Asymmetric Synthesis

DOI: 10.1002/ange.201301741

A Catalytic Asymmetric Synthesis of Polysubstituted Piperidines Using a Rhodium(I)-Catalyzed [2+2+2] Cycloaddition Employing a Cleavable Tether**

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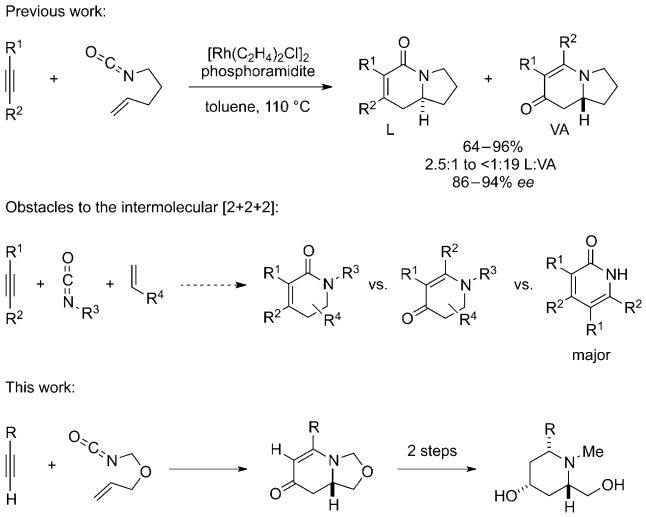
Due to their prevalence in drug targets and natural products, the asymmetric synthesis of nitrogen-containing heterocycles is an important focus of the synthetic community. Our group has a longstanding interest in the catalytic asymmetric synthesis of such moieties (Scheme 1). In 2006, we reported



Scheme 1. Previous and envisioned [2+2+2] cycloadditions.

the rhodium(I)-catalyzed asymmetric [2+2+2] cycloaddition between alkenyl isocyanates and alkynes. This catalytic, asymmetric method allows facile access to indolizidines and quinolizidines, important scaffolds in natural products and pharmaceutical targets, in good yields with high enantioselectivities.[1,2] Extension of this methodology to the synthesis of monocyclic nitrogen-containing heterocycles would be useful, as piperidines are present in numerous compounds with interesting biological activities,[3] such as alkaloid 241D,[4] isosolenopsin A[5] and palinavir[6] (Figure 1). Recently, several new methods have been reported for the synthesis of polysubstituted piperidines,[7,8] highlighted by Bergman and Ellman's recent contribution.[9] Catalytic asymmetric approaches to polysubstituted piperidines, however, remain

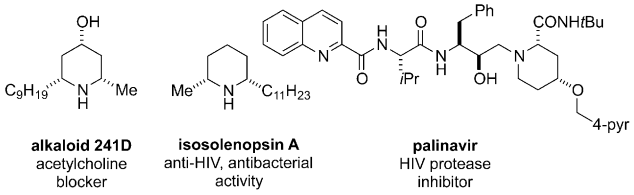


Figure 1. Piperidine-containing compounds.

scarce with the notable exception of the powerful aza-Diels–Alder reaction.[10] Complementary approaches to piperidines relying on the union of two or more fragments with concomitant control of stereochemistry in the process would be of significant value.[11,12] Herein, we report a partial solution to this problem relying on an asymmetric rhodium-catalyzed cycloaddition of an alkyne, alkene and isocyanate, bringing three components together wherein two of the three are attached by a removal linker.

We sought to develop a catalytic asymmetric method to access piperidine scaffolds utilizing the rhodium(I)-catalyzed [2+2+2] cycloaddition. While the fully intermolecular reaction faces several challenges, such as competitive insertion of the alkene component over insertion of a second alkyne to form a pyridone and regioselectivity of π component insertion, the use of a cleavable tether in the isocyanate backbone provides a solution to these obstacles (Scheme 1).[13–15] Products of net intermolecular [2+2+2] cycloaddition would be accessed after cleavage of the tether, allowing for the synthesis of substituted piperidine scaffolds in a catalytic asymmetric fashion. Here, we report the use of a cleavable tether in the rhodium-catalyzed [2+2+2] cycloaddition between oxygen-linked alkenyl isocyanates and alkynes to access piperidine scaffolds after cleavage of the tether. The products are obtained in high enantioselectivity and yield. Differentially substituted piperidines with functional group handles for further manipulation can be accessed in a short sequence, in which the stereocenter introduced in a catalytic asymmetric fashion controls the diastereoselectivity of two more stereocenters.

Our investigations began with the oxygen-linked alkenyl isocyanate shown to participate in the rhodium(I)-catalyzed

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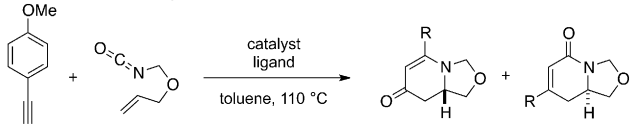
[**] We thank NIGMS (GM80442) for generous support and Roche and Amgen for unrestricted support. We thank Johnson Matthey for a generous loan of Rh salts.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301741.

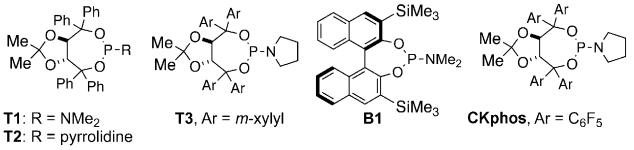
Table 1: Reaction optimization.[a,b]



1a 2 3 4

Entry	Ligand	3:4[b]	Yield 3 [%]	*ee* 3[c] [%]
1	**T1**	2.7:1	53	88
2	**T2**	>19:1	20	91
3	**T3**	>19:1	33	93
4	**B1**	1:1	30	40
5	**CKphos**	>19:1	77	94

[a] Reaction conditions: 1.6 equiv **1a**, 1.0 equiv **2**, 0.05 equiv $[Rh(C_2H_4)_2Cl]_2$, 0.10 equiv ligand, reaction concentration: 0.05 M. [b] Determined by ^{1}H NMR spectroscopy after purification. [c] *ee* values were determined by HPLC analysis on a chiral stationary phase.



T1: R = NMe_2
T2: R = pyrrolidine
T3, Ar = *m*-xylyl
B1
CKphos, Ar = C_6F_5

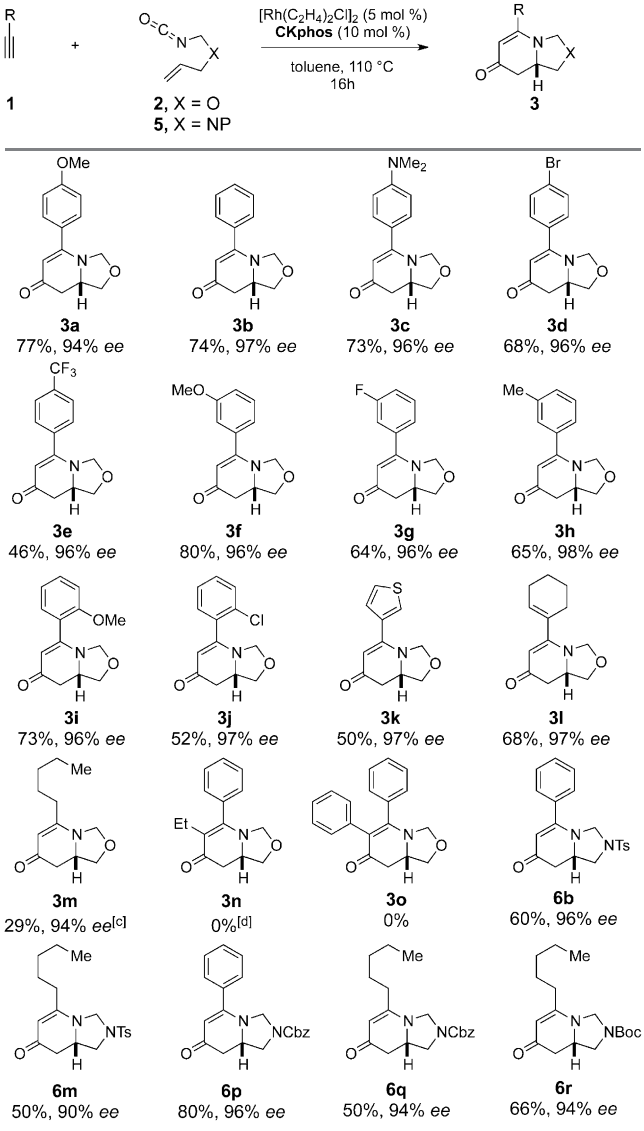
[2+2+2] cycloaddition (Table 1).[1f] As with previous rhodium(I)-catalyzed [2+2+2] cycloadditions, $[Rh(C_2H_4)_2Cl]_2$ proved to be the most efficient precatalyst.[16,17] A variety of TADDOL-based phosphoramidite ligands provided the vinylogous amide. However, poor product selectivity (Table 1, entry 1) and low yield (entries 2 and 3) are observed. BINOL-based phosphoramidite ligands such as Guiphos **B1** provided vinylogous amide with low enantioselectivity (entry 4). The recently developed electron-withdrawing phosphoramidite **CKphos** proved to be the best ligand (entry 5).[18] Using **CKphos**, vinylogous amide was obtained in 77% yield and 94% *ee*. As expected with **CKphos**, product selectivity favored **3** over **4** by >19:1.[19]

With optimal conditions in hand, the alkyne scope was explored (Table 2). Aryl alkynes with electron-donating and electron-withdrawing groups participate in the reaction with moderate to high yield and high enantioselectivity (**3a**–**3j**). Substitution at the *ortho*- and *meta*- positions (**3f**–**3j**) is tolerated without decrease in yield or enantioselectivity. Heteroaromatic alkynes and enynes are also competent substrates in the reaction, providing **3k** and **3l** with high enantioselectivity. In all cases, product selectivity is >19:1 favoring vinylogous amide.

Alkyl and internal alkynes do not undergo the desired reaction with oxygen-linked alkenyl isocyanates under the standard conditions.[20] Excess alkyne (5.0 equivalents) or prolonged reaction times (48 h) do not lead to cycloadduct formation. However, in the case of 1-heptyne, we found that with slow addition of the isocyanate, **3m** could be isolated in modest yield. Interestingly, isocyanates with a *N*-Ts linker provide the desired products with both aromatic and alkyl alkynes (Table 2). Importantly, the reaction also tolerates Cbz and Boc protecting groups on nitrogen (**6p**–**6r**, Table 2).

Vinylogous amide products **8** containing a tetrasubstituted carbon could be obtained when alkenyl isocyanate **7** was used

Table 2: Alkyne scope.[a,b]



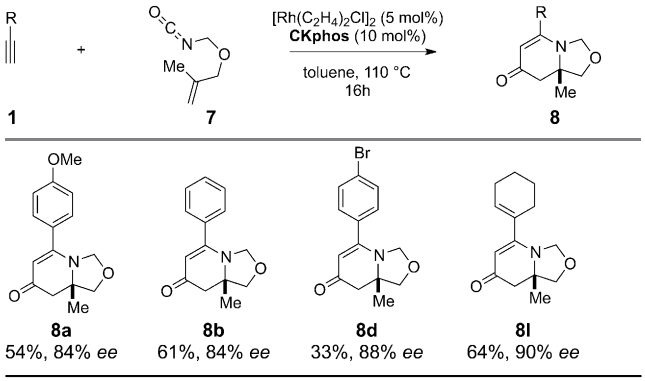
[a] Reaction conditions: 1.6 equiv **1**, 1.0 equiv **2**. [b] Yields for isolated vinylogous amide product. In all cases product selectivity is >19:1 (**3**:**4**). *ee* values were determined by HPLC analysis on a chiral stationary phase. [c] Slow addition of **2** was required. [d] **3n** could be obtained in 16% yield with the use of **B1** as ligand.

in the reaction (Table 3).[1c] These reactions proceed in slightly lower yield and enantioselectivity. A variety of alkynes are tolerated, including aryl alkynes with electron donating or withdrawing substituents and enynes. Substrates bearing a homologous tether afford vinylogous amides **10** with a 6,6-bicyclic ring system (Table 4).

We then turned our attention to cleavage of the tether. Unfortunately, a one-step cleavage of the tether proved problematic.[21] We found that reduction of the vinylogous amide allows cleavage of the aminal. 5% Palladium on carbon under a hydrogen atmosphere affords bicyclic aminals with high diastereoselectivity (>19:1, Table 5).[1b]

A screen of a variety of conditions to cleave the aminal revealed reductive amination as an effective method to

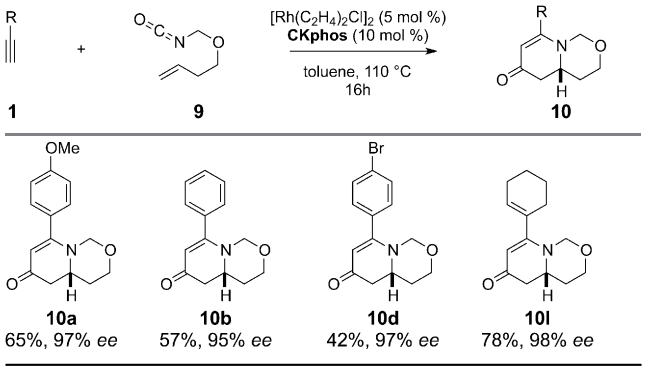
Table 3: 1,1-Disubstituted alkenyl isocyanates.[a,b]



8a 54%, 84% *ee* | **8b** 61%, 84% *ee* | **8d** 33%, 88% *ee* | **8l** 64%, 90% *ee*

[a] Reaction conditions: 1.6 equiv **1**, 1.0 equiv **7**. [b] See Table 2.

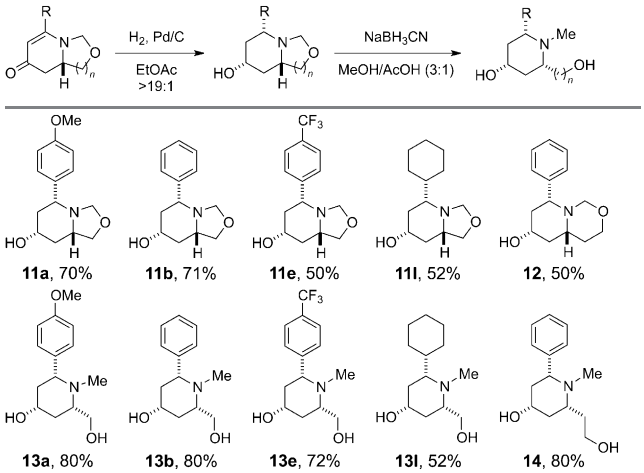
Table 4: Homologous alkenyl isocyanates.[a,b]



10a 65%, 97% *ee* | **10b** 57%, 95% *ee* | **10d** 42%, 97% *ee* | **10l** 78%, 98% *ee*

[a] Reaction conditions: 1.6 equiv **1**, 1.0 equiv **9**. [b] See Table 2.

Table 5: Access to trisubstituted piperidines.[a]



11a, 70% | **11b**, 71% | **11e**, 50% | **11l**, 52% | **12**, 50%

13a, 80% | **13b**, 80% | **13e**, 72% | **13l**, 52% | **14**, 80%

[a] Reaction conditions: 5 mol% Pd/C in EtOAc for 24–36 h at 23 °C; 2.0 equiv $NaCNBH_3$ in MeOH/AcOH for 24 h at 23 °C.

provide the *N*-methylpiperidinol products. Thus, treatment of the aminal with sodium cyanoborohydride in a mixture of methanol and acetic acid (3:1) at ambient temperature provides the desired product.[22] Using vinylogous amide **31** in this two-step procedure affords piperidinol **121** with alkyl substitution. This presents a solution to the incorporation of alkyl alkynes in the reported [2+2+2] cycloaddition.

An X-ray crystal structure was obtained of compound **13a**. The protons of the three tertiary carbons are all on the same face of the piperidinol ring, confirming the stereochemistry of the reduction of the vinyologous amide with Pd/C.[23]

In conclusion, we present a route to access piperidinol scaffolds based on the rhodium(I)-catalyzed asymmetric [2+2+2] cycloaddition between alkynes and an oxygen-linked alkenyl isocyanate. The cycloaddition proceeds with good yield and high enantioselectivity for a variety of substrates. The stereocenter introduced in a catalytic, asymmetric fashion is then used to control diastereoselectivity in a subsequent hydrogenation to afford diastereoselectivities of $>19{:}1$. Piperidinol scaffolds with functional group handles for further manipulation can then be accessed following reductive amination.

Experimental Section

Standard [2+2+2] conditions: In a glove box, a round bottom flask was charged with chlorobisethylene rhodium(I) dimer (0.005 mmol) and CKphos (0.01 mmol). The flask was equipped with a reflux condensor and septum. Outside the glove box, toluene (1 mL) was added, and the mixture was stirred for 15 min. after which time alkenyl isocyanate (0.10 mmol) and alkyne (0.16 mmol) in toluene (1 mL) were added dropwise. The reaction mixture was heated to reflux and stirred for 16 h. Upon completion of the reaction, the flask was cooled to 23 °C, solvent removed via rotary evaporation, and the crude material was subjected to column chromatography (EtOAc to 20:1 EtOAc:MeOH).

Received: February 28, 2013
Published online: April 19, 2013

Keywords: asymmetric synthesis · cycloaddition · heterocycles

[1] a) R. T. Yu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2782–2783; b) R. T. Yu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 12370–12371; c) E. E. Lee, T. Rovis, *Org. Lett.* **2008**, *10*, 1231–1234; d) R. T. Yu, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 3262–3263; e) R. K. Friedman, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10775–10782; f) D. M. Dalton, K. M. Oberg, R. T. Yu, E. E. Lee, S. Perreault, M. E. Oinen, M. L. Pease, G. Malik, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 15717–15728; g) M. E. Oinen, R. T. Yu, T. Rovis, *Org. Lett.* **2009**, *11*, 4934–4937.

[2] a) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625–649; b) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165.

[3] a) G. M. Strunz, J. A. Findlay in *The Alkaloids*, *Vol. 26* (Ed.: A. Brossi), Academic Press, New York, **1985**, p. 89; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; c) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166–187.

[4] a) M. W. Edwards, J. W. Daly, *J. Nat. Prod.* **1988**, *51*, 1188–1197; b) M. W. Edwards, H. M. Garaffo, J. W. Daly, *Synthesis* **1994**, 1167–1170.

[5] T. H. Jones, M. S. Blum, H. M. Fales, *Tetrahedron* **1982**, *38*, 1949–1958.

[6] a) P. C. Anderson, F. Soucy, C. Yoakim, P. Lavallee, P. L. Beaulieu, US Patent 5614533A 19970325, **1997**; b) D. Lamarre, G. Croteau, E. Wardrop, L. Bourgon, D. Thibeault, C. Clouette, M. Vaillancourt, E. Cohen, C. Pargellis, C. Yoakim, P. C. Anderson, *Antimicrob. Agents Chemother.* **1997**, *41*, 965–971.

[7] For select recent examples of polysubstituted piperidine syntheses in which two or more components are united to form the azacycle, see: a) H. M. Peltier, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 7342 – 7345; b) T. Kobayashi, F. Hasegawa, K. Tanaka, S. Katsumura, *Org. Lett.* **2006**, *8*, 3813 – 3816; c) M. Takahashi, G. C. Micalizio, *J. Am. Chem. Soc.* **2007**, *129*, 7514 – 7516; d) Y. Wang, S. Zhu, D. Ma, *Org. Lett.* **2011**, *13*, 1602 – 1605; e) H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011 – 4014; f) S. Duttwyler, C. Lu, A. L. Rheingold, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 4064 – 4067; g) K. Y. T. Ho, C. Aïssa, *Chem. Eur. J.* **2012**, *18*, 3486 – 3489; h) N. Ishida, T. Yuhki, M. Murakami, *Org. Lett.* **2012**, *14*, 3898; i) P. Kumar, J. Louie, *Org. Lett.* **2012**, *14*, 2026 – 2029.

[8] For recent syntheses of substituted 4-piperidinols, see: a) F. A. Davis, A. Rao, P. J. Carroll, *Org. Lett.* **2003**, *5*, 3855 – 3857; b) C. Gnamm, C. M. Krauter, K. Brödner, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 2050 – 2054; c) L. Cui, C. Li, L. Zhang, *Angew. Chem.* **2010**, *122*, 9364 – 9367; *Angew. Chem. Int. Ed.* **2010**, *49*, 9178 – 9181; d) T. C. Coombs, G. H. Lushington, J. Douglas, J. Aubé, *Angew. Chem.* **2011**, *123*, 2786 – 2789; *Angew. Chem. Int. Ed.* **2011**, *50*, 2734 – 2737.

[9] S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman, J. A. Ellman, *Science* **2013**, *339*, 678 – 682.

[10] For an excellent recent review, see: G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902 – 923.

[11] Catalytic asymmetric methods are poorly represented in the above list, outside of the aza-Diels–Alder reaction. Stereocontrol through a chiral auxiliary has been explored by Micalizio (2 steps) and Zhang (4 steps) (refs. [7c] and [8c], respectively). The two catalytic asymmetric examples are Ma's prolinol-catalyzed coupling of aldehydes and allylic amines bearing a nitro group on the olefin and Helmchen's Ir-catalyzed allylic amination reaction which provides trisubstituted piperidinols in 8 steps from allylic carbonates; see Refs. [7d] and [8b].

[12] For reviews of piperidine synthesis, see: a) V. Baliah, R. Jeyaraman, L. Chandrasekaran, *Chem. Rev.* **1983**, *83*, 379 – 423; b) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825 – 1872; c) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953 – 2989; d) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701 – 1729; e) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642 – 2713.

[13] Use of alkenes with a tethered coordinating group such as a thioether, pyridine, amine, or second alkene did not provide the desired product.

[14] For reviews on the use of cleavable tethers, see: a) L. Fensterbank, M. Malacria, S. Sieburth, *Synthesis* **1997**, 813 – 854; b) D. Gauthier, Jr., K. S. Zandi, K. J. Shea, *Tetrahedron* **1998**, *54*, 2289 – 2338; c) S. Bracegirdle, E. A. Anderson, *Chem. Soc. Rev.* **2010**, *39*, 4114 – 4129.

[15] Murakami has reported a fully intermolecular asymmetric [2+2+2] cycloaddition between an allene and two equivalents of isocyanate catalyzed by Ni; see: T. Miura, M. Morimoto, M. Murakami, *J. Am. Chem. Soc.* **2010**, *132*, 15836 – 15838.

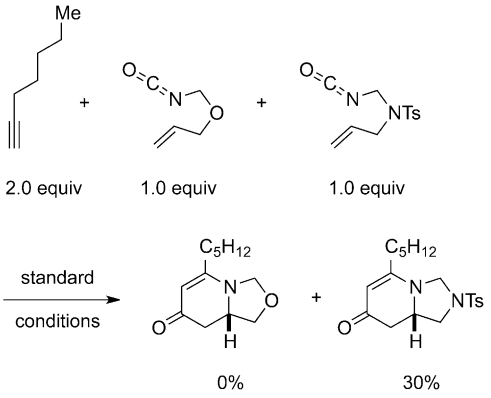
[16] Chlorocyclooctadienerhodium(I) dimer is also a competent catalyst, but provided slightly lower yield (60%, 92% *ee*) of the desired vinylogous amide product with **CKphos**.

[17] $Rh(PPh_3)_3Cl$, $[Rh(cod)_2]BF_4$, $Ni(cod)_2$, $Pd(PPh_3)_4$, or $[Ir(cod)Cl]_2$ did not provide any observed product.

[18] a) D. M. Dalton, A. K. Rappé, T. Rovis, *Chem. Sci.* **2013**, *4*, 2062 – 2070; b) S. Perreault, T. Rovis, *Synthesis* **2013**, 719 – 728; c) D. M. Dalton, T. Rovis, submitted.

[19] Attempts to access **4** as the major product resulted in either no reaction or decomposition of **2**.

[20] The reasons behind this observation are unclear. We note, however, that the presence of **2** does not prevent other cycloadditions from occurring with heptyne as per the following experiment:



[21] Acidic conditions led to a mixture of unidentified byproducts. Also, variation of the heteroatom tether did not alleviate the problems with one-pot cleavage.

[22] Direct reductive amination of the vinylogous amide leads to observed formation of the desired product, albeit in poor diastereoselectivity.

[23] See the Supporting Information for X-ray structure and data.

