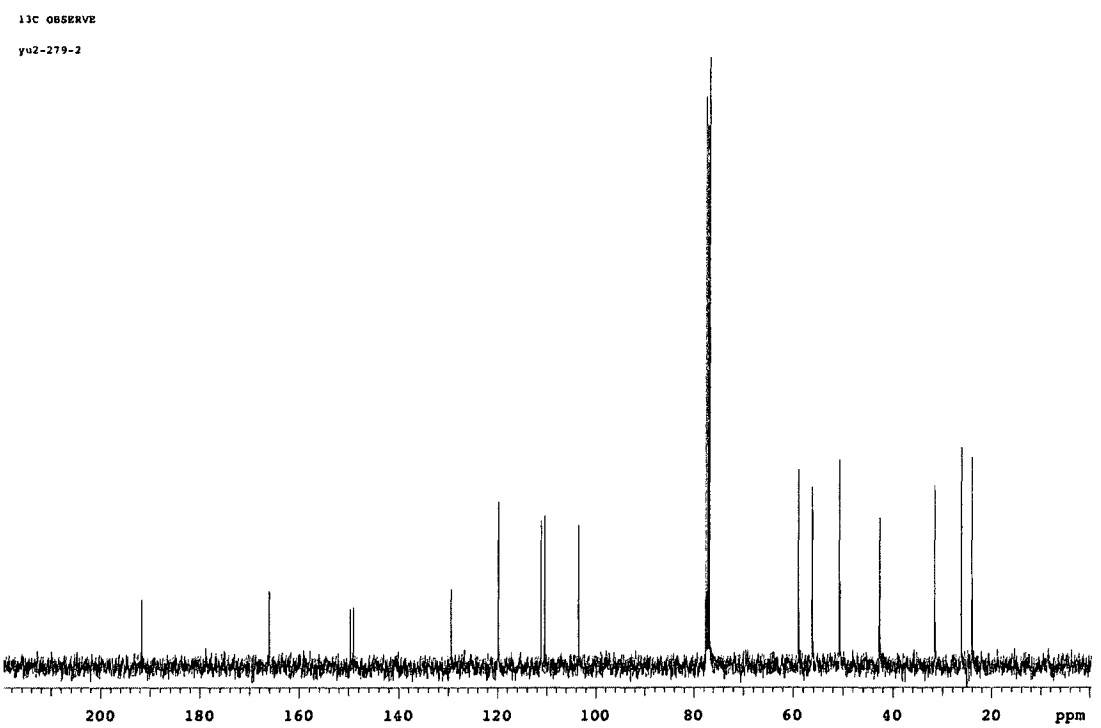
yu2-208-1

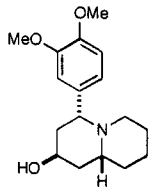




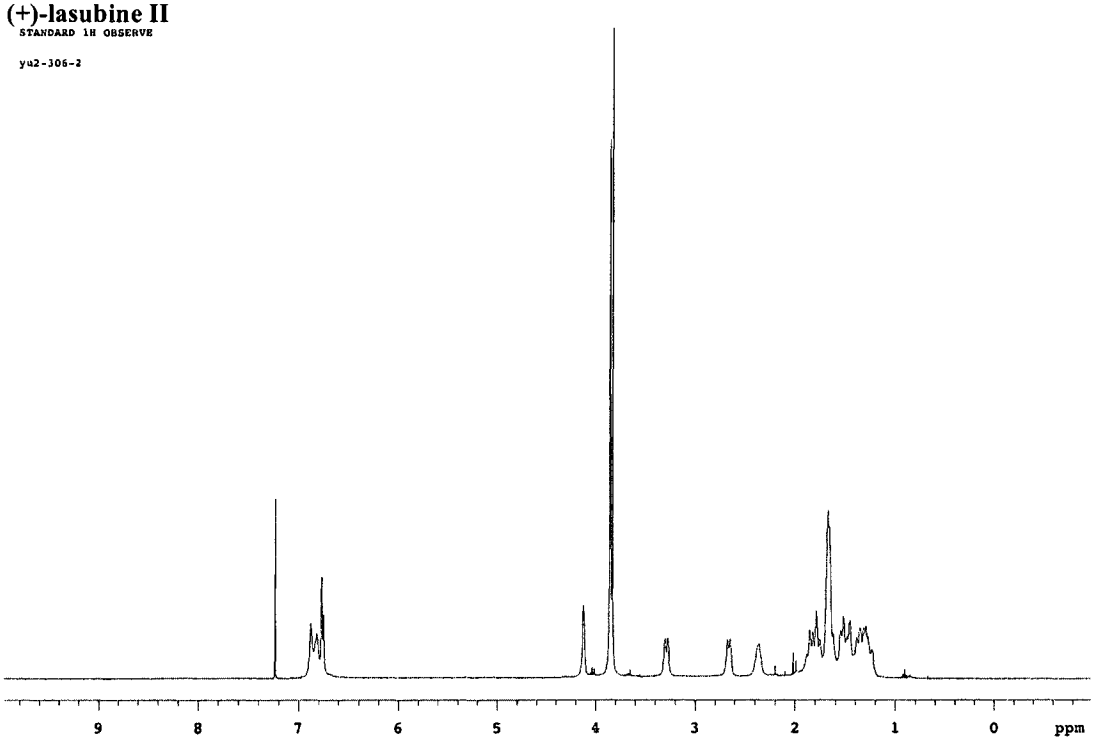
35c

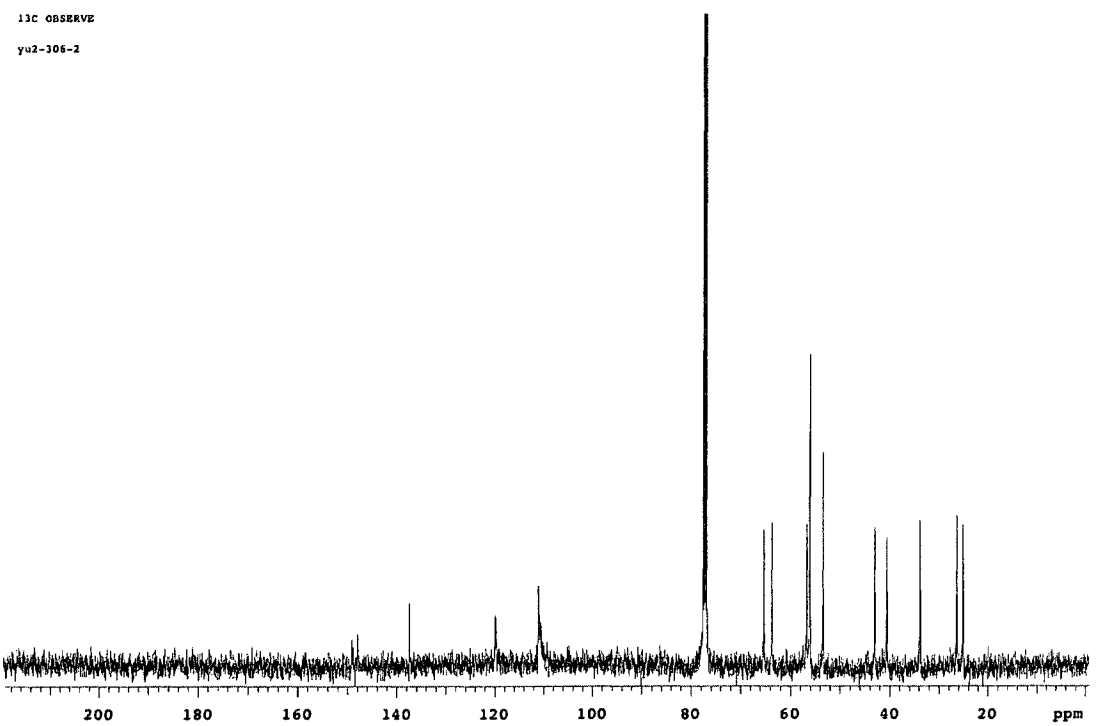






(+)-lasubine II





Crystal Structure Data for 18k

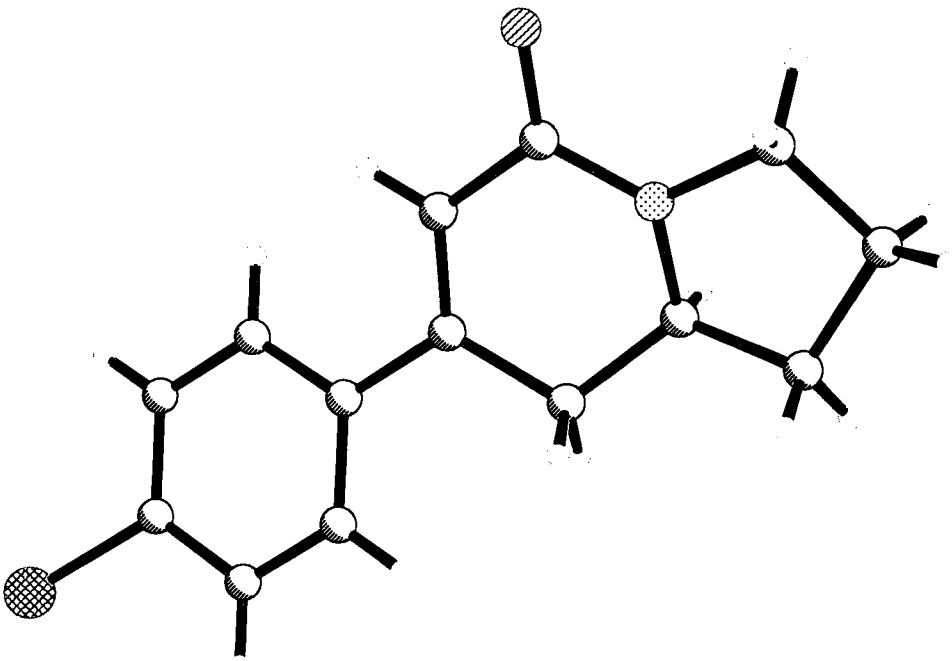


Table 1. Crystal data and structure refinement for **18k**.

Identification code	rovis22a	
Empirical formula	C14 H14 Br N O	
Formula weight	292.17	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.2073(5) Å	α= 90°.
	b = 7.8184(4) Å	β= 91.258(3)°.
	c = 12.9408(6) Å	γ = 90°.
Volume	1234.79(10) $Å^3$	
Z	4	
Density (calculated)	1.572 Mg/m^3	
Absorption coefficient	3.311 mm^{-1}	
F(000)	592	
Crystal size	0.17 x 0.15 x 0.11 mm^3	

Theta range for data collection	1.57 to 35.41°.
Index ranges	-19<=h<=19, -12<=k<=12, -21<=l<=19
Reflections collected	50738
Independent reflections	10905 [R(int) = 0.0466]
Completeness to theta = 35.41°	99.1 %
Absorption correction	multi-scan
Max. and min. transmission	0.7183 and 0.6062
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10905 / 1 / 308
Goodness-of-fit on F^2	0.940
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0719
R indices (all data)	R1 = 0.0722, wR2 = 0.0811
Absolute structure parameter	0.005(5)
Largest diff. peak and hole 0.415 and -0.553 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **18k**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1A)	11295(1)	11742(1)	7916(1)	37(1)
N(1A)	17817(1)	11759(3)	11237(1)	23(1)
O(1A)	16938(1)	11933(3)	12752(1)	34(1)
C(1A)	17819(1)	11803(3)	10101(1)	22(1)
C(2A)	18879(1)	10840(3)	9887(2)	33(1)
C(3A)	19650(1)	11386(4)	10774(2)	36(1)
C(4A)	18903(1)	11572(3)	11703(2)	27(1)
C(5A)	16909(1)	11934(3)	11800(1)	24(1)
C(6A)	15870(1)	12096(2)	11199(1)	24(1)
C(7A)	15775(1)	11685(3)	10195(1)	18(1)
C(8A)	16776(1)	11087(3)	9635(1)	22(1)
C(9A)	14701(1)	11718(3)	9646(1)	19(1)
C(10A)	13749(1)	11235(2)	10149(2)	22(1)
C(11A)	12736(1)	11285(3)	9643(2)	26(1)
C(12A)	12675(1)	11793(3)	8623(2)	24(1)
C(13A)	13601(1)	12305(3)	8101(2)	27(1)

C(14A)	14611(1)	12256(2)	8618(2)	23(1)
Br(1)	8590(1)	9294(1)	7116(1)	34(1)
N(1)	2124(1)	9645(2)	3705(1)	24(1)
O(1)	3018(1)	9083(2)	2230(1)	31(1)
C(1)	2117(1)	10323(3)	4764(1)	24(1)
C(2)	996(1)	9774(3)	5120(2)	33(1)
C(3)	271(1)	9885(3)	4142(2)	31(1)
C(4)	1027(1)	9390(4)	3257(2)	29(1)
C(5)	3044(1)	9482(3)	3159(1)	24(1)
C(6)	4082(1)	9704(3)	3743(1)	24(1)
C(7)	4145(1)	9776(2)	4780(1)	20(1)
C(8)	3100(1)	9726(3)	5387(1)	25(1)
C(9)	5207(1)	9747(2)	5349(1)	20(1)
C(10)	6185(1)	10219(3)	4874(2)	25(1)
C(11)	7181(1)	10117(3)	5396(2)	27(1)
C(12)	7213(1)	9537(3)	6408(2)	25(1)
C(13)	6265(1)	9090(3)	6908(2)	26(1)
C(14)	5267(1)	9199(3)	6381(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for **18k**.

Br(1A)-C(12A)	1.9006(17)	C(7A)-C(8A)	1.509(2)
N(1A)-C(5A)	1.346(2)	C(9A)-C(10A)	1.396(2)
N(1A)-C(4A)	1.452(2)	C(9A)-C(14A)	1.397(3)
N(1A)-C(1A)	1.471(2)	C(10A)-C(11A)	1.387(2)
O(1A)-C(5A)	1.231(2)	C(11A)-C(12A)	1.379(3)
C(1A)-C(8A)	1.505(2)	C(12A)-C(13A)	1.388(3)
C(1A)-C(2A)	1.528(3)	C(13A)-C(14A)	1.391(2)
C(2A)-C(3A)	1.529(3)	Br(1)-C(12)	1.9053(17)
C(3A)-C(4A)	1.532(2)	N(1)-C(5)	1.347(2)
C(5A)-C(6A)	1.480(2)	N(1)-C(4)	1.461(2)
C(6A)-C(7A)	1.340(2)	N(1)-C(1)	1.468(2)
C(7A)-C(9A)	1.477(2)	O(1)-C(5)	1.242(2)
		C(1)-C(8)	1.506(2)
		C(1)-C(2)	1.515(2)
		C(2)-C(3)	1.532(3)
		C(3)-C(4)	1.536(3)
		C(5)-C(6)	1.471(2)

C(6)-C(7)	1.344(3)	C(13A)-C(12A)-Br(1A)	119.61(15)
C(7)-C(9)	1.477(2)	C(12A)-C(13A)-C(14A)	118.71(19)
C(7)-C(8)	1.512(2)	C(13A)-C(14A)-C(9A)	121.13(16)
C(9)-C(14)	1.403(3)	C(5)-N(1)-C(4)	123.14(16)
C(9)-C(10)	1.404(2)	C(5)-N(1)-C(1)	123.06(15)
C(10)-C(11)	1.380(3)	C(4)-N(1)-C(1)	113.30(13)
C(11)-C(12)	1.386(3)	N(1)-C(1)-C(8)	111.52(14)
C(12)-C(13)	1.383(2)	N(1)-C(1)-C(2)	101.90(15)
C(13)-C(14)	1.385(2)	C(8)-C(1)-C(2)	117.63(16)
		C(1)-C(2)-C(3)	103.98(15)
C(5A)-N(1A)-C(4A)	122.76(15)	C(2)-C(3)-C(4)	104.83(14)
C(5A)-N(1A)-C(1A)	123.94(14)	N(1)-C(4)-C(3)	103.30(15)
C(4A)-N(1A)-C(1A)	113.27(13)	O(1)-C(5)-N(1)	121.82(16)
N(1A)-C(1A)-C(8A)	111.81(14)	O(1)-C(5)-C(6)	122.08(15)
N(1A)-C(1A)-C(2A)	100.96(14)	N(1)-C(5)-C(6)	116.01(16)
C(8A)-C(1A)-C(2A)	117.18(17)	C(7)-C(6)-C(5)	123.19(15)
C(1A)-C(2A)-C(3A)	103.68(17)	C(6)-C(7)-C(9)	121.79(15)
C(2A)-C(3A)-C(4A)	104.38(14)	C(6)-C(7)-C(8)	119.16(15)
N(1A)-C(4A)-C(3A)	103.80(15)	C(9)-C(7)-C(8)	118.82(15)
O(1A)-C(5A)-N(1A)	122.35(16)	C(1)-C(8)-C(7)	112.67(15)
O(1A)-C(5A)-C(6A)	122.15(15)	C(14)-C(9)-C(10)	118.05(15)
N(1A)-C(5A)-C(6A)	115.50(16)	C(14)-C(9)-C(7)	120.36(15)
C(7A)-C(6A)-C(5A)	122.98(15)	C(10)-C(9)-C(7)	121.57(17)
C(6A)-C(7A)-C(9A)	121.29(15)	C(11)-C(10)-C(9)	121.26(19)
C(6A)-C(7A)-C(8A)	119.06(14)	C(10)-C(11)-C(12)	119.21(16)
C(9A)-C(7A)-C(8A)	119.57(15)	C(13)-C(12)-C(11)	121.17(16)
C(1A)-C(8A)-C(7A)	112.30(15)	C(13)-C(12)-Br(1)	119.26(15)
C(10A)-C(9A)-C(14A)	118.43(15)	C(11)-C(12)-Br(1)	119.55(13)
C(10A)-C(9A)-C(7A)	120.63(16)	C(12)-C(13)-C(14)	119.38(18)
C(14A)-C(9A)-C(7A)	120.94(15)	C(13)-C(14)-C(9)	120.91(15)
C(11A)-C(10A)-C(9A)	121.02(18)		
C(12A)-C(11A)-C(10A)	119.19(16)		
C(11A)-C(12A)-C(13A)	121.50(16)		
C(11A)-C(12A)-Br(1A)	118.88(13)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for **18k**. The anisotropic

displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1A)	19(1)	48(1)	45(1)	-8(1)	-6(1)	1(1)
N(1A)	19(1)	35(1)	15(1)	-1(1)	2(1)	2(1)
O(1A)	30(1)	59(1)	14(1)	-4(1)	4(1)	5(1)
C(1A)	21(1)	28(1)	16(1)	3(1)	4(1)	-2(1)
C(2A)	19(1)	58(1)	22(1)	-3(1)	6(1)	3(1)
C(3A)	18(1)	62(2)	28(1)	-1(1)	3(1)	-5(1)
C(4A)	20(1)	37(1)	24(1)	0(1)	-1(1)	0(1)
C(5A)	22(1)	34(1)	18(1)	-1(1)	4(1)	2(1)
C(6A)	21(1)	31(1)	20(1)	0(1)	6(1)	2(1)
C(7A)	18(1)	20(1)	17(1)	3(1)	4(1)	-1(1)
C(8A)	19(1)	29(1)	18(1)	-1(1)	3(1)	4(1)
C(9A)	18(1)	20(1)	20(1)	-1(1)	4(1)	0(1)
C(10A)	21(1)	23(1)	23(1)	2(1)	6(1)	1(1)
C(11A)	17(1)	22(1)	40(1)	-3(1)	8(1)	0(1)
C(12A)	17(1)	25(1)	31(1)	-5(1)	-1(1)	0(1)
C(13A)	22(1)	35(1)	22(1)	1(1)	-1(1)	-1(1)
C(14A)	20(1)	29(1)	21(1)	1(1)	2(1)	-2(1)
Br(1)	18(1)	47(1)	37(1)	-8(1)	-6(1)	0(1)
N(1)	18(1)	36(1)	16(1)	-3(1)	0(1)	4(1)
O(1)	27(1)	50(1)	17(1)	-2(1)	1(1)	7(1)
C(1)	20(1)	34(1)	18(1)	-2(1)	4(1)	3(1)
C(2)	20(1)	56(2)	22(1)	-1(1)	4(1)	1(1)
C(3)	18(1)	47(1)	29(1)	-5(1)	2(1)	5(1)
C(4)	18(1)	43(1)	26(1)	-8(1)	-3(1)	7(1)
C(5)	20(1)	31(1)	19(1)	2(1)	3(1)	5(1)
C(6)	18(1)	37(1)	18(1)	1(1)	5(1)	1(1)
C(7)	18(1)	22(1)	20(1)	2(1)	4(1)	0(1)
C(8)	18(1)	41(1)	16(1)	-3(1)	4(1)	0(1)
C(9)	17(1)	23(1)	21(1)	-2(1)	3(1)	0(1)
C(10)	20(1)	32(1)	23(1)	3(1)	6(1)	-1(1)
C(11)	18(1)	33(1)	30(1)	1(1)	6(1)	-2(1)
C(12)	15(1)	26(1)	32(1)	-6(1)	-2(1)	-1(1)

C(13)	20(1)	35(1)	23(1)	1(1)	-2(1)	-4(1)
C(14)	17(1)	35(1)	19(1)	2(1)	1(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **18k**.

	x	y	z	U(eq)
H(1AA)	17899	12992	9875	26
H(2AA)	19170	11168	9224	39
H(2AB)	18761	9614	9893	39
H(3AA)	20005	12463	10618	43
H(3AB)	20208	10525	10905	43
H(4AA)	18944	10566	12141	32
H(4AB)	19101	12570	12111	32
H(6AA)	15254	12501	11532	29
H(8AA)	16808	9847	9656	26
H(8AB)	16715	11432	8916	26
H(10A)	13795	10873	10833	27
H(11A)	12104	10981	9988	31
H(13A)	13546	12674	7419	32
H(14A)	15237	12588	8274	28
H(1A)	2133	11574	4729	29
H(2A)	733	10536	5652	39
H(2B)	1016	8616	5389	39
H(3A)	-11	11035	4046	37
H(3B)	-342	9098	4180	37
H(4A)	916	8208	3053	35
H(4B)	904	10121	2660	35
H(6A)	4726	9799	3377	29
H(8A)	2975	8564	5620	30
H(8B)	3188	10444	5994	30
H(10B)	6162	10608	4195	30
H(11B)	7823	10433	5072	32
H(13B)	6297	8719	7590	31

H(14B)	4628	8905	6716	29

Crystal Structure Data for 19k

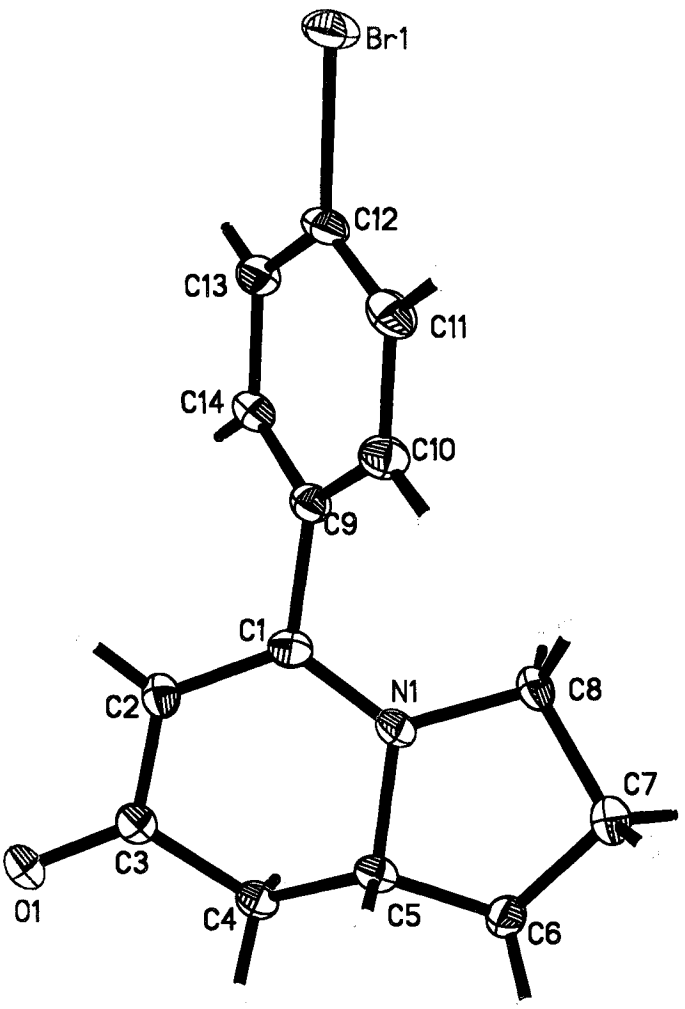


Table 1. Crystal data and structure refinement for **19k**.

Identification code	rovis23a
Empirical formula	C14 H14 Br N O
Formula weight	292.17

Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.5864(8) Å	α= 90°.
	b = 8.6454(6) Å	β= 100.668(4)°.
	c = 17.4451(12) Å	γ = 90°.
Volume	1865.5(2) $Å^3$	
Z	6	
Density (calculated)	1.560 Mg/m^3	
Absorption coefficient	3.288 mm^{-1}	
F(000)	888	
Crystal size	0.13 x 0.09 x 0.09 mm^3	
Theta range for data collection	1.65 to 31.53°.	
Index ranges	-18<=h<=18, -12<=k<=12, -25<=l<=25	
Reflections collected	55388	
Independent reflections	12412 [R(int) = 0.0498]	
Completeness to theta = 31.53°	99.7 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.7541 and 0.6783	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12412 / 1 / 461	
Goodness-of-fit on F^2	0.744	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0806	
R indices (all data)	R1 = 0.0482, wR2 = 0.0895	
Absolute structure parameter	-0.006(5)	
Largest diff. peak and hole	0.583 and -0.511 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **19k**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	1341(1)	7216(1)	6210(1)	28(1)
N(1)	-2477(2)	7614(2)	2761(1)	17(1)
O(1)	-992(2)	9676(2)	1119(1)	20(1)

C(1)	-1439(2)	8026(3)	2933(1)	16(1)
C(2)	-933(2)	8835(3)	2412(1)	18(1)
C(3)	-1423(2)	9005(3)	1610(1)	17(1)
C(4)	-2506(2)	8183(3)	1364(1)	19(1)
C(5)	-3156(2)	8132(3)	2016(1)	18(1)
C(6)	-4096(2)	6989(3)	1899(1)	20(1)
C(7)	-4206(2)	6535(3)	2730(2)	21(1)
C(8)	-3043(2)	6476(3)	3173(1)	20(1)
C(9)	-808(2)	7681(3)	3729(1)	17(1)
C(10)	-1182(2)	8187(3)	4394(1)	21(1)
C(11)	-539(2)	8024(3)	5129(1)	22(1)
C(12)	463(2)	7337(3)	5196(1)	20(1)
C(13)	849(2)	6772(3)	4552(1)	20(1)
C(14)	192(2)	6954(3)	3819(1)	18(1)
Br(1A)	2976(1)	5554(1)	13079(1)	20(1)
N(1A)	238(2)	7837(2)	9512(1)	14(1)
O(1A)	2189(2)	9322(2)	8017(1)	28(1)
C(1A)	1309(2)	7987(3)	9751(1)	15(1)
C(2A)	1974(2)	8625(3)	9283(1)	20(1)
C(3A)	1605(2)	8835(3)	8463(1)	21(1)
C(4A)	460(2)	8293(3)	8144(1)	20(1)
C(5A)	-288(2)	8421(3)	8735(1)	17(1)
C(6A)	-1326(2)	7471(3)	8553(1)	21(1)
C(7A)	-1598(2)	7136(3)	9353(1)	21(1)
C(8A)	-488(2)	6830(3)	9863(1)	17(1)
C(9A)	1764(2)	7455(3)	10557(1)	15(1)
C(10A)	1341(2)	8031(3)	11190(1)	17(1)
C(11A)	1734(2)	7483(3)	11940(1)	17(1)
C(12A)	2546(2)	6368(3)	12059(1)	17(1)
C(13A)	2998(2)	5823(3)	11437(1)	18(1)
C(14A)	2599(2)	6373(3)	10687(1)	17(1)
Br(1B)	5095(1)	7231(1)	9810(1)	41(1)
N(1B)	6128(2)	5254(2)	6176(1)	19(1)
O(1B)	3274(2)	4358(3)	4680(1)	30(1)
C(1B)	5172(2)	5403(3)	6412(1)	18(1)
C(2B)	4204(2)	5029(3)	5935(1)	23(1)

C(3B)	4132(2)	4687(3)	5123(1)	22(1)
C(4B)	5192(2)	4883(4)	4817(2)	29(1)
C(5B)	6177(2)	4495(4)	5430(2)	27(1)
C(6B)	7266(2)	4964(4)	5261(2)	29(1)
C(7B)	7955(2)	5175(4)	6078(2)	31(1)
C(8B)	7174(2)	5950(3)	6527(2)	24(1)
C(9B)	5165(2)	5896(3)	7230(1)	18(1)
C(10B)	5825(2)	5115(3)	7847(1)	20(1)
C(11B)	5780(2)	5502(4)	8614(1)	24(1)
C(12B)	5103(2)	6672(3)	8757(2)	24(1)
C(13B)	4435(2)	7461(3)	8163(2)	23(1)
C(14B)	4473(2)	7053(3)	7392(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for **19k**.

Br(1)-C(12)	1.906(2)	C(13)-C(14)	1.397(3)
N(1)-C(1)	1.334(3)	Br(1A)-C(12A)	1.896(2)
N(1)-C(8)	1.477(3)	N(1A)-C(1A)	1.342(3)
N(1)-C(5)	1.487(3)	N(1A)-C(8A)	1.475(3)
O(1)-C(3)	1.240(3)	N(1A)-C(5A)	1.482(3)
C(1)-C(2)	1.391(3)	O(1A)-C(3A)	1.239(3)
C(1)-C(9)	1.496(3)	C(1A)-C(2A)	1.387(3)
C(2)-C(3)	1.429(3)	C(1A)-C(9A)	1.490(3)
C(3)-C(4)	1.527(3)	C(2A)-C(3A)	1.431(3)
C(4)-C(5)	1.519(3)	C(3A)-C(4A)	1.520(4)
C(5)-C(6)	1.526(3)	C(4A)-C(5A)	1.523(3)
C(6)-C(7)	1.532(3)	C(5A)-C(6A)	1.526(3)
C(7)-C(8)	1.525(4)	C(6A)-C(7A)	1.526(3)
C(9)-C(14)	1.389(3)	C(7A)-C(8A)	1.533(3)
C(9)-C(10)	1.400(3)	C(9A)-C(14A)	1.394(3)
C(10)-C(11)	1.391(3)	C(9A)-C(10A)	1.403(3)
C(11)-C(12)	1.380(4)	C(10A)-C(11A)	1.394(3)
C(12)-C(13)	1.393(3)	C(11A)-C(12A)	1.392(3)
		C(12A)-C(13A)	1.398(3)
		C(13A)-C(14A)	1.396(3)
		Br(1B)-C(12B)	1.902(3)
		N(1B)-C(1B)	1.348(3)

N(1B)-C(5B)	1.469(3)	C(14)-C(9)-C(1)	120.6(2)
N(1B)-C(8B)	1.474(3)	C(10)-C(9)-C(1)	120.3(2)
O(1B)-C(3B)	1.239(3)	C(11)-C(10)-C(9)	120.3(2)
C(1B)-C(2B)	1.381(3)	C(12)-C(11)-C(10)	119.2(2)
C(1B)-C(9B)	1.490(3)	C(11)-C(12)-C(13)	122.2(2)
C(2B)-C(3B)	1.433(3)	C(11)-C(12)-Br(1)	117.81(18)
C(3B)-C(4B)	1.535(4)	C(13)-C(12)-Br(1)	120.01(19)
C(4B)-C(5B)	1.517(4)	C(12)-C(13)-C(14)	117.6(2)
C(5B)-C(6B)	1.510(4)	C(9)-C(14)-C(13)	121.7(2)
C(6B)-C(7B)	1.536(4)	C(1A)-N(1A)-C(8A)	126.32(19)
C(7B)-C(8B)	1.521(4)	C(1A)-N(1A)-C(5A)	120.21(19)
C(9B)-C(14B)	1.390(3)	C(8A)-N(1A)-C(5A)	112.03(18)
C(9B)-C(10B)	1.405(3)	N(1A)-C(1A)-C(2A)	122.5(2)
C(10B)-C(11B)	1.389(3)	N(1A)-C(1A)-C(9A)	116.8(2)
C(11B)-C(12B)	1.375(4)	C(2A)-C(1A)-C(9A)	120.6(2)
C(12B)-C(13B)	1.386(4)	C(1A)-C(2A)-C(3A)	121.3(2)
C(13B)-C(14B)	1.400(3)	O(1A)-C(3A)-C(2A)	123.4(2)
		O(1A)-C(3A)-C(4A)	120.5(2)
C(1)-N(1)-C(8)	127.5(2)	C(2A)-C(3A)-C(4A)	115.9(2)
C(1)-N(1)-C(5)	119.77(19)	C(3A)-C(4A)-C(5A)	113.1(2)
C(8)-N(1)-C(5)	112.06(19)	N(1A)-C(5A)-C(4A)	111.56(19)
N(1)-C(1)-C(2)	122.3(2)	N(1A)-C(5A)-C(6A)	103.12(18)
N(1)-C(1)-C(9)	119.0(2)	C(4A)-C(5A)-C(6A)	115.6(2)
C(2)-C(1)-C(9)	118.6(2)	C(7A)-C(6A)-C(5A)	103.86(19)
C(1)-C(2)-C(3)	121.7(2)	C(6A)-C(7A)-C(8A)	103.26(19)
O(1)-C(3)-C(2)	124.0(2)	N(1A)-C(8A)-C(7A)	102.99(18)
O(1)-C(3)-C(4)	120.4(2)	C(14A)-C(9A)-C(10A)	119.7(2)
C(2)-C(3)-C(4)	115.3(2)	C(14A)-C(9A)-C(1A)	120.4(2)
C(5)-C(4)-C(3)	112.31(19)	C(10A)-C(9A)-C(1A)	119.9(2)
N(1)-C(5)-C(4)	111.21(19)	C(11A)-C(10A)-C(9A)	119.9(2)
N(1)-C(5)-C(6)	103.15(19)	C(12A)-C(11A)-C(10A)	119.9(2)
C(4)-C(5)-C(6)	115.5(2)	C(11A)-C(12A)-C(13A)	120.7(2)
C(5)-C(6)-C(7)	104.08(19)	C(11A)-C(12A)-Br(1A)	118.11(18)
C(8)-C(7)-C(6)	104.01(19)	C(13A)-C(12A)-Br(1A)	121.12(18)
N(1)-C(8)-C(7)	103.60(19)	C(14A)-C(13A)-C(12A)	119.1(2)
C(14)-C(9)-C(10)	119.0(2)	C(9A)-C(14A)-C(13A)	120.7(2)

C(1B)-N(1B)-C(5B)	120.0(2)	N(1B)-C(8B)-C(7B)	102.7(2)
C(1B)-N(1B)-C(8B)	127.8(2)	C(14B)-C(9B)-C(10B)	119.5(2)
C(5B)-N(1B)-C(8B)	111.7(2)	C(14B)-C(9B)-C(1B)	121.1(2)
N(1B)-C(1B)-C(2B)	122.1(2)	C(10B)-C(9B)-C(1B)	119.3(2)
N(1B)-C(1B)-C(9B)	118.9(2)	C(11B)-C(10B)-C(9B)	119.9(2)
C(2B)-C(1B)-C(9B)	118.9(2)	C(12B)-C(11B)-C(10B)	119.2(2)
C(1B)-C(2B)-C(3B)	122.1(2)	C(11B)-C(12B)-C(13B)	122.5(2)
O(1B)-C(3B)-C(2B)	123.5(2)	C(11B)-C(12B)-Br(1B)	118.4(2)
O(1B)-C(3B)-C(4B)	121.4(2)	C(13B)-C(12B)-Br(1B)	119.1(2)
C(2B)-C(3B)-C(4B)	114.9(2)	C(12B)-C(13B)-C(14B)	118.0(2)
C(5B)-C(4B)-C(3B)	112.4(2)	C(9B)-C(14B)-C(13B)	120.8(2)
N(1B)-C(5B)-C(6B)	104.0(2)		
N(1B)-C(5B)-C(4B)	111.3(2)		
C(6B)-C(5B)-C(4B)	117.2(2)		
C(5B)-C(6B)-C(7B)	103.2(2)		
C(8B)-C(7B)-C(6B)	102.8(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **19k**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	33(1)	33(1)	14(1)	3(1)	-3(1)	-2(1)
N(1)	20(1)	19(1)	12(1)	2(1)	4(1)	1(1)
O(1)	25(1)	18(1)	18(1)	4(1)	7(1)	1(1)
C(1)	19(1)	16(1)	12(1)	-3(1)	2(1)	2(1)
C(2)	20(1)	18(1)	16(1)	-1(1)	5(1)	-3(1)
C(3)	18(1)	16(1)	17(1)	1(1)	6(1)	3(1)
C(4)	21(1)	24(1)	12(1)	2(1)	2(1)	-1(1)
C(5)	20(1)	20(1)	15(1)	3(1)	2(1)	2(1)
C(6)	16(1)	25(1)	18(1)	1(1)	4(1)	-1(1)
C(7)	22(1)	21(1)	21(1)	0(1)	8(1)	-2(1)
C(8)	21(1)	24(1)	17(1)	4(1)	8(1)	-1(1)
C(9)	20(1)	17(1)	14(1)	1(1)	2(1)	-2(1)
C(10)	23(1)	22(1)	17(1)	-1(1)	3(1)	3(1)

C(11)	31(1)	21(1)	15(1)	-1(1)	6(1)	-1(1)
C(12)	26(1)	19(1)	12(1)	2(1)	0(1)	-2(1)
C(13)	21(1)	20(1)	18(1)	3(1)	2(1)	1(1)
C(14)	24(1)	15(1)	14(1)	1(1)	4(1)	0(1)
Br(1A)	21(1)	25(1)	12(1)	3(1)	-1(1)	-1(1)
N(1A)	16(1)	14(1)	11(1)	1(1)	1(1)	0(1)
O(1A)	31(1)	34(1)	21(1)	7(1)	9(1)	-5(1)
C(1A)	18(1)	12(1)	13(1)	-2(1)	1(1)	0(1)
C(2A)	18(1)	23(1)	16(1)	2(1)	2(1)	-6(1)
C(3A)	25(1)	18(1)	20(1)	3(1)	6(1)	-2(1)
C(4A)	26(1)	22(1)	12(1)	3(1)	2(1)	0(1)
C(5A)	18(1)	16(1)	14(1)	2(1)	-1(1)	0(1)
C(6A)	19(1)	21(1)	19(1)	0(1)	-4(1)	0(1)
C(7A)	15(1)	22(1)	25(1)	1(1)	2(1)	2(1)
C(8A)	20(1)	14(1)	17(1)	1(1)	2(1)	-2(1)
C(9A)	17(1)	15(1)	13(1)	1(1)	2(1)	-2(1)
C(10A)	18(1)	16(1)	16(1)	-1(1)	0(1)	-1(1)
C(11A)	20(1)	20(1)	13(1)	-1(1)	3(1)	-3(1)
C(12A)	19(1)	19(1)	13(1)	2(1)	0(1)	-3(1)
C(13A)	17(1)	20(1)	17(1)	1(1)	1(1)	-1(1)
C(14A)	18(1)	21(1)	13(1)	1(1)	5(1)	-1(1)
Br(1B)	32(1)	72(1)	20(1)	-16(1)	7(1)	-9(1)
N(1B)	19(1)	22(1)	17(1)	-3(1)	4(1)	0(1)
O(1B)	28(1)	44(1)	16(1)	2(1)	-1(1)	-6(1)
C(1B)	19(1)	18(1)	17(1)	0(1)	5(1)	1(1)
C(2B)	19(1)	32(1)	16(1)	-3(1)	3(1)	-4(1)
C(3B)	25(1)	25(1)	15(1)	5(1)	2(1)	0(1)
C(4B)	28(2)	43(2)	17(1)	-1(1)	4(1)	3(1)
C(5B)	28(1)	37(2)	17(1)	-4(1)	7(1)	5(1)
C(6B)	24(1)	47(2)	18(1)	7(1)	8(1)	11(1)
C(7B)	24(1)	45(2)	26(1)	4(1)	8(1)	3(1)
C(8B)	18(1)	28(1)	27(1)	1(1)	5(1)	-1(1)
C(9B)	17(1)	19(1)	18(1)	-2(1)	4(1)	-2(1)
C(10B)	16(1)	23(1)	20(1)	0(1)	2(1)	-1(1)
C(11B)	20(1)	33(1)	16(1)	5(1)	-1(1)	-1(1)
C(12B)	22(1)	34(1)	18(1)	-7(1)	4(1)	-11(1)

C(13B)	24(1)	21(1)	25(1)	-6(1)	8(1)	-2(1)
C(14B)	22(1)	21(1)	22(1)	-1(1)	4(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **19k**.

	x	y	z	U(eq)
H(2A)	-259	9277	2590	21
H(4A)	-2924	8713	918	23
H(4B)	-2378	7134	1205	23
H(5A)	-3434	9170	2088	22
H(6A)	-3937	6092	1606	24
H(6B)	-4754	7471	1626	24
H(7A)	-4622	7299	2955	25
H(7B)	-4554	5534	2736	25
H(8A)	-3001	6764	3715	24
H(8B)	-2738	5450	3150	24
H(10A)	-1864	8634	4344	25
H(11A)	-782	8375	5570	26
H(13A)	1520	6291	4607	24
H(14A)	429	6578	3381	21
H(2AA)	2672	8923	9507	23
H(4AA)	482	7224	7979	24
H(4AB)	165	8905	7688	24
H(5AA)	-478	9511	8785	20
H(6AA)	-1900	8054	8232	25
H(6AB)	-1211	6519	8285	25
H(7AA)	-2063	6238	9336	25
H(7AB)	-1949	8016	9545	25
H(8AA)	-483	7110	10402	20
H(8AB)	-284	5751	9839	20
H(10C)	799	8777	11109	20
H(11C)	1455	7862	12361	21
H(13C)	3557	5104	11522	22

H(14C)	2893	6014	10269	20
H(2BA)	3578	4999	6147	27
H(4BA)	5178	4215	4368	35
H(4BB)	5248	5943	4647	35
H(5BA)	6186	3374	5514	33
H(6BA)	7216	5921	4966	35
H(6BB)	7563	4164	4973	35
H(7BA)	8201	4187	6308	37
H(7BB)	8577	5828	6061	37
H(8BA)	7360	5721	7080	29
H(8BB)	7165	7062	6454	29
H(10B)	6292	4342	7743	24
H(11B)	6203	4975	9025	28
H(13B)	3974	8237	8274	27
H(14B)	4031	7564	6984	26

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Chapter 3 Experimental

Asymmetric Synthesis of Bicyclic Amidines via Rhodium-Catalyzed [2+2+2] Cycloaddition of Carbodiimides

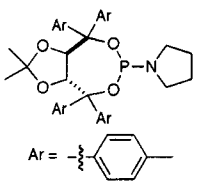
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine (peptide synthesis grade) was purchased from Fisher Scientific and used without further purification. Column chromatography was performed on Silicycle Inc. silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm) and/or potassium permanganate.

Alkynes **1a – 1d, 1f, 1h – 1o, 1s, 1t**, and **27** were purchased from Aldrich Chemicals Co. and used without further purification. Alkynes **1e** and **1g** are known compounds and can be synthesized from the corresponding aryl bromide or iodide via a typical Sonogashira procedure described previously.[1] Alkyne **1p** was prepared by a typical methylation using (trimethylsilyl)diazomethane solution (2.0 M in Et_2O) of the corresponding carboxylic acid, which was purchased from Aldrich Chemicals Co. Alkyne **1q** and **1r** were prepared by typical TBS-protection of the corresponding alcohols, which were purchased from Aldrich Chemicals Co. Alkyne **1u** was prepared according to literature.[2] $[Rh(C_2H_4)_2Cl]_2$ and **L1** were purchased from Strem Chemical, Inc. and used without further purification. Synthesis of **L2** was described previously while **L4 – L6** can be synthesized by the procedure described within. All racemate products are obtained via

the same cycloaddition using the *rac*-**L4** as the ligand. Carbodiimides **2a – 2f**, **21**, and **24** can be synthesized by the procedures described within.

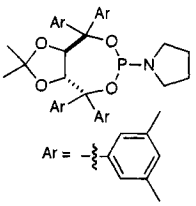
General procedure for synthesis of ligands:

To a flame-dried round bottom flask charged with a magnetic stir bar was added 4 Å molecular sieves, the diol (2.11 mmol) and 9 ml of THF. To the reaction mixture was added Et_3N (3.40 eq, 7.17 mmol) and phosphorus trichloride (1.2 eq, 2.53 mmol) dropwise at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 40 minutes. A solution of amine (10 eq, 21.10 mmol) in 11 ml of THF was added slowly at 0 °C. The reaction was allowed to stir overnight at ambient temperature before it was diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo and the resulting crude material was purified by flash column chromatography (4:96 EtOAc:Hexane) to afford the desired phosphoramidite as a white solid.

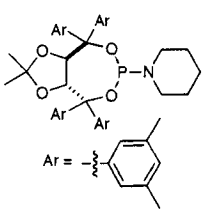


1-[4,4,8,8-Tetrakis-(4-methyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-pyrrolidine (L4). Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid (45%). R_f = 0.50 (90:10 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -109.4 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.1 Hz), 7.46 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.1 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 7.11-7.01 (6H, m) 7.04 (2H, d, 8.1 Hz), 5.15 (1H, dd, *J* = 8.5, 3.4 Hz), 4.76 (1H, d, *J* = 8.5 Hz), 3.41-3.37 (2H, m), 3.25-3.21 (2H, m), 2.31 (3H, s), 2.31 (3H, s), 2.30 (3H, s), 2.28 (3H, s) 1.83-1.78 (4H, m), 1.31 (3H, s), 0.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.2, 139.6, 139.5, 137.0, 136.8, 136.6, 129.1, 129.0, 128.8, 128.5, 128.4, 128.0, 127.2, 127.2, 126.3, 111.6, 83.1, 82.8, 82.6, 81.6, 81.1, 45.2,

45.0, 27.8, 26.2, 26.2, 25.6, 21.3, 21.3, 21.2; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.74; IR (Thin Film) 2924, 2862, 1507, 1452, 1377, 1247, 1161, 1044, 907 cm^{-1}.



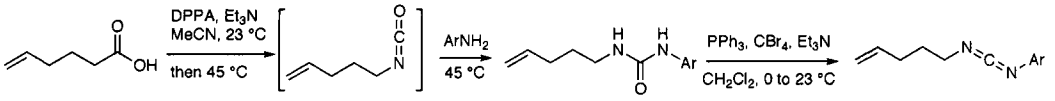
1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-pyrrolidine (L5). Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid (50%). R_f = 0.50 (90:10 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -108.0 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, s), 7.16 (2H, s), 7.04 (2H, s), 7.02 (2H, s), 6.84 (3H, s), 6.80 (1H, s), 5.08 (1H, dd, *J* = 8.5, 2.5 Hz), 4.74 (1H, d, *J* = 8.0 Hz), 3.47-3.35 (2H, m), 3.35-3.15 (2H, m), 2.27 (6H, s), 2.25 (12H, s), 2.24 (6H, s), 1.86-1.72 (4H, m), 1.32 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.9, 142.2, 142.1, 137.3, 136.9, 136.7, 136.3, 129.2, 128.9, 128.7, 127.9, 127.0, 126.8, 125.3, 125.2, 111.7, 83.1 (d, *J* = 4.5 Hz), 82.9, 82.7, 81.8, 81.1 (d, *J* = 5.5 Hz), 45.1 (d, *J* = 19.0 Hz), 27.9, 26.3, 26.2, 25.7, 21.9, 21.8; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.40; IR (Thin Film) 2917, 2866, 1601, 1456, 1379, 1214, 1159, 1042, 854 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 678.3707, found 678.3702.



(*R*,*R*)-1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-piperidine (L6) Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid (52%); R_f = 0.50 (90:10 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -108.0 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, s), 7.20 (2H, s), 7.04 (4H, s), 6.84 (3H, s), 6.79 (1H, s), 5.02 (1H, dd, *J* = 8.5, 3.0 Hz), 4.67 (1H, d, *J* = 8.5 Hz), 3.34-3.27 (2H, m), 3.20-3.08 (2H, m), 2.26 (6H, s), 2.26 (6H, s), 2.25 (6H, s), 2.24 (6H, s), 1.65-1.50 (6H, m), 1.37 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.0, 142.1, 137.3,

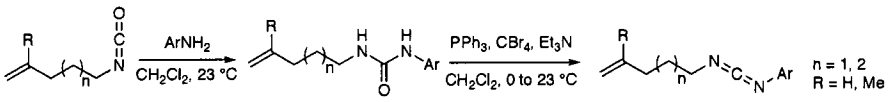
136.9, 136.7, 136.4, 129.2, 128.9, 128.8, 128.7, 127.1, 126.8, 125.3, 111.5, 83.3, 82.9, 82.7, 81.4, 81.3, 81.2, 77.4, 45.3, 45.1, 27.9, 27.2, 27.2, 25.7, 25.5, 21.9, 21.8, 21.7; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.76; IR (Thin Film) 2931, 2851, 1600, 1448, 1370, 1215, 1159, 1040, 940 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 692.3863, found 692.3843.

General procedure for synthesis of carbodiimides:

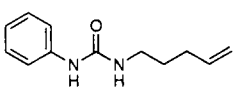


Procedure A: To a solution of 5-hexenoic acid (5.26 mmol) in 6 ml of MeCN (ca. 1 M) was added 0.77 ml of Et_3N (1.06 eq, 5.57 mmol) slowly, followed by 1.2 ml of diphenyl phosphoryl azide (1.06 eq, 5.57 mmol) dropwise at ambient temperature. The reaction mixture was stirred at ambient temperature for 30 minutes before heated to 45 °C in an oil bath. The reaction mixture was stirred at 45 °C for additional two hours to ensure complete conversion to the isocyanate. The amine (1.2 eq, 6.31 mmol) was added, and the resulting reaction mixture was stirred at 45 °C for 12 hours fitted with a reflux condenser. The reaction was diluted with Et_2O (40 ml), washed with 1M HCl (2x20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The urea was then purified by silica gel flash chromatography (70:30 Hexane:EtOAc). To a solution of the urea (1.76 mmol) in 14 ml of CH_2Cl_2 was added triphenyl phosphine (2.0 eq, 3.53 mmol), 1.0 ml of Et_3N (4.0 eq, 7.05 mmol), followed by a solution of CBr_4 (2.0 eq, 3.53 mmol) in 5 ml of CH_2Cl_2 slowly at 0 °C. The reaction mixture was stirred at ambient temperature for 12 hours and then concentrated *in vacuo*. The target carbodiimide was purified by silica gel flash chromatography (96:4

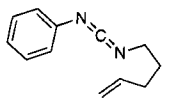
Hexane:EtOAc). Note: Two consecutive purifications of flash chromatography are recommended, as the purity of carbodiimides is vital to the success of cycloaddition.



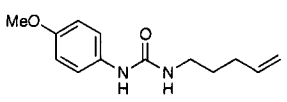
Procedure B: To a solution of isocyanate[3] (2.70 mmol) in 12 ml of CH_2Cl_2 was added the amine (1.05 eq, 2.83 mmol). The reaction mixture was stirred at ambient temperature for 12 hours and then concentrated *in vacuo*. The crude material was dissolved in Et_2O followed by addition of Hexane. The urea was then precipitated and filtered as a white solid. To a solution of the urea (1.76 mmol) in 14 ml of CH_2Cl_2 was added triphenyl phosphine (2.0 eq, 3.53 mmol), 1.0 ml of Et_3N (4.0 eq, 7.05 mmol), followed by a solution of CBr_4 (2.0 eq, 3.53 mmol) in 5 ml of CH_2Cl_2 slowly at 0 °C. The reaction mixture was stirred at ambient temperature for 12 hours and then concentrated *in vacuo*. The target carbodiimide was purified by silica gel flash chromatography (96:4 Hexane:EtOAc). Note: Two consecutive purifications of flash chromatography are recommended, as the purity of carbodiimides is vital to the success of cycloaddition.



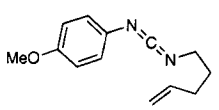
1-(pent-4-enyl)-3-phenylurea. Procedure B yielded a white solid (81%); R_f = 0.56 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.26 – 7.22 (m, 4H), 7.01 (m, 1H), 5.73 (ddt, 1H, *J* = 6.6, 10.2, 16.6 Hz), 5.58 (m, 1H), 4.99 – 4.92 (m, 2H), 3.18 (dt, 2H, *J* = 6.4, 6.4 Hz), 2.03 (dt, 2H, *J* = 7.2, 7.2 Hz), 1.54 (tt, 2H, *J* = 7.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 139.1, 138.0, 129.3, 123.5, 120.8, 115.3, 39.9, 31.2, 29.5; IR (Thin Film) 3338, 2925, 1647, 1596, 1558, 1500, 1443, 1310, 1240 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 205.13353, found 205.13350.



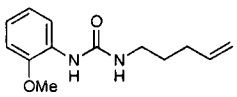
***N*-((pent-4-enylimino)methylene)aniline (2a).** Procedure B yielded an clear oil (66%); R_f = 0.63 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 2H, *J* = 7.5 Hz), 7.13 – 7.09 (m, 3H), 5.80 (ddt, 1H, *J* = 6.8, 10.2, 17.0 Hz), 5.07 (dm, 1H, *J* = 17.1 Hz), 5.02 (dm, 1H, *J* = 10.0 Hz), 3.44 (t, 2H, *J* = 6.8 Hz), 2.20 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.78 (tt, 2H, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 137.4, 136.3, 129.6, 124.8, 123.7, 115.9, 46.3, 31.0, 30.6; IR (Thin Film) 2931, 2135, 1595, 1502, 1344, 1153 cm^{-1}.



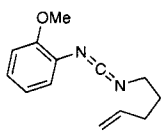
1-(4-methoxyphenyl)-3-(pent-4-enyl)urea. Procedure A yielded a white solid (52%); R_f = 0.33 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 2H, *J* = 7.7 Hz), 6.92 (m, 1H), 6.79 (d, 2H, *J* = 7.8 Hz), 5.73 (m, 1H), 5.16 (m, 1H), 4.97 – 4.89 (m, 2H), 3.74 (s, 3H), 3.16 (m, 2H), 2.01 (dt, 2H, *J* = 6.2, 6.2 Hz), 1.52 (tt, 2H, *J* = 6.6, 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 156.8, 138.1, 131.4, 124.5, 115.2, 114.6, 55.7, 40.0, 31.3, 29.5; IR (Thin Film) 3313, 2938, 1634, 1570, 1513, 1297, 1246, 1176, 1030 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 235.14410, found 235.14350.



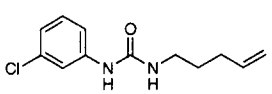
4-methoxy-*N*-((pent-4-enylimino)methylene)aniline (2b). Procedure A yielded an clear oil (46%); R_f = 0.26 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 5.80 (ddt, 1H, *J* = 6.6, 10.0, 16.8 Hz), 5.05 (dm, 1H, *J* = 17.3 Hz), 5.01 (dm, 1H, *J* = 10.0 Hz), 3.78 (s, 3H), 3.40 (t, 2H, *J* = 6.8 Hz), 2.19 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.76 (tt, 2H, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 137.5, 137.3, 133.2, 124.5, 115.8, 114.8, 55.7, 46.4, 31.0, 30.6; IR (Thin Film) 2936, 2129, 1582, 1507, 1289, 1240, 1170, 1033 cm^{-1}.



1-(2-methoxyphenyl)-3-(pent-4-enyl)urea. Procedure A yielded a white solid (59%); R_f = 0.53 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, 1H, *J* = 1.9, 7.7 Hz), 7.03 (s, 1H), 6.98 – 6.90 (m, 2H), 6.84 (dd, 2H, *J* = 1.7, 7.7 Hz), 5.78 (ddt, 1H, *J* = 6.6, 10.2, 17.1 Hz), 5.21 (m, 1H), 5.01 (dm, 1H, *J* = 17.0 Hz), 4.96 (dm, 1H, *J* = 10.2 Hz), 3.81 (s, 3H), 3.26 (dt, 2H, *J* = 6.7, 6.7 Hz), 2.09 (dt, 2H, *J* = 7.2, 7.2 Hz), 1.62 (tt, 2H, *J* = 7.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 148.5, 138.1, 128.9, 122.7, 121.4, 119.9, 115.3, 110.4, 55.8, 40.0, 31.3, 29.5; IR (Thin Film) 3326, 2933, 1640, 1602, 1564, 1462, 1284, 1252, 1170, 1025 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 235.14410, found 235.14318.

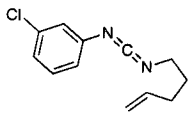


2-methoxy-*N*-((pent-4-enylimino)methylene)aniline (2c). Procedure A yielded an clear oil (72%); R_f = 0.29 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (ddd, 1H, *J* = 1.5, 7.7, 7.7 Hz), 7.02 (dd, 1H, *J* = 1.6, 8.1 Hz), 6.89 – 6.85 (m, 2H), 5.81 (ddt, 1H, *J* = 6.6, 10.0, 16.8 Hz), 5.07 (dm, 1H, *J* = 17.0 Hz), 5.00 (dm, 1H, *J* = 10.2 Hz), 3.89 (s, 3H), 3.41 (t, 2H, *J* = 6.8 Hz), 2.20 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.77 (tt, 2H, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 137.7, 137.1, 129.1, 125.5, 124.8, 121.2, 115.6, 111.3, 56.1, 46.4, 31.1, 30.4; IR (Thin Film) 2936, 2135, 1589, 1502, 1464, 1344, 1245, 1109, 1027 cm^{-1}.

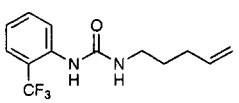


1-(3-chlorophenyl)-3-(pent-4-enyl)urea. Procedure A yielded a yellow oil (51%); R_f = 0.63 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.33 (s, 1H), 7.13 – 7.11 (m, 2H), 6.96 (m, 1H), 5.77 (m, 1H), 5.73 (ddt, 1H, *J* = 6.6, 10.0, 16.8 Hz), 5.00 – 4.85 (m, 2H), 3.18 (dt, 2H, *J* = 6.8, 6.8 Hz), 2.03 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.53 (tt, 2H, *J* = 7.2, 7.2 Hz); ^{13}C NMR (100 MHz,

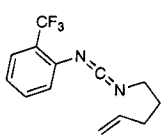
$CDCl_3$) δ 156.5, 140.4, 137.8, 134.8, 130.2, 123.1, 120.1, 118.0, 115.4, 39.9, 31.2, 29.3; IR (Thin Film) 3326, 2931, 1653, 1595, 1558, 1475, 1271, 1233, 1093, 1074 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 239.09456, found 239.09391.



3-chloro-*N*-((pent-4-enylimino)methylene)aniline (2d). Procedure A yielded an clear oil (55%); R_f = 0.57 (10:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.08 – 7.06 (m, 2H), 6.96 (dm, 1H, *J* = 8.1 Hz), 5.80 (ddt, 1H, *J* = 6.8, 10.2, 17.1 Hz), 5.09 – 5.01 (m, 2H), 3.46 (t, 2H, *J* = 6.8 Hz), 2.20 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.78 (tt, 2H, *J* = 6.8, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 137.2, 134.9, 134.8, 130.4, 124.9, 123.9, 121.9, 116.0, 46.2, 31.0, 30.5; IR (Thin Film) 2936, 2140, 1589, 1485, 1344, 1164, 1109 cm^{-1}.

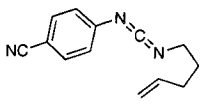


1-(pent-4-enyl)-3-(2-(trifluoromethyl)phenyl)urea. Procedure A yielded a white solid (70%); R_f = 0.47 (7:3 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, *J* = 7.9 Hz), 7.56 (d, 1H, *J* = 7.7 Hz), 7.47 (dd 1H, *J* = 7.7, 7.7 Hz), 7.20 – 7.16 (m, 2H), 6.85 (m, 1H), 5.75 (ddt, 1H, *J* = 6.6, 10.2, 16.8 Hz), 5.01 – 4.92 (m, 2H), 3.17 (dt, 2H, *J* = 6.8, 6.8 Hz), 2.04 (dt, 2H, *J* = 6.8, 6.8 Hz), 1.56 (tt, 2H, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 137.9, 136.5, 133.0, 129.6, 126.3, 125.5, 124.0, 120.4, 115.4, 40.2, 31.2, 29.1; IR (Thin Film) 3326, 2938, 1650, 1564, 1456, 1322, 1284, 1175, 1119, 1030 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 273.12092, found 273.12023.

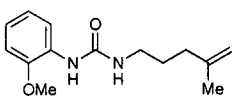


***N*-((pent-4-enylimino)methylene)-2-(trifluoromethyl)aniline (2e).** Procedure A yielded an clear oil (60%); R_f = 0.52 (95:5 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H, *J* = 7.9 Hz), 7.46 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.25 (d, 1H, *J* = 7.7 Hz), 7.15 (dd, 1H, *J* = 7.7, 7.7 Hz), 5.79 (ddt, 1H, *J* = 6.8, 10.2, 17.0 Hz),

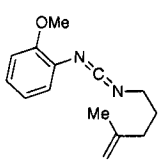
5.05 (dm, 1H, J = 17.3 Hz), 5.01 (dm, 1H, J = 10.8 Hz), 3.47 (t, 2H, J = 6.8 Hz), 2.19 (dt, 2H, J = 7.0, 7.0 Hz), 1.78 (tt, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.3, 132.8, 132.6, 127.0, 126.9, 125.5, 124.1, 122.4, 116.0, 46.0, 30.9, 30.4; IR (Thin Film) 2942, 2151, 1581, 1507, 1462, 1315, 1130, 1056 cm^{-1}.



4-((pent-4-enylimino)methyleneamino)benzonitrile (2f). After a quick flash chromatography, the crude urea was converted to the target carbodiimide according to Procedure A as an clear oil (25% overall); R_f = 0.18 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.3 Hz), 7.12 (d, 2H, J = 8.3 Hz), 5.79 (ddt, 1H, J = 6.6, 10.2, 17.1 Hz), 5.08 – 5.01 (m, 2H), 3.50 (t, 2H, J = 6.8 Hz), 2.19 (dt, 2H, J = 7.0, 7.0 Hz), 1.79 (tt, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 137.0, 133.6, 132.5, 124.3, 119.1, 116.2, 107.7, 46.0, 30.9, 30.4; IR (Thin Film) 2936, 2230, 2150, 1594, 1507, 1340, 1155 cm^{-1}.

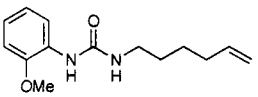


1-(2-methoxyphenyl)-3-(4-methylpent-4-enyl)urea. Procedure B yielded a white solid (67%); R_f = 0.54 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, 1H, J = 7.7 Hz), 6.98 – 6.90 (m, 3H), 6.84 (d, 2H, J = 7.9 Hz), 5.15 (m, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 3.82 (s, 3H), 3.25 (dt, 2H, J = 6.7, 6.7 Hz), 2.05 (t, 2H, J = 7.6 Hz), 1.70 (s, 3H), 1.67 (tt, 2H, J = 7.3, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.5, 145.3, 128.8, 122.7, 121.4, 120.0, 110.5, 110.4, 55.8, 40.3, 35.2, 28.2, 22.6; IR (Thin Film) 3326, 2938, 1640, 1602, 1558, 1462, 1431, 1246, 1106, 1025 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 249.15975, found 249.15873.

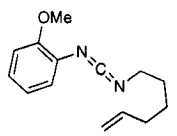


2-methoxy-*N*-((4-methylpent-4-enylimino)methylene)aniline (21). Procedure B yielded an clear oil (68%); R_f = 0.34 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (ddd, 1H, J = 1.5, 7.7, 7.7 Hz), 7.02 (dd,

1H, J = 1.5, 8.3 Hz), 6.88 – 6.85 (m, 2H), 4.75 (s, 1H), 4.71 (s, 1H), 3.89 (s, 3H), 3.40 (t, 2H, J = 6.8 Hz), 2.15 (t, 2H, J = 7.5 Hz), 1.82 (tt, 2H, J = 7.0, 7.0 Hz), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 144.9, 137.1, 129.2, 125.5, 124.8, 121.2, 111.3, 110.8, 56.0, 46.6, 35.1, 29.2, 22.6; IR (Thin Film) 2940, 2131, 1588, 1501, 1465, 1347, 1245, 1107, 1020 cm^{-1}.



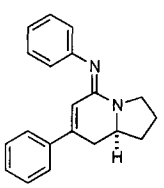
1-(hex-5-enyl)-3-(2-methoxyphenyl)urea. Procedure B yielded a white solid (80%); R_f = 0.53 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, 1H, J = 1.9, 7.7 Hz), 7.00 (s, 1H), 6.99 – 6.90 (m, 2H), 6.84 (dd, 2H, J = 1.7, 7.7 Hz), 5.77 (ddt, 1H, J = 6.8, 10.2, 17.1 Hz), 5.13 (m, 1H), 4.99 (dm, 1H, J = 17.1 Hz), 4.94 (dm, 1H, J = 10.2 Hz), 3.81 (s, 3H), 3.25 (dt, 2H, J = 6.7, 6.7 Hz), 2.05 (dt, 2H, J = 7.0, 7.0 Hz), 1.58 – 1.48 (m, 2H), 1.46 – 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.4, 138.7, 128.9, 122.6, 121.4, 119.8, 114.9, 110.3, 55.8, 40.4, 33.6, 29.8, 26.3; IR (Thin Film) 3319, 2931, 1640, 1602, 1551, 1456, 1240, 1214, 1170, 1030 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 249.15975, found 249.15959.



***N*-((hex-5-enylimino)methylene)-2-methoxyaniline (24).** Procedure B yielded an clear oil (70%); R_f = 0.32 (95:5 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, 1H, J = 7.5, 7.5 Hz), 7.02 (d, 1H, J = 8.1 Hz), 6.89 – 6.85 (m, 2H), 5.80 (ddt, 1H, J = 6.8, 10.2, 17.1 Hz), 5.01 (dm, 1H, J = 17.1 Hz), 4.96 (dm, 1H, J = 10.2 Hz), 3.88 (s, 3H), 3.40 (t, 2H, J = 6.8 Hz), 2.10 (dt, 2H, J = 6.9, 6.9 Hz), 1.74 – 1.66 (m, 2H), 1.58 – 1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 138.6, 137.1, 129.2, 125.5, 124.8, 121.2, 115.0, 111.3, 56.1, 47.0, 33.5, 30.8, 26.3; IR (Thin Film) 2936, 2132, 1594, 1501, 1464, 1342, 1242, 1107, 1025 cm^{-1}.

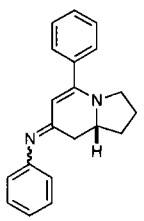
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl carbodiimides and terminal alkynes:

A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (1.8 mg, 0.0048 mmol) and the phosphoramidite ligand **L5** (6.5 mg, 0.0097 mmol), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml toluene was added via syringe and the resulting yellow solution was stirred at ambient temperature under argon flow for 15 minutes. To this solution was added a solution of alkyne **1** (0.322 mmol) and carbodiimide **2**, **21,** or **24** (0.161 mmol) in 1 ml of toluene via syringe or cannula. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 3 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo (no heat!), and purified by flash column chromatography (gradient elution typically 50:50 Hex:EtOAC, then 100% EtOAc, followed by 60:40:4 Hex:EtOAc:Et_3N). Evaporation of solvent afforded the analytically pure product **3**, **22**, or **25**. The minor products **4**, **23**, **26** were much more polar (basic), requiring 96:4 EtOAc:Et_3N for isolation. The minor products were typically a 2:1 or 3:1 mixture of imine isomers, and often contaminated with other by-products. For characterization purpose, products that can be isolated relatively clean such as **4aa, 4ab, 4ac, 23a, 4ne, 4nc**, and **4ue** analytical data are provided.[4] Others are not provided due to the impurities.

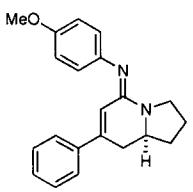


(*S*,*E*)-*N*-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3aa). General procedure with alkyne **1a** and carbodiimide **2a** yielded 32.5 mg of the cycloadduct (70%); R_f = 0.46 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 430.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0

ml/min, Major: 8.34 minutes, Minor: 7.22 minutes, 254 nm detection light, *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 7H), 6.99 (t, 1H, *J* = 7.5 Hz), 6.88 (d, 2H, *J* = 7.5 Hz), 6.42 (d, 1H, *J* = 2.6 Hz), 3.78 (m, 1H), 3.70 (m, 1H), 3.64 (m, 1H), 2.92 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.59 (ddd, 1H, *J* = 2.8, 13.2, 16.0 Hz), 2.29 (ddd, 1H, *J* = 5.5, 5.5, 11.3 Hz), 2.14 (m, 1H), 1.94 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.7, 145.4, 139.2, 129.0, 128.8, 126.0, 123.4, 122.0, 114.6, 56.4, 45.6, 33.8, 33.7, 23.3; IR (Thin Film) 2959, 1629, 1573, 1454, 1350, 1328 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 289.16992, found 289.16896.

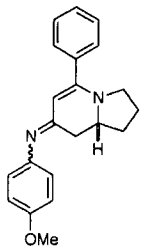


(*R*)-*N*-(5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (4aa). General procedure with alkyne **1a** and carbodiimide **2a** yielded 8.5 mg of the cycloadduct (18%) as a 3:1 mixture of the imine isomers; R_f = 0.28 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2967, 1600, 1575, 1489, 1452, 1235, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 289.16992, found 289.1702.

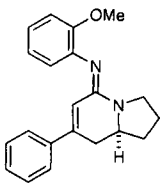


(*S*,*E*)-4-methoxy-*N*-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3ab). General procedure with alkyne **1a** and carbodiimide **2b** yielded 36.0 mg of the cycloadduct (70%); R_f = 0.43 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 329.0 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH with 0.1% diethyl amine, 1.0 ml/min, Major: 9.05 minutes, Minor: 8.06 minutes, 254 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 6.83 – 6.78 (m, 4H), 6.42 (d, 1H, *J* = 2.1 Hz), 3.79 (s, 3H), 3.75 (m, 1H), 3.68 (m, 1H), 3.60 (m, 1H), 2.90 (dd, 1H, *J* = 4.1, 16.2 Hz), 2.56 (m, 1H), 2.27 (ddd, 1H, *J* = 5.7, 5.7, 11.5 Hz), 2.13 (m, 1H), 1.92 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100

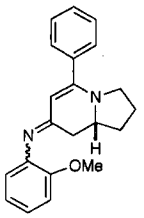
MHz, $CDCl_3$) δ 155.1, 152.5, 145.1, 144.0, 139.3, 128.9, 128.8, 125.9, 124.1, 114.6, 114.1, 56.4, 55.6, 45.5, 33.8, 33.6, 23.2; IR (Thin Film) 2954, 1627, 1571, 1496, 1446, 1322, 1235 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 319.18048, found 319.17926.



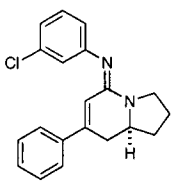
(*R*)-4-methoxy-*N*-(5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (4ab). General procedure with alkyne **1a** and carbodiimide **2b** yielded 9.2 mg of the cycloadduct (18%) as a 3:1 mixture of the imine isomers; R_f = 0.17 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2961, 1600, 1581, 1544, 1489, 1452, 1235, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 319.18048, found 319.1812.



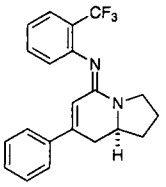
(*S*,*E*)-2-methoxy-*N*-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3ac). General procedure with alkyne **1a** and carbodiimide **2c** yielded 35.0 mg of the cycloadduct (68%); R_f = 0.49 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 330.1 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.35 minutes, Minor: 8.67 minutes, 210 nm detection light, *ee* = 98%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 6.96 (m, 1H), 6.88 – 6.83 (m, 2H), 6.77 (d, 1H, *J* = 7.5 Hz), 6.34 (m, 1H), 3.83 (m, 1H), 3.81 (s, 3H), 3.75 – 3.63 (m, 2H), 2.89 (dd, 1H, *J* = 4.0, 16.2 Hz), 2.57 (ddd, 1H, *J* = 2.3, 12.2, 15.8 Hz), 2.27 (ddd, 1H, *J* = 6.0, 6.0, 11.5 Hz), 2.12 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 146.1, 139.0, 134.3, 129.7, 129.2, 128.9, 126.0, 123.5, 121.9, 121.7, 114.3, 56.4, 45.5, 33.8, 33.7, 23.2; IR (Thin Film) 2946, 1635, 1579, 1491, 1441, 1328, 1240 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 319.18048, found 319.17991.



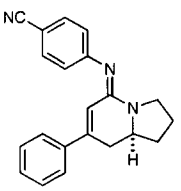
(*R*)-2-methoxy-*N*-(5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (4ac). General procedure with alkyne **1a** and carbodiimide **2c** yielded 7.2 mg of the cycloadduct (14%) as a 3:1 mixture of the imine isomers; R_f = 0.15 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2955, 1600, 1575, 1551, 1489, 1452, 1235, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 319.18048, found 319.1801.



(*S*,*E*)-3-chloro-*N*-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3ad). General procedure with alkyne **1a** and carbodiimide **2d** yielded 34.9 mg of the cycloadduct (67%); R_f = 0.60 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 391.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexane:iPrOH, 1.0 ml/min, Major: 8.90 minutes, Minor: 8.21 minutes, 254 nm detection light, *ee* = 97%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 5H), 7.15 (dd, 1H, *J* = 7.9, 8.1 Hz), 6.94 (d, 1H, *J* = 8.1 Hz), 6.93 (s, 1H), 6.74 (d, 1H, *J* = 7.9 Hz), 6.36 (d, 1H, *J* = 2.3 Hz), 3.76 – 3.67 (m, 2H), 3.57 (m, 1H), 2.92 (dd, 1H, *J* = 4.1, 16.2 Hz), 2.57 (ddd, 1H, *J* = 2.6, 13.6, 16.0 Hz), 2.28 (m, 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 146.1, 139.0, 134.3, 129.7, 129.2, 128.9, 126.0, 123.5, 121.9, 121.7, 114.3, 56.4, 45.5, 33.8, 33.7, 23.3; IR (Thin Film) 2959, 1623, 1573, 1447, 1353, 1328, 1278 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 323.13095, found 323.12911.

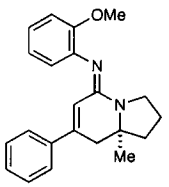


(*S*,*E*)-*N*-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-(trifluoromethyl)aniline (3ae). General procedure with alkyne **1a** and carbodiimide **2e** yielded 47.0 mg of the cycloadduct (82%); R_f = 0.56 (EtOAc); $[\alpha]_D^{20}$ = – 212.7 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexane:iPrOH, 1.0 ml/min, Major: 5.24 minutes, Minor: 5.54 minutes, 210 nm detection light, *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 1H, *J* = 7.7 Hz), 7.38 – 7.32 (m, 6H), 7.01 (dd, 1H, *J* = 7.5, 7.7 Hz), 6.81 (d, 1H, *J* = 7.9 Hz), 6.16 (d, 1H, *J* = 2.6 Hz), 3.76 – 3.68 (m, 2H), 3.62 (m, 1H), 2.90 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.58 (m, 1H), 2.29 (m, 1H), 2.13 (m, 1H), 1.94 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 150.2, 146.1, 139.1, 132.1, 129.0, 128.8, 126.5, 126.4, 126.1, 126.0, 124.7, 123.4, 123.1, 121.3, 114.7, 56.4, 45.3, 33.9, 33.7, 23.2; IR (Thin Film) 2963, 1633, 1578, 1559, 1443, 1248, 1126 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 357.15730, found 357.15647.

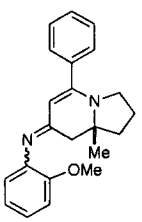


(*S*,*E*)-4-(7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylideneamino)benzonitrile (3af). General procedure with alkyne **1a** and carbodiimide **2f** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 28.0 mg of the cycloadduct (55%); R_f = 0.12 (EtOAc); $[\alpha]_D^{20}$ = – 413.2 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 11.26 minutes, Minor: 12.37 minutes, 210 nm detection light, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J* = 8.3 Hz), 7.38 – 7.34 (m, 5H), 6.88 (d, 2H, *J* = 8.3 Hz), 6.29 (d, 1H, *J* = 2.6 Hz), 3.78 – 3.70 (m, 2H), 3.56 (m, 1H), 2.95 (dd, 1H, *J* = 4.3, 16.4 Hz), 2.60 (ddd, 1H, *J* = 2.8, 13.4, 16.2 Hz), 2.32 (ddd, 1H, *J* = 6.0, 6.0, 11.9 Hz), 2.15 (m, 1H), 1.93 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 152.0, 146.8, 138.7, 133.1, 129.4, 129.0, 125.9, 124.0, 120.4, 114.1, 104.2, 56.3, 45.6, 33.7,

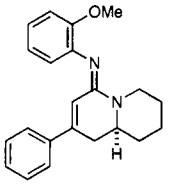
23.2; IR (Thin Film) 2963, 2218, 1626, 1553, 1456, 1322, 1273, 1163 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 314.16468, found 314.16517.



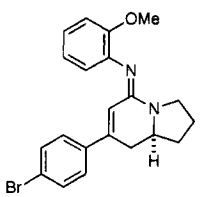
(*S*,*E*)-2-methoxy-*N*-(8a-methyl-7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (22a). General procedure with alkyne **1a** and carbodiimide **21** yielded 34.3 mg of the cycloadduct (64%); R_f = 0.44 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 249.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 6.74 minutes, Minor: 8.76 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 6.95 (m, 1H), 6.87 – 6.83 (m, 2H), 6.77 (d, 1H, *J* = 7.7 Hz), 6.30 (m, 1H), 3.79 (s, 3H), 3.79 – 3.65 (m, 2H), 2.83 (d, 1H, *J* = 16.2 Hz), 2.77 (dd, 1H, *J* = 2.1, 16.2 Hz), 2.11 – 2.04 (m, 3H), 1.93 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.8, 143.3, 140.4, 139.9, 128.7, 126.0, 124.6, 122.6, 120.8, 114.7, 111.5, 60.2, 55.9, 45.1, 40.9, 40.8, 23.1, 21.7; IR (Thin Film) 2963, 1626, 1578, 1486, 1431, 1236, 1169 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 333.19614, found 333.19614.



(*R*)-2-methoxy-*N*-(8a-methyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (23a). General procedure with alkyne **1a** and carbodiimide **21** yielded 10.8 mg of the cycloadduct (20%) as a 2:1 mixture of the imine isomers; R_f = 0.36 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2967, 1600, 1575, 1551, 1489, 1452, 1241, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 333. 19614, found 333.1963.

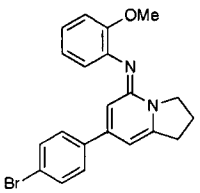


(*S*,*E*)-2-methoxy-*N*-(2-phenyl-1*H*-quinolizin-4(6*H*,7*H*,8*H*,9*H*,9a*H*)-ylidene)aniline (25a). General procedure with alkyne **1a** and carbodiimide **24** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 23.0 mg of the cycloadduct (43%); R_f = 0.55 (65:35:4 Hex/EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 240.1 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 20.39 minutes, Minor: 11.03 minutes, 210 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 5H), 6.97 (m, 1H), 6.89 – 6.86 (m, 2H), 6.74 (d, 1H, *J* = 6.6 Hz), 6.26 (d, 1H, *J* = 1.7 Hz), 4.62 (dm, 1H, *J* = 12.8 Hz), 3.79 (s, 3H), 3.37 (m, 1H), 2.78 (dd, 1H, *J* = 4.9, 17.1 Hz), 2.71 (dd, 1H, *J* = 3.2, 13.2 Hz), 2.61 (ddd, 1H, *J* = 1.7, 10.4, 16.8 Hz), 1.87 – 1.80 (m, 3H), 1.72 – 1.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 151.7, 143.4, 140.4, 139.1, 128.9, 128.7, 125.8, 123.6, 122.8, 121.0, 113.7, 111.6, 56.0, 55.1, 45.3, 34.6, 33.6, 24.8, 24.1; IR (Thin Film) 2930, 1637, 1581, 1489, 1440, 1328, 1260 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 333.19614, found 333.19535.

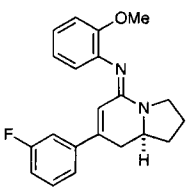


(*S*,*E*)-*N*-(7-(4-bromophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3bc). General procedure with alkyne **1b** and carbodiimide **2c** yielded 47.7 mg of the cycloadduct (75%); R_f = 0.45 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 345.1 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.44 minutes, Minor: 9.03 minutes, 210 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 8.3 Hz), 7.20 (d, 2H, *J* = 8.3 Hz), 6.98 (m, 1H), 6.88 – 6.83 (m, 2H), 6.77 (d, 1H, *J* = 7.2 Hz), 6.32 (m, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.75 – 3.63 (m, 2H), 2.83 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.55 (ddd, 1H, *J* = 2.3, 13.2, 15.8 Hz), 2.27 (ddd, 1H, *J* = 6.0, 6.0, 11.5 Hz), 2.24 (m,

1H), 1.92 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 143.7, 138.1, 131.9, 127.5, 124.5, 123.0, 120.8, 115.5, 111.3, 56.4, 55.9, 45.7, 33.6, 23.2; IR (Thin Film) 2938, 1620, 1578, 1431, 1320, 1230, 1108 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 397.09100, found 397.08916. X-ray data is attached at the end of this manuscript.

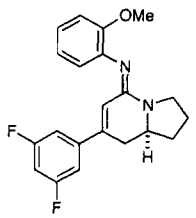


(*E*)-*N*-(7-(4-bromophenyl)-2,3-dihydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (20). R_f = 0.38 (96:4 EtOAc/Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.5 Hz), 7.24 (d, 2H, *J* = 8.6 Hz), 6.99 – 6.88 (m, 4H), 6.26 (s, 1H), 5.98 (s, 1H), 4.22 (t, 2H, *J* = 7.3 Hz), 3.78 (s, 3H), 3.04 (t, 2H, *J* = 7.8 Hz), 2.23 (tt, 2H, *J* = 7.7, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.4, 151.0, 147.6, 138.1, 132.0, 128.4, 124.0, 123.1, 122.8, 121.4, 111.8, 108.5, 97.8, 55.9, 50.0, 31.8, 21.5; IR (NaCl, $CDCl_3$) 1643, 1560, 1484, 1232, 1026 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 395.07535, found 395.07499.

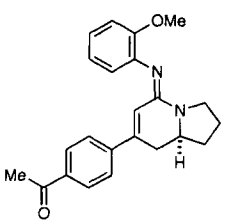


(*S*,*E*)-*N*-(7-(3-fluorophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3cc). General procedure with alkyne **1c** and carbodiimide **2c** yielded 41.9 mg of the cycloadduct (77%); R_f = 0.48 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 359.1 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 11.83 minutes, Minor: 8.45 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.12 (d, 1H, *J* = 7.9 Hz), 7.04 -- 6.95 (m, 3H), 6.88 – 6.83 (m, 2H), 6.74 (dd, 1H, *J* = 1.7, 7.7 Hz), 6.34 (d, 1H, *J* = 2.4 Hz), 3.82 (m, 1H), 3.81 (s, 3H), 3.73 – 3.61 (m, 2H), 2.83 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.55 (ddd, 1H, *J* = 2.6, 13.0, 15.8 Hz), 2.27 (ddd, 1H, *J* = 5.8, 5.8, 11.3 Hz), 2.12 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.8, 152.2, 152.1, 143.3, 141.8, 141.7, 139.9, 130.3, 130.2, 124.3, 122.8, 121.6, 120.8,

116.2, 115.7, 115.5, 113.0, 112.8, 111.3, 56.3, 55.9, 45.5, 33.8, 33.6, 23.2; IR (Thin Film) 2953, 1636, 1579, 1485, 1435, 1328, 1247, 1109 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 337.17106, found 337.17014.

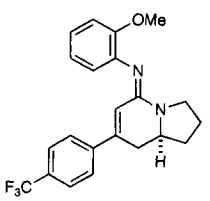


(*S*,*E*)-*N*-(7-(3,5-difluorophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3dc). General procedure with alkyne **1d** and carbodiimide **2c** yielded 37.7 mg of the cycloadduct (66%); R_f = 0.43 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 341.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 11.40 minutes, Minor: 8.20 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (m, 1H), 6.89 – 6.86 (m, 4H), 6.75 – 6.71 (m, 2H), 6.33 (d, 1H, *J* = 2.6 Hz), 3.81 (m, 1H), 3.81 (s, 3H), 3.73 – 3.60 (m, 2H), 2.78 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.54 (ddd, 1H, *J* = 2.6, 13.0, 16.0 Hz), 2.27 (ddd, 1H, *J* = 6.2, 6.2, 12.1 Hz), 2.13 (m, 1H), 1.92 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 152.2, 151.7, 142.2, 139.7, 124.2, 123.0, 120.8, 117.0, 111.4, 109.0, 108.8, 104.2, 103.9, 103.7, 56.2, 55.9, 45.6, 33.7, 33.6, 23.2; IR (Thin Film) 2938, 1626, 1596, 1443, 1322, 1242, 1120 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 355.16164, found 355.16026.

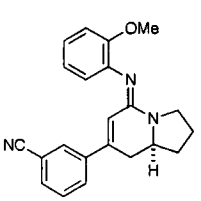


(*S*,*E*)-1-(4-(5-(2-methoxyphenylimino)-1,2,3,5,8,8a-hexahydroindolizin-7-yl)phenyl)ethanone (3ec). General procedure with alkyne **1e** and carbodiimide **2c** yielded 45.2 mg of the cycloadduct (78%); R_f = 0.37 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 352.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 25.11 minutes, Minor: 17.29 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 2H, *J* = 7.0 Hz), 7.42 (d, 2H, *J* = 7.0 Hz), 6.97 (m, 1H), 6.88 – 6.82 (m,

2H), 6.74 (d, 1H, J = 7.5 Hz), 6.42 (m, 1H), 3.82 (m, 1H), 3.81 (s, 3H), 3.75 – 3.66 (m, 2H), 2.88 (dd, 1H, J = 4.1, 16.0 Hz), 2.59 (m, 1H), 2.57 (s, 3H), 2.28 (ddd, 1H, J = 6.6, 6.6, 11.9 Hz), 2.13 (m, 1H), 1.92 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 152.2, 152.0, 143.9, 143.3, 139.8, 136.9, 128.8, 126.1, 124.3, 122.9, 120.8, 117.1, 111.3, 56.3, 55.9, 45.6, 33.7, 26.9, 23.2; IR (Thin Film) 2954, 1683, 1627, 1577, 1434, 1353, 1271, 1235, 1116 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 361.19105, found 361.19049.

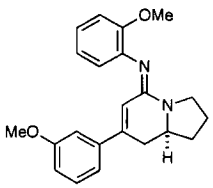


(*S*,*E*)-2-methoxy-*N*-(7-(4-(trifluoromethyl)phenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3fc). General procedure with alkyne **1f** and carbodiimide **2c** yielded 42.5 mg of the cycloadduct (68%); R_f = 0.44 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 303.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 9.49 minutes, Minor: 7.13 minutes, 210 nm detection light, *ee* = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.3 Hz), 7.43 (d, 2H, J = 8.1 Hz), 6.98 (m, 1H), 6.88 – 6.83 (m, 2H), 6.76 (d, 1H, J = 6.8 Hz), 6.38 (d, 1H, J = 2.3 Hz), 3.83 (m, 1H), 3.80 (s, 3H), 3.78 – 3.63 (m, 2H), 2.86 (dd, 1H, J = 4.3, 16.0 Hz), 2.60 (ddd, 1H, J = 2.4, 13.2, 15.8 Hz), 2.28 (ddd, 1H, J = 5.8, 5.8, 11.3 Hz), 2.14 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 152.0, 143.3, 142.9, 131.1, 130.5 126.2, 125.7, 125.7, 124.4, 123.1, 120.8, 117.0, 111.4, 56.3, 55.9, 45.7, 33.7, 33.6, 23.2; IR (Thin Film) 2948, 1625, 1581, 1439, 1328, 1235, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 387.16787, found 387.16857.



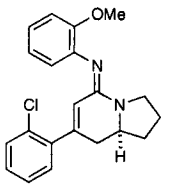
(*S*,*E*)-3-(5-(2-methoxyphenylimino)-1,2,3,5,8,8a-hexahydroindolizin-7-yl)benzonitrile (3gc). General procedure with alkyne **1g** and

carbodiimide **2c** yielded 34.3 mg of the cycloadduct (62%); R_f = 0.49 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 280.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 21.14 minutes, Minor: 15.22 minutes, 210 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.57 – 7.54 (m, 2H), 7.42 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.98 (m, 1H), 6.89 – 6.84 (m, 2H), 6.73 (dd, 1H, *J* = 7.5 Hz), 6.35 (d, 1H, *J* = 2.3 Hz), 3.82 (m, 1H), 3.81 (s, 3H), 3.76 – 3.61 (m, 2H), 2.82 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.59 (ddd, 1H, *J* = 2.6, 13.2, 15.8 Hz), 2.28 (m, 1H), 2.12 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.7, 142.2, 140.8, 139.7, 132.0, 130.2, 129.7, 129.5, 124.2, 123.0, 120.9, 118.7, 117.1, 113.1, 111.4, 56.2, 55.9, 45.6, 33.7, 33.6, 23.2; IR (Thin Film) 2953, 2225, 1629, 1573, 1485, 1435, 1328, 1234, 1115 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 344.17573, found 344.17469.

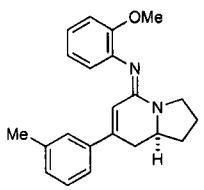


(*S*,*E*)-2-methoxy-*N*-(7-(3-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3hc). General procedure with alkyne **1h** and carbodiimide **2c** yielded 38.8 mg of the cycloadduct (69%); R_f = 0.40 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 280.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 15.51 minutes, Minor: 11.07 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.98 – 6.93 (m, 2H), 6.87 – 6.84 (m, 2H), 6.83 (s, 1H), 6.77 (dd, 1H, *J* = 7.5 Hz), 6.33 (m, 1H), 3.82 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 – 3.63 (m, 2H), 2.86 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.56 (ddd, 1H, *J* = 2.1, 13.0, 15.6 Hz), 2.26 (ddd, 1H, *J* = 6.0, 6.0, 11.7 Hz), 2.12 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 152.5, 152.4, 144.7, 140.9, 129.8, 124.5, 122.9, 120.8, 118.5, 115.5, 113.8, 112.0, 111.3, 56.4, 55.9, 55.5, 45.7, 33.9, 33.6, 23.2; IR (Thin Film)

2947, 1633, 1583, 1490, 1440, 1328, 1253, 1116 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 349.19105, found 349.19044.

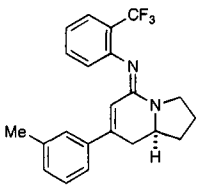


(*S*,*E*)-*N*-(7-(2-chlorophenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3ic). General procedure with alkyne **1i** and carbodiimide **2c** yielded 20.1 mg of the cycloadduct (35%); R_f = 0.42 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 62.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 9.44 minutes, Minor: 8.31 minutes, 210 nm detection light, *ee* = 31%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1H), 7.20 – 7.14 (m, 2H), 7.07 (m, 1H), 6.90 (m, 1H), 6.82 – 6.74 (m, 3H), 5.99 (d, 1H, *J* = 2.6 Hz), 3.84 – 3.74 (m, 2H), 3.78 (s, 3H), 3.63 (m, 1H), 2.70 (dd, 1H, *J* = 4.3, 16.1 Hz), 2.58 (ddd, 1H, *J* = 2.8, 13.0, 16.0 Hz), 2.21 (ddd, 1H, *J* = 5.5, 5.5, 11.5 Hz), 2.09 (m, 1H), 1.89 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 145.4, 140.1, 130.0, 129.8, 129.3, 127.0, 124.4, 122.8, 120.7, 119.4, 111.1, 56.6, 55.8, 45.6, 35.7, 33.5, 23.3; IR (Thin Film) 2936, 1641, 1577, 1440, 1234 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 352.13424, found 352.13397.

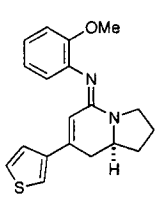


(*S*,*E*)-2-methoxy-*N*-(7-*m*-tolyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3lc). General procedure with alkyne **1l** and carbodiimide **2c** yielded 32.8 mg of the cycloadduct (61%); R_f = 0.47 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 349.2 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 11.50 minutes, Minor: 8.21 minutes, 210 nm detection light, *ee* = 98%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.2 – 7.16 (m, 3H), 7.11 (d, 1H, *J* = 7.3 Hz), 6.97 (m, 1H), 6.88 – 6.83 (m, 2H), 6.78 (d, 1H, *J* = 7.5 Hz), 6.32 (d, 1H, *J* = 2.1 Hz), 3.84 (m, 1H), 3.82 (s, 3H), 3.74 – 3.63 (m, 2H), 2.88 (dd, 1H, *J* = 4.3,

16.2 Hz), 2.57 (ddd, 1H, J = 2.6, 13.2, 16.0 Hz), 2.32 (s, 3H), 2.26 (ddd, 1H, J = 5.8, 5.8, 11.7 Hz), 2.12 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.4, 145.0, 139.4, 138.4, 129.6, 128.7, 126.7, 124.5, 123.1, 122.8, 120.8, 115.1, 111.2, 56.4, 55.9, 45.7, 33.9, 33.7, 23.2, 21.7; IR (Thin Film) 2942, 1631, 1569, 1489, 1439, 1322, 1235, 1114 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 333.19614, found 333.19545.

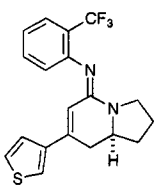


(*S*,*E*)-*N*-(7-*m*-tolyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-(trifluoromethyl)aniline (3le). General procedure with alkyne **1l** and carbodiimide **2e** yielded 44.0 mg of the cycloadduct (74%); R_f = 0.51 (EtOAc); $[\alpha]_D^{20}$ = – 230.2 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexane:iPrOH, 1.0 ml/min, Major: 4.81 minutes, Minor: 5.41 minutes, 210 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 7.5 Hz), 7.33 (dd, 1H, J = 7.6, 7.6 Hz), 7.18 (dd, 1H, J = 7.0, 7.0 Hz), 7.14 – 7.08 (m, 3H), 6.98 (dd, 1H, J = 7.5, 7.5 Hz), 6.79 (d, 1H, J = 7.5 Hz), 6.11 (m, 1H), 3.74 – 3.65 (m, 2H), 3.58 (m, 1H), 2.86 (dm, 1H, J = 6.4 Hz), 2.55 (m, 1H), 2.30 (s, 3H), 2.25 (m, 1H), 2.10 (m, 1H), 1.91 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 146.3, 139.2, 138.4, 132.1, 129.8, 128.7, 126.6, 126.5, 126.4, 124.7, 123.1, 121.2, 114.5, 56.4, 45.3, 34.1, 33.7, 23.2, 21.6; IR (Thin Film) 2961, 1631, 1594, 1563, 1439, 1310, 1124 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 371.17296, found 371.1734.

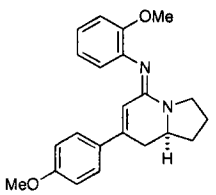


(*S*,*E*)-2-methoxy-*N*-(7-(thiophen-3-yl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3mc). General procedure with alkyne **1m** and carbodiimide **2c** yielded 30.6 mg of the cycloadduct (58%); R_f = 0.46 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 311.5 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column

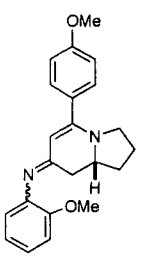
80:20 hexane:iPrOH, 1.0 ml/min, Major: 16.30 minutes, Minor: 10.22 minutes, 210 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.10 (d, 1H, *J* = 4.9 Hz), 6.98 (m, 1H), 6.88 – 6.86 (m, 2H), 6.78 (d, 1H, *J* = 7.5 Hz), 6.32 (m, 1H), 3.82 (m, 1H), 3.80 (s, 3H), 3.72 – 3.64 (m, 2H), 2.89 (dd, 1H, *J* = 4.0, 16.2 Hz), 2.50 (ddd, 1H, *J* = 1.7, 10.2, 15.3 Hz), 2.27 (ddd, 1H, *J* = 5.8, 5.8, 11.3 Hz), 2.10 (m, 1H), 1.91 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.4, 141.0, 139.3, 126.6, 125.4, 124.9, 122.8, 120.8, 113.8, 111.3, 56.2, 55.9, 45.7, 33.6, 23.2; IR (Thin Film) 2948, 1625, 1575, 1495, 1439, 1328, 1235, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 325.13691, found 325.13691.



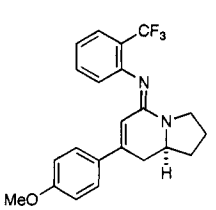
(*S*,*E*)-*N*-(7-(thiophen-3-yl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-(trifluoromethyl)aniline (3me). General procedure with alkyne **1m** and carbodiimide **2e** yielded 46.1 mg of the cycloadduct (79%); R_f = 0.46 (EtOAc); $[\alpha]_D^{20}$ = – 265.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexane(with 0.01% diethyl amine):iPrOH, 1.0 ml/min, Major: 6.31 minutes, Minor: 6.66 minutes, 254 nm detection light, *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 6.8 Hz), 7.34 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.25 – 7.23 (m, 2H), 7.04 (m, 1H), 6.99 (dd, 1H, *J* = 7.5, 7.5 Hz), 6.78 (d, 1H, *J* = 7.5 Hz), 6.11 (m, 1H), 3.74 – 3.64 (m, 2H), 3.57 (m, 1H), 2.88 (dm, 1H, *J* = 16.2 Hz), 2.49 (m, 1H), 2.26 (m, 1H), 2.08 (m, 1H), 1.91 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 140.8, 132.1, 126.7, 126.4, 125.3, 124.7, 123.1, 121.3, 113.1, 56.2, 45.4, 33.8, 33.7, 23.1; IR (Thin Film) 2967, 1631, 1587, 1563, 1439, 1315, 1247, 1123, 1031 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 363.11373, found 363.11471.



(*S*,*E*)-2-methoxy-*N*-(7-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3nc). General procedure with alkyne **1n** and carbodiimide **2c** yielded 11.2 mg of the cycloadduct (20%); R_f = 0.43 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 165.2 (c = 0.73, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 18.71 minutes, Minor: 12.56 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 2H, *J* = 8.8 Hz), 6.98 (m, 1H), 6.88 – 6.78 (m, 5H), 6.27 (m, 1H), 3.85 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.75 – 3.66 (m, 2H), 2.89 (dd, 1H, *J* = 4.0, 16.0 Hz), 2.52 (ddd, 1H, *J* = 2.4, 11.6, 16.0 Hz), 2.27 (ddd, 1H, *J* = 6.0, 6.0, 11.2 Hz), 2.12 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 160.3, 152.9, 152.5, 140.1, 131.4, 127.3, 124.7, 122.9, 120.8, 114.1, 113.3, 111.3, 56.5, 55.9, 55.5, 45.8, 33.6, 23.2; IR (Thin Film) 2954, 1627, 1577, 1515, 1440, 1241, 1179, 1116 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 349.19105, found 349.18953.

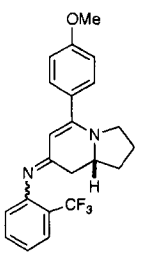


(*R*)-2-methoxy-*N*-(5-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (4nc). General procedure with alkyne **1n** and carbodiimide **2c** yielded 29.3 mg of the cycloadduct (52%) as a 2:1 mixture of the imine isomers; R_f = 0.17 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2954, 1602, 1577, 1509, 1453, 1247, 1172, 1116 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 349.19105, found 349.18960.

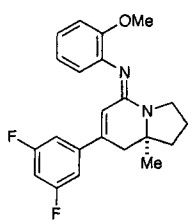


(*S*,*E*)-*N*-(7-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-(trifluoromethyl)aniline (3ne). General procedure with alkyne **1n** and carbodiimide **2e** yielded 23.0 mg of the cycloadduct

(37%); R_f = 0.79 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 236.7 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 4.98 minutes, Minor: 5.45 minutes, 210 nm detection light, *ee* = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 7.9 Hz), 7.34 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.32 – 7.23 (m, 2H), 6.98 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.84 – 6.78 (m, 3H), 6.06 (m, 1H), 3.77 (s, 3H), 3.75 – 3.63 (m, 2H), 3.58 (m, 1H), 2.87 (dd, 1H, *J* = 4.0, 16.2 Hz), 2.41 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 1.91 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 151.6, 145.5, 132.1, 131.3, 127.3, 126.4, 124.8, 121.2, 114.1, 112.9, 56.4, 55.6, 45.3, 33.8, 33.7, 23.2; IR (Thin Film) 2945, 1631, 1557, 1510, 1439, 1247, 1179, 1124 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 387.16787, found 387.16883.

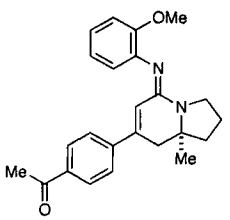


(*R*)-*N*-(5-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)-2-(trifluoromethyl)aniline (4ne). General procedure with alkyne **1n** and carbodiimide **2e** yielded 22.3 mg of the cycloadduct (36%) as a 3:1 mixture of the imine isomers; R_f = 0.56 (96:4 EtOAc/Et_3N); *ee* not determined; For its ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$), see ref 4; IR (Thin Film) 2961, 1600, 1563, 1513, 1443, 1247, 1172, 1117 cm^{-1}; HRMS (ESI) *m/e* calcd (M+H$^+$) 387.16787, found 387.16797.

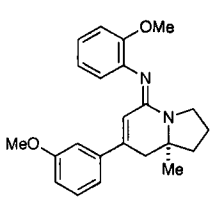


(*S,E*)-*N*-(7-(3,5-difluorophenyl)-8a-methyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (22d). General procedure with alkyne **1d** and carbodiimide **21** yielded 47.0 mg of the cycloadduct (79%); R_f = 0.53 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 253.6 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 6.41 minutes, Minor: 7.96 minutes, 210 nm detection light, *ee* = 98%; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.97 (m, 1H), 6.88 – 6.83 (m, 4H), 6.75 – 6.70 (m, 2H), 6.29 (m, 1H), 3.78 (s, 3H), 3.78 – 3.64 (m, 2H), 2.76 – 2.68 (m, 2H), 2.11 – 2.06 (m, 3H), 1.93 (m, 1H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.1, 152.1, 151.0, 124.4, 122.9, 120.9, 116.3, 111.6, 109.0, 108.8, 104.2, 103.9, 103.7, 60.1, 55.9, 45.1, 40.8, 40.6, 23.2, 21.7; IR (Thin Film) 2969, 1626, 1585, 1571, 1431, 1242, 1174, 1120 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 369.17729, found 369.17689.

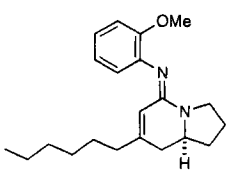


(*S*,*E*)-1-(4-(5-(2-methoxyphenylimino)-8a-methyl-1,2,3,5,8,8a-hexahydroindolizin-7-yl)phenyl)ethanone (22e). General procedure with alkyne **1e** and carbodiimide **21** yielded 45.0 mg of the cycloadduct (74%); R_f = 0.43 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 245.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 13.21 minutes, Minor: 16.64 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.1 Hz), 6.96 (m, 1H), 6.88 – 6.84 (m, 2H), 6.76 (d, 1H, *J* = 7.5 Hz), 6.38 (m, 1H), 3.79 (s, 3H), 3.79 – 3.65 (m, 2H), 2.83 – 2.78 (m, 2H), 2.58 (s, 3H), 2.14 – 2.06 (m, 3H), 1.93 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 152.2, 151.3, 144.4, 142.1, 140.2, 136.9, 128.8, 126.1, 124.5, 122.8, 120.9, 116.5, 111.5, 60.1, 55.9, 45.1, 40.9, 40.6, 26.9, 23.2, 21.7; IR (Thin Film) 2967, 1680, 1625, 1569, 1427, 1266, 1111 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 375.20670, found 375.20550.

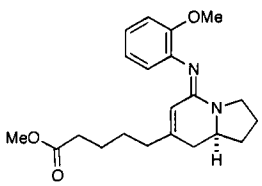


(*S*,*E*)-2-methoxy-*N*-(7-(3-methoxyphenyl)-8a-methyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (22h). General procedure with alkyne **1h** and carbodiimide **21** yielded 38.7 mg of the cycloadduct (66%); R_f = 0.49 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 244.0 (c = 1, $CHCl_3$);

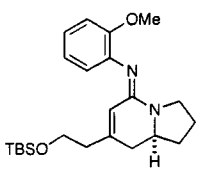
HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 7.95 minutes, Minor: 10.68 minutes, 210 nm detection light, *ee* = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, 1H, *J* = 8.0, 8.0 Hz), 6.96 – 6.92 (m, 2H), 6.86 – 6.82 (m, 4H), 6.77 (d, 1H, *J* = 7.7 Hz), 6.29 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.78 – 3.63 (m, 2H), 2.81 – 2.73 (m, 2H), 2.11 – 2.06 (m, 3H), 1.92 (m, 1H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 159.8, 152.3, 151.7, 143.2, 141.4, 129.8, 124.6, 122.6, 120.8, 118.5, 115.0, 113.7, 112.1, 111.4, 60.2, 55.9, 55.5, 45.1, 40.9, 23.1, 21.7; IR (Thin Film) 2957, 1626, 1577, 1492, 1430 1242, 1162, 1108 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 363.20670, found 363.20638.



(*S*,*E*)-*N*-(7-hexyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3oc). General procedure with alkyne **1o** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 38.8 mg of the cycloadduct (74%); R_f = 0.41 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 211.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 8.59 minutes, Minor: 7.05 minutes, 230 nm detection light, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 1H), 6.85 – 6.82 (m, 2H), 6.74 (d, 1H, *J* = 7.0 Hz), 5.72 (m, 1H), 3.79 (s, 3H), 3.77 (m, 1H), 3.62 – 3.51 (m, 2H), 2.29 (dd, 1H, *J* = 4.5, 16.2 Hz), 2.18 – 2.14 (m, 2H), 2.10 – 2.05 (m, 3H), 1.85 (m, 1H), 1.61 (m, 1H), 1.37 – 1.21 (m, 8H), 0.86 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.4, 149.3, 124.5, 122.5, 120.6, 114.5, 111.2, 56.5, 55.8, 45.5, 37.2, 34.7, 33.6, 31.8, 29.0, 27.2, 23.2, 22.8, 14.3; IR (Thin Film) 2928, 1651, 1583, 1490, 1440, 1322, 1247, 1116 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 327.24309, found 327.24281.

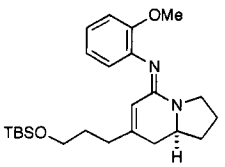


(*S*,*E*)-methyl 5-(5-(2-methoxyphenylimino)-1,2,3,5,8,8a-hexahydroindolizin-7-yl)pentanoate (3pc). General procedure with alkyne **1p** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 39.0 mg of the cycloadduct (68%); R_f = 0.42 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 212.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 19.00 minutes, Minor: 13.29 minutes, 230 nm detection light, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.85 – 6.81 (m, 2H), 6.70 (d, 1H, *J* = 7.7 Hz), 5.73 (m, 1H), 3.78 (s, 3H), 3.73 (m, 1H), 3.64 (s, 3H), 3.61 – 3.51 (m, 2H), 2.30 – 2.25 (m, 3H), 2.19 – 2.14 (m, 2H), 2.10 – 2.03 (m, 3H), 1.84 (m, 1H), 1.64 – 1.54 (m, 3H), 1.44 – 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 152.6, 152.3, 148.1, 140.3, 124.4, 122.4, 120.6, 115.0, 111.2, 56.4, 55.8, 51.7, 45.4, 36.8, 34.6, 33.9, 33.6, 26.7, 24.5, 23.2; IR (Thin Film) 2942, 1736, 1649, 1575, 1489, 1439, 1328, 1235, 1173 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 357.21726, found 357.21669.

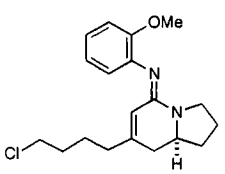


(*S*,*E*)-*N*-(7-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3qc). General procedure with alkyne **1q** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 49.3 mg of the cycloadduct (76%); R_f = 0.48 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 169.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 8.24 minutes, Minor: 5.98 minutes, 230 nm detection light, *ee* = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.84 – 6.81 (m, 2H), 6.70 (d, 1H, *J* = 7.7 Hz), 5.78 (d, 1H, *J* = 1.7 Hz), 3.79 (s, 3H), 3.73 (m, 1H), 3.65 (m, 2H), 3.62 – 3.52 (m, 2H), 2.38 (dd, 1H, *J* = 4.3, 16.4 Hz), 2.28 (t, 2H, *J* =

6.4 Hz), 2.21 – 2.13 (m, 2H), 2.04 (m, 1H), 1.85 (m, 1H), 1.60 (m, 1H), 0.85 (s, 9H), 0.003 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.4, 146.4, 140.3, 124.4, 122.4, 120.7, 116.0, 111.2, 61.8, 56.3, 55.8, 45.4, 40.4, 35.3, 33.6, 26.1, 23.1, 18.4, -5.22; IR (Thin Film) 2947, 1652, 1577, 1490, 1465, 1434, 1328, 1253, 1097 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 401.26188, found 401.26217.

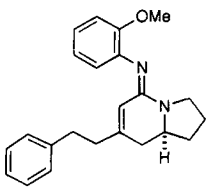


***(S,E)-N*-(7-(3-(tert-butyldimethylsilyloxy)propyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3rc).** General procedure with alkyne **1r** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 48.5 mg of the cycloadduct (73%); R_f = 0.49 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 181.1 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 7.21 minutes, Minor: 5.69 minutes, 230 nm detection light, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.85 – 6.81 (m, 2H), 6.71 (d, 1H, *J* = 7.6 Hz), 5.75 (m, 1H), 3.79 (s, 3H), 3.73 (m, 1H), 3.62 – 3.51 (m, 4H), 2.30 (dd, 1H, *J* = 4.4, 16.4 Hz), 2.20 – 2.10 (m, 5H), 2.05 (m, 1H), 1.85 (m, 1H), 1.66 – 1.56 (m, 3H), 0.86 (s, 9H), 0.006 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.4, 148.6, 140.4, 124.4, 122.4, 120.7, 114.6, 111.2, 62.6, 56.4, 55.8, 45.4, 34.9, 33.6, 30.5, 26.1, 23.2, 18.5, -5.13; IR (Thin Film) 2940, 1654, 1579, 1441, 1322, 1252, 1102 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 415.27753, found 415.27832.

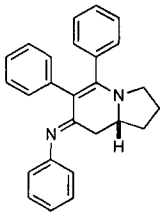


***(S,E)-N*-(7-(4-chlorobutyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-methoxyaniline (3sc).** General procedure with alkyne **1s** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 32.1 mg of the cycloadduct (60%); R_f = 0.46 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 179.6 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15

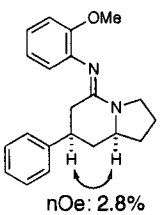
hexane:iPrOH, 1.0 ml/min, Major: 13.88 minutes, Minor: 11.04 minutes, 230 nm detection light, *ee* = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.86 – 6.83 (m, 2H), 6.73 (d, 1H, *J* = 7.5 Hz), 5.74 (m, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.62 – 3.53 (m, 2H), 3.49 (t, 2H, *J* = 6.4 Hz), 2.30 (dd, 1H, *J* = 4.5, 16.4 Hz), 2.20 – 2.05 (m, 5H), 1.86 (m, 1H), 1.74 – 1.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.4, 140.0, 124.4, 122.6, 120.7, 115.1, 111.2, 56.4, 55.8, 45.5, 44.8, 36.3, 34.6, 33.6, 32.0, 24.4, 23.2; IR (Thin Film) 2942, 1649, 1581, 1489, 1439, 1328, 1241, 1173, 1118 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 333.17281, found 333.17217.



(*S*,*E*)-2-methoxy-*N*-(7-phenethyl-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)aniline (3tc). General procedure with alkyne **1t** and carbodiimide **2c** in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% **L5** yielded 39.3 mg of the cycloadduct (70%); R_f = 0.47 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 219.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 17.02 minutes, Minor: 12.63 minutes, 230 nm detection light, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.18 (m, 1H), 7.10 (d, 2H, *J* = 7.9 Hz), 6.93 (m, 1H), 6.84 – 6.78 (m, 2H), 6.58 (d, 1H, *J* = 7.7 Hz), 5.75 (m, 1H), 3.78 (s, 3H), 3.74 (m, 1H), 3.61 – 3.52 (m, 2H), 2.72 – 2.61 (m, 2H), 2.42 – 2.38 (m, 2H), 2.31 (dd, 1H, *J* = 4.5, 16.4 Hz), 2.22 – 2.14 (m, 2H), 2.04 (m, 1H), 1.85 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.4, 147.7, 141.2, 140.2, 128.6, 128.5, 126.3, 124.4, 122.4, 120.6, 115.2, 111.2, 56.3, 55.8, 45.4, 39.0, 35.0, 33.8, 33.6, 23.2; IR (Thin Film) 2930, 1649, 1581, 1489, 1439, 1328, 1247, 1118 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 342.21179, found 342.21059.

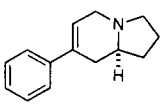


(*R*,*E*)-*N*-(5,6-diphenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)aniline (28). General procedure with alkyne **27** and carbodiimide **2a** yielded 39.0 mg of the cycloadduct (66%); R_f = 0.51 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = + 630.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 10.66 minutes, Minor: 7.28 minutes, 210 nm detection light, *ee* = 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 6.89 (m, 13H), 6.71 (d, 2H, *J* = 7.9 Hz), 3.82 (dddd, 1H, *J* = 3.6, 7.0, 7.0, 14.5 Hz), 3.30 (ddd, 1H, *J* = 3.5, 7.5, 10.9 Hz), 2.95 (ddd, 1H, *J* = 7.5, 7.5, 10.4 Hz), 2.69 (dd, 1H, *J* = 3.8, 15.1 Hz), 2.27 (dd, 1H, *J* = 14.9, 14.9 Hz), 2.21 (m, 1H), 1.92 – 1.73 (m, 2H), 1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 153.9, 152.9, 138.9, 137.3, 133.0, 130.0, 128.6, 128.1, 127.9, 127.2, 125.0, 122.1, 121.0, 56.5, 49.9, 32.8, 32.5, 24.4; IR (Thin Film) 2968, 1578, 1536, 1481, 1446, 1312, 1201 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 364.19395, found 364.19352.

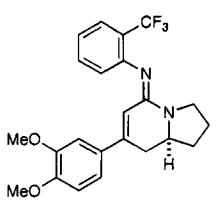


(*E*)-2-methoxy-*N*-((7*R*,8a*S*)-7-phenylhexahydroindolizin-5(1*H*)-ylidene)aniline (29). A mixture of **3ac** (29.1 mg, 0.0914 mmol) and 34 mg of 10% Pd/C in 3 ml of MeOH was stirred at ambient temperature under hydrogen atmosphere (1 atm) for 3 hours. The reaction mixture was filtered through celite and concentrated *in vacuo*. Upon purification by column chromatography 27.0 mg (92%) of the desired product was isolated; R_f = 0.44 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 155.0 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.19 – 7.12 (m, 3H), 6.87 (ddd, 1H, *J* = 1.7, 7.7, 7.7 Hz), 6.82 – 6.74 (m, 3H), 3.79 (s, 3H), 3.74 – 3.66 (m, 2H), 3.54 (dddd, 1H, *J* = 4.1, 4.1, 10.9, 10.9 Hz), 2.94 (dddd, 1H, *J* = 3.3, 5.3, 12.2, 17.7 Hz), 2.55 (dd, 1H, *J* = 5.3, 16.8 Hz), 2.27 – 2.20 (m,

2H), 2.12 (m, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.66 – 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 151.6, 145.0, 140.5, 128.8, 126.9, 126.8, 124.1, 122.4, 121.1, 111.5, 59.3, 55.8, 46.4, 39.9, 36.8, 34.3, 33.7, 22.8; IR (Thin Film) 2932, 1602, 1584, 1462, 1443, 1320, 1242, 1110 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 321.19614, found 321.19721.

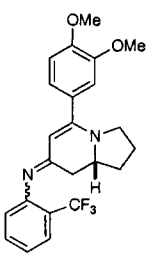


(*S*)-7-phenyl-1,2,3,5,8,8a-hexahydroindolizine (30). To a solution of **3ac** (33.0 mg, 0.104 mmol) in 2 ml of anhydrous THF was added 0.5 ml of 1M DIBAL solution (in hexane) at 0 °C. The reaction mixture was stirred at ambient temperature until the disappearance of starting material. The reaction was quenched with H_2O and then 2N NaOH, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Upon purification by column chromatography 15.0 mg (72%) of the desired product was isolated; R_f = 0.36 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = + 85.3 (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H, *J* = 7.6 Hz), 7.32 (t, 2H, *J* = 7.6 Hz), 7.23 (t, 1H, *J* = 7.2 Hz), 6.08 (m, 1H), 3.69 (dm, 1H, *J* = 16.4 Hz), 3.25 (ddd, 1H, *J* = 2.0, 8.8, 8.8 Hz), 2.93 (dm, 1H, *J* = 16.4 Hz), 2.67 (ddd, 1H, *J* = 2.8, 2.8, 16.0 Hz), 2.40 (m, 1H), 2.30 (m, 1H), 2.20 (q, 1H, 8.9 Hz), 2.07 (m, 1H), 1.92 (m, 1H), 1.80 (m, 1H), 1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 135.9, 128.5, 127.1, 125.4, 122.6, 60.4, 54.5, 53.1, 35.0, 31.1, 21.7; IR (Thin Film) 2960, 2910, 2779, 1496, 1446, 1384, 1328, 1147 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 200.14337, found 200.14313.



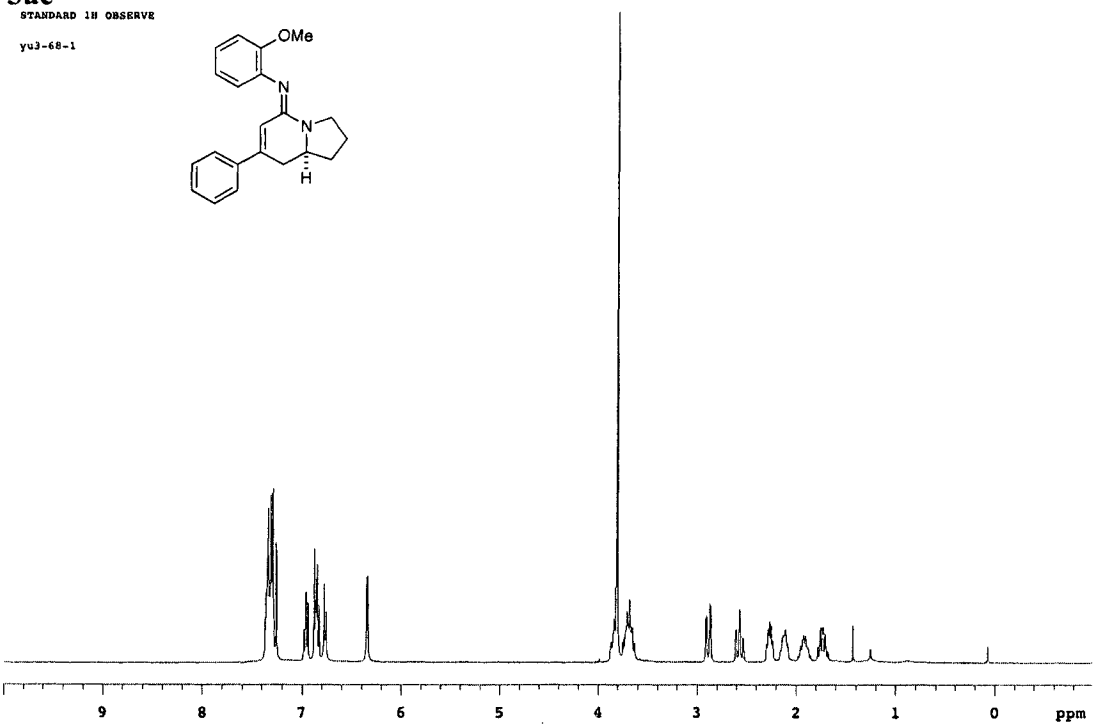
(*S*,*E*)-*N*-(7-(3,4-dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-ylidene)-2-(trifluoromethyl)aniline (3ue). General procedure with alkyne **1u** (1.5 mmol) and carbodiimide **2e** (1.0 mmol) yielded

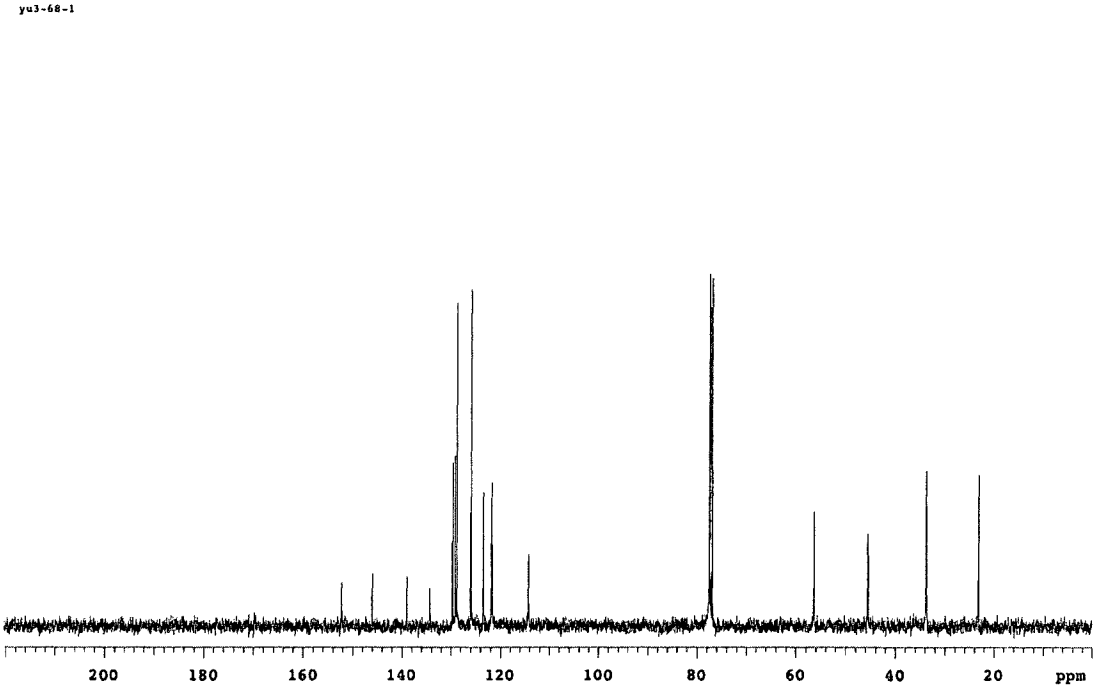
240.2 mg of the cycloadduct (58%); R_f = 0.65 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 243.0 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 [hexane (containing 0.01% diethyl amine):iPrOH], 1.0 ml/min, Major: 6.27 minutes, Minor: 6.98 minutes, 330 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1H, *J* = 7.9 Hz), 7.32 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.97 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.91 (m, 1H), 6.80 – 6.76 (m, 3H), 6.06 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.75 – 3.65 (m, 2H), 3.58 (m, 1H), 2.86 (dd, 1H, *J* = 4.3, 16.2 Hz), 2.50 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 1.91 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 150.0, 149.0, 145.7, 132.0, 131.9, 126.4, 124.7, 121.2, 119.0, 113.3, 111.1, 109.1, 56.4, 56.1, 56.1, 45.3, 34.0, 33.7, 23.2; IR (Thin Film) 2962, 1629, 1585, 1563, 1440, 1317, 1255, 1146, 1123 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 416.17116, found 416.17151.



(*R*)-*N*-(5-(3,4-dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ylidene)-2-(trifluoromethyl)aniline (4ue). General procedure with alkyne **1u** and carbodiimide **2e** yielded 163.3 mg of the cycloadduct (39%) as a 2.7:1 mixture of the imine isomers; R_f = 0.50 (96:4 EtOAc/Et_3N); *ee* not determined; See attached spectra for its ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$); IR (Thin Film) 2963, 1598, 1545, 1513, 1450, 1319, 1259, 1126 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 416.17116, found 416.17093.

3ac

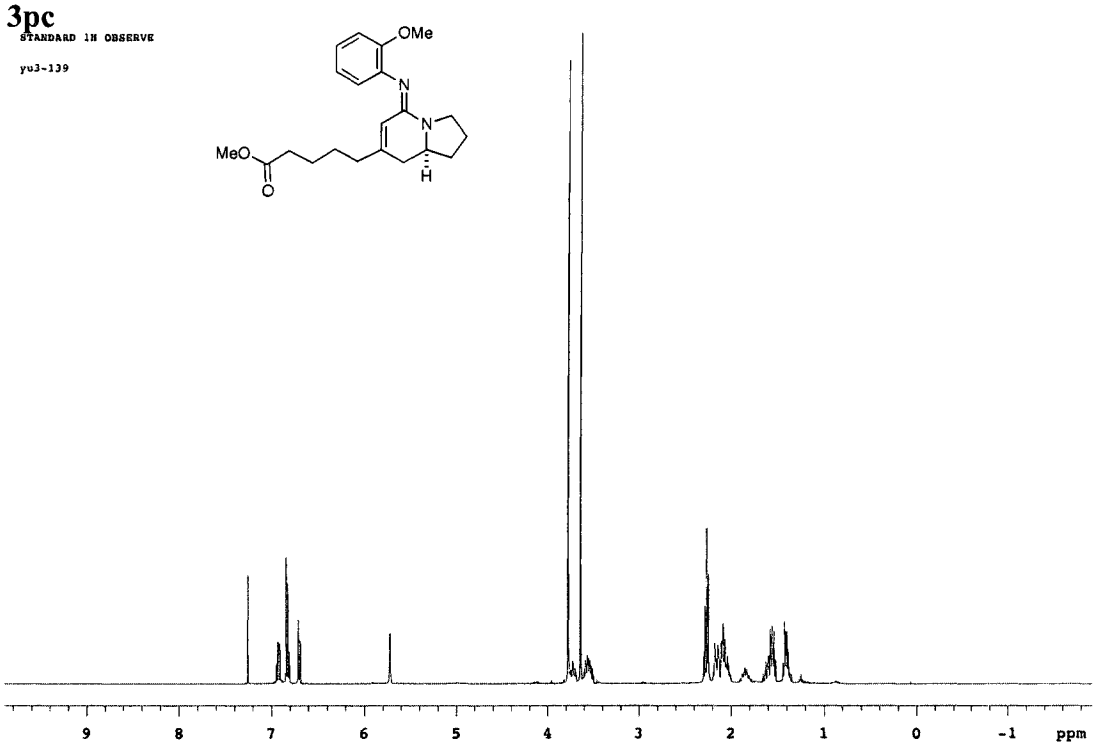




3pc

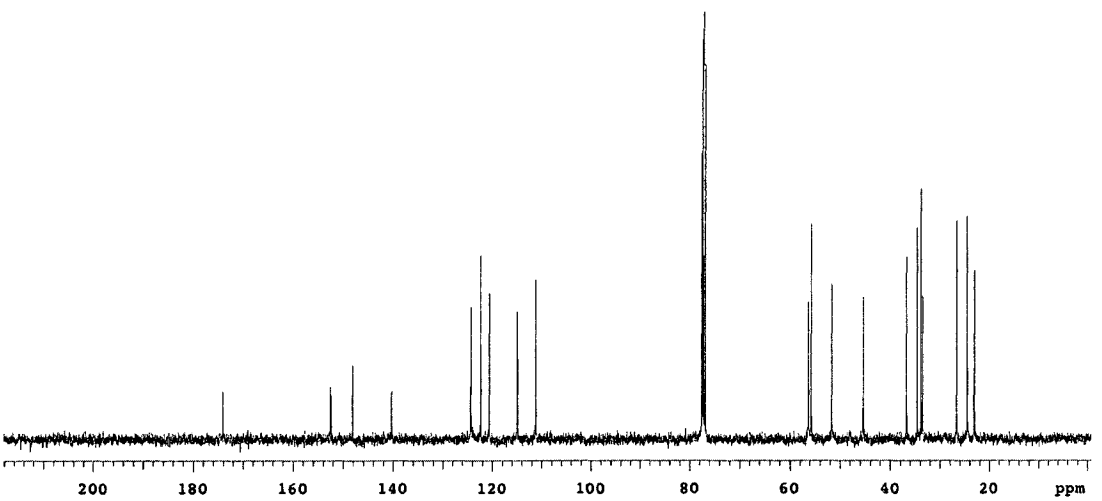
STANDARD 1H OBSERVE

yu3-139

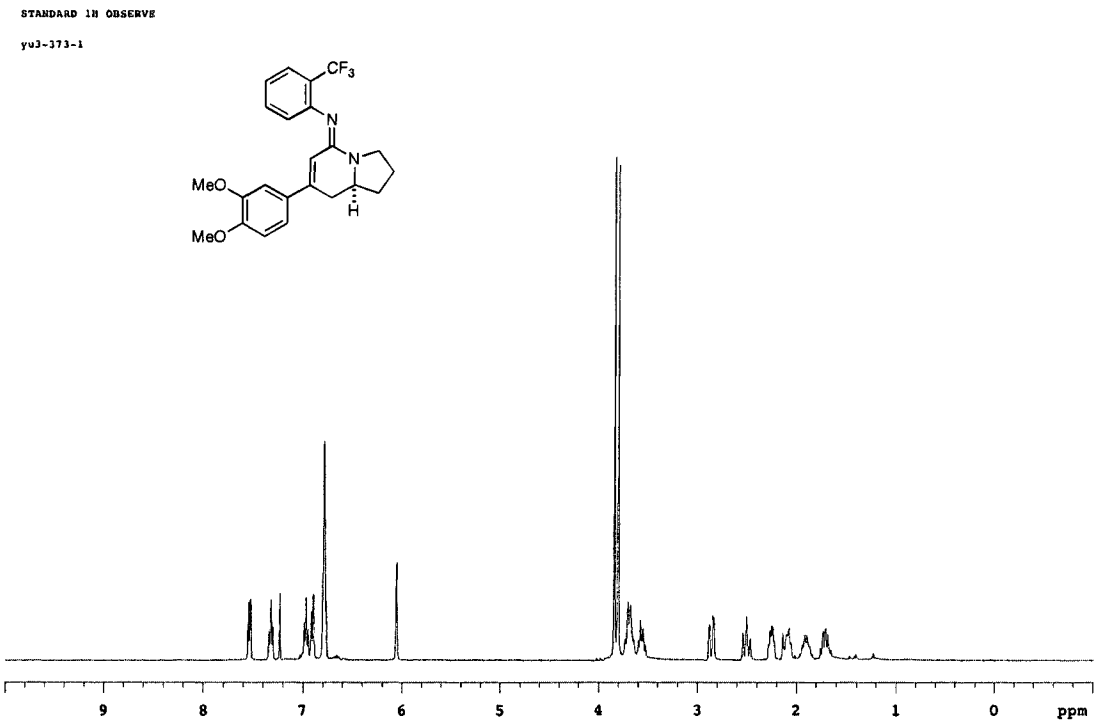


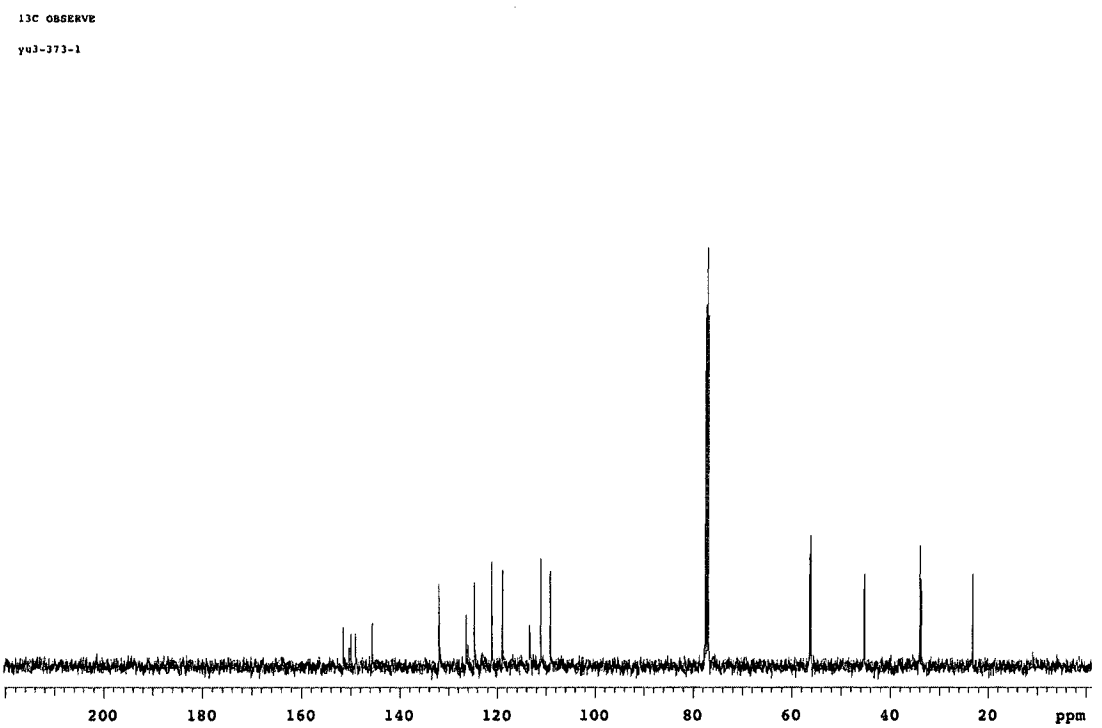
13C OBSERVE

yu3-139
yu3-139

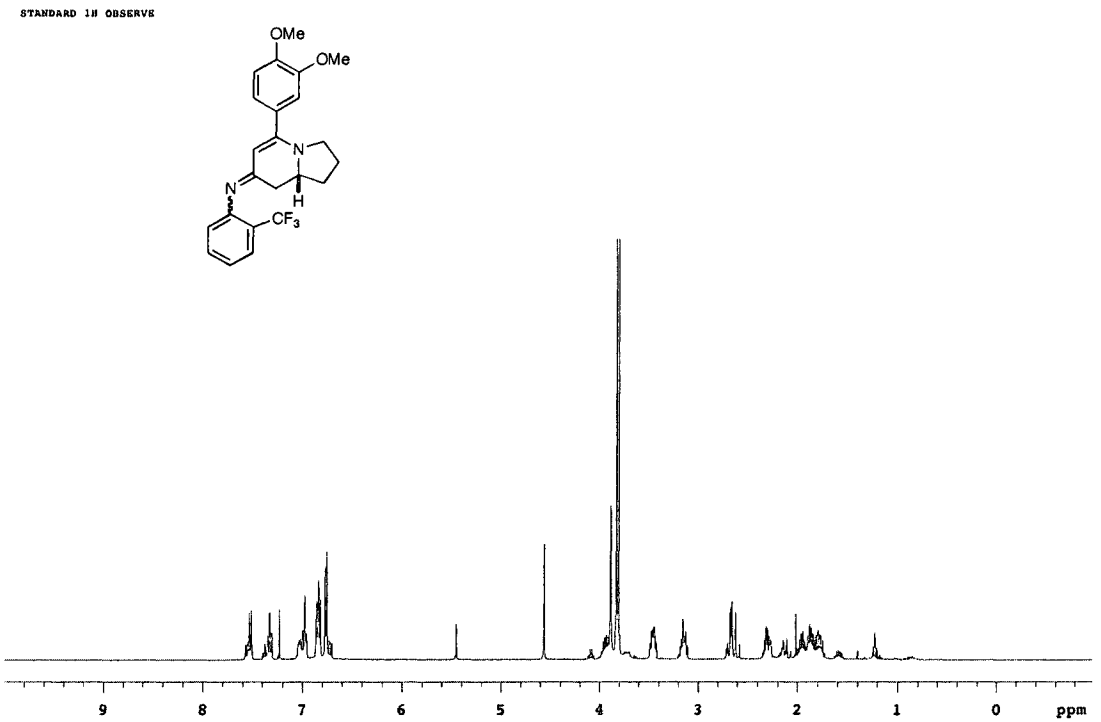


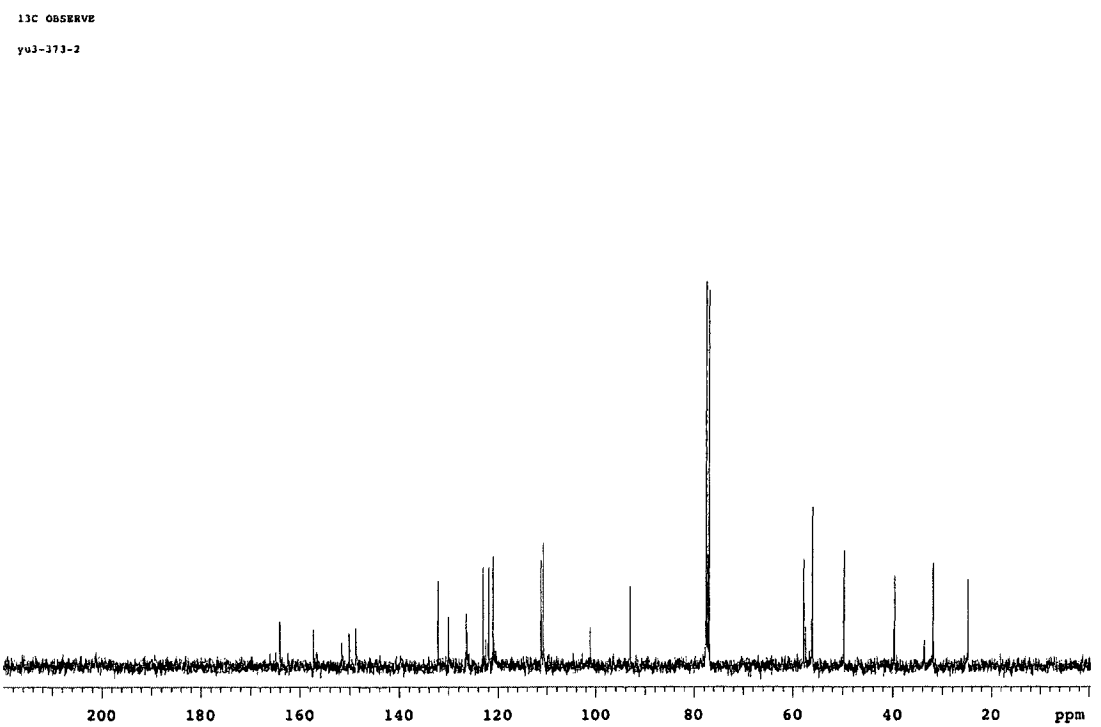
3ue





4ue





Crystal Structure Data for 3bc

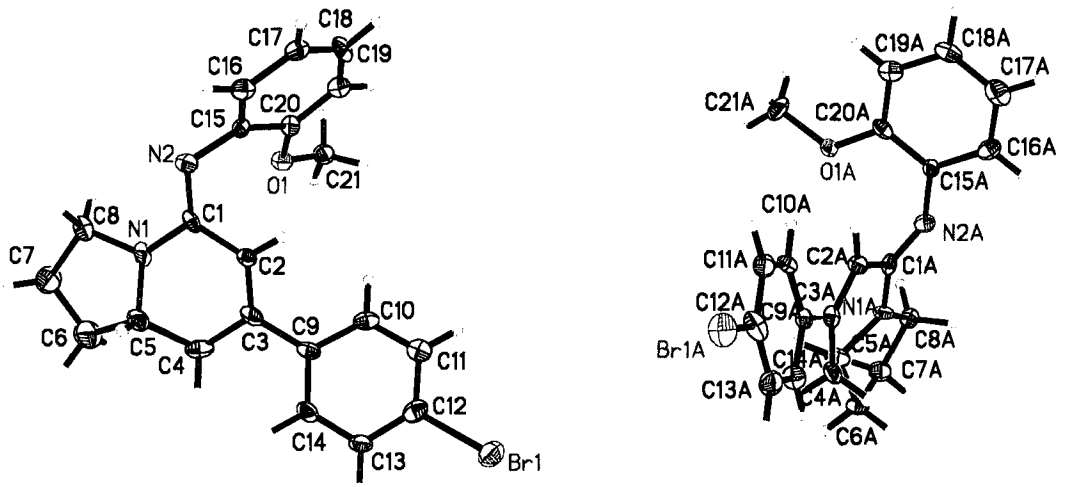


Table 1. Crystal data and structure refinement for rovis29_0m (**3bc**).

Identification code	rovis29_0m	
Empirical formula	C21 H21 Br N2 O	
Formula weight	397.31	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.4508(13) Å	α= 90°.
	b = 14.332(3) Å	β= 90°.
	c = 38.051(8) Å	γ = 90°.
Volume	3518.0(13) $Å^3$	
Z	8	
Density (calculated)	1.500 Mg/m^3	
Absorption coefficient	2.348 mm^{-1}	
F(000)	1632	
Crystal size	0.27 x 0.26 x 0.04 mm^3	
Theta range for data collection	3.50 to 30.03°.	
Index ranges	-3<=h<=9, -20<=k<=19, -47<=l<=53	
Reflections collected	22084	
Independent reflections	10257 [R(int) = 0.1359]	

Completeness to theta = 30.03°	99.7 %
Absorption correction	multi-scan
Max. and min. transmission	0.9161 and 0.5729
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10257 / 0 / 452
Goodness-of-fit on F^2	0.923
Final R indices [I>2sigma(I)]	R1 = 0.0705, wR2 = 0.1039
R indices (all data)	R1 = NaN, wR2 = 0.1405
Absolute structure parameter	-0.016(19)
Largest diff. peak and hole	0.580 and -0.573 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rovis29_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	6942(1)	1906(1)	9840(1)	34(1)
N(1)	-4066(10)	-430(4)	8700(2)	22(2)
N(2)	-4005(10)	789(5)	8314(2)	21(2)
O(1)	-264(8)	525(4)	7987(1)	21(1)
C(1)	-3191(12)	376(5)	8581(2)	16(2)
C(2)	-1368(12)	688(5)	8784(2)	17(2)
C(3)	-476(13)	201(6)	9034(2)	21(2)
C(4)	-1302(12)	-773(5)	9122(2)	29(2)
C(5)	-3555(13)	-848(5)	9045(2)	27(2)
C(6)	-4437(14)	-1821(6)	9009(2)	45(2)
C(7)	-6198(14)	-1747(6)	8747(2)	45(3)
C(8)	-5943(13)	-846(5)	8548(2)	21(2)
C(9)	1370(13)	559(5)	9229(2)	19(2)
C(10)	2785(13)	1157(5)	9058(2)	22(2)
C(11)	4423(12)	1554(6)	9238(2)	22(2)
C(12)	4651(12)	1359(6)	9590(2)	25(2)
C(13)	3366(12)	748(6)	9764(2)	25(2)
C(14)	1711(13)	372(6)	9583(2)	25(2)
C(15)	-2933(12)	1559(5)	8165(2)	19(2)
C(16)	-3856(13)	2434(6)	8161(2)	23(2)

C(17)	-2835(12)	3187(6)	7993(2)	24(2)
C(18)	-1019(13)	3045(6)	7815(2)	25(2)
C(19)	-70(12)	2168(5)	7810(2)	19(2)
C(20)	-1002(12)	1434(5)	7986(2)	18(2)
C(21)	1536(13)	343(6)	7776(2)	24(2)
Br(1A)	8267(1)	6859(1)	9885(1)	33(1)
N(1A)	19162(9)	4583(5)	8687(2)	17(2)
N(2A)	18968(10)	5791(5)	8303(2)	19(2)
O(1A)	15297(8)	5531(4)	7948(1)	21(1)
C(1A)	18143(12)	5312(5)	8553(2)	18(2)
C(2A)	16175(11)	5592(5)	8735(2)	18(2)
C(3A)	15619(12)	5207(5)	9047(2)	15(2)
C(4A)	16957(11)	4457(5)	9207(2)	23(2)
C(5A)	18192(13)	3926(5)	8935(2)	23(2)
C(6A)	20053(11)	3372(5)	9062(2)	20(2)
C(7A)	21352(13)	3295(6)	8733(2)	26(2)
C(8A)	21086(12)	4224(5)	8543(2)	20(2)
C(9A)	13775(13)	5564(5)	9240(2)	19(2)
C(10A)	12229(12)	6090(5)	9080(2)	18(2)
C(11A)	10607(12)	6470(5)	9267(2)	22(2)
C(12A)	10464(13)	6315(6)	9628(2)	24(2)
C(13A)	11941(12)	5774(6)	9797(2)	28(2)
C(14A)	13570(13)	5395(5)	9601(2)	23(2)
C(15A)	17886(12)	6553(5)	8145(2)	17(2)
C(16A)	18764(13)	7448(6)	8154(2)	21(2)
C(17A)	17804(13)	8187(7)	7987(2)	29(2)
C(18A)	15990(13)	8051(7)	7797(2)	25(2)
C(19A)	15122(12)	7167(6)	7781(2)	21(2)
C(20A)	16082(13)	6406(5)	7954(2)	19(2)
C(21A)	13456(12)	5348(6)	7748(2)	28(2)

Table 3. Bond lengths [Å] and angles [°] for rovis29_0m.

Br(1)-C(12)	1.924(9)
N(1)-C(1)	1.365(9)
N(1)-C(8)	1.468(10)
N(1)-C(5)	1.478(9)

N(2)-C(1)	1.288(9)	C(4A)-C(5A)	1.513(10)
N(2)-C(15)	1.421(9)	C(5A)-C(6A)	1.518(10)
O(1)-C(20)	1.387(9)	C(6A)-C(7A)	1.510(10)
O(1)-C(21)	1.435(9)	C(7A)-C(8A)	1.526(10)
C(1)-C(2)	1.476(10)	C(9A)-C(10A)	1.391(10)
C(2)-C(3)	1.312(10)	C(9A)-C(14A)	1.403(10)
C(3)-C(9)	1.494(12)	C(10A)-C(11A)	1.377(10)
C(3)-C(4)	1.531(11)	C(11A)-C(12A)	1.394(11)
C(4)-C(5)	1.486(11)	C(12A)-C(13A)	1.387(11)
C(5)-C(6)	1.512(11)	C(13A)-C(14A)	1.398(11)
C(6)-C(7)	1.516(11)	C(15A)-C(20A)	1.388(11)
C(7)-C(8)	1.505(11)	C(15A)-C(16A)	1.402(10)
C(9)-C(14)	1.390(10)	C(16A)-C(17A)	1.381(11)
C(9)-C(10)	1.411(11)	C(17A)-C(18A)	1.389(11)
C(10)-C(11)	1.380(11)	C(18A)-C(19A)	1.387(11)
C(11)-C(12)	1.378(10)	C(19A)-C(20A)	1.415(10)
C(12)-C(13)	1.376(11)		
C(13)-C(14)	1.381(11)	C(1)-N(1)-C(8)	123.6(7)
C(15)-C(16)	1.388(10)	C(1)-N(1)-C(5)	123.1(6)
C(15)-C(20)	1.431(11)	C(8)-N(1)-C(5)	111.7(6)
C(16)-C(17)	1.418(10)	C(1)-N(2)-C(15)	118.2(7)
C(17)-C(18)	1.367(11)	C(20)-O(1)-C(21)	116.6(6)
C(18)-C(19)	1.399(11)	N(2)-C(1)-N(1)	118.9(7)
C(19)-C(20)	1.385(10)	N(2)-C(1)-C(2)	126.8(7)
Br(1A)-C(12A)	1.891(8)	N(1)-C(1)-C(2)	114.3(7)
N(1A)-C(1A)	1.335(9)	C(3)-C(2)-C(1)	124.6(8)
N(1A)-C(8A)	1.451(9)	C(2)-C(3)-C(9)	121.8(8)
N(1A)-C(5A)	1.472(9)	C(2)-C(3)-C(4)	119.3(8)
N(2A)-C(1A)	1.289(9)	C(9)-C(3)-C(4)	118.8(7)
N(2A)-C(15A)	1.430(9)	C(5)-C(4)-C(3)	111.3(6)
O(1A)-C(20A)	1.353(9)	N(1)-C(5)-C(4)	111.3(6)
O(1A)-C(21A)	1.435(9)	N(1)-C(5)-C(6)	102.1(6)
C(1A)-C(2A)	1.500(10)	C(4)-C(5)-C(6)	116.9(7)
C(2A)-C(3A)	1.360(10)	C(5)-C(6)-C(7)	106.1(7)
C(3A)-C(9A)	1.488(11)	C(8)-C(7)-C(6)	108.0(7)
C(3A)-C(4A)	1.507(10)	N(1)-C(8)-C(7)	103.9(7)

C(14)-C(9)-C(10)	117.4(8)
C(14)-C(9)-C(3)	122.8(8)
C(10)-C(9)-C(3)	119.8(7)
C(11)-C(10)-C(9)	121.3(7)
C(12)-C(11)-C(10)	118.6(8)
C(13)-C(12)-C(11)	122.2(8)
C(13)-C(12)-Br(1)	119.1(6)
C(11)-C(12)-Br(1)	118.7(7)
C(12)-C(13)-C(14)	118.3(7)
C(13)-C(14)-C(9)	122.1(8)
C(16)-C(15)-N(2)	119.8(7)
C(16)-C(15)-C(20)	118.8(7)
N(2)-C(15)-C(20)	121.1(7)
C(15)-C(16)-C(17)	119.5(8)
C(18)-C(17)-C(16)	120.6(8)
C(17)-C(18)-C(19)	121.1(8)
C(20)-C(19)-C(18)	119.0(7)
C(19)-C(20)-O(1)	124.4(7)
C(19)-C(20)-C(15)	120.9(7)
O(1)-C(20)-C(15)	114.6(7)
C(1A)-N(1A)-C(8A)	123.6(6)
C(1A)-N(1A)-C(5A)	122.4(6)
C(8A)-N(1A)-C(5A)	112.3(6)
C(1A)-N(2A)-C(15A)	121.2(7)
C(20A)-O(1A)-C(21A)	119.1(6)
N(2A)-C(1A)-N(1A)	119.7(7)
N(2A)-C(1A)-C(2A)	123.1(7)
N(1A)-C(1A)-C(2A)	116.8(7)
C(3A)-C(2A)-C(1A)	121.2(7)
C(2A)-C(3A)-C(9A)	120.2(7)
C(2A)-C(3A)-C(4A)	119.4(7)
C(9A)-C(3A)-C(4A)	120.3(7)
C(3A)-C(4A)-C(5A)	112.6(6)
N(1A)-C(5A)-C(4A)	110.0(6)
N(1A)-C(5A)-C(6A)	101.7(6)
C(4A)-C(5A)-C(6A)	117.4(6)
C(7A)-C(6A)-C(5A)	102.3(6)
C(6A)-C(7A)-C(8A)	105.5(6)
N(1A)-C(8A)-C(7A)	103.0(6)
C(10A)-C(9A)-C(14A)	117.1(8)
C(10A)-C(9A)-C(3A)	123.0(7)
C(14A)-C(9A)-C(3A)	119.9(8)
C(11A)-C(10A)-C(9A)	122.2(7)
C(10A)-C(11A)-C(12A)	119.8(8)
C(13A)-C(12A)-C(11A)	120.1(8)
C(13A)-C(12A)-Br(1A)	120.3(6)
C(11A)-C(12A)-Br(1A)	119.6(7)
C(12A)-C(13A)-C(14A)	119.0(8)
C(13A)-C(14A)-C(9A)	121.8(8)
C(20A)-C(15A)-C(16A)	119.4(7)
C(20A)-C(15A)-N(2A)	120.9(7)
C(16A)-C(15A)-N(2A)	119.4(7)
C(17A)-C(16A)-C(15A)	120.5(8)
C(16A)-C(17A)-C(18A)	120.7(9)
C(19A)-C(18A)-C(17A)	119.3(9)
C(18A)-C(19A)-C(20A)	120.5(8)
O(1A)-C(20A)-C(15A)	117.6(7)
O(1A)-C(20A)-C(19A)	122.9(7)
C(15A)-C(20A)-C(19A)	119.5(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for rovis29_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	31(1)	42(1)	31(1)	-2(1)	-6(1)	-3(1)
N(1)	20(3)	6(4)	38(4)	0(3)	2(3)	-6(3)
N(2)	21(4)	20(4)	20(4)	3(3)	3(3)	5(3)
O(1)	20(3)	23(3)	18(3)	1(2)	3(2)	4(3)
C(1)	19(4)	7(4)	23(4)	1(3)	11(4)	0(3)
C(2)	16(4)	19(4)	16(4)	2(3)	6(3)	2(3)
C(3)	24(4)	26(5)	14(4)	4(4)	13(4)	4(4)
C(4)	33(5)	26(4)	26(4)	6(4)	-4(4)	8(4)
C(5)	33(5)	23(4)	24(4)	6(3)	-2(4)	-12(4)
C(6)	56(6)	30(5)	48(5)	6(5)	-12(5)	-19(5)
C(7)	39(5)	26(5)	69(6)	20(5)	-15(5)	-9(5)
C(8)	22(4)	13(4)	29(5)	-2(4)	10(4)	3(4)
C(9)	25(4)	19(5)	14(4)	3(3)	4(4)	6(4)
C(10)	29(4)	14(4)	24(4)	4(3)	-6(4)	11(4)
C(11)	22(4)	20(5)	24(4)	-2(3)	7(4)	11(4)
C(12)	20(4)	29(5)	28(5)	1(4)	-3(4)	11(4)
C(13)	21(4)	36(5)	16(4)	11(4)	2(4)	3(4)
C(14)	20(4)	35(5)	21(4)	9(4)	7(4)	0(4)
C(15)	18(4)	23(5)	15(4)	1(3)	-5(4)	-7(4)
C(16)	28(5)	19(5)	21(4)	-1(4)	-5(4)	0(4)
C(17)	30(4)	14(4)	29(4)	1(4)	-12(4)	-1(5)
C(18)	36(5)	14(5)	26(4)	-2(4)	1(4)	-13(4)
C(19)	23(4)	20(5)	15(4)	-5(3)	2(3)	5(4)
C(20)	16(4)	16(4)	21(4)	-2(3)	1(3)	2(3)
C(21)	20(4)	23(5)	29(4)	6(4)	-1(4)	3(4)
Br(1A)	26(1)	35(1)	38(1)	-6(1)	10(1)	3(1)
N(1A)	16(3)	25(4)	12(3)	8(3)	2(3)	3(3)
N(2A)	17(4)	19(4)	21(4)	2(3)	-2(3)	6(3)
O(1A)	17(3)	16(3)	29(3)	8(2)	-5(2)	-2(2)
C(1A)	16(4)	21(4)	16(4)	-7(3)	1(4)	-5(3)
C(2A)	14(4)	20(4)	19(4)	3(3)	1(3)	2(3)

C(3A)	17(4)	7(4)	22(4)	-6(3)	1(3)	-2(3)
C(4A)	24(4)	14(4)	29(4)	6(3)	1(4)	-4(3)
C(5A)	30(4)	19(4)	21(4)	2(3)	1(4)	8(4)
C(6A)	20(4)	20(4)	21(4)	4(3)	0(3)	8(3)
C(7A)	27(4)	22(5)	30(4)	6(4)	-5(4)	4(4)
C(8A)	19(4)	15(4)	25(4)	-1(4)	-3(3)	5(3)
C(9A)	24(4)	13(4)	19(4)	-1(3)	-3(4)	-6(4)
C(10A)	23(4)	14(4)	18(4)	6(3)	0(3)	0(3)
C(11A)	19(4)	16(4)	31(5)	1(4)	-3(4)	1(3)
C(12A)	29(4)	13(4)	30(5)	-6(4)	13(4)	1(4)
C(13A)	27(4)	35(5)	21(4)	-3(4)	0(4)	-8(4)
C(14A)	22(4)	24(5)	22(4)	-2(4)	5(4)	1(4)
C(15A)	20(4)	15(5)	15(4)	0(3)	-1(3)	-5(3)
C(16A)	21(4)	26(5)	16(4)	-5(4)	0(4)	5(4)
C(17A)	37(5)	31(5)	18(4)	-3(4)	11(4)	-3(5)
C(18A)	34(5)	24(5)	18(4)	6(4)	9(3)	7(5)
C(19A)	22(4)	27(5)	15(4)	-1(4)	9(3)	7(4)
C(20A)	27(4)	10(4)	20(4)	1(3)	4(3)	1(3)
C(21A)	15(4)	35(5)	33(5)	0(4)	-11(4)	0(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for rovis29_0m.

	x	y	z	U(eq)
H(2B)	-800	1282	8730	21
H(4A)	-539	-1244	8982	34
H(4B)	-1059	-906	9374	34
H(5A)	-4342	-509	9232	32
H(6A)	-4955	-2048	9238	54
H(6B)	-3363	-2258	8923	54
H(7A)	-6159	-2282	8582	53
H(7B)	-7547	-1754	8871	53
H(8A)	-5763	-963	8293	26
H(8B)	-7158	-434	8583	26

H(10A)	2607	1290	8816	27
H(11A)	5374	1953	9120	26
H(13A)	3610	588	10003	29
H(14A)	775	-27	9703	30
H(16A)	-5162	2528	8271	27
H(17A)	-3418	3795	8003	29
H(18A)	-391	3551	7694	30
H(19A)	1195	2076	7686	23
H(21A)	1917	-317	7797	36
H(21B)	2689	732	7857	36
H(21C)	1232	489	7530	36
H(2AB)	15302	6047	8629	21
H(4AA)	16065	4014	9337	27
H(4AB)	17924	4745	9377	27
H(5AA)	17241	3502	8802	28
H(6AA)	20804	3709	9250	24
H(6AB)	19635	2750	9149	24
H(7AA)	20863	2773	8584	31
H(7AB)	22826	3188	8793	31
H(8AA)	22257	4650	8593	24
H(8AB)	20977	4132	8285	24
H(10B)	12293	6191	8833	22
H(11B)	9591	6837	9151	26
H(13B)	11847	5663	10043	34
H(14B)	14564	5012	9716	27
H(16B)	20030	7547	8276	25
H(17B)	18389	8793	8002	35
H(18B)	15351	8559	7678	30
H(19B)	13872	7071	7654	25
H(21D)	13094	4686	7768	42
H(21E)	13703	5505	7501	42
H(21F)	12314	5729	7839	42

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[1] Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006,** *128,* 12370.

[2] (a) Lawrence, N. J.; Ghani, F. A.; Hepworth, L. A.; Hadfield, J. A.; McGown, A. T.; Pritchard, R. G. *Synthesis* **1999,** 1656. (b) Fang, Z.; Song, Y.; Sarkar, T.; Hamel, E.; Fogler, W. E.; Agoston, G. E.; Fanwick, P. E.; Cushman, M. *J. Org. Chem.* **2008**, *73*, 4241.

[3] (a) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006,** *128,* 2782. (b) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.

[4] Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008,** *130,* 3262.

Chapter 4 Experimental

The Missing Piece: A Catalyst-Controlled Cycloaddition of Alkenyl Isocyanates and Terminal Alkyl Alkynes for the Construction of 5-Alkyl Indolizinones, and Application to the Synthesis of Indolizidine (–)-209D

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine (peptide synthesis grade) was purchased from Fisher Scientific and used without further purification. Column chromatography was performed on Silicycle Inc. silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm) and/or potassium permanganate.

Infrared spectra (IR) were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were obtained on Varian Unity 400 spectrometers. Chemical shifts are expressed in ppm values. Proton chemical shifts in $CDCl_3$ were referenced to 7.24 ppm ($CHCl_3$) or 0.00 ppm (TMS). Carbon chemical shifts were referenced to 77.0 ppm ($CDCl_3$). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplet; b, broad; *J*, coupling constant in Hz. High resolution mass spectra (HRMS) were recorded on a Agilent Technologies 6210 Time of Flight LC/MS. HPLC spectra were obtained on an Agilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter.

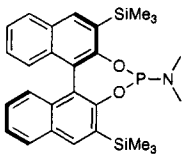
Alkynes **1a – 1c, 1f – 1h, 1j – 14l** and **1n** were purchased from Aldrich Chemicals Co. and used without further purification. Alkyne **1d** and **1i** were prepared by typical TBS and TIPS-protection of the corresponding alcohols respectively, which were purchased from Aldrich Chemicals Co. Alkyne **1e** is a known compound,[1] which can be prepared by a typical peptide coupling condition (EDC, HOAt, and DIPEA) of the corresponding carboxylic acid and *N,O*-dimethyl hydroxy amine. Alkyne **1m** can be prepared by the procedure described within. $[Rh(C_2H_4)_2Cl]_2$ and ligands **L1, L2, L4,** and **L6** were purchased from Strem Chemical, Inc. and used without further purification. Ligand **L3** was prepared according to a literature procedure.[2] Ligands **L5, L7 – L13** can be synthesized by one of the two procedures described within. All racemate products are obtained via the same cycloaddition using the *rac*-**L13** as the ligand. Alkenyl isocyanate **2** can be synthesized by the procedures described within. The synthesis of isocyanates **5** and **7** can be found in our previous report.[3]

General procedure for synthesis of ligands:

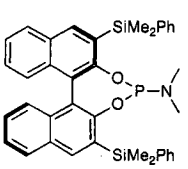
Method A: To a flame-dried round bottom flask charged with a magnetic stir bar was added the diol (1.00 mmol), 7 ml of toluene, and hexamethylphosphorus triamide HMPA (1.20 eq, 1.20 mmol). The reaction flask was then fitted with a reflux condenser. The resulting mixture was stirred at 110 °C for 36h. The reaction mixture was allowed to cool to ambient temperature and concentrated in *vacuo*. The crude material was purified by flash column chromatography on silica gel (typically 96:4 Hex:EtOAc or 10:1 Hex:CH_2Cl_2) to afford the desired phosphoramidite as a white solid.

Method B (from de Vries and coworkers' report): [4] To a flame-dried round bottom flask charged with a magnetic stir bar was added the diol (0.74 mmol), 5 ml of toluene,

hexamethylphosphorus triamide (1.20 eq, 0.89 mmol), and a catalytic amount of NH_4Cl (7 mg). The reaction flask was then fitted with a reflux condenser. The resulting mixture was stirred at 110 °C for 24h. The reaction mixture was allowed to cool to ambient temperature and concentrated in *vacuo*. The crude material was dissolved in a solution of PhMe:Et_3N (95:5), and purified by flash column chromatography on silica gel (typically 96:4 Hex:EtOAc or 10:1 Hex:CH_2Cl_2) to afford the desired phosphoramidite as a white solid.

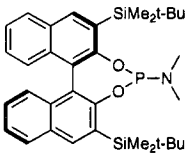


***O,O'-(R)*-3,3'-bis(trimethylsilyl)-1,1'-binaphthyl-2,2'-diyl-*N,N*-dimethylphosphoramidite (L5).** Method A with 1.00 mmol of the diol,[5] 7 ml of toluene, and 1.20 mmol of HMPT yielded a white solid (70%). R_f = 0.77 (10:1 Hexane:EtOAc); $[\alpha]_D^{20}$ = -703.2 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.00 (s, 1H), 7.87 (d, 2H, J = 8.1 Hz), 7.36 – 7.32 (m, 2H), 7.20 – 7.08 (m, 4H), 2.46 (m, 6H), 0.42 (s, 9H), 0.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 136.9, 134.2, 134.0, 132.8, 132.4, 131.0, 130.3, 128.5, 128.4, 127.0, 126.9, 126.4, 124.6, 124.4, 122.8, 121.7, 36.4, 0.22, 0.19, -0.05; ^{31}P NMR (75 MHz, $CDCl_3$) δ 149.40; IR (Thin Film) 2954, 1247, 1224, 1092, 839 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 503.18657, found 503.18609.

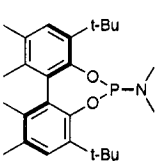


***O,O'-(R)*-3,3'-bis(dimethylphenylsilyl)-1,1'-binaphthyl-2,2'-diyl-*N,N*-dimethylphosphoramidite (L9).** Method A with 0.35 mmol of the diol,[6] 5 ml of toluene, and 0.42 mmol of HMPT yielded a white solid (50%). R_f = 0.33 (4:1 Hexane:CH_2Cl_2); $[\alpha]_D^{20}$ = -366.0 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.85 (s, 1H), 7.82 (d, 1H, J = 8.1 Hz), 7.76 (d, 1H, J = 8.3 Hz), 7.63 – 7.59 (m, 4H), 7.36 – 7.29 (m, 8H), 7.17 – 7.13 (m, 3H), 7.09 (d, 1H, J = 8.3

Hz), 2.22 (br d, 6H, J = 7.0 Hz), 0.69 (s, 3H), 0.69 (s, 3H), 0.67 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 138.7, 138.6, 138.3, 138.0, 134.6, 134.4, 134.1, 131.2, 130.9, 130.5, 130.1, 129.2, 129.2, 128.6, 128.5, 128.0, 127.9, 127.0, 127.0, 126.6, 126.5, 124.6, 124.4, 122.8, 121.7, 36.2, -0.74, -0.98, -1.62; ^{31}P NMR (75 MHz, $CDCl_3$) δ 149.77; IR (Thin Film) 2950, 2893, 1427, 1385, 1224, 1196, 1092, 968 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 627.21787, found 627.21792.



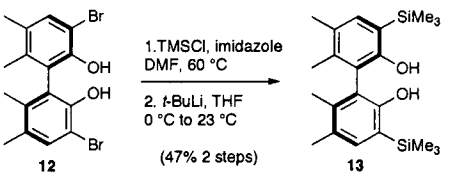
***O,O'-(R)*-3,3'-bis(dimethyl-*tert*-butylsilyl)-1,1'-binaphthyl-2,2'-diyl-*N,N*-dimethylphosphoramidite (L10).** Method A with 0.35 mmol of the diol,[6] 5 ml of toluene, and 0.42 mmol of HMPT yielded a white solid (80%). R_f = 0.73 (4:1 Hexane:CH_2Cl_2); $[\alpha]_D^{20}$ = -566.1 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 8.00 (s, 1H), 7.87 (d, 2H, J = 8.3 Hz), 7.35 (m, 2H), 7.20 – 7.12 (m, 3H), 7.05 (d, 1H, J = 8.5 Hz), 2.43 (m, 6H), 0.89 (s, 9H), 0.82 (s, 9H), 0.46 (s, 3H), 0.44 (s, 6H), 0.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 138.2, 137.9, 134.3, 134.0, 130.7, 130.3, 130.0, 129.7, 128.5, 128.5, 126.8, 126.7, 126.6, 126.5, 124.5, 124.3, 122.9, 121.9, 36.5, 27.4, 27.2, 17.9, 17.7, -2.69, -2.82, -3.49, -4.29, -4.42; ^{31}P NMR (75 MHz, $CDCl_3$) δ 148.59; IR (Thin Film) 2954, 2894, 1386, 1255, 1225, 1201, 1092, 968 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 587.28047, found 587.28105.



***O,O'-(R)*-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl-*N,N*-dimethylphosphoramidite (L13).** Method B with 0.74 mmol of the diol (purchased from Strem Chemical, Inc.), 5 ml of toluene, 0.89 mmol of HMPT, and 7 mg of NH_4Cl yielded a white solid (60%). R_f = 0.75 (20:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.08 (s, 1H), 2.50 – 2.30

(m, 6H), 2.26 (s, 3H), 2.24 (s, 3H), 1.88 (s, 3H), 1.78 (s, 3H), 1.43 (s, 9H), 1.39 (s, 9H); ^{31}P NMR (75 MHz, $CDCl_3$) δ 141.07. All spectra data match with the literature.[4]

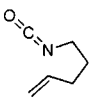
***O,O'-(R)*-3,3'-Bis(trimethylsilyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl-*N,N*-dimethylphosphoramidite (L12).** Method B with 0.24 mmol of the diol **13**, 4 ml of toluene, 0.36 mmol of HMPT, and 3 mg of NH_4Cl yielded a white solid (53%). R_f = 0.85 (20:1 Hexane:EtOAc); $[\alpha]_D^{20}$ = -449.9 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.13 (s, 1H), 2.40 (d, 6H, J = 8.5 Hz), 2.25 (s, 3H), 2.24 (s, 3H), 1.96 (s, 3H), 1.87 (s, 3H), 0.28 (s, 9H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 138.7, 138.0, 135.7, 135.4, 132.4, 131.3, 129.1, 127.8, 127.0, 36.4, 20.4, 20.4, 17.6, 17.4, 0.33, 0.30, 0.15; ^{31}P NMR (75 MHz, $CDCl_3$) δ 143.25; IR (Thin Film) 2952, 2887, 1433, 1388, 1245, 1211, 1026, 979 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 459.21787, found 459.21796.



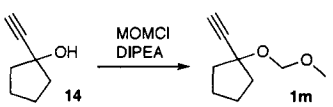
***(R)*-3,3'-Bis(trimethylsilyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl (13).** Diol **13** was prepared from **12**[7] using a literature protocol[6a] (47%). R_f = 0.53 (4:1 Hexane:CH_2Cl_2); $[\alpha]_D^{20}$ = +32.4 (c=0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 4.69 (s, 2H), 2.23 (s, 6H), 1.85 (s, 6H), 0.26 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 138.5, 136.8, 128.7, 122.3, 119.5, 20.0, 16.6, -0.76; IR (Thin Film) 3530, 2952, 1435, 1363, 1244, 1033, 939 cm^{-1}.

General procedure for synthesis of alkenyl isocyanates:

In a flame-dried round bottom flask under Ar atmosphere, triethylamine (23.22 mmol, 1.06 eq) was added to a stirring solution of carboxylic acid (21.90 mmol) in dichloromethane (23.0 mL) at 0 °C. Diphenylphosphoryl azide (23.22 mmol, 1.06 eq) was then slowly added. After 4 hours, the reaction was concentrated under vacuum and rapidly purified by flash chromatography (20:1 Hex:EtOAc, solvent removal was carried out with the rotovap bath temperature less than 23 °C). The resulting acyl azide was slowly converted to the desired isocyanate by sitting in neat at ambient temperature for 24 hours followed by gently heating at 35 °C for 3-6 hours.



5-isocyanatopent-1-ene (2). The starting hexenoic acid was purchased from Wako or Aldrich. Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (76%); ^{1}H NMR (400 MHz, $CDCl_3$) d 5.75 (ddt, 1H, J = 6.8, 10.2, 17.1 Hz), 5.05 (dm, 1H, J = 17.1 Hz), 5.00 (dm, 1H, J = 10.2 Hz), 3.29 (t, 2H, J = 6.6 Hz), 2.14 (dt, 2H, J = 7.0, 7.0 Hz), 1.69 (tt, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 137.0, 116.1, 42.4, 30.7, 30.4; IR (NaCl, $CHCl_3$) 2955, 2279, 1644, 1516, 1434, 1358 cm^{-1}.

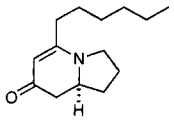


1-ethynyl-1-(methoxymethoxy)cyclopentane (1m). The starting alcohol **14** was purchased from Aldrich. To a solution of **14** (0.5 ml, 4.37 mmol) in 10 ml of diisopropylethylamine was added MOMCl (1.4 ml, 17.46 mmol) at 0 °C. After stirring at ambient temperature for 12 hours, the reaction was poured into a ice slurry-1M HCl solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and

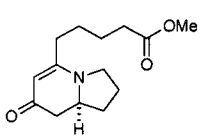
concentrated in *vacuo*. Purification with flash chromatography yielded 435 mg of the target alkyne as a clear oil (65%); R_f = 0.37 (20:1 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 2H), 3.37 (s, 3H), 2.48 (s, 1H), 2.11 – 2.02 (m, 2H), 1.93 – 1.88 (m, 2H), 1.82 – 1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.7, 85.1, 80.4, 73.5, 56.1, 40.8, 23.2; IR (Thin Film) 2925, 1702 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 154.09938, found 154.09939.

General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and terminal alkyl alkynes:

A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (2.6 mg, 0.0068 mmol) and the phosphoramidite ligand **L** (0.0135 mmol), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml toluene was added via syringe and the resulting yellow solution was stirred at ambient temperature under argon flow for 15 minutes. To this solution was added a solution of alkyne **1** (0.54 mmol) and isocyanate **2** or **5** (0.270 mmol) in 2 ml of toluene via syringe or cannula. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 12 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 10:1 EtOAc:MeOH). Evaporation of solvent afforded the analytically pure product **3** or **6**.

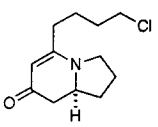


(*S*)-5-hexyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3a). General procedure with alkyne **1a**, isocyanate **2**, and ligand **L13** yielded 45.0 mg of the cycloadduct (75%); R_f = 0.04 (EtOAc); $[\alpha]_D^{20}$ = – 450.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 24.30 minutes, Minor: 27.65 minutes, 330 nm detection light, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 3.68 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.8 Hz), 3.53 (m, 1H), 3.39 (m, 1H), 2.34 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.26 – 2.15 (m, 4H), 2.05 (m, 1H), 1.84 (m, 1H), 1.62 (m, 1H), 1.51 – 1.44 (m, 2H), 1.32 – 1.23 (m, 6H), 0.83 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 164.8, 97.3, 59.3, 46.7, 41.5, 33.8, 32.7, 31.7, 29.2, 27.3, 24.0, 22.7, 14.2; IR (Thin Film) 2928, 2869, 1623, 1545, 1266, 1241 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 221.17796, found 221.17828.

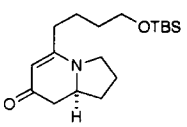


(*S*)-methyl 5-(7-oxo-1,2,3,7,8,8a-hexahydroindolizin-5-yl)pentanoate (3b). General procedure with alkyne **1b**, isocyanate **2**, and ligand **L13** yielded 45.3 mg of the cycloadduct (66%); R_f = 0.14 (10:1 EtOAc/MeOH); $[\alpha]_D^{20}$ = – 382.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 29.06 minutes, Minor: 34.98 minutes, 330 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (s, 1H), 3.69 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.8 Hz), 3.62 (s, 3H), 3.53 (m, 1H), 3.39 (m, 1H), 2.35 (dd, 1H, *J* = 4.7, 15.8 Hz), 2.32 – 2.26 (m, 3H), 2.23 – 2.18 (m, 3H), 2.06 (m, 1H), 1.85 (m, 1H), 1.68 – 1.60 (m, 3H), 1.57 – 1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 173.9, 164.0, 97.3, 59.3, 51.8, 46.8, 41.5, 33.8, 33.4, 32.7, 26.7, 24.7, 24.0; IR (Thin

Film) 2951, 2874, 1735, 1619, 1541, 1267, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 251.15214, found 251.15267.

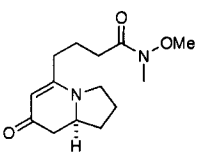


(*S*)-5-(4-chlorobutyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3c). General procedure with alkyne **1c**, isocyanate **2**, and ligand **L13** yielded 35.5 mg of the cycloadduct (57%); R_f = 0.04 (EtOAc); $[\alpha]_D^{20}$ = – 402.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 21.51 minutes, Minor: 24.77 minutes, 330 nm detection light, *ee* = 94%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1H), 3.70 (dddd, 1H, *J* = 5.1, 5.1, 10.4, 15.8 Hz), 3.58 – 3.51 (m, 3H), 3.44 (m, 1H), 2.37 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.76 – 2.19 (m, 4H), 2.08 (m, 1H), 1.91 – 1.78 (m, 3H), 1.72 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 163.7, 97.5, 59.4, 46.8, 44.6, 41.5, 32.9, 32.7, 32.0, 24.4, 24.0; IR (Thin Film) 2956, 2874, 1618, 1541, 1268, 1241 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 227.10769, found 227.10827.

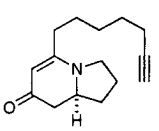


(*S*)-5-(4-(*tert*-butyldimethylsilyloxy)butyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3d). General procedure with alkyne **1d**, isocyanate **2**, and ligand **L13** yielded 54.2 mg of the cycloadduct (62%); R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = – 230.7 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 15.43 minutes, Minor: 18.19 minutes, 330 nm detection light, *ee* = 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 3.70 (dddd, 1H, *J* = 5.5, 5.5, 10.4, 15.8 Hz), 3.59 (t, 2H, *J* = 5.8 Hz), 3.55 (m, 1H), 3.41 (m, 1H), 2.36 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.28 – 2.20 (m, 4H), 2.06 (m, 1H), 1.85 (m, 1H), 1.69 – 1.51 (m, 5H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 164.6, 97.4, 62.7, 59.3, 46.8, 41.5, 33.6, 32.7, 32.5, 26.1, 24.0, 23.7,

18.5, -5.1; IR (Thin Film) 2929, 2857, 1626, 1546, 1248, 1102 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 323.22806, found 323.22815.

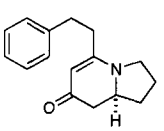


(*S*)-*N*-methoxy-*N*-methyl-4-(7-oxo-1,2,3,7,8,8a-hexahydroindolizin-5-yl)butanamide (3e). General procedure with alkyne **1e**, isocyanate **2**, and ligand **L13** yielded 38.5 mg of the cycloadduct (66%); Colume conditions: gradient elution 96:4 EtOAc:Et_3N followed by 10:1:0.4 EtOAc:MeOH:Et_3N; R_f = 0.09 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 382.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 10.82 minutes, Minor: 13.59 minutes, 330 nm detection light, *ee* = 90%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H), 3.68 (dddd, 1H, *J* = 5.1, 5.1, 10.4, 15.8 Hz), 3.64 (s, 3H), 3.62 (m, 1H), 3.46 (m, 1H), 3.13 (s, 3H), 2.47 (t, 2H, *J* = 6.4 Hz), 2.38 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.31 – 2.20 (m, 4H), 2.07 (m, 1H), 1.89 – 1.81 (m, 3H), 1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 164.3, 97.6, 61.5, 59.3, 47.0, 41.1, 33.4, 32.6, 30.9, 24.0, 21.8; IR (Thin Film) 2964, 2869, 1659, 1614, 1538, 1270, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 266.16304, found 266.16348.

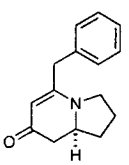


(*S*)-5-(hept-6-ynyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3f). General procedure with alkyne **1f**, isocyanate **2**, and ligand **L13** yielded 34.2 mg of the cycloadduct (55%); R_f = 0.23 (10:1 EtOAc/MeOH); $[\alpha]_D^{20}$ = – 310.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 48.17 minutes, Minor: 53.60 minutes, 330 nm detection light, *ee* = 91%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (s, 1H), 3.71 (dddd, 1H, *J* = 5.3, 5.3, 10.7, 16.0 Hz), 3.56 (m, 1H), 3.42 (m, 1H), 2.40 (dd, 1H, *J* = 4.9, 16.2 Hz), 2.29 – 2.14 (m, 6H), 2.08 (m, 1H), 1.91 (t, 1H, *J* = 2.7 Hz), 1.86 (m, 1H), 1.65 (m, 1H),

1.57 – 1.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 164.8, 97.3, 84.4, 68.7, 59.3, 46.9, 41.2, 33.6, 32.7, 28.5, 28.2, 26.8, 24.0, 18.4; IR (Thin Film) 2937, 2863, 1617, 1541, 1268, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 231.16231, found 231.16284.

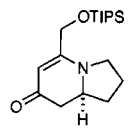


(*S*)-5-phenethyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3g). General procedure with alkyne **1g**, isocyanate **2**, and ligand **L13** yielded 36.7 mg of the cycloadduct (56%); R_f = 0.22 (10:1 EtOAc/MeOH); $[\alpha]_D^{20}$ = – 350.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 29.46 minutes, Minor: 25.28 minutes, 330 nm detection light, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 5.02 (s, 1H), 3.69 (dddd, 1H, *J* = 5.3, 5.3, 10.7, 15.8 Hz), 3.37 (m, 1H), 3.20 (m, 1H), 2.86 – 2.82 (m, 2H), 2.51 (t, 2H, *J* = 7.9 Hz), 2.39 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.29 – 2.19 (m, 2H), 1.98 (m, 1H), 1.74 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 164.1, 140.4, 128.8, 128.6, 126.8, 97.3, 59.3, 46.9, 41.3, 35.6, 34.1, 32.6, 23.9; IR (Thin Film) 2940, 2869, 1618, 1540, 1267, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 241.14666, found 241.14713.

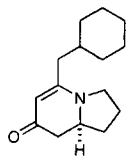


(*S*)-5-benzyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3h). General procedure with alkyne **1h**, isocyanate **2**, and ligand **L13** yielded 32.0 mg of the cycloadduct (52%); R_f = 0.25 (10:1 EtOAc/MeOH); $[\alpha]_D^{20}$ = – 388.7 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 21.41 minutes, Minor: 24.53 minutes, 330 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 4.93 (s, 1H), 3.75 (dddd, 1H, *J* = 5.3, 5.3, 10.7, 16.0 Hz), 3.57 (s, 2H), 3.45 (m, 1H), 3.28 (m, 1H), 2.42 (dd, 1H, *J* = 4.7, 16.0 Hz), 2.33 – 2.20 (m, 2H), 2.00 (m, 1H), 1.79 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 162.5, 135.6, 129.0, 128.9, 127.3, 99.6, 59.5, 47.0, 41.3,

40.4, 32.6, 24.0; IR (Thin Film) 2966, 2877, 1619, 1542, 1267, 1241 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 227.13101, found 227.13111.

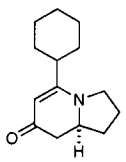


(*S*)-5-((triisopropylsilyloxy)methyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3i). General procedure with alkyne **1i**, isocyanate **2**, and ligand **L13** yielded 38.8 mg of the cycloadduct (44%); R_f = 0.20 (EtOAc); $[\alpha]_D^{20}$ = – 248.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 13.92 minutes, Minor: 12.71 minutes, 330 nm detection light, *ee* = 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.35 (d, 1H, *J* = 14.4 Hz), 4.29 (d, 1H, *J* = 14.4 Hz), 3.75 (m, 1H), 3.62 (m, 1H), 3.41 (m, 1H), 2.46 (dd, 1H, *J* = 4.5, 16.2 Hz), 2.34 – 2.21 (m, 2H), 2.10 (m, 1H), 1.87 (m, 1H), 1.63 (m, 1H), 1.13 – 1.02 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 162.8, 95.9, 62.9, 59.5, 46.3, 41.2, 32.3, 24.4, 18.1, 12.1; IR (Thin Film) 2942, 2866, 1615, 1539, 1264, 1240 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 323.22806, found 323.22825.

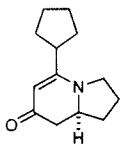


(*S*)-5-(cyclohexylmethyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3j). General procedure with alkyne **1j**, isocyanate **2**, and ligand **L13** yielded 45.4 mg of the cycloadduct (72%); R_f = 0.06 (EtOAc); $[\alpha]_D^{20}$ = – 376.2 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 12.79 minutes, Minor: 15.21 minutes, 330 nm detection light, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 3.69 (dddd, 1H, *J* = 5.3, 5.3, 10.7, 16.0 Hz), 3.55 (m, 1H), 3.40 (m, 1H), 2.36 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.27 – 2.19 (m, 2H), 2.09 – 2.02 (m, 3H), 1.84 (m, 1H), 1.73 – 1.59 (m, 6H), 1.49 (m, 1H), 1.22 – 1.07 (m, 3H), 0.96 – 0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 164.0, 98.7, 59.3, 47.2, 41.6, 41.2, 36.8, 33.5, 32.6, 26.4, 26.3, 23.9; IR (Thin Film) 2923,

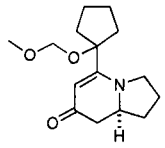
2850, 1623, 1541, 1266, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 233.17796, found 233.17857.



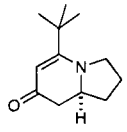
(*S*)-5-cyclohexyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3k). General procedure with alkyne **1k**, isocyanate **2**, and ligand **L13** yielded 51.0 mg of the cycloadduct (86%); R_f = 0.06 (EtOAc); $[\alpha]_D^{20}$ = – 375.9 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 15.50 minutes, Minor: 18.47 minutes, 330 nm detection light, *ee* = 91%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 3.68 (dddd, 1H, *J* = 5.3, 5.3, 10.4, 15.8 Hz), 3.59 (m, 1H), 3.42 (m, 1H), 2.35 (dd, 1H, *J* = 4.7, 15.8 Hz), 2.27 – 2.13 (m, 3H), 2.07 (m, 1H), 1.91 – 1.58 (m, 7H), 1.32 – 1.14 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 169.0, 94.9, 59.4, 46.5, 41.9, 41.5, 32.6, 31.4, 31.3, 26.6, 26.4, 26.0, 24.0; IR (NaCl, $CDCl_3$) 2929, 2854, 1621, 1536, 1264, 1244 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 219.16231, found 219.1626.



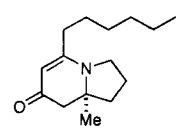
(*S*)-5-cyclopentyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3l). General procedure with alkyne **1l**, isocyanate **2**, and ligand **L13** yielded 48.4 mg of the cycloadduct (87%); R_f = 0.06 (EtOAc); $[\alpha]_D^{20}$ = – 433.5 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 14.34 minutes, Minor: 16.46 minutes, 330 nm detection light, *ee* = 89%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 3.68 (dddd, 1H, *J* = 5.3, 5.3, 10.7, 16.0 Hz), 3.59 (m, 1H), 3.42 (m, 1H), 2.64 (p, 1H, *J* = 7.9 Hz), 2.33 (dd, 1H, *J* = 4.9, 16.0 Hz), 2.25 – 2.17 (m, 2H), 2.05 (m, 1H), 1.92 – 1.79 (m, 3H), 1.75 – 1.46 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 169.1, 94.3, 59.4, 47.1, 42.4, 41.3, 32.7, 31.8, 31.6, 25.7, 24.0; IR (NaCl, $CDCl_3$) 2955, 2870, 1620, 1532, 1268, 1244 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 205.14666, found 205.14700.



(*S*)-5-(1-(methoxymethoxy)cyclopentyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3m). General procedure with alkyne **1m**, isocyanate **2**, and ligand **L13** yielded 43.2 mg of the cycloadduct (60%); R_f = 0.10 (EtOAc); $[\alpha]_D^{20}$ = – 338.6 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexane(containing 0.01% of diethylamine):iPrOH, 1.0 ml/min, Major: 43.14 minutes, Minor: 41.37 minutes, 330 nm detection light, *ee* = 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 1H), 4.49 (d, 1H, *J* = 6.5 Hz), 4.45 (d, 1H, *J* = 6.5 Hz), 4.07 (ddd, 1H, *J* = 1.7, 8.1, 10.4 Hz), 3.70 (dddd, 1H, *J* = 5.1, 5.1, 10.2, 15.8 Hz), 3.43 (ddd, 1H, *J* = 6.8, 10.9, 10.9 Hz), 3.31 (s, 3H), 2.35 (dd, 1H, *J* = 4.3, 16.0 Hz), 2.25 – 2.16 (m, 2H), 2.15 – 1.97 (m, 3H), 1.87 – 1.57 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 163.1, 98.7, 93.1, 88.1, 60.4, 56.6, 49.3, 41.6, 37.2, 36.0, 31.9, 24.9, 23.4, 23.1; IR (NaCl, $CDCl_3$) 2956, 2875, 1614, 1530, 1462, 1269, 1160, 1031 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 265.16779, found 265.16848.



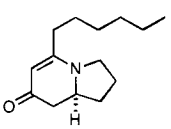
(*S*)-5-*tert*-butyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3n). General procedure with alkyne **1n**, isocyanate **2**, and ligand **L5** yielded 34.4 mg of the cycloadduct (66%); R_f = 0.08 (EtOAc); $[\alpha]_D^{20}$ = – 527.1 (c = 1.0, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 13.53 minutes, Minor: 15.79 minutes, 330 nm detection light, *ee* = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 2.31 – 2.17 (m, 3H), 2.03 (m, 1H), 1.81 (m, 1H), 1.59 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 170.8, 97.7, 61.1, 50.2, 41.4, 36.3, 31.4, 29.1, 25.2; IR (NaCl, $CDCl_3$) 2968, 2875, 1625, 1517, 1275, 1254 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 193.14666, found 193.14691.



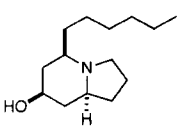
(*S*)-5-hexyl-8a-methyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (6). General procedure with alkyne **1a**, isocyanate **5**, and ligand **L13** yielded

45.6 mg of the cycloadduct (72%); R_f = 0.07 (EtOAc); $[\alpha]_D^{20}$ = – 36.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 8.64 minutes, Minor: 7.86 minutes, 330 nm detection light, *ee* = 27%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, s), 3.60-3.52 (1H, m), 3.47-3.39 (1H, m), 2.48 (1H, d, *J* = 16.0 Hz), 2.28 (1H, d, *J* = 16.0 Hz), 2.20-2.10 (2H, m), 2.08-1.94 (3H, m), 1.84-1.74 (1H, m), 1.52-1.40 (2H, m), 1.35-1.20 (6H, m), 1.17 (3H, s), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 163.2, 96.2, 63.1, 48.0, 46.5, 39.7, 34.1, 31.7, 29.1, 27.3, 22.7, 22.4, 20.0, 14.2; IR (Thin Film) 2957, 2928, 2870, 1625, 1544, 1487, 1267, 1213 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 235.19361, found 235.19369.

Synthesis of Indolizidine (–)-209D

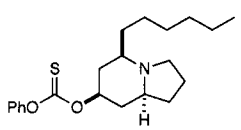


(*S*)-5-hexyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3a). General procedure with alkyne **1a** (2.80 mmol), isocyanate **2** (1.40 mmol), Rh-dimer (13.5 mg, 0.035 mmol) and ligand **L13** (30.2 mg, 0.070 mmol) in 20 ml of toluene at 100 °C yielded 206.0 mg of the cycloadduct (66%, 91% *ee*).

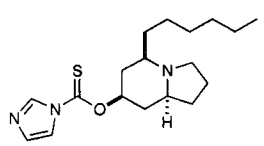


(5*R*,7*S*,8a*S*)-5-hexyloctahydroindolizin-7-ol (9). A mixture of **3a** (181.9 mg, 0.822 mmol) and 119 mg of 10% Pd/C in 23 ml of MeOH was stirred at ambient temperature under hydrogen atmosphere (1 atm) for 24 hours. The reaction mixture was filtered through celite and concentrated *in vacuo*. Upon purification by column chromatography (10:1 EtOAc:Et_3N), 151.3 mg of the desired product was isolated as a white solid (82%); R_f = 0.48 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 78.4 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (m, 1H), 3.17 (m, 1H), 2.07 (m, 1H), 2.00 (m, 1H), 1.98 – 1.90 (m, 3H), 1.86 – 1.75 (m, 2H), 1.70 – 1.58 (m, 3H), 1.45 (m, 1H),

1.35 – 1.15 (m, 11H), 0.84 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 63.1, 60.8, 50.7, 40.4, 34.5, 32.0, 30.1, 29.8, 25.8, 22.8, 21.4, 14.3; IR (NaCl, $CDCl_3$) 2915, 2854, 2773, 1463, 1358, 1025 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 225.20926, found 225.20975.

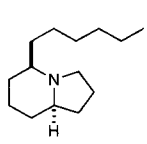


***O*-(5*R*,7*S*,8a*S*)-5-hexyloctahydroindolizin-7-yl *O*-phenyl carbonothioate (10).** To a stirring solution of alcohol **9** (123.3 mg, 0.547 mmol) in 10 ml of CH_2Cl_2 was added DMAP (102.9 mg, 0.842 mmol) and then PhOC(S)Cl (0.09 ml, 0.066 mmol). The resulting mixture was stirred at ambient temperature for 24h. The mixture was diluted with EtOAc and concentrated to approximately 1 ml. Flash column chromatography (10:1 Hex:EtOAc followed by EtOAc) gave the desired product as a yellow oil (64 mg, 32%); R_f = 0.20 (EtOAc); $[\alpha]_D^{20}$ = – 25.5 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, 2H, J = 7.7, 7.7 Hz), 7.26 (t, 1H, J = 7.5 Hz), 7.08 (d, 2H, J = 7.7 Hz), 5.23 (dddd, 1H, J = 4.7, 4.7, 11.1, 11.1 Hz), 3.20 (m, 1H), 2.39 (m, 1H), 2.29 (m, 1H), 2.10 – 1.97 (m, 3H), 1.87 – 1.79 (m, 2H), 1.73 – 1.60 (m, 2H), 1.55 – 1.45 (m, 3H), 1.40 – 1.22 (m, 9H), 0.86 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 153.5, 129.7, 126.7, 122.2, 82.7, 62.6, 60.5, 50.6, 35.7, 35.5, 34.5, 32.0, 30.1, 29.8, 25.6, 22.8, 21.4, 14.3; IR (NaCl, $CDCl_3$) 2930, 2858, 1588, 1486, 1291, 1199, 1009 cm^{-1}; HRMS (FAB+) *m/e* calcd ($M+H^+$) 362.215376, found 362.215390.



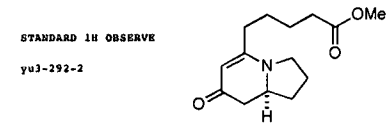
***O*-(5*R*,7*S*,8a*S*)-5-hexyloctahydroindolizin-7-yl 1*H*-imidazole-1-carbothioate (11).** A solution of alcohol **9** (35 mg, 0.155 mmol), DMAP (56.8 mg, 0.465 mmol), and thiocarbonyldiimidazolide (83 mg, 0.465 mmol) in a minimum amount of CH_2Cl_2 was evaporated to dryness. The resulting solid was heated

at 55 °C for 3h under Ar. Flash column chromatography (50:50 Hex:EtOAc followed by 50:50:4 Hex:EtOAc:Et_3N) gave the desired product as a yellow oil (40.4 mg, 77%); R_f = 0.47 (50:50:4 Hex/EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 45.1 (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.58 (s, 1H), 6.99 (s, 1H), 5.47 (dddd, 1H, *J* = 4.7, 4.7, 11.1, 11.1 Hz), 3.21 (m, 1H), 2.38 (m, 1H), 2.27 (m, 1H), 2.14 – 2.00 (m, 3H), 1.90 – 1.61 (m, 4H), 1.55 – 1.44 (m, 3H), 1.40 – 1.19 (m, 9H), 0.85 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 137.1, 130.9, 118.0, 81.9, 62.5, 60.3, 50.6, 35.7, 35.4, 34.4, 31.9, 30.1, 29.8, 25.5, 22.8, 21.4, 14.3; IR (NaCl, $CDCl_3$) 2929, 2858, 1463, 1387, 1329, 1286, 1232, 979 cm^{-1}; HRMS (ESI) *m/e* calcd (M^+) 335.20313, found 335.2033.



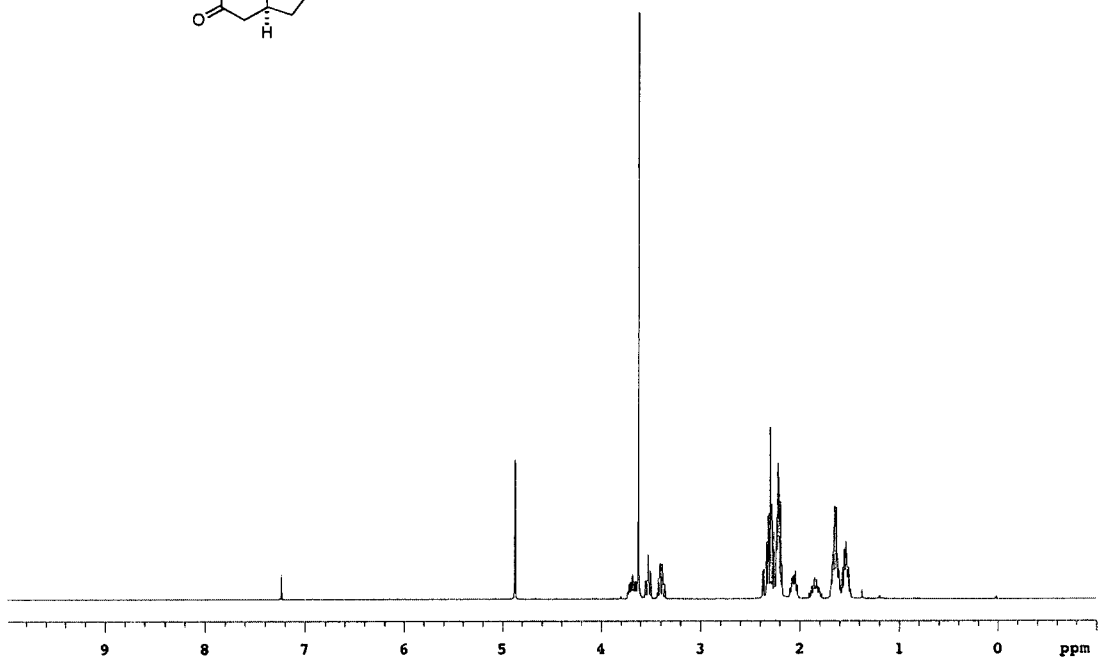
Indolizidine (–)-209D. To a solution of **11** (40.8 mg, 0.122 mmol) in 4 ml of toluene was added *n*Bu_3SnH (4 eq) and AIBN (0.5 eq). The resulting mixture was heated at 100 °C for 1 hour. After addition of extra *n*Bu_3SnH (4 eq) and AIBN (0.5 eq), the reaction was heated at 100 °C for additional 20 minutes. Flash column chromatography (50:50 Hex:EtOAc followed by 50:50:4 Hex:EtOAc:Et_3N) gave the desired natural product (18.2 mg, 71%); 79% from **10**; R_f = 0.44 (96:4 EtOAc/Et_3N); $[\alpha]_D^{20}$ = – 66.5 (c = 1, $CHCl_3$); lit.[8] $[\alpha]^{26}_D$ = -80.4° (c 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 3.23 (m, 1H), 1.98 – 1.55 (m, 10H), 1.45 – 1.05 (m, 13H), 0.85 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.2, 64.1, 51.7, 34.8, 32.1, 31.2, 31.0, 30.7, 29.9, 26.0, 24.9, 22.8, 20.6, 14.3; IR (NaCl, $CDCl_3$) 2929, 2857, 1458, 1380, 1129 cm^{-1}; HRMS (ESI) *m/e* calcd (M^+) 209.21435, found 209.21465.

3b



STANDARD 1H OBSERVE

yu3-292-2



13C OBSERVE

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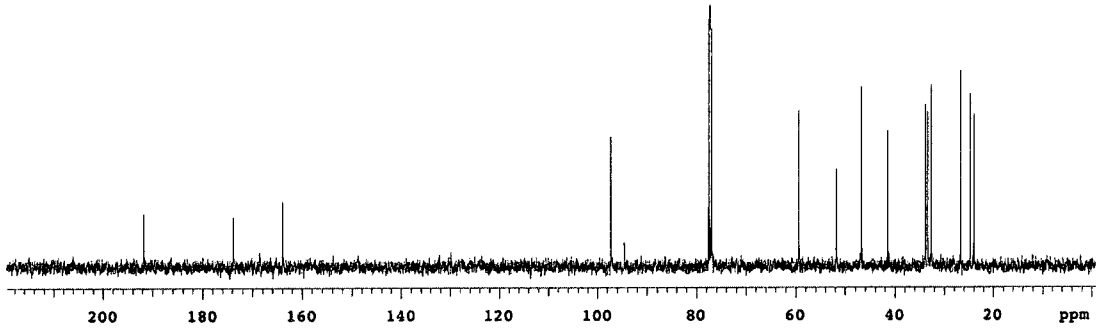
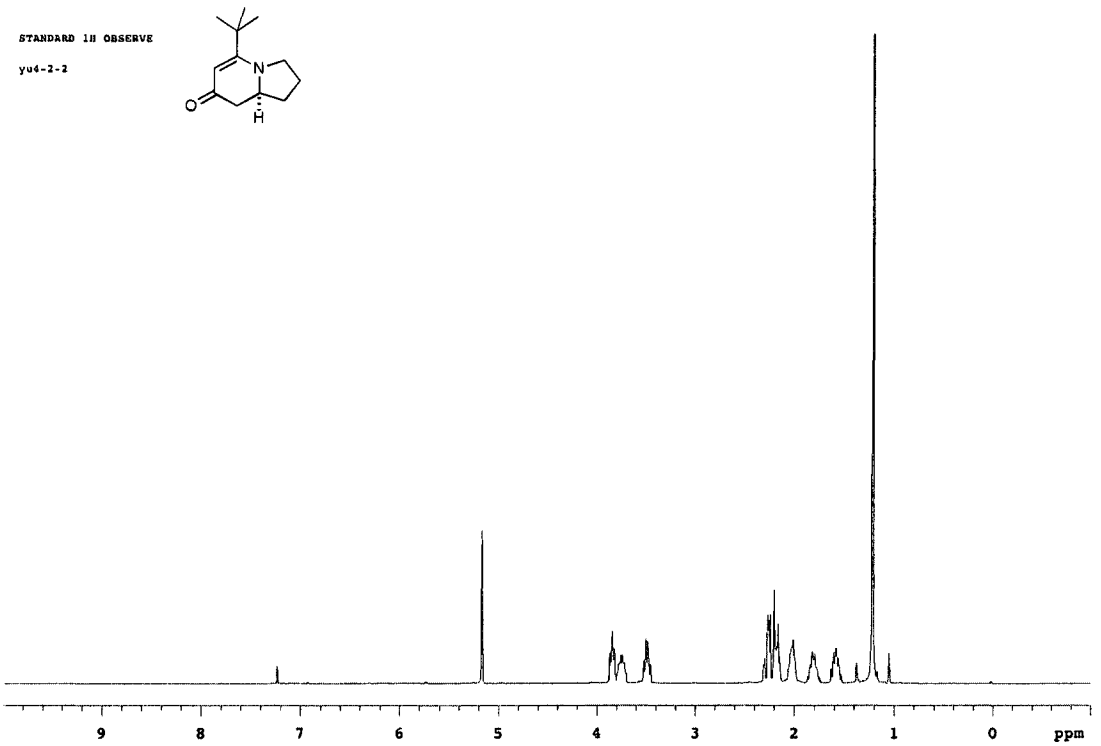
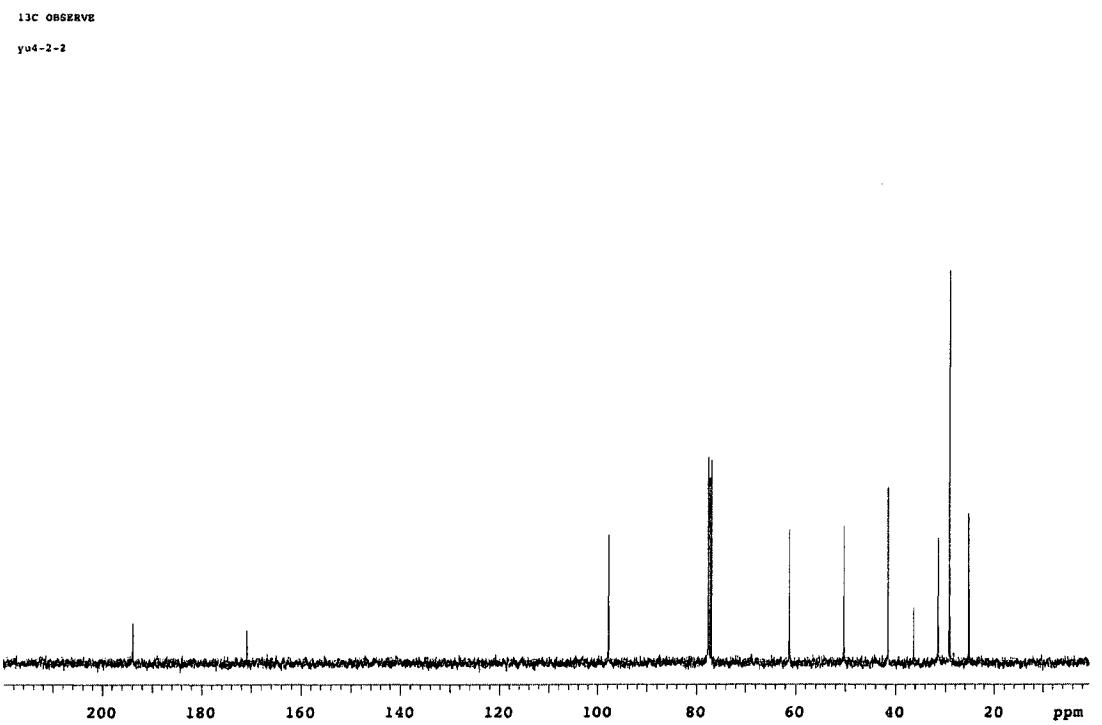


3n

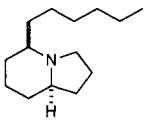


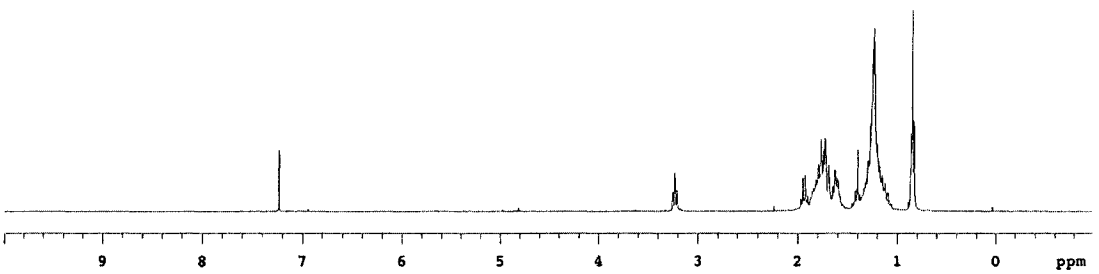


209D

STANDARD 1H OBSERVE

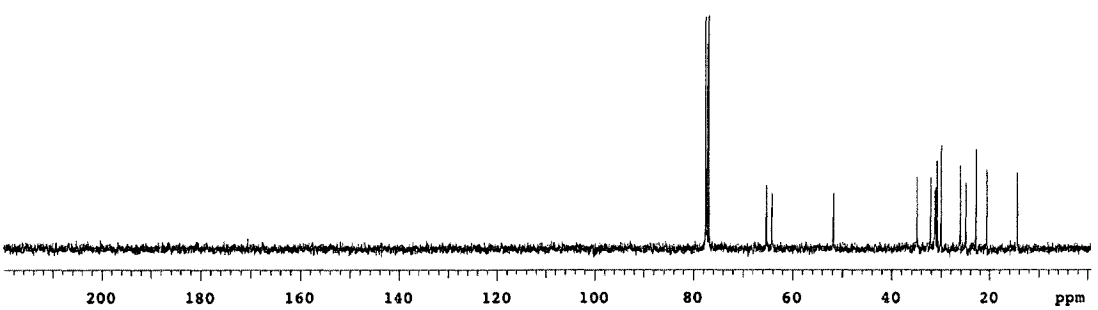
yu4-26





13C OBSERVE

yu4-26



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Chapter 5 Experimental

Highyl Enantioselective Rhodium-Catalyzed [4+2+2] Cycloadditions Utilizing Dienyl Isocyanates: A New Method for the Synthesis of Nitrogen-Containing Eight-Membered Rings

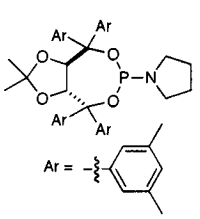
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine (peptide synthesis grade) was purchased from Fisher Scientific and used without further purification. Column chromatography was performed on Silicycle Inc. silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm) and/or potassium permanganate.

Infrared spectra (IR) were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were obtained on Varian Unity 400 spectrometers. Chemical shifts are expressed in ppm values. Proton chemical shifts in $CDCl_3$ were referenced to 7.24 ppm ($CHCl_3$) or 0.00 ppm (TMS). Carbon chemical shifts were referenced to 77.0 ppm ($CDCl_3$). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplet; b, broad; *J*, coupling constant in Hz. High resolution mass spectra (HRMS) were recorded on a Agilent Technologies 6210 Time of Flight LC/MS. HPLC spectra were obtained on an Agilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter.

Alkynes **14a – 14c, 14e – 14f, 14h** and **14k – 14l** were purchased from Aldrich Chemicals Co. and used without further purification. Alkyne **29** was purchased from Wako and used without further purification. Alkyne **14g** and **14j** were prepared by typical TIPS and TBS-protection of the corresponding alcohols respectively, which were purchased from Aldrich Chemicals Co. Alkyne **14h** can be prepared by the procedure described within. $[Rh(C_2H_4)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. Ligands **L1 – L3** can be synthesized by the procedure described within. All racemate products are obtained via the same cycloaddition using the *rac*-**L2** as the ligand. Alkenyl isocyanates **15, 33** and **36** can be synthesized by the procedures described within.

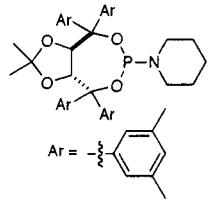
General procedure for synthesis of ligands:

To a flame-dried round bottom flask charged with a magnetic stir bar was added 4 Å molecular sieves, the diol (2.11 mmol) and 9 ml of THF. To the reaction mixture was added Et_3N (3.40 eq, 7.17 mmol) and phosphorus trichloride (1.2 eq, 2.53 mmol) dropwise at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 40 minutes. A solution of amine (10 eq, 21.10 mmol) in 11 ml of THF was added slowly at 0 °C. The reaction was allowed to stir overnight at ambient temperature before it was diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo and the resulting crude material was purified by flash column chromatography (4:96 EtOAc:Hexane) to afford the desired phosphoramidite as a white solid.

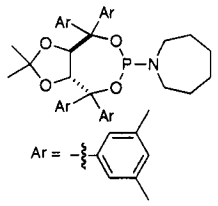


1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-pyrrolidine (L1). Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid

(50%). R_f = 0.50 (90:10 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -108.0 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, s), 7.16 (2H, s), 7.04 (2H, s), 7.02 (2H, s), 6.84 (3H, s), 6.80 (1H, s), 5.08 (1H, dd, *J* = 8.5, 2.5 Hz), 4.74 (1H, d, *J* = 8.0 Hz), 3.47-3.35 (2H, m), 3.35-3.15 (2H, m), 2.27 (6H, s), 2.25 (12H, s), 2.24 (6H, s), 1.86-1.72 (4H, m), 1.32 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.9, 142.2, 142.1, 137.3, 136.9, 136.7, 136.3, 129.2, 128.9, 128.7, 127.9, 127.0, 126.8, 125.3, 125.2, 111.7, 83.1 (d, *J* = 4.5 Hz), 82.9, 82.7, 81.8, 81.1 (d, *J* = 5.5 Hz), 45.1 (d, *J* = 19.0 Hz), 27.9, 26.3, 26.2, 25.7, 21.9, 21.8; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.40; IR (Thin Film) 2917, 2866, 1601, 1456, 1379, 1214, 1159, 1042, 854 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 678.3707, found 678.3702.

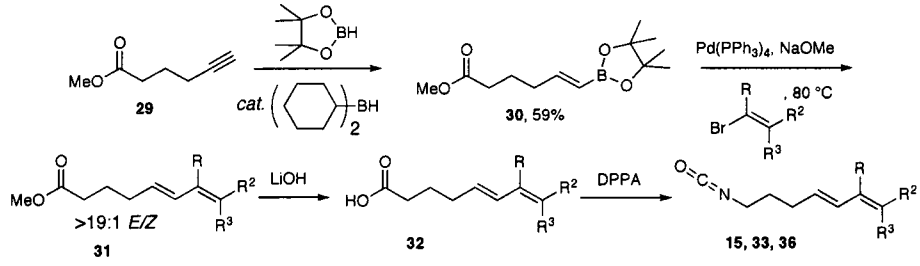


(*R*,*R*)-1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-piperidine (L2) Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid (52%); R_f = 0.67 (95:5 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -108.0 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, s), 7.20 (2H, s), 7.04 (4H, s), 6.84 (3H, s), 6.79 (1H, s), 5.02 (1H, dd, *J* = 8.5, 3.0 Hz), 4.67 (1H, d, *J* = 8.5 Hz), 3.34-3.27 (2H, m), 3.20-3.08 (2H, m), 2.26 (6H, s), 2.26 (6H, s), 2.25 (6H, s), 2.24 (6H, s), 1.65-1.50 (6H, m), 1.37 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.0, 142.1, 137.3, 136.9, 136.7, 136.4, 129.2, 128.9, 128.8, 128.7, 127.1, 126.8, 125.3, 111.5, 83.3, 82.9, 82.7, 81.4, 81.3, 81.2, 77.4, 45.3, 45.1, 27.9, 27.2, 27.2, 25.7, 25.5, 21.9, 21.8, 21.7; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.76; IR (Thin Film) 2931, 2851, 1600, 1448, 1370, 1215, 1159, 1040, 940 cm^{-1}; HRMS (ESI) *m/e* calcd ($M+H^+$) 692.3863, found 692.3843.



(*R*,*R*)-1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-azepane (L3) Flash Chromatography (96:4 Hexanes:EtOAc) yielded a white solid (49%); R_f = 0.69 (95:5 Hexanes:EtOAc); $[\alpha]_D^{20}$ = -96.4 (c=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, s), 7.21 (2H, s), 7.05 (4H, s), 6.85-6.80 (4H, m), 5.07 (1H, dd, *J* = 8.5, 3.7 Hz), 4.66 (1H, d, *J* = 8.5 Hz), 3.42-3.34 (2H, m), 3.30-3.22 (2H, m), 2.27 (6H, s), 2.26 (6H, s), 2.26 (6H, s), 2.25 (6H, s), 1.80-1.65 (8H, m), 1.41 (3H, s), 0.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.0, 142.3, 142.1, 137.2, 136.9, 136.7, 136.4, 129.1, 129.0, 128.9, 128.7, 127.2, 126.7, 125.3, 111.4, 83.5, 83.5, 83.0, 82.7, 81.4, 81.3, 81.1, 47.2, 47.0, 31.5, 31.5, 28.0, 27.3, 25.6, 21.9, 21.8, 21.8; ^{31}P NMR (75 MHz, $CDCl_3$) δ 141.33; IR (Thin Film) 2919, 1600, 1452, 1380, 1211, 1159, 1040 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 705.3947, found 705.3949.

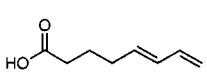
General procedure for synthesis of dienyl isocyanates:



Vinyl boronic ester **30** to dienes **32**: Vinyl boronic ester **30** was prepared from alkyne **29** (20 mmol scale) according to literature procedures.[1] To a flame-dried seal-tube charged with a magnetic stir bar and $Pd(PPh_3)_4$ (5 mol%, 0.39 mmol) was added 8 ml of benzene, boronic ester **30** (7.87 mmol dissolved in 8ml of benzene), NaOMe (15.74 mmol, 25 wt%

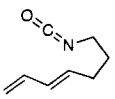
solution in MeOH), and the corresponding vinyl bromide (9.45 mmol) under an inert atmosphere. The reaction tube was sealed and heated at 80 °C. After 12 hours, the reaction mixture was cooled to ambient temperature, diluted with ether, filtered through a pad of celite, and concentrated in *vacuo*. The crude material was purified by flash column chromatography (15:1 Hexane:EtOAc) to yield a relatively clean **31**. The resulting ester **31** was treated with LiOH (10 eq) in 30 ml of MeOH/H_2O (3/1) and stirred at ambient temperature for 16 hours. The reaction was then quenched with 1M HCl, extracted (EtOAcx3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting dienoic acid **32** was purified by flash chromatography (gradient elution: 10:1 Hex:EtOAc, then 1:1 Hex:EtOAc).

Synthesis of target isocyanates: In a flame-dried round bottom flask under Ar atmosphere, triethylamine (5.58 mmol, 1.06 eq) was added to a stirring solution of carboxylic acid **32** (5.27 mmol) in dichloromethane (9.5 mL) at 0 °C. Diphenylphosphoryl azide (5.58 mmol, 1.06 eq) was then slowly added. After 4 hours, the reaction was concentrated under vacuum and rapidly purified by flash chromatography (20:1 Hex:EtOAc, solvent removal was carried out with the rotovap bath temperature less than 23 °C). The resulting acyl azide was slowly converted to the desired isocyanate by sitting in neat at ambient temperature for 12 hours followed by gently heating at 35 °C for 3-6 hours.

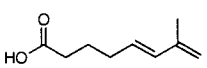


(*E*)-octa-5,7-dienoic acid (32). Procedure yielded a colorless oil (70% from **30**); R_f = 0.41 (7:3 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (ddd, 1H, *J* = 10.2, 10.2, 16.9 Hz), 6.05 (dd, 1H, *J* = 10.4, 15.1 Hz), 5.63 (dt, 1H, *J* = 7.0, 15.1 Hz), 5.08 (dm, 1H, *J* = 16.8 Hz), 4.96 (dm, 1H, *J* = 10.2 Hz), 2.34 (t, 2H, *J* =

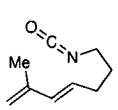
7.5 Hz), 2.12 (dt, 2H, J = 7.0, 7.0 Hz), 1.72 (tt, 2H, J = 7.5, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 137.2, 133.7, 132.2, 115.6, 33.6, 31.9, 24.2; IR (Thin Film) 2937, 1709, 1414, 1241 cm^{-1}; HRMS (ESI) *m/e* calcd (M-) 140.08373, found 140.08337.



(*E*)-7-isocyanatohepta-1,3-diene (15). Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (ddd, 1H, J = 10.2, 10.2, 17.1 Hz), 6.06 (dd, 1H, J = 10.5, 15.1 Hz), 5.62 (dt, 1H, J = 7.0, 14.7 Hz), 5.10 (dm, 1H, J = 16.8 Hz), 4.98 (dm, 1H, J = 10.0 Hz), 3.29 (t, 2H, J = 6.6 Hz), 2.17 (dt, 2H, J = 7.3, 7.3 Hz), 1.69 (tt, 2H, J = 6.8, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 133.0, 132.5, 115.9, 42.4, 30.7, 29.5; IR (Thin Film) 2952, 2273, 1603, 1440, 1006 cm^{-1}.

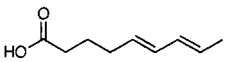


(*E*)-7-methylocta-5,7-dienoic acid (32b). Procedure yielded a colorless oil (50% from **30**); R_f = 0.41 (7:3 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, 1H, J = 15.6 Hz), 5.58 (dt, 1H, J = 6.8, 15.8 Hz), 4.86 (br s, 2H), 2.35 (t, 2H, J = 7.5 Hz), 2.15 (dt, 2H, J = 7.0, 7.0 Hz), 1.80 (s, 3H), 1.74 (tt, 2H, J = 7.5, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 142.1, 134.1, 129.3, 115.1, 33.6, 32.1, 24.4, 18.8; IR (Thin Film) 2937, 1709, 1416, 1242 cm^{-1}; HRMS (ESI) *m/e* calcd (M-) 154.09938, found 154.09925.

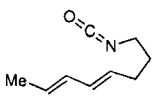


(*E*)-7-isocyanato-2-methylhepta-1,3-diene (33). Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, 1H, J = 15.6 Hz), 5.57 (dt, 1H,

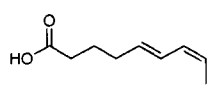
J = 7.0, 14.8 Hz), 4.87 (br s, 2H), 3.29 (t, 2H, J = 6.6 Hz), 2.19 (dt, 2H, J = 7.0, 7.0 Hz), 1.81 (s, 3H), 1.70 (tt, 2H, J = 6.9, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 134.4, 128.6, 115.3, 42.5, 31.0, 29.7, 18.8; IR (Thin Film) 2947, 2269, 1609, 1438, 967 cm^{-1}.



(5*E*,7*E*)-nona-5,7-dienoic acid (32c). Procedure yielded a colorless oil (50% from **30**); R_f = 0.53 (10:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, 1H, J = 11.1, 14.9 Hz), 5.94 (dd, 1H, J = 10.9, 10.9 Hz), 5.59 (dt, 1H, J = 7.0, 14.5 Hz), 5.38 (m, 1H), 2.35 (t, 2H, J = 7.6 Hz), 2.15 (dt, 2H, J = 7.1, 7.1 Hz), 1.77 – 1.70 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 132.7, 129.4, 126.7, 124.9, 33.6, 32.2, 24.4, 13.5; IR (Thin Film) 2935, 1709, 1411, 1235 cm^{-1}; HRMS (ESI) *m/e* calcd (M-) 154.09938, found 154.10005.

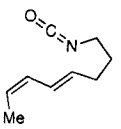


(2*E*,4*E*)-8-isocyanatooct-2,4-diene ((*E*,*E*)-36). Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dd, 1H, J = 11.1, 14.9 Hz), 5.95 (dd, 1H, J = 11.1, 11.1 Hz), 5.57 (dt, 1H, J = 7.0, 14.7 Hz), 5.40 (m, 1H), 3.30 (t, 2H, J = 6.6 Hz), 2.19 (dt, 2H, J = 7.1, 7.1 Hz), 1.73 – 1.66 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 129.2, 127.0, 125.2, 42.5, 30.9, 29.8, 13.5; IR (Thin Film) 2937, 2272, 1437, 1354, 984 cm^{-1}.

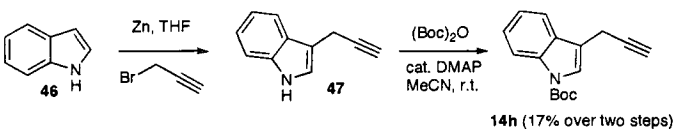


(5*E*,7*Z*)-nona-5,7-dienoic acid (32d). Procedure yielded a colorless oil (69% from **30**); R_f = 0.53 (10:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.95 (m, 2H), 5.55 (m, 1H), 5.47 (m, 1H), 2.33 (t, 2H, J = 7.6 Hz), 2.09 (dt, 2H, J = 7.1,

7.1 Hz), 1.74 – 1.66 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 131.7, 131.6, 130.3, 127.8, 33.5, 31.9, 24.5, 18.2; IR (Thin Film) 2933, 1705, 1414, 1269 cm^{-1}; HRMS (ESI) *m/e* calcd (M-) 154.09938, found 154.09974.



(2*Z*,4*E*)-8-isocyanatooocta-2,4-diene ((*E,Z*)-36). Flash chromatography of the acyl azide (96:4 Hex/EtOAc) and subsequent thermal conversion yielded a clear liquid (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 – 5.96 (m, 2H), 5.59 (m, 1H), 5.46 (m, 1H), 3.28 (t, 2H, *J* = 6.7 Hz), 2.13 (dt, 2H, *J* = 7.3, 7.3 Hz), 1.72 – 1.64 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 131.4, 129.5, 128.0, 42.4, 30.9, 29.5, 18.2; IR (Thin Film) 2934, 2272, 1439, 1355, 989 cm^{-1}.

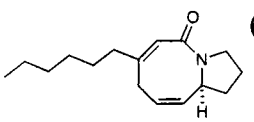


***tert*-butyl 3-(prop-2-ynyl)-1*H*-indole-1-carboxylate (14h).** To a solution of indole **46** (585 mg, 5 mmol) and propargyl bromide (2.4 ml, 20 mmol) in 6 ml of THF was added zinc dust (1.3 g, 20 mmol) at ambient temperature. After stirring for 12 hours, the reaction was diluted with EtOAc, filtered through a pad of celite, and concentrated in *vacuo*. After a quick flash chromatography (10:1 Hex/EtOAc), the resulting **46/47** mixture (~70% conversion) was subjected to a typical Boc-protection condition in the presence of cat. DMAP (0.03 eq) and $(Boc)_2O$ (1.1 eq). Aqueous work-up (partitioned between H_2O and EtOAc) followed by flash chromatography (20:1 Hex/EtOAc) yielded 220 mg of the target alkyne (17%); R_f = 0.37 (10:1 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.54 (d, 2H, *J* = 7.2 Hz), 7.31 (dd, 1H, *J* = 8.3, 8.3 Hz), 7.24

(dd, 1H, J = 8.1, 8.1 Hz), 3.60 (m, 2H), 2.14 (m, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.8, 123.6, 122.7, 119.0, 115.9, 115.5, 83.8, 80.7, 70.0, 28.4, 15.4; IR (Thin Film) 3298, 2979, 1732, 1453, 1368, 1254, 1159, 1081 cm^{-1}.

General procedure for the Rh-catalyzed [4+2+2] cycloaddition of dienyl isocyanates and terminal alkynes:

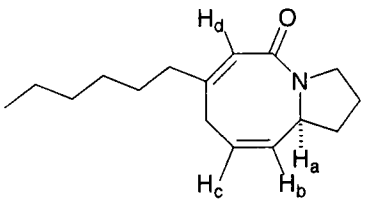
A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (3.5 mg, 0.0089 mmol) and the phosphoramidite ligand **L2** (12.4 mg, 0.0179 mmol), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 2.0 ml toluene was added via syringe and the resulting yellow solution was stirred at ambient temperature under argon flow for 15 minutes. To this solution was added a solution of alkyne **14** (0.268 mmol) and isocyanate **15,** or **33** (0.179 mmol) in 3 ml of toluene via syringe or cannula. After an additional 2 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 12 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc). Evaporation of solvent afforded the analytically pure product **16** or **34**.



(*S*,6*Z*,9*Z*)-7-hexyl-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16b). General procedure with alkyne **14b** and isocyanate **15** yielded 32.6 mg of the cycloadduct (74%); R_f = 0.33 (EtOAc); $[\alpha]_D^{20}$ = – 135.3 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min,

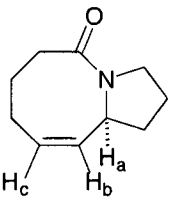
Major: 7.23 minutes, Minor: 8.49 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.72 (m, 1H), 5.34 (ddd, 1H, *J* = 2.6, 2.6, 11.1 Hz) 4.59 (br s, 1H), 3.48 (m, 1H), 3.37 (m, 1H), 3.18 (dm, 1H, *J* = 14.7 Hz), 2.40 (dd, 1H, *J* = 9.6, 14.7 Hz), 2.05 – 1.76 (m, 6H), 1.40 – 1.35 (m, 2H), 1.27 – 1.20 (m, 6H), 0.84 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 143.8, 133.6, 127.9, 121.9, 57.2, 45.3, 38.2, 33.8, 31.9, 30.8, 29.1, 27.7, 23.4, 22.8, 14.3; IR (Thin Film) 2927, 2855, 1657, 1618, 1411 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 247.19361, found 247.19381.

HSQC of **16b** was also recorded and attached after its ^{1}H and ^{13}C spectra. HSQC indicated 4 CH carbons at 57.2, 121.9, 127.9, and 133.6 ppm correlating to protons at 4.59, 5.89, 5.72, and 5.34 ppm respectively. All data are consistent with the desired bicyclic azocine structure, and match well with the literature compound **48** (Shown below). The absolute configuration of **16** was assigned by analogy to **48**, which was prepared from L-proline.[2]



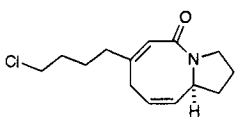
16b, $[\alpha]_D^{20}$= –135.3

H_a = 4.59 ppm (br s)
H_b = 5.34 ppm
H_c = 5.72 ppm
H_d = 5.89 ppm



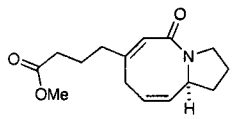
48, $[\alpha]_D^{20}$= –64.8

H_a = 4.45 ppm (br s)
H_b = 5.44 ppm
H_c = 5.67 ppm

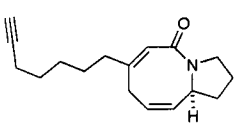


(*S*,6*Z*,9*Z*)-7-(4-chlorobutyl)-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16c). General procedure with alkyne **14c** and

isocyanate **15** yielded 31.3 mg of the cycloadduct (69%); R_f = 0.29 (EtOAc); $[\alpha]_D^{20}$ = – 105.8 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 6.07 minutes, Minor: 6.86 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.73 (m, 1H), 5.37 (m, 1H), 4.59 (br s, 1H), 3.51 (m, 1H), 3.50 (t, 2H, *J* = 6.4 Hz), 3.37 (m, 1H), 3.20 (dm, 1H, *J* = 14.7 Hz), 2.41 (dd, 1H, *J* = 9.6, 14.7 Hz), 2.08 (t, 2H, *J* = 7.3 Hz), 2.01 – 1.70 (m, 6H), 1.60 – 1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 142.9, 133.8, 127.7, 122.4, 57.2, 45.4, 45.0, 37.2, 33.9, 32.2, 30.7, 24.9, 23.4; IR (Thin Film) 2942, 2869, 1656, 1614, 1415 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 253.12334, found 253.12341.

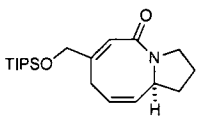


methyl 4-((*S*,6*Z*,9*Z*)-5-oxo-1,2,3,5,8,10a-hexahydropyrrolo[1,2-*a*]azocin-7-yl)butanoate (16d). General procedure with alkyne **14d** and isocyanate **15** yielded 33.1 mg of the cycloadduct (70%); R_f = 0.18 (EtOAc); $[\alpha]_D^{20}$ = – 104.0 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 8.04 minutes, Minor: 9.25 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 5.73 (m, 1H), 5.36 (m, 1H), 4.59 (br s, 1H), 3.63 (s, 3H), 3.49 (m, 1H), 3.36 (m, 1H), 3.20 (dm, 1H, *J* = 14.7 Hz), 2.41 (dd, 1H, *J* = 9.4, 14.7 Hz), 2.27 (t, 2H, *J* = 7.5 Hz), 2.08 (t, 2H, *J* = 7.6 Hz), 2.00 – 1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.6, 142.5, 133.8, 127.7, 122.7, 57.1, 51.8, 45.4, 37.3, 33.9, 33.6, 30.6, 23.4, 23.0; IR (Thin Film) 2950, 2876, 1735, 1655, 1614, 1416 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 263.15214, found 263.15189.

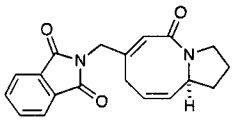


(*S*,6*Z*,9*Z*)-7-(hept-6-ynyl)-1,2,3,10a-tetrahydropyrrolo[1,2-

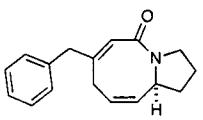
***a*]azocin-5(8*H*)-one (16e).** General procedure with alkyne **14e** and isocyanate **15** yielded 25.3 mg of the cycloadduct (55%); R_f = 0.34 (EtOAc); $[\alpha]_D^{20}$ = – 104.5 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 13.02 minutes, Minor: 14.77 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.71 (m, 1H), 5.34 (ddd, 1H, *J* = 2.6, 2.6, 10.9 Hz), 4.59 (br s, 1H), 3.47 (m, 1H), 3.36 (m, 1H), 3.19 (dm, 1H, *J* = 14.7 Hz), 2.39 (dd, 1H, *J* = 9.6, 14.7 Hz), 2.14 (ddd, 2H, *J* = 2.6, 7.0, 7.0 Hz), 2.04 (t, 2H, *J* = 6.8 Hz), 2.00 – 1.75 (m, 5H), 1.52 – 1.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 143.4, 133.7, 127.8, 122.2, 84.7, 68.4, 57.2, 45.3, 38.0, 33.8, 30.8, 28.5, 28.4, 27.2, 23.4, 18.5; IR (Thin Film) 2932, 2856, 1657, 1614, 1417 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 257.17796, found 257.17816.



(*S*,6*E*,9*Z*)-7-((triisopropylsilyloxy)methyl)-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16g). General procedure with alkyne **14g** and isocyanate **15** yielded 51.5 mg of the cycloadduct (82%); R_f = 0.50 (EtOAc); $[\alpha]_D^{20}$ = – 90.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 4.86 minutes, Minor: 5.28 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 5.67 (m, 1H), 5.36 (ddd, 1H, *J* = 2.8, 2.8, 11.1 Hz), 4.59 (br s, 1H), 4.15 – 4.06 (m, 2H), 3.50 (m, 1H), 3.37 (m, 1H), 3.14 (dm, 1H, *J* = 14.9 Hz), 2.31 (dd, 1H, *J* = 9.6, 14.9 Hz), 2.01 – 1.76 (m, 4H), 1.10 – 0.97 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.6, 134.0, 127.5, 120.3, 65.3, 57.0, 45.4, 33.9, 27.2, 23.4, 18.2, 12.1; IR (Thin Film) 2943, 2865, 1666, 1621, 1414 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 349.24371, found 349.24347.

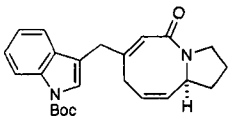


2-(((*S*,6*E*,9*Z*)-5-oxo-1,2,3,5,8,10a-hexahydropyrrolo[1,2-*a*]azocin-7-yl)methyl)isoindoline-1,3-dione (16h). General procedure with alkyne **14h** and isocyanate **15** yielded 37.4 mg of the cycloadduct (65%); R_f = 0.27 (EtOAc); $[\alpha]_D^{20}$ = – 53.3 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 44.51 minutes, Minor: 41.43 minutes, 210 nm detection light, *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2H), 7.72 – 7.69 (m, 2H), 6.09 (s, 1H), 5.53 (m, 1H), 5.36 (br d, 1H, *J* = 11.1 Hz), 4.63 (br s, 1H), 4.32 (d, 1H, *J* = 15.3 Hz), 4.19 (d, 1H, *J* = 15.3 Hz), 3.46 (m, 1H), 3.35 (m, 1H), 3.22 (dm, 1H, *J* = 15.1 Hz), 2.54 (dd, 1H, *J* = 9.6, 15.3 Hz), 2.01 – 1.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.0, 136.5, 134.4, 132.0, 126.6, 124.8, 123.6, 56.9, 45.3, 43.0, 33.9, 28.8, 23.3; IR (Thin Film) 2969, 2876, 1714, 1666, 1617, 1421, 1391 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 322.13174, found 322.13178.

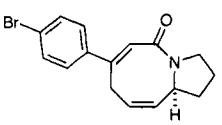


(*S*,6*E*,9*Z*)-7-benzyl-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16f). General procedure with alkyne **14f** and isocyanate **15** yielded 31.0 mg of the cycloadduct (68%); R_f = 0.31 (EtOAc); $[\alpha]_D^{20}$ = – 111.6 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 8.55 minutes, Minor: 9.92 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 5H), 5.84 (s, 1H), 5.58 (m, 1H), 5.31 (br d, 1H, *J* = 10.9 Hz), 4.60 (br s, 1H), 3.48 (m, 1H), 3.36 (m, 1H), 3.34 (s, 2H), 3.17 (dm, 1H, *J* = 14.7 Hz), 2.44 (dd, 1H, *J* = 9.6, 14.7 Hz), 2.01 – 1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 142.8, 138.1, 133.7, 129.6, 128.6, 127.7, 126.7, 123.7, 57.1, 45.3, 43.9, 33.9, 30.3, 23.4; IR

(Thin Film) 2967, 2876, 1658, 1615, 1416 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 253.14666, found 253.1467.

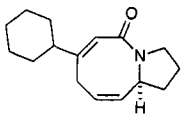


***tert*-butyl 3-(((*S*,6*E*,9*Z*)-5-oxo-1,2,3,5,8,10a-hexahydropyrrolo[1,2-*a*]azocin-7-yl)methyl)-1*H*-indole-1-carboxylate (16i).** General procedure with alkyne **14i** and isocyanate **15** yielded 40.0 mg of the cycloadduct (57%); R_f = 0.36 (EtOAc); $[\alpha]_D^{20}$ = – 84.6 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 6.83 minutes, Minor: 6.03 minutes, 230 nm detection light, *ee* = 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J* = 6.4 Hz), 7.40 – 7.37 (m, 2H), 7.27 (t, 1H, *J* = 7.3 Hz), 7.17 (t, 1H, *J* = 7.5 Hz), 5.86 (s, 1H), 5.68 (m, 1H), 5.34 (br d, 1H, *J* = 10.9 Hz), 4.55 (br s, 1H), 3.50 – 3.33 (m, 4H), 3.25 (dm, 1H, *J* = 14.5 Hz), 2.53 (dd, 1H, *J* = 9.6, 14.7 Hz), 1.98 – 1.75 (m, 4H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.7, 149.8, 141.5, 135.8, 134.0, 130.6, 127.7, 124.6, 123.4, 122.7, 119.0, 116.9, 115.5, 83.8, 57.1, 45.4, 33.9, 33.0, 30.6, 28.4, 23.4; IR (Thin Film) 2975, 1731, 1659, 1614, 1452, 1420, 1369, 1157 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 392.20999, found 392.21139.

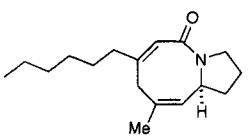


(*S*,6*E*,9*Z*)-7-(4-bromophenyl)-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16k). General procedure with alkyne **14k** and isocyanate **15** yielded 20.2 mg of the cycloadduct (35%); R_f = 0.33 (EtOAc); $[\alpha]_D^{20}$ = – 22.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 15.06 minutes, Minor: 10.83 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 8.5 Hz), 7.25 (d, 2H, *J* = 8.1 Hz), 6.42 (s, 1H), 5.93 (m, 1H),

5.47 (ddd, 1H, J = 2.6, 2.6, 11.1 Hz), 4.67 (br s, 1H), 3.58 – 3.45 (m, 3H), 2.93 (dd, 1H, J = 9.3, 14.3 Hz), 2.03 – 1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 139.8, 139.1, 134.4, 131.9, 128.2, 127.8, 123.7, 122.4, 57.0, 45.5, 33.9, 30.1, 23.4; IR (Thin Film) 2967, 2880, 1636, 1606, 1417 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 317.04153, found 317.04174.

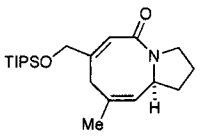


(*S*,6*E*,9*Z*)-7-cyclohexyl-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (16l). General procedure with alkyne **14l** and isocyanate **15** yielded 16.9 mg of the cycloadduct (39%); R_f = 0.29 (EtOAc); *ee* = n.d.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.71 (m, 1H), 5.33 (m, 1H), 4.57 (br s, 1H), 3.48 (m, 1H), 3.37 (m, 1H), 3.12 (dm, 1H, J = 14.9 Hz), 2.50 (dd, 1H, J = 9.6, 14.9 Hz), 1.98 – 1.63 (m, 9H), 1.26 – 1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 148.1, 133.3, 128.6, 120.5, 57.0, 45.8, 45.3, 33.8, 32.2, 31.7, 29.4, 26.7, 26.5, 26.3, 23.4; IR (Thin Film) 2925, 2851, 1651, 1614, 1413 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 245.17796, found 245.17807.

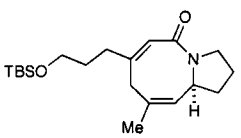


(*S*,6*Z*,9*Z*)-7-hexyl-9-methyl-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (34b). General procedure with alkyne **14b** and isocyanate **33** yielded 29.0 mg of the cycloadduct (62%); R_f = 0.34 (EtOAc); $[\alpha]_D^{20}$ = – 147.4 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 97:3 hexane:iPrOH, 1.0 ml/min, Major: 6.91 minutes, Minor: 7.74 minutes, 210 nm detection light, *ee* = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.11 (s, 1H), 4.53 (br s, 1H), 3.48 (m, 1H), 3.35 – 3.29 (m, 2H), 2.20 (d, 1H, J = 14.3 Hz), 2.01 (t, 2H, J = 7.5 Hz), 1.98 – 1.79 (m, 3H), 1.78 (s, 3H), 1.72 (m, 1H), 1.40 – 1.34 (m, 2H), 1.28 – 1.23 (m, 6H), 0.84 (t, 3H, J = 6.7 Hz); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 169.9, 143.3, 136.2, 127.3, 121.9, 57.0, 45.2, 38.0, 36.4, 34.2, 31.9, 29.1, 27.7, 27.5, 23.5, 22.7, 14.3; IR (Thin Film) 2927, 2857, 1656, 1618, 1411 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 261.20926, found 261.20921.

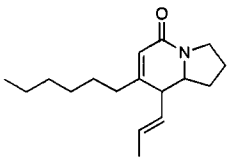


(*S*,6*E*,9*Z*)-9-methyl-7-((triisopropylsilyloxy)methyl)-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (34g). General procedure with alkyne **14g** and isocyanate **33** yielded 33.2 mg of the cycloadduct (51%); R_f = 0.58 (EtOAc); $[\alpha]_D^{20}$ = – 109.5 (c = 1, $CHCl_3$); HPLC analysis – Chiracel AS-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 20.40 minutes, Minor: 18.71 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 5.12 (s, 1H), 4.51 (br s, 1H), 4.13 (d, 1H, *J* = 15.1 Hz), 4.05 (d, 1H, *J* = 15.3 Hz), 3.50 (m, 1H), 3.35 (m, 1H), 3.27 (br d, 1H, *J* = 14.7 Hz), 2.27 – 2.11 (m, 2H), 2.00 – 1.71 (m, 6H), 1.11 – 0.98 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.2, 135.6, 127.5, 120.4, 65.2, 56.9, 45.3, 34.2, 32.7, 27.7, 23.5, 18.2, 12.2; IR (Thin Film) 2942, 2865, 1667, 1623, 1415 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 363.25936, found 363.25981.

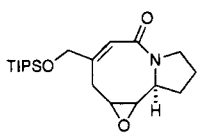


(*S*,6*Z*,9*Z*)-7-(3-(*tert*-butyldimethylsilyloxy)propyl)-9-methyl-1,2,3,10a-tetrahydropyrrolo[1,2-*a*]azocin-5(8*H*)-one (34j). General procedure with alkyne **14j** and isocyanate **33** yielded 33.6 mg of the cycloadduct (54%); R_f = 0.45 (EtOAc); $[\alpha]_D^{20}$ = – 111.9 (c = 1, $CHCl_3$); HPLC analysis – Chiracel OJ-H column 95:5 hexane:iPrOH, 1.0 ml/min, Major: 5.06 minutes, Minor: 5.54 minutes, 210 nm detection light, *ee* = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.11 (s, 1H), 4.52 (br s, 1H), 3.57 (t, 2H, *J* = 6.0 Hz), 3.47 (m, 1H), 3.34 – 3.29 (m, 2H), 2.22 (d, 1H, *J* = 14.5 Hz),

2.08 (t, 2H, J = 7.5 Hz), 2.00 – 1.71 (m, 7H), 1.64 – 1.58 (m, 2H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 142.9, 136.1, 127.3, 121.9, 62.6, 57.0, 45.2, 36.5, 34.2, 34.1, 30.8, 27.8, 26.1, 23.5, 18.5, -5.1; IR (Thin Film) 2953, 2856, 1658, 1619, 1410, 1101 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 349.24371, found 349.24375.



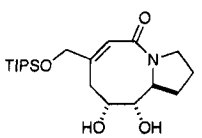
(*E*)-7-hexyl-8-(prop-1-enyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one ((*E*)-37). General procedure with alkyne **14b** and isocyanate **(*E*,*E*)-36** yielded 21.5 mg of the cycloadduct (46%); R_f = 0.31 (EtOAc); *ee* = n.d.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 – 5.70 (m, 2H), 5.17 (dd, 1H, J = 10.6, 10.6 Hz), 3.64 (m, 1H), 3.44 (m, 1H), 3.39 (m, 1H), 3.21 (dd, 1H, J = 11.4, 11.4 Hz), 2.11 – 2.01 (m, 3H), 1.95 (m, 1H), 1.75 – 1.64 (m, 4H), 1.53 (m, 1H), 1.39 – 1.21 (m, 8H), 0.84 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 156.6, 128.6, 127.6, 120.8, 61.5, 44.6, 43.2, 34.2, 32.8, 31.8, 29.1, 27.1, 22.9, 22.7, 14.3, 13.6; IR (Thin Film) 2927, 2858, 1666, 1611, 1443, 1354 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 261.20926, found 261.20967.



(9a*S*,*E*)-3-((triisopropylsilyloxy)methyl)-1a,2,7,8,9,9a-hexahydrooxireno[2,3-*c*]pyrrolo[1,2-*a*]azocin-5(9b*H*)-one (42). To a solution of azocine **16g** (0.063 mmol) in CH_2Cl_2 (2 ml) was added *m*CPBA (0.095 mmol) at ambient temperature. After stirring for 12 hours, reaction was quenched by sat. $Na_2S_2O_3$, then by sat. $NaHCO_3$. Reaction was extracted with CH_2Cl_2 (x2), dried over $MgSO_4$, and concentrated in *vacuo*. Flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc) yielded 12.0 mg as the major diastereomer (52%, R_f = 0.54 in EtOAc), and 4.8 mg as the minor diastereomer (21%, R_f = 0.42 in EtOAc);

The major epoxide: $[\alpha]_D^{20}$ = – 39.0 (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.23 – 4.14 (m, 3H), 3.59 (m, 1H), 3.39 (m, 1H), 3.12 (m, 1H), 2.82 (d, 1H, *J* = 4.3 Hz), 2.49 (dd, 1H, *J* = 7.9, 13.9 Hz), 2.41 (dd, 1H, *J* = 6.3, 14.1 Hz), 2.19 – 2.07 (m, 3H), 1.89 (m, 1H), 1.14 – 0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 145.6, 120.9, 66.5, 60.0, 55.7, 51.4, 46.8, 32.5, 29.0, 23.2, 18.2, 12.1; IR (Thin Film) 2943, 2866, 1665, 1624, 1413, 1096 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 365.23862, found 365.23902.

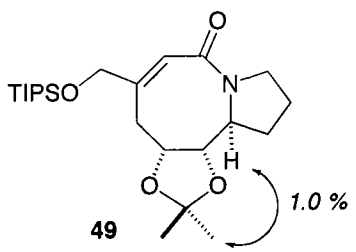
The minor epoxide: $[\alpha]_D^{20}$ = – 41.2 (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 4.23 (dd, 1H, *J* = 1.7, 15.6 Hz), 4.13 (m, 1H), 4.08 (dd, 1H, *J* = 1.9, 15.8 Hz), 3.47 (m, 2H), 3.11 (t, 1H, *J* = 4.9 Hz), 2.80 – 2.74 (m, 2H), 2.38 (dd, 1H, *J* = 5.5, 14.9 Hz), 2.10 – 1.94 (m, 4H), 1.14 – 1.03 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 144.0, 122.4, 66.6, 58.9, 58.4, 56.6, 45.1, 33.0, 27.6, 23.5, 18.2, 12.1; IR (Thin Film) 2943, 2866, 1672, 1626, 1412, 1113 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 365.23862, found 365.23915.



(9*R*,10*S*,10a*S*,*E*)-9,10-dihydroxy-7-((triisopropylsilyloxy)methyl)-2,3,8,9,10,10a-hexahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (43). To a solution of azocine **16g** (0.086 mmol) and *N*-methylmorpholine oxide (1 eq, 0.086 mmol) in acetone (1 ml) was added a solution of OsO_4 (4% wt. in H_2O, 0.0086 mmol) in acetone (0.5 ml) at 0 °C, followed by addition of 0.3 ml of H_2O. Reaction mixture was stirred at 0 °C for two hours, then at ambient temperature for 12 hours. Reaction was quenched by sat. $NaHSO_3$, extracted with EtOAc (x2), dried over $MgSO_4$, and concentrated in *vacuo*. Flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by

100% EtOAc) yielded 24.2 mg of the target diol (72%); R_f = 0.14 (EtOAc); $[\alpha]_D^{20}$ = – 33.6 (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.19 (d, 1H, *J* = 13.0 Hz), 4.12 (d, 1H, *J* = 13.0 Hz), 4.08 – 3.98 (m, 3H), 3.67 (ddd, 1H, *J* = 8.7, 8.7, 12.6 Hz), 3.44 (m, 1H), 3.38 (m, 1H), 2.78 (d, 1H, *J* = 7.2 Hz), 2.64 (dd, 1H, *J* = 9.6, 16.0 Hz), 2.43 (d, 1H, *J* = 16.0 Hz), 2.33 (m, 1H), 1.99 – 1.92 (m, 2H), 1.78 (m, 1H), 1.16 – 1.04 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 142.9, 122.5, 72.6, 68.4, 66.3, 58.6, 45.6, 32.6, 28.0, 21.9, 18.1, 12.1; IR (Thin Film) 3389, 2942, 2865, 1583, 1454 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 383.24919, found 383.24937.

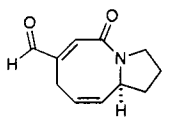
To determine the relative stereochemistry of **43**, the corresponding acetonide **49** was prepared by treating the diol with 2,2-dimethoxypropane (1 ml) and $TsOH{\cdot}H_2O$ at 0 °C. NOE experiment of **49** suggests the ***(R,R,S)*-43** diastereomer (shown below).



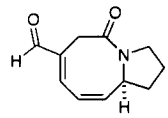
49

(3a*R*,11a*S*,11b*S*,*E*)-2,2-dimethyl-5-((triisopropylsilyloxy)methyl)-3a,4,9,10,11,11a-hexahydro-[1,3]dioxolo[4,5-*c*]pyrrolo[1,2-*a*]azocin-7(11b*H*)-one (49). R_f = 0.44 (EtOAc); $[\alpha]_D^{20}$ = – 82.7 (c = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 4.46 (dd, 1H, *J* = 1.9, 16.0 Hz), 4.24 (dd, 1H, *J* = 6.0, 6.0 Hz), 4.08 (dd, 1H, *J* = 2.1, 16.0 Hz), 4.04 (m, 1H), 3.79 – 3.71 (m, 2H), 3.33 (ddd, 1H, *J* = 3.0, 7.9, 11.5 Hz), 2.71 (d, 1H, *J* = 14.7 Hz), 2.29 (dd, 1H, *J* = 6.8, 14.9 Hz), 2.12 (m, 1H), 1.98 – 1.91 (m, 2H), 1.82 (m, 1H), 1.35 (s, 3H), 1.31 (s, 3H), 1.15 – 1.04 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

170.2, 145.0, 120.8, 76.3, 72.5, 66.8, 58.6, 45.6, 28.7, 27.9, 27.8, 25.8, 21.8, 18.3, 18.3, 12.2; IR (Thin Film) 2941, 2866, 1623, 1413 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 423.28049, found 423.28042.



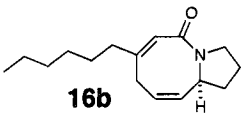
(*S*,6*E*,9*Z*)-5-oxo-1,2,3,5,8,10a-hexahydropyrrolo[1,2-*a*]azocine-7-carbaldehyde (44). To a solution of azocine **16g** (0.246 mmol) in 6 ml of THF was added TBAF (1.0 M THF solution, 5 eq, 1.23 mmol) at 0 °C. Reaction mixture was stirred at 0 °C for two hours before subjected to flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc) to yield the corresponding alcohol. To the alcohol dissolved in 3.5 ml of chloroform was added MnO_2 (10 eq). The reaction flask fitted with a west condenser was then immersed in 50 °C oil bath for 12 hours. The reaction mixture was cooled to ambient temperature, filted through a pad of celite, and concentrated in *vacuo*. Flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc) yielded 29.6 mg of the target aldehyde (63% over two steps); R_f = 0.33 (EtOAc); $[\alpha]_D^{20}$ = – 142.5 (c = 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.93 (s, 1H), 5.74 (m, 1H), 5.36 (ddd, 1H, *J* = 2.6, 2.6, 11.1 Hz), 4.50 (br s, 1H), 3.52 (m, 1H), 3.47 (m, 1H), 3.23 (dd, 1H, *J* = 9.4, 14.9 Hz), 2.88 (dm, 1H, *J* = 14.9 Hz), 2.05 – 1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 166.7, 142.3, 140.6, 133.6, 127.5, 56.2, 45.6, 34.0, 23.2, 22.1; IR (Thin Film) 2952, 2873, 1689, 1641, 1613, 1431 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 191.09463, found 191.09473.



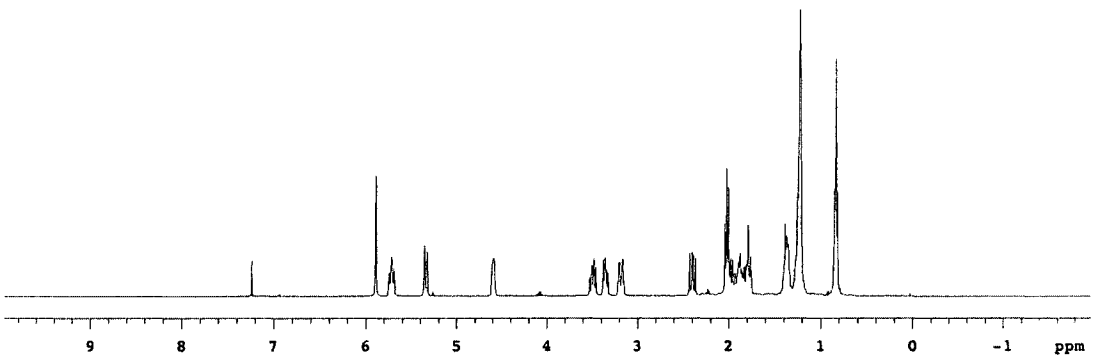
(*S*,7*E*,9*Z*)-5-oxo-1,2,3,5,6,10a-hexahydropyrrolo[1,2-*a*]azocine-7-carbaldehyde (45). To a solution of azocine **16g** (0.23 mmol) in 6 ml of THF was added TBAF (1.0 M THF solution, 5 eq, 1.15 mmol) at 0 °C. Reaction mixture was stirred at ambient temperature for 24 hours before subjected to flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc) to yield the corresponding alcohol. To the alcohol dissolved in 3 ml of chloroform was added MnO_2 (10 eq). The reaction flask fitted with a west condenser was then immersed in 50 °C oil bath for 12 hours. The reaction mixture was cooled to ambient temperature, filted through a pad of celite, and concentrated in *vacuo*. Flash column chromatography (gradient elution typically 50:50 Hex:EtOAc followed by 100% EtOAc) yielded 25.0 mg of the target aldehyde (57% over two steps); R_f = 0.23 (EtOAc); $[\alpha]_D^{20}$ = + 193.4 (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 6.85 (d, 1H, *J* = 5.1 Hz), 6.29 (dm, 1H, *J* = 11.7 Hz), 5.89 (dd, 1H, *J* = 5.3, 11.7 Hz), 4.44 (m, 1H), 3.66 (m, 1H), 3.63 (d, 1H, *J* = 13.0 Hz), 3.38 (ddd, 1H, *J* = 6.8, 6.8, 12.4 Hz), 3.30 (d, 1H, *J* = 13.2 Hz), 2.23 (m, 1H), 1.92 – 1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 168.1, 145.9, 140.0, 139.7, 127.9, 57.5, 47.7, 35.5, 33.9, 23.0; IR (Thin Film) 2972, 2876, 1681, 1643, 1425 cm^{-1}; HRMS (ESI) *m/e* calcd (M+) 191.09463, found 191.09493.

STANDARD 1H OBSERVE

yu3-445

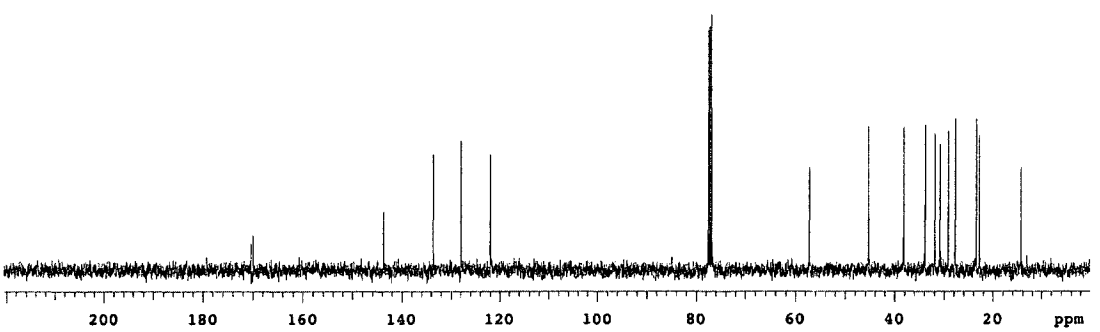


16b

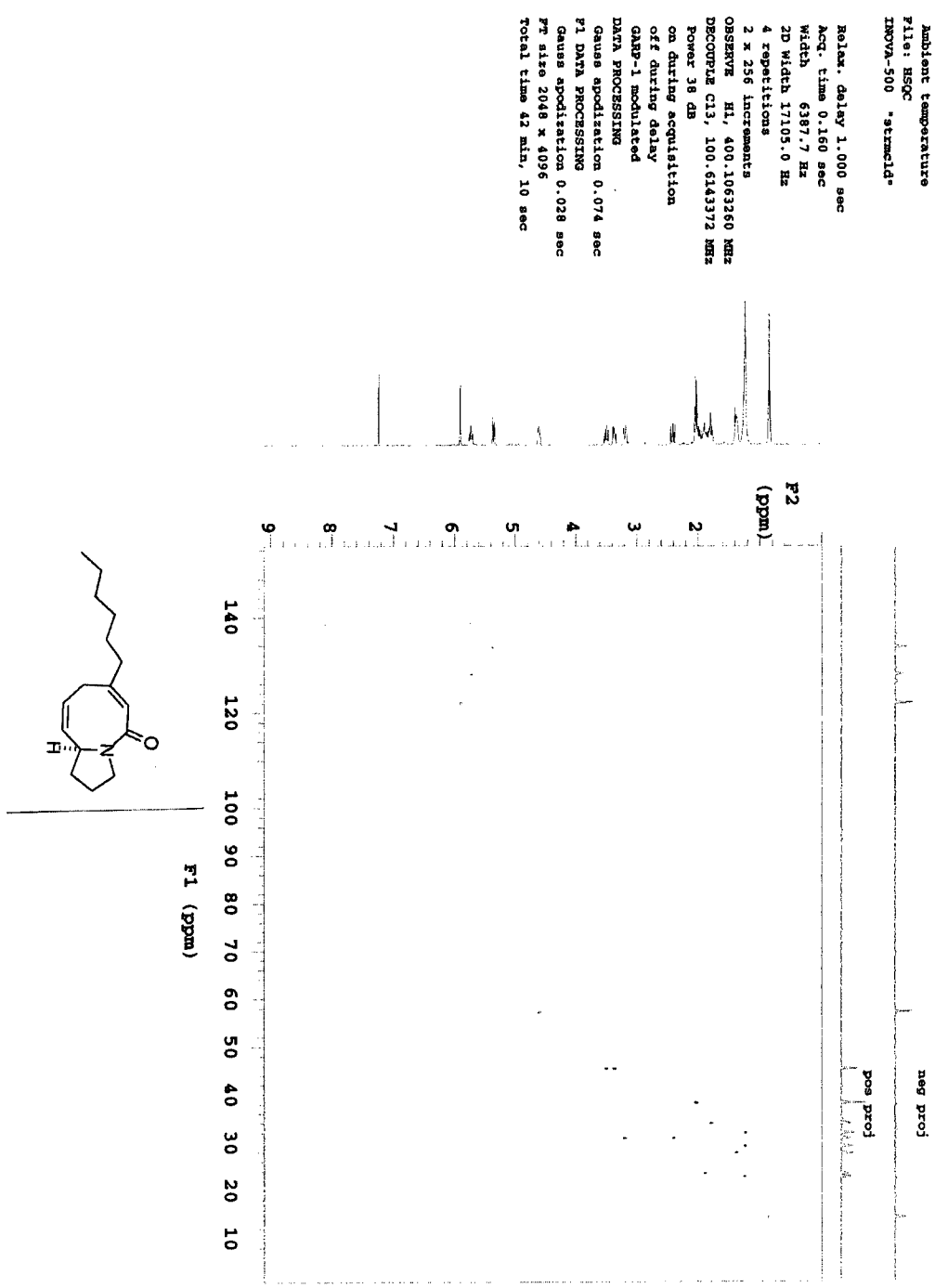


13C OBSERVE

yu3-445

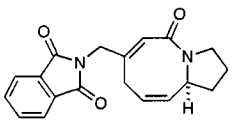


HSQC of **16b**

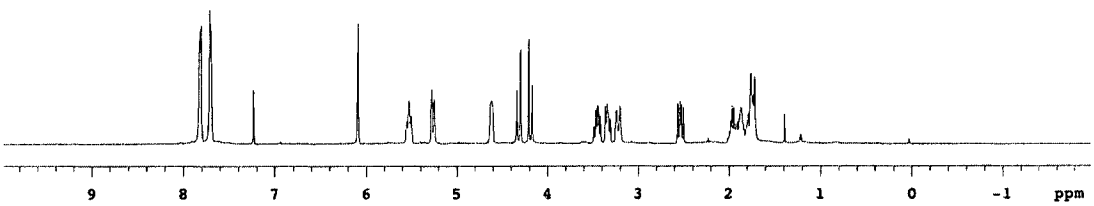


STANDARD 1H OBSERVE

yu3-477

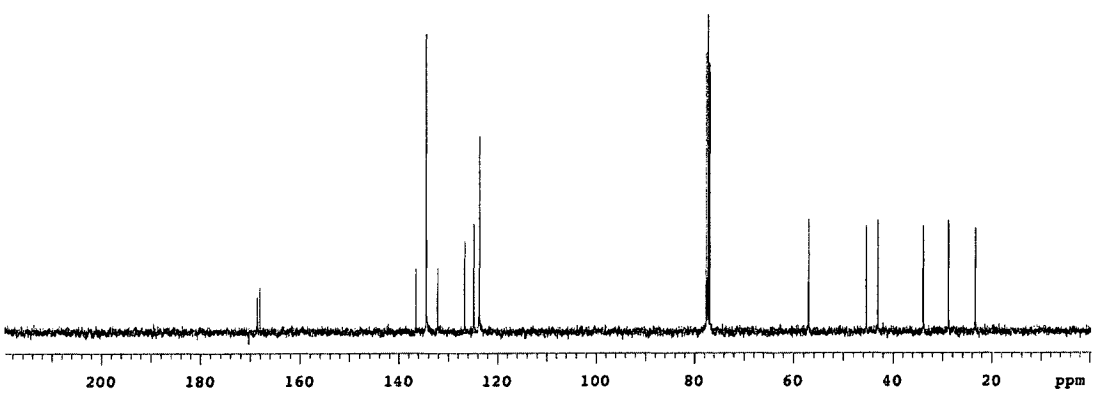


16h



13C OBSERVE

yu3-477



References:

[1] (a) Shirakawa, K.; Arase, A.; Hoshi, M. *Synthesis* **2004**, 1814. For the exact compound, see: (b) Fujita, M.; Lee, H. J.; Okuyama, T. *Org. Lett.* **2006**, *8*, 1399.

[2] Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron* **1996**, *52*, 10597.