Asymmetric Catalysis

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Total Synthesis of Indolizidine Alkaloid (−)-209D: Overriding Substrate Bias in the Asymmetric Rhodium-Catalyzed [2+2+2] Cycloaddition**

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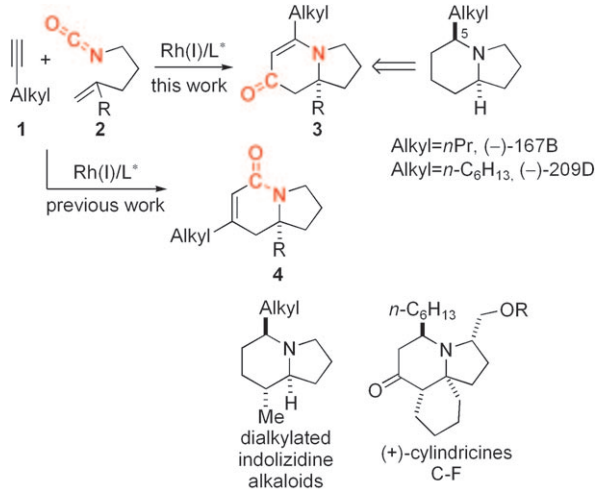
Indolizidine frameworks possessing an alkyl group substituted at the 5-position (indolizidine numbering)[1] represent a large class of naturally occurring compounds.[2] Alkaloids ranging from structurally simple indolizidine 167B and 209D to more complex marine alkaloids, such as cylindricines[3] (Scheme 1) and the immunosuppressant FR901483,[4] all contain such ring systems. Most 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.[5] Herein, we detail the development of an enantioselective rhodium-catalyzed [2+2+2] cycloaddition of terminal alkyl alkynes and alkenyl isocyanates to generate various 5-alkyl indolizinones (**3**). As part of a program directed toward developing a universal strategy to indolizidine alkaloids, the synthetic utility herein is demonstrated by an expedient synthesis of (−)-209D.

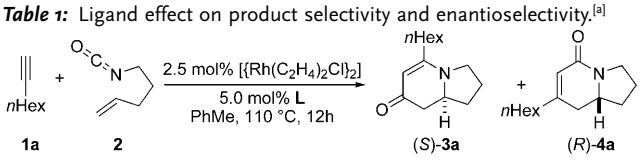


Scheme 1. [2+2+2] Cycloaddition strategies to access the framework of various indolizidine alkaloids. L* = ligand.

We have been exploring the use of neutral rhodium(I)/taddol-derived phosphoramidite complexes (see Table 1 for ligand structures) as enantioselective catalysts for various [2+2+2] cycloadditions, including reactions of terminal alkynes with isocyanates[6] or carbodiimides.[7] In previous studies, the use of terminal alkyl alkynes with these catalysts provides efficient cycloadditions to afford various bicyclic lactams **4** (Scheme 1) in good yields and enantioselectivities, whereas the 5-alkyl indolizinone cycloadducts **3**, resulting from a CO migration process, can only be observed as minor components. Herein, we report a new Rh·L* system to achieve a catalyst-controlled cycloaddition en route to 5-alkyl indolizinones **3**.

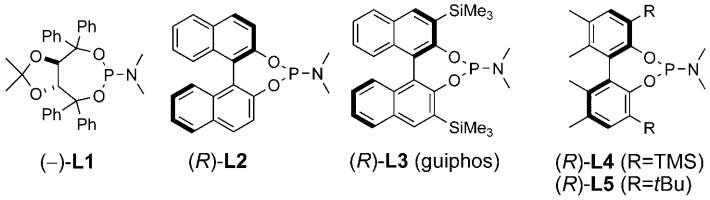
To tune product selectivity through ligand design, we began our study by examining the cycloaddition of 1-octyne (**1a**) and alkenyl isocyanate **2** using various phosphoramidite ligands[8] (Table 1). Switching from taddol-derived ligands such as (−)-**L1** to binol-derived (*R*)-**L2** led to a complete inversion of product selectivity (Table 1, entry 1 versus 2) favoring the indolizinone **3a**. Formation of **3** is thought to proceed through the initial metalacycle **I** (Scheme 2) and a

Table 1: Ligand effect on product selectivity and enantioselectivity.[a]



Entry	L	3:4[b]	Yield of 3 [%][c]	ee [%] of 3[d]
1	(−)-**L1**	1:3.2	20	73[e]
2	(*R*)-**L2**	2.2:1	22	72
3	(*R*)-**L3**	3.8:1	60	96
4	(*R*)-**L4**	3.5:1	50	94
5	(*R*)-**L5**	6.2:1	75	91

[a] Reaction conditions: **1** (2 equiv), **2** (0.27 mmol), Rh/**L** in PhMe (0.07 M) at 110 °C. [b] Product selectivity determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c] Yield of isolated product. [d] Determined by HPLC methods using a chiral stationary phase. [e] Other enantiomer. TMS = trimethylsilyl.



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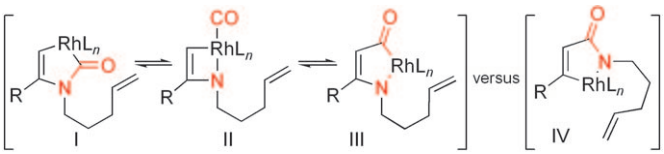
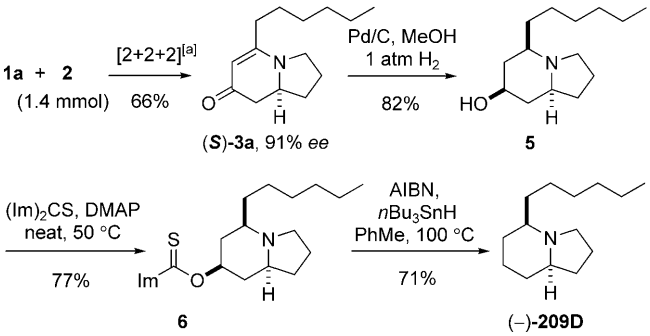


Scheme 2. Proposed mechanism of the [2+2+2] cycloaddition.

subsequent CO migration process via **II** to arrive at **III**. The migratory insertion of the pendant alkene into the Rh–N bond and subsequent reductive elimination gives rise to cycloadducts **3**. The selectivity in the formation of two initial metalacycles (**I** versus **IV**) is reflected in the product selectivity between **3** and **4**. Despite the low yield and poor *ee* value, the fundamental difference in product selectivity prompted additional investigation into the binol-derived phosphoramidites. Ligands possessing substitution at both the 3- and 3′-position of the binol backbone positively impact the reaction efficiency toward the desired indolizinone **3a**. Additional exploration led to the discovery of guiphos ((*R*)-**L3**). This TMS-substituted phosphoramidite (*R*)-**L3** provides a much improved reaction having product selectivity of approximately 4:1, good chemical yield, and most importantly an excellent 96% *ee* for **3a** (Table 1, entry 3). Although the TMS-substituted biphenol-derived phosphoramidite (*R*)-**L4** behaves no differently than guiphos (Table 1, entry 4), the corresponding ligand possessing *tert*-butyl groups at the 3,3′-positions ((*R*)-**L5**)[9,10] proved superior. The precatalyst $[\{Rh(C_2H_4)_2Cl\}_2]$, modified with (*R*)-**L5**, provides a clean reaction to furnish the desired indolizinone **3a** with a good product ratio (6.2:1) in excellent yield and enantioselectivity (Table 1, entry 5).

Indolizidine 209D belongs to a family of 22 natural products, commonly referred to as gephyrotoxins, isolated from the skin secretions of neotropical frogs.[11] 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, both to prepare them in greater quantities, and as a tool to validate new methodologies.[12] The key intermediate 5-hexyl indolizinone **3a** can be prepared conveniently by the cycloaddition protocol in one step and is suitable for scale-up (Scheme 3). The resulting vinylogous amide functionality readily undergoes a diastereoselective hydrogenation to afford enantioenriched amino alcohol **5** as a single diastereomer. Barton–McCombie deoxygenation via **6** completes the four-step enantioselective synthesis of (−)-209D, which also confirms the absolute configuration of **3a**: $[\alpha]_D^{22} = -66.5°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2); lit.[10a] $[\alpha]_D^{26} = -80.4°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2). Considering that alkenyl isocyanate **2** can be prepared in one step from commercially available 5-hexenoic acid, this constitutes the shortest synthesis of 209D reported to date.[10]

The newly developed Rh/phosphoramidite (*R*)-**L5** catalyst promotes the enantioselective synthesis of 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



Scheme 3. Synthesis of indolizidine (−)-209D. [a] See entry 1 of Table 2 for the reaction conditions. Im = imidazole, DMAP = 4-dimethylaminopyridine, AIBN = 2,2′-azobis(isobutyronitrile).

all react smoothly to afford cycloadducts in good product ratios and excellent enantioselectivities (Table 2, entries 2–7). The cycloaddition is highly sensitive to both electronic and steric effects on the alkyne partner. The product selectivity shifts more toward formation of the bicyclic lactams **4** when electron-withdrawing substituents are 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 5:1 ratio obtained using **1g** (Table 2, entry 8 versus entry 7). In a more extreme case, the cycloaddition of the TIPS-protected propargyl alcohol **1i** furnishes a 1.6:1 product mixture slightly favoring the indolizinone **3i** (Table 2, entry 9). In contrast, the reaction with the more sterically hindered alkyne **1j** improves the product selectivity to provide the desired cycloadduct **3j** in a high yield and excellent enantioselectivity (Table 2, entry 10). 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 product ratios of 14:1 (Table 2, entries 11 and 12). Even more impressively, the rhodium catalyst modified by ligand (*R*)-**L5** promotes the cycloaddition of tertiary alkyl-substituted alkynes to gain access to highly congested 5-alkyl indolizinones (Table 2, entries 13 and 14). 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 (*R*)-**L5** produces the best product selectivity and high overall reactivity, whereas the use of guiphos ((*R*)-**L3**) usually gives the best level of enantiocontrol. Although guiphos ((*R*)-**L3**) 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 (Table 2, entry 15). This protocol can also be applied to the synthesis of 5,9-dialkyl indolizinones [Eq. (1)]. 1,1-Disubstituted alkenyl isocyanate **7** participates in the cycloaddition with 1-octyne (**1a**) quite efficiently to provide the corresponding cycloadduct **8** in good product ratio and yield of the isolated product. Interestingly, whereas the product selectivity stays relatively unchanged as those

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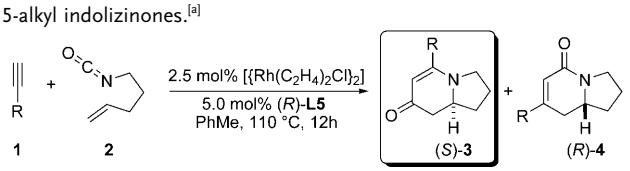
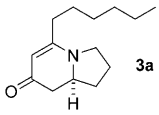
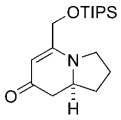
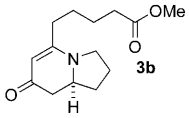
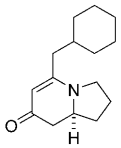
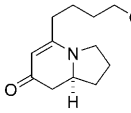
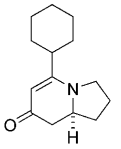
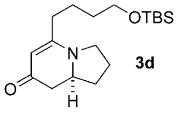
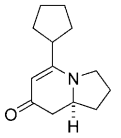
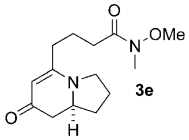
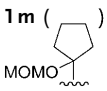
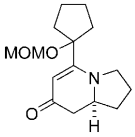
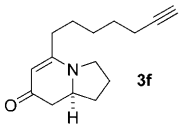
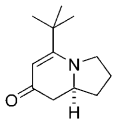
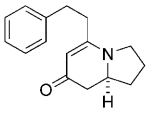
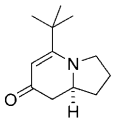
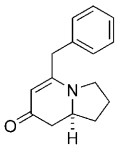
Table 2: Enantioselective synthesis of 5-alkyl indolizinones.[a]

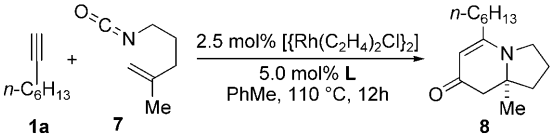


Entry	1 (R)	Major product	3:4 ratio[b] yield [%][c] and *ee* [%][d] of 3	Entry	1 (R)	Major product	3:4 ratio[b] yield [%][c] and *ee* [%][d] of 3
1[e]	**1a** (*n*Hex)	 **3a**	6:1 66, 91	9	**1i** (-CH_2OTIPS)	 **3i**	1.6:1 44, 87
2	**1b** (-$(CH_2)_4CO_2CH_3$)	 **3b**	5:1 66, 90	10	**1j** (CH_2Cy)	 **3j**	8:1 72, 91
3	**1c** (-$(CH_2)_4$Cl)	 **3c**	5:1 57, 94	11	**1k** (Cy)	 **3k**	14:1 86, 91
4	**1d** (-$(CH_2)_4$OTBS)	 **3d**	5:1 62, 90	12	**1l** (*c*Pent)	 **3l**	14:1 87, 89
5	**1e** (-$(CH_2)_3$CON$(OCH_3)(CH_3)$)	 **3e**	5:1 54, 90	13	**1m** 	 **3m**	>20:1 60, 81
6	**1f** (-$(CH_2)_5$C≡CH)	 **3f**	5:1 55, 91	14	**1n** (*t*Bu)	 **3n**	10:1 67, 79
7	**1g** (-$(CH_2)_2$Ph)	 **3g**	5:1 56, 91	15[f]	**1n** (*t*Bu)	 **3n**	6:1 66, 88
8	**1h** (Bn)	 **3h**	3:1 52, 90				

[a]–[d] See Table 1. [e] 1.4 mmol scale (**2**) at 100 °C. [f] guiphos ((*R*)-**L3**) used as the ligand. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Cy = cyclohexyl, MOM = methoxymethyl.

obtained with the unsubstituted alkenyl isocyanate **2**, a profound effect on the enantioselectivity is observed. The use of guiphos ((*R*)-**L3**) here provides a partial solution, improving the enantioselectivity significantly.

In conclusion, we have developed an efficient catalyst system that promotes cycloadditions between terminal alkyl alkynes and alkenyl isocyanates involving a CO migration process. This previously unattainable process allows access to various 5-alkyl indolizinones including an enantioselective



(1)

(*R*)-**L5**: 6.3 : 1 ratio, 72%, 27% *ee*
(*R*)-**L3**: 3.4 : 1 ratio, 53%, 72% *ee*

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synthesis of indolizidine (−)-209D. Additional studies on the reaction scope, as well as applications to the synthesis of alkaloids are ongoing.

Experimental Section

General procedure: In an inert atmosphere (N_2) glove box, 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 (*R*)-**L5** (5.8 mg, 0.0136 mmol), and then fitted with a flame-dried reflux condenser. The system was sealed using a standard septum. Upon removal of the flask from the glove box, toluene (1.0 mL) was added by syringe and the resulting yellow solution was stirred at ambient temperature under argon flow for 5 min. Alkyne **1** (0.54 mmol) and isocyanate **2** (30 mg, 0.27 mmol) in 2 mL of toluene, were added to this solution by syringe. After an additional portion of toluene (1 mL) was added to wash the remaining residue down the sides of the flask, the resulting solution was placed in an oil bath, heated to 110 °C, and maintained at reflux for 12 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by column chromatography.

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