

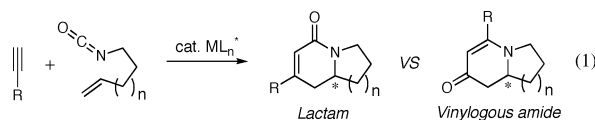
Enantioselective Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates and Terminal Alkynes: Application to the Total Synthesis of (+)-Lasubine II

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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.¹ In light of potentially providing a general and efficient route to many indole and quinolizidine alkaloid natural products,² our group has focused on developing a catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and alkynes.^{3,4} Previously, we have disclosed a Rh(I)/P(4-MeO-C₆H₄)₃-catalyzed [2+2+2] cycloaddition between pen-tenyl isocyanate **2** and a variety of internal alkynes.⁵ The cycloaddition reaction includes a CO migration process to afford *vinyllogous amides* as the major products in good yields. 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 *vinyllogous amides* using chiral phosphoramidites⁶ as ligands (eq 1). The synthetic utility is demonstrated in an expedient asymmetric total synthesis of (+)-lasubine II.

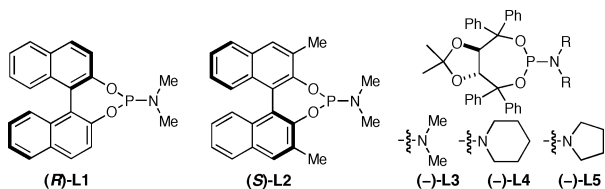


Under our previously reported reaction conditions, the use of phenyl acetylene **1a** or other terminal alkynes often results in sluggish reactions and poor isolated yields (entry 1, Table 1), partly due to the competitive Rh-catalyzed head-to-tail dimerization of terminal alkynes.⁷ Attempts to improve the reaction led to the

Table 1. Ligand Screen^a

entry	ligand	3a : 4a ^b	yield (%) ^c	ee (%) of 3a ^d	ee (%) of 4a ^d
1	P(4-MeO-C ₆ H ₄) ₃	1 : 1	< 20	-	-
2	L1	1 : 2.2	32	5	55 ^e
3	L2	1 : 4.5	50	45 ^e	8
4	L3	1 : 7.0	80	83	94
5	L4	1 : 3.3	76	90	81
6	L5	1 : 7.3	87	89	94

^a Conditions: **1** (2 equiv), **2**, Rh catalyst (5 mol %), **L** (10 mol %) in PhMe at 110 °C for 16 h. ^b Lactam-vinyllogous amide product selectivity determined by ¹H NMR of the unpurified reaction mixture. ^c Combined isolated yield. ^d Determined by HPLC using a chiral stationary phase. ^e Other enantiomer.

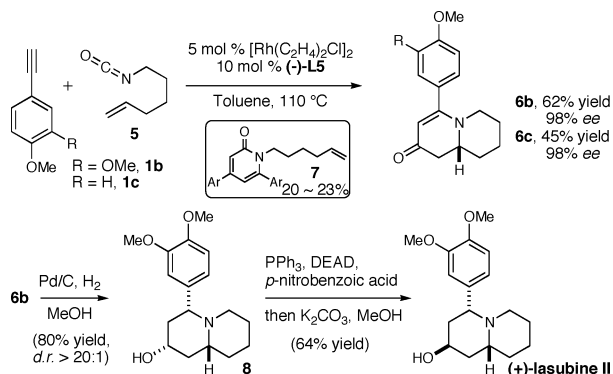
Table 2. Scope of the Cycloaddition with Aryl Acetylenes^a

entry	Ar	3 : 4 ^b	yield (%) ^c	ee (%) of 3 ^{d,e}	ee (%) of 4 ^{d,e}
1	3,4-OMe-C ₆ H ₃ , 1b	< 1 : 20	72	-	94
2	<i>p</i> -OMe-C ₆ H ₄ , 1c	< 1 : 20	70	-	90
3	<i>o</i> -OMe-C ₆ H ₄ , 1d	< 1 : 20	64	-	94
4 ^f	<i>p</i> -NMe ₂ -C ₆ H ₄ , 1e	< 1 : 20	78	-	87
5	<i>m</i> -Tol, 1f	1 : 8.3	65	-	94
6 ^f	2-thienyl, 1g	1 : 9.0	64	-	86
7	2-indolyl, R = H, 1h	< 1 : 20	65	-	90
8	2-indolyl, R = Boc, 1i	< 1 : 20	85	-	91
9	Ph, 1a	1 : 7.3	86	89	94
10	<i>p</i> -Br-C ₆ H ₄ , 1j	1 : 3.2	72	90	89
11	<i>p</i> -Cl-C ₆ H ₄ , 1k	1 : 3.8	65	93	90
12	<i>m</i> -F-C ₆ H ₄ , 1l	1 : 1.8	68	94	94
13	<i>p</i> -Ac-C ₆ H ₄ , 1m	1 : 1.5	65	94	81
14	<i>p</i> -CF ₃ -C ₆ H ₄ , 1n	2.5 : 1	50	94	-
15	2-phenyl, 1o	< 1 : 20	96	-	92

^{a-d} See Table 1. ^e Absolute configuration assigned by analogy to (S)-**3j** and (R)-**4j** (established by X-ray analysis). ^f **L3** used as the ligand.

discovery of Rh(I)/phosphoramidite complexes as more efficient catalysts. Treatment of **1a** and isocyanate **2** with 5 mol % [Rh-(C₂H₄)₂Cl]₂ and 10 mol % BINOL-derived ligand **L1** (MONOPHOS) furnishes the cycloadducts **3a/4a** in 32% combined yield with a 1:2.2 product selectivity, favoring the *vinyllogous amide* **4a** with a moderate enantioselectivity (entry 2). While the bulkier ligand **L2** increases both the reactivity and *lactam-vinyllogous amide* selectivity, the enantioselectivity of **4a** decreases significantly (entry 3). Conversely, TADDOL-derived phosphoramidites are found to be much superior ligands. The cycloaddition generally proceeds cleanly to furnish the cycloadducts in high yields and enantioselectivity (entries 4–6). The commercially available **L3** affords (R)-**4a** with very good *lactam-vinyllogous amide* selectivity (entry 4). Replacing the dimethylamino group with the more rigid piperidinyl as in **L4** increases the production of the *lactam* (S)-**3a** (entry 5). The pyrrolidinyl-substituted ligand **L5** is the current standard, providing a slightly better product selectivity and reactivity (entry 6).⁸ It is noteworthy that the cycloaddition proceeds in a highly regioselective manner, as both (S)-**3a** and (R)-**4a** are isolated as single regioisomers (>20:1 by ¹H NMR).

Table 2 summarizes the scope of the enantioselective [2+2+2] cycloaddition of isocyanate **2** with a variety of aryl acetylenes. Electron-rich substituted aryl acetylenes readily participate in the cycloaddition to afford almost exclusively the *vinyllogous amide* **4** products in good yields and high enantiomeric excess (entries 1–5). Heteroaryl acetylenes including both free and protected indoles also undergo the cycloaddition efficiently (entries 6–8). Electron-

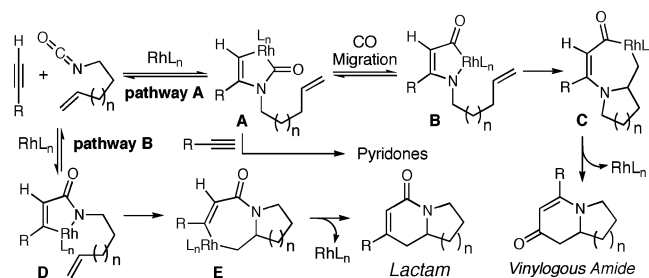
Scheme 1. Total Synthesis of (+)-Lasubine II

withdrawing substituted aryl acetylenes also participate readily in the cycloaddition (up to 94% ee), with the product selectivity gradually shifting toward increased amount of *lactam* **3** with increasing electron-withdrawing ability (entries 10–14).⁹ The reaction is not restricted to aryl acetylenes, as the cyclic enyne **10** also participates to generate exclusively the corresponding *vinylous amide* **4** in high efficiency (entry 15).

Asymmetric syntheses of quinolizinones **6** can also be achieved in moderate to good yields with excellent enantiocontrol (Scheme 1). The reactions are accompanied by varying amounts of pyridones **7** as side products,¹⁰ suggesting that the alkene moiety is the last 2π component incorporated. To demonstrate the synthetic utility of this methodology, enantioenriched **6b** undergoes a diastereoselective hydrogenation followed by a Mitsunobu to complete the total synthesis of (+)-lasubine II¹¹ in only three steps from isocyanate **5**.

In contrast to the *vinylous amide* selectivity observed for most aryl acetylenes, reactions with alkyl acetylenes provide primarily *lactam* products, presumably due to the electronic differences between the alkyl and aryl groups (Table 3). By employing **L4**, cycloadditions with primary alkyl acetylenes proceed smoothly to afford *lactams* **3** with excellent product selectivity (up to >20:1), good enantioselectivity (up to 87% ee), and good isolated yields (entries 1–6). The more sterically hindered cyclohexyl acetylene (entry 7) furnishes both types of products in an approximately 1:1 ratio with excellent enantioselectivity for **4v** (95% ee), suggesting that both sterics and electronics play a role in governing product selectivity.

A proposed mechanism is outlined in Scheme 2. An initial oxidative cyclization between the isocyanate and alkyne in an orientation where a C–N bond is formed provides metalacycle **A**. A CO migration^{12,13} to **B** followed by olefin insertion and reductive elimination furnishes the *vinylous amides* (pathway A). In a different orientation, metallacycle **D** is formed with a C–C bond

Scheme 2. Proposed Mechanism

formation (pathway B). Subsequent olefin insertion and reductive elimination provides the *lactams*.

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.

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Supporting Information Available: Detailed experimental procedures and compound characterization (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) These reaction conditions provide inferior results with internal alkynes. For example, Rh(I)/**L5** provides the vinylous amide in 28% yield and 9% ee when using diphenylacetylene as the alkyne partner.
- (9) This effect may be partially rationalized through Hoffmann's theoretical study if one considers orbital coefficients in the LUMO of the alkyne. See: Stockis, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 2952.
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- (13) Conducting the cycloaddition under 1 atm of CO leads to no reaction.

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Table 3. Scope of the Cycloaddition with Alkyl Acetylenes^a

entry	R	3 : 4 ^b	yield (%) ^c	ee (%) of 3 ^d
1	nHex, 1p	5.0 : 1	78	80
2	(CH ₂) ₄ CO ₂ Me, 1q	5.8 : 1	65	80
3	CH ₂ CH ₂ Ph, 1r	> 20 : 1	47	84
4	Bn, 1s	> 20 : 1	50	84
5	CH ₂ CH ₂ OTBS, 1t	> 20 : 1	65	87
6	CH ₂ OMe, 1u	> 20 : 1	46	76
7 ^f	cyclohexyl, 1v	1.2 : 1	82	77, 95 ^g

^{a-d} See Table 1. ^e ee (%) of **4v**. ^f **L3** used as the ligand.