

# Catalytic, Asymmetric Indolizidinone Aza-Quaternary Stereocenter Synthesis: Expedient Synthesis of the Cylindricine Alkaloid Core

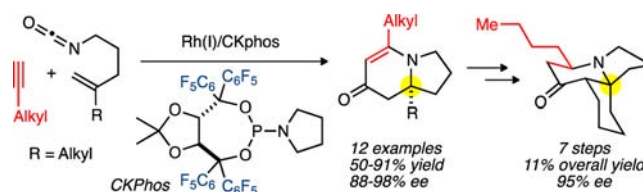
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## ABSTRACT



The Rh(I)•CKphos catalyzed [2 + 2 + 2] cycloaddition of 1,1-disubstituted alkenyl isocyanates and alkyl alkynes selectively forms previously inaccessible vinylogous amide indolizidinone cycloadducts, establishing an aza-quaternary stereocenter with excellent enantioselectivities (up to 98% ee). This advance enables a seven step catalytic, asymmetric synthesis of the tricyclic core of the cylindricine alkaloids with excellent control of product selectivity as well as regio- and enantioselectivity.

Efficient, selective N-heterocycle synthesis is a vital area of research due to the abundance and biological importance of molecules that contain such motifs. Transition metal catalysis offers efficient access to complex N-heterocycles through [2 + 2 + 2] cycloadditions with N-containing  $\pi$ -components, such as isocyanates.<sup>1</sup> We have made a

number of contributions in this area<sup>2</sup> and found that alkyl alkynes give lactam products while aryl alkynes provide vinylogous amides with 1,1-disubstituted alkenyl isocyanates (Scheme 1).<sup>3</sup> A limitation of our methodology was the ability to synthesize vinylogous amide cycloadducts with alkyl alkynes (Scheme 1).<sup>4</sup> Alkyl substituted vinylogous amide indolizidinones are valuable synthetic targets due to the abundance (> 200) of indolizidine and quinolizidine natural products<sup>5</sup> that have 5-alkyl substituents. A number of tricyclic indolizidine and quinolizidine alkaloids, including the cylindricines,<sup>6</sup> lepadiformines,<sup>7</sup> fascicularin,<sup>8</sup> and FR901483,<sup>9</sup> have 5,9-alkyl substitution with

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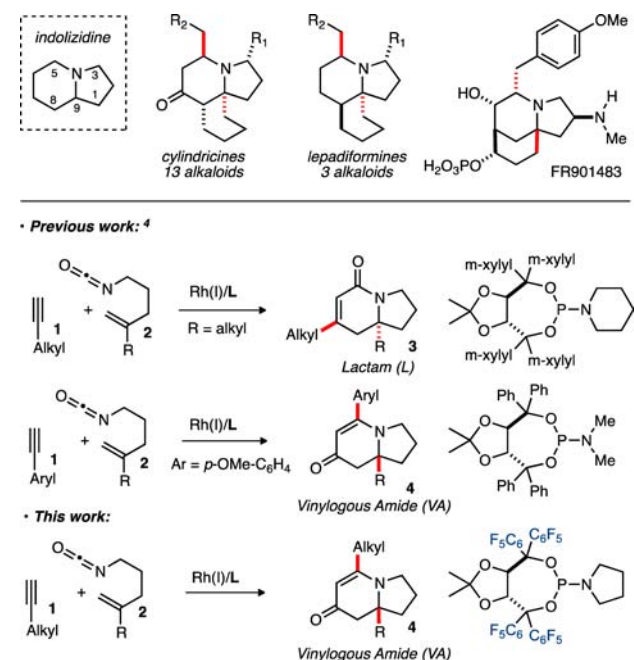
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C9 being a tetrasubstituted aza-quaternary stereocenter (Scheme 1).

**Scheme 1.** Rh(I) Catalyzed Cycloadditions of 1,1-Disubstituted Alkenyl Isocyanates and Alkynes, and Select Natural Products Accessible from the Alkyl-Substituted Vinylogous Amide Scaffold



Due to their interesting architecture and biological activity many methods to synthesize these tricyclic alkaloids have been developed. Most of these syntheses are racemic<sup>10</sup> or use chiral starting materials<sup>11</sup> and take advantage of an aza-Michael addition (single or double) to form the functionalized piperidine core. Shibasaki<sup>12</sup> (5 steps, 82% *ee*) and Zhang<sup>13</sup> (10 steps, 87% *ee*) have reported catalytic asymmetric approaches to the cylindricines. While Shibasaki's approach is very efficient, it uses the traditional aza-Michael addition to synthesize the

cylindricine core; Zhang's synthesis does not incorporate the 5-alkyl side chain. We saw asymmetric Rh(I) catalyzed [2 + 2 + 2] cycloadditions as a complementary approach to the aza-Michael synthesis of the tricyclic cylindricine core because it easily accesses a variety of analogs.

Crucial to the development of an efficient route to the cylindricine molecules was the design of a perfluorinated Taddol phosphoramidite, CKphos,<sup>14</sup> that overrides substrate based control of product selectivity in the [2 + 2 + 2] cycloaddition. This discovery allows for the highly selective formation of vinylogous amide indolizidinones with a wide range of alkynes, including alkyl alkynes. Herein, we report that Rh(I)•CKphos catalyzed cycloadditions are a highly enantioselective method to form tetrasubstituted N-stereocenters from 1,1-disubstituted alkenyl isocyanates and alkyl alkynes. Furthermore, Rh(I)•CKphos was used to synthesize the tricyclic cylindricine core in 7 steps, 95% *ee*, and 11% overall yield.

**Table 1.** Ligand Screen for Rh(I) Catalyzed Cycloadditions of 1,1-Disubstituted Alkenyl Isocyanates and Alkynes

entry	ligand (L)	3:4	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>T2</b>	6.5:1	88	91
2	<b>B1</b>	1:3.4	53	72
3	<b>B2</b>	1:6.3	72	27
4	<b>CKphos</b>	1:>19	61	90

**T2** Ar = *m*-Xylyl  
**B1** Ar = *p*-Tolyl  
**B2** Ar = *t*-Bu  
**CKphos** Ar = C<sub>6</sub>F<sub>5</sub>  
**R** = *p*-Tolyl, *m*-Xylyl, *t*-Bu

<sup>a</sup> Reaction conditions: **1**, **2** (1.3 equiv), [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> (2.5 mol %), **L** (5 mol %) in PhMe at 110 °C for 16 h. <sup>b</sup> The combined isolated yield is reported. <sup>c</sup> The enantiomeric excess shown is of the major product.

Vinylogous amide formation with 1,1-disubstituted alkenes previously required aryl acetylenes because alkyl alkynes produced a lactam cycloadduct (Table 1).<sup>4</sup> A screen of ligands revealed that this inherent substrate bias of product selectivity could be altered by the phosphoramidite on rhodium. *m*-Xylyl Taddol phosphoramidite **T2** provides lactam **3** in 6.5:1 selectivity. Guiphos **B1** and *t*-BuBiaryl **B2** modestly favor vinylogous amide, but in the case of **B2** the enantioselectivity is poor (27%). CKPhos provides vinylogous amide **4** with excellent product (1: > 19) and enantioselectivity (90%) and good yield (61%).

We found that Rh(I)•CKphos provides a selective means of forming vinylogous amides from alkyl alkynes and 1,1-disubstituted alkenes (Figure 1). A variety of

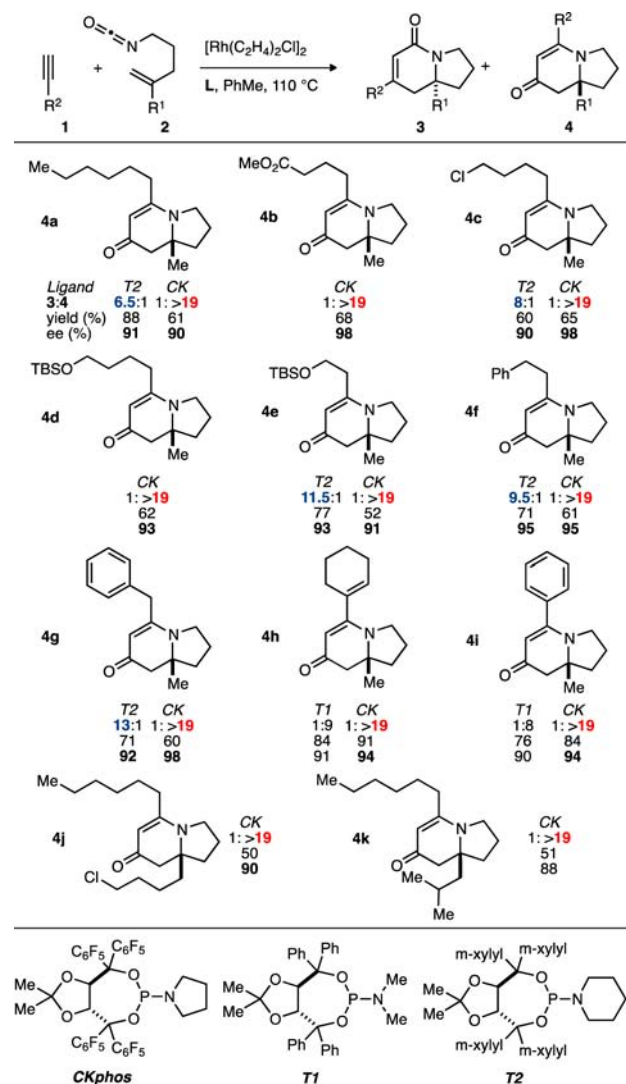
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**Figure 1.** Isocyanate and alkyne substrate scope. Reaction conditions: 1, 2 (1.3 equiv), [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> (2.5 mol %), L (5 mol %) in PhMe at 110 °C for 16 h. The combined isolated yield is reported. The enantiomeric excess shown is of the major product. For T1 and T2, the results were previously reported;<sup>4</sup> 2 equiv of 2 were used.

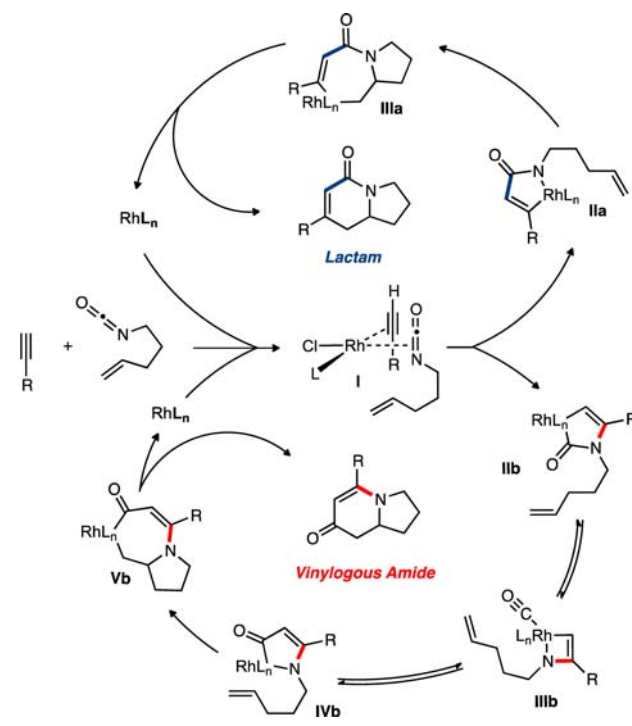
functional groups are tolerated on the alkyne, including esters, chlorides, silyl ethers, aryls, and alkenes. Larger 1,1-disubstituted alkenes provide the vinylogous amide in lower yields, and an increase in pyridone byproduct is seen.<sup>3</sup> Presumably, the increase in steric bulk on the alkene slows alkene coordination and subsequent migratory insertion, allowing a second alkyne moiety to incorporate prior to alkene insertion.

The proposed mechanism for the formation of lactam **3** and vinylogous amide **4** is illustrated in Scheme 2.<sup>2g</sup> Coordination of the alkyne and isocyanate orthogonal to the square plane precedes oxidative cyclization, which establishes both lactam and vinylogous amide pathways. Oxidative cyclization is the first irreversible step based on competition experiments between mono- and disubstituted

alkenyl isocyanates.<sup>15</sup> For lactam, oxidative cyclization results in five-membered rhodacycle **IIa** and C–C bond formation. Migratory insertion of the alkene into **IIa** provides seven-membered rhodacycle **IIIa**, which is followed by reductive elimination to form lactam **3** and regenerates the active catalyst.

For vinylogous amide **4**, oxidative cyclization gives rhodacycle **IIb** and forms a C–N bond. The pendent alkene cannot insert into rhodacycle **IIb** due to a strained geometry in the transition state; thus, a reversible CO migration<sup>16</sup> occurs through a highly reactive, four-membered rhodacycle **IIIb** to form enamine **IVb**. Migratory insertion of the alkene into **IVb** provides seven-membered metallacycle **Vb**. Reductive elimination forms a vinylogous amide and regenerates the active catalyst.

**Scheme 2.** Proposed Mechanistic Cycle for Product Formation

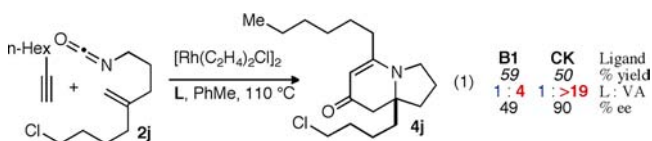


To showcase the ability of this methodology to rapidly and enantioselectively assemble indolizidines from simple starting materials, we sought to apply the Rh(I)•CKphos catalyzed cycloaddition of 1,1-disubstituted alkenyl isocyanates (**2j**) with alkyl alkynes to afford alkyl-substituted indolizidinone **4j** (eq 1) that could be further functionalized to the tricyclic core. Early attempts at the cycloaddition with **2j** found that Guiphos **B1** gives modest product and

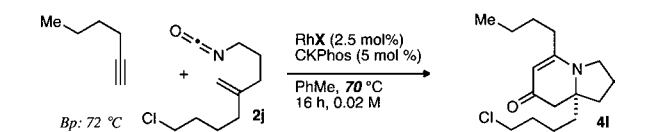
(15) A competition experiment between a monosubstituted pentenyl isocyanate and 1,1-disubstituted methyl pentenyl isocyanate with benzyl acetylene gives a 1:1 ratio of vinylogous amide products. See Supporting Information for further details. This finding is consistent with previously reported competition experiments with aryl acetylenes as discussed in ref 2g.

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enantioselectivity. CKphos maintains good yield and excellent selectivities with 1-octyne.



**Table 2.** Optimization of Reaction Conditions at 70 °C



entry	precatalyst	additive	3:4	% conversion <sup>b</sup>	% ee
1	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$		1: >19	33	90
2	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	AgOTf <sup>a</sup>	1: >19	28	96
3	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	AgOTs <sup>a</sup>	1: >19	69	95
4	$[\text{Rh}(\text{cod})\text{Cl}]_2$		1: >19	4	

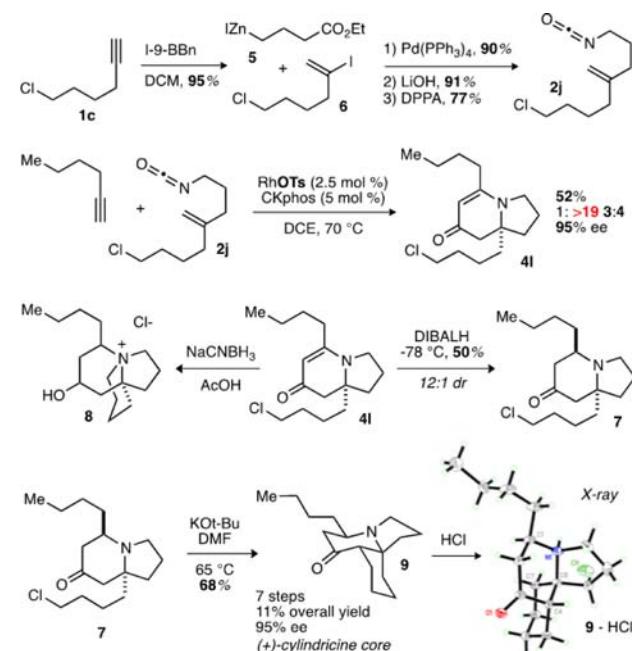
<sup>a</sup> 1,2-Dichloroethane (DCE) was used as solvent with 4 Å MS. <sup>b</sup> <sup>1</sup>H NMR conversion reported after 16 h based on isocyanate conversion.

For our synthesis of the tricyclic core of these alkaloids, 1-hexyne was chosen since *n*-butyl is the smallest alkyl chain found in the cylindricine alkaloids, and we anticipated it would be more challenging to synthesize. Indeed, the low boiling point proved problematic under our standard reaction conditions and low yields were seen in the cycloaddition with **2j** (Table 2). To improve the yield a variety of precatalysts were screened. We determined that  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$  is the most effective precatalyst and tosylate is the best counterion for the synthesis of **4l**, improving conversion and enantioselectivity at lower temperatures.

With an improved catalyst for the synthesis of **4l**, we investigated conditions for vinylogous amide reduction. Under acidic conditions, sodium cyanoborohydride reduces vinylogous amide **4l** to the tertiary amine, which is N-alkylated to form ammonium chloride **8** (Scheme 3). On the other hand, Diisobutylaluminum hydride (DIBAL-H) selectively reduces vinylogous amide **4l** in 1,4 fashion to indolizidine **7** with moderate yields and good diastereoselectivity (12:1). Once isolated, **7** slowly decomposes by N-alkylation. However, if **7** is immediately subjected to potassium *tert*-butoxide (KO<sup>t</sup>-Bu) in polar protic (*t*-BuOH) or aprotic (DMSO, DMF) solvents with heat (65 °C) the *cis*-decalin system **9** is obtained.<sup>17</sup> Alkylation in DMF provides the highest yield of the cylindricine core (68%). Both the relative and absolute stereochemistry of **9** were

(17) A related alkylation was carried out by Padwa and co-workers; see ref 10c.

**Scheme 3.** Synthesis of the Cylindricine Core Framework



confirmed by X-ray analysis of the hydrochloride salt (**9·HCl**). In summary, the (+)-cylindricine core was synthesized enantioselectively in 7 steps, 95% ee, and 11% overall yield from simple commercially available starting materials.

In conclusion, we have developed an enantioselective Rh(I)•CKphos catalyzed cycloaddition of 1,1-disubstituted alkenyl isocyanates and alkynes that overcomes substrate control of product selectivity to access vinylogous amide cycloadducts. This contribution is significant because the vinylogous amide cycloadduct was previously only accessible with aryl acetylenes, and a greater number of C<sub>5</sub> alkyl-substituted indolizidine natural products are found in biological systems. We applied the method to the synthesis of the tricyclic core of the cylindricine alkaloids in 7 steps, 11% overall yield, and 95% ee.

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**Supporting Information Available.** Detailed experimental procedures and characterization of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.