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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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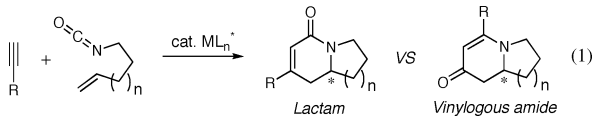
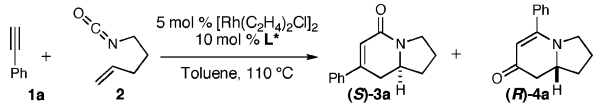
Cycloaddition reactions of [*m*+*n*+*o*] type catalyzed by transition metals are powerful methods to construct polycyclic carbocycles and heterocycles of structural and functional complexity.[1] In light of potentially providing a general and efficient route to many indo- and quinolizidine alkaloid natural 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-C_5H_4)$_3$-catalyzed [2+2+2] cycloaddition between pentenyl isocyanate **2** and a variety of internal alkynes.[5] The cycloaddition reaction includes a CO migration process to afford *vinylogous 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 *vinylogous amides* using chiral phosphoramidites[6] as ligands (eq 1). The synthetic utility is demonstrated in an expedient asymmetric total synthesis of (+)-lasubine II.



(1)

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_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	**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−vinylogous amide product selectivity determined by ^{1}H NMR of the unpurified reaction mixture. [c] Combined isolated yield. [d] Determined by HPLC using a chiral stationary phase. [e] Other enantiomer.

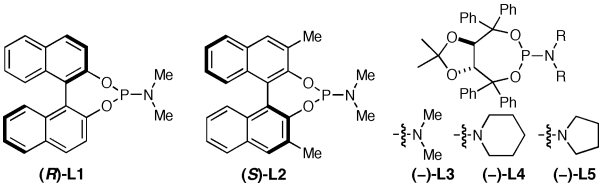
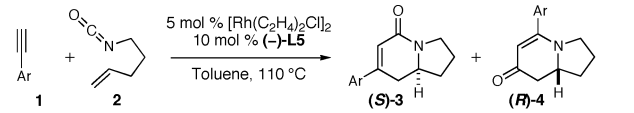


Table 2. Scope of the Cycloaddition with Aryl Acetylenes[a]



entry	Ar	**3 : 4**[b]	yield (%)[c]	*ee* (%) of **3**[d,e]	*ee* (%) of **4**[d,e]
1	3,4-OMe-C_6H_3, **1b**	< 1 : 20	72	-	94
2	*p*-OMe-C_6H_4, **1c**	< 1 : 20	70	-	90
3	*o*-OMe-C_6H_4, **1d**	< 1 : 20	64	-	94
4[f]	*p*-NMe_2-C_6H_4, **1e**	< 1 : 20	78	-	87
5	*m*-Tol, **1f**	1 : 8.3	65	-	94
6[f]	 , **1g**	1 : 9.0	64	-	86
7	 R = H, **1h**	< 1 : 20	65	-	90
8	R = Boc, **1i**	< 1 : 20	85	-	91
9	Ph, **1a**	1 : 7.3	86	89	94
10	*p*-Br-C_6H_4, **1j**	1 : 3.2	72	90	89
11	*p*-Cl-C_6H_4, **1k**	1 : 3.8	65	93	90
12	*m*-F-C_6H_4, **1l**	1 : 1.8	68	94	94
13	*p*-Ac-C_6H_4, **1m**	1 : 1.5	65	94	81
14	*p*-CF_3-C_6H_4, **1n**	2.5 : 1	50	94	-
15	 , **1o**	< 1 : 20	96	-	92

[a–d] See Table 1. [e] Absoloute 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-(C_2H_4)$_2$Cl]$_2$ 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 *vinylogous amide* **4a** with a moderate enantioselectivity (entry 2). While the bulkier ligand **L2** increases both the reactivity and *lactam*-*vinylogous 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*-*vinylogous 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 ^{1}H 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 *vinylogous 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-

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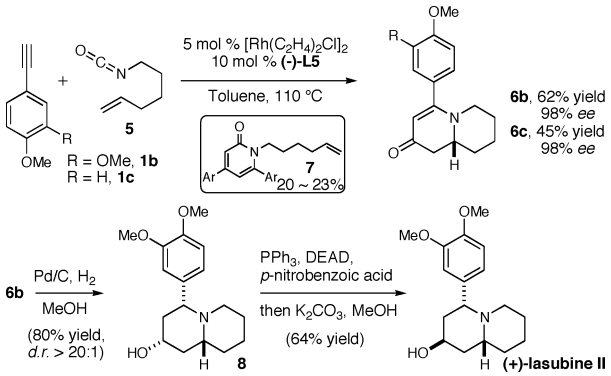
Scheme 1. Total Synthesis of (+)-Lasubine II



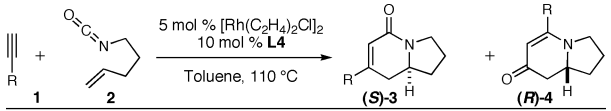
withdrawing substituted aryl acetylenes also participate readily in the cycloaddition (up to 94% ee), with the product selectivity gradually shifting toward increased amount of *lactam* **3** with increasing electron-withdrawing ability (entries 10−14).[9] The reaction is not restricted to aryl acetylenes, as the cyclic enyne **1o** also participates to generate exclusively the corresponding *vinylogous 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 II[11] in only three steps from isocyanate **5**.

In contrast to the *vinylogous 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 *vinylogous amides* (pathway A). In a different orientation, metallacycle **D** is formed with a C−C bond

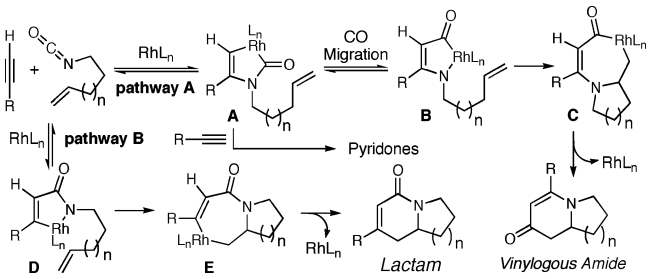
Table 3. Scope of the Cycloaddition with Alkyl Acetylenes[a]



entry	R	**3** : **4**[b]	yield (%)[c]	*ee* (%) of **3**[d]
1	*n*Hex, **1p**	5.0 : 1	78	80
2	$(CH_2)_4CO_2Me$, **1q**	5.8 : 1	65	80
3	CH_2CH_2Ph, **1r**	> 20 : 1	47	84
4	Bn, **1s**	> 20 : 1	50	84
5	CH_2CH_2OTBS, **1t**	> 20 : 1	65	87
6	CH_2OMe, **1u**	> 20 : 1	46	76
7[f]	 , **1v**	1.2 : 1	82	77, 95[e]

[a−d] See Table 1. [e] ee (%) of **4v**. [f] **L3** used as the ligand.

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 vinylogous 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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