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Ruthenium-Catalyzed Alkene–Alkyne Coupling of Disubstituted Olefins: Application to the Stereoselective Synthesis of Trisubstituted Enecarbamates

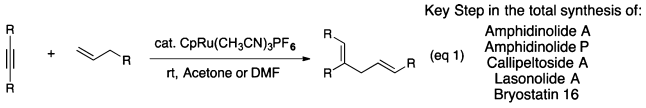
Barry M. Trost* and James J. Cregg

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: The Ru-catalyzed alkene–alkyne coupling reaction has been demonstrated to be an enabling methodology for the synthesis of complex molecules. However, to date, it has been limited to monosubstituted olefins. Herein we report the first general utilization of disubstituted olefins in the Ru-catalyzed alkene–alkyne coupling reaction by employing carbamate directing groups. The products are stereodefined trisusbstituted enecarbamates. The elaboration of these structures toward the asymmetric synthesis of complex aminocyclopentitols and 1,2-amino alcohols is discussed.

The alkene–alkyne coupling reaction between olefins and alkynes catalyzed by ruthenium (+2) complexes has been demonstrated to be a highly atom-economic reaction for the regio-, diastereo-, and chemoselective synthesis of 1,4-dienes (eq 1).[1] The reaction represents the ideal addition reaction, forming



one C–C bond and two stereodefined olefins, without the need of any premetalated reagents. The utility of the reaction has been demonstrated by its use as a key step in a number of total syntheses (eq 1).[2] However, to date, the intermolecular reaction has been limited to monosubstituded olefins.[3] Thus, given the success of the reaction as a powerful tool for the rapid construction of molecular complexity, we became interested in finding a way to facilitate the reaction using disubstituted olefins.

Considering that the mechanism of the reaction is believed to proceed through a ruthenacyclopentene intermediate,[1] we postulated that when using disubstituted olefins this intermediate was destabilized due to detrimental steric interactions (Figure 1). To alleviate this problem we hoped that a Lewis basic directing group could coordinate the cationic ruthenium center and increase the stability of the complex. Herein we report the success of such a strategy; employing carbamates as directing groups, we were able to facilitate the coupling of branched disubstituted olefins under extremely mild conditions. This methodology represents the first general example of disubstituted olefins being used as substrates in the Ru-catalyzed alkene–alkyne coupling reaction. The resultant trisubstituted enecarbamates are formed with complete stereoselectivity,

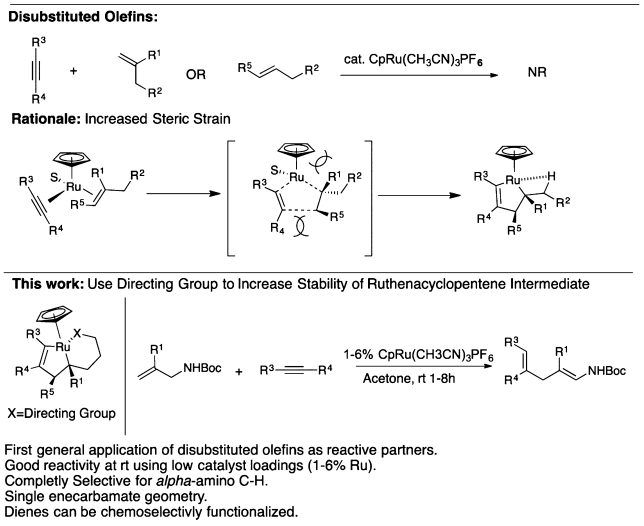


Figure 1. Utilization of carbamate directing groups to facilitate the Ru-catalyzed alkene–alkyne coupling reaction of disubstituted olefins.

require no stoichiometric metals, and are synthesized from readily available alkenes and alkynes.

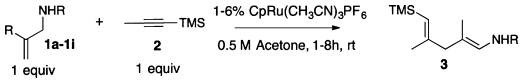
Enecarbamates are excellent substrates for a diverse range of synthetic transformations; including hydrogenation,[4] dihydroxylation,[5] halogenation,[6] cyclopropanation,[7] amination,[8] aminoxylation,[9] in Diels–Alder reactions,[10] as imine surrogates,[11] as nucleophiles in stereoselective C–C bond forming reactions,[12] and as amino acid precursors via hydroformylation.[13] In addition, they represent key structural motifs in a variety of bioactive natural products.[14] However, the available methods for the stereoselective synthesis of more highly susbstituted enecarbamates remains a challenge. The synthesis of β,β'-trisubstituted enecarbamates are limited to the carbometalation of ynamides[15] or the cross coupling of carbamates with preformed stereodefined vinyl halides and triflates.[16] In addition, for the carbometalation of ynamides, the directing groups required to obtain good regioselectivities are difficult to remove.

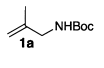
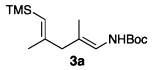
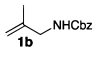
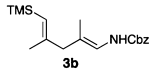
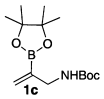
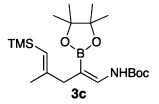
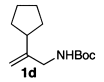
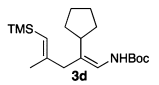
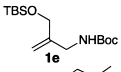
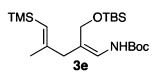
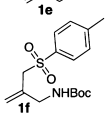
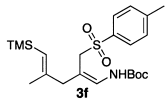
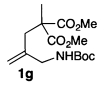
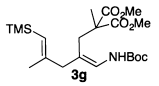
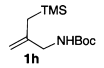
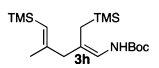
Thus, during our initial screening of carbamate directing groups we were interested in finding a more synthetically versatile group. Gratifyingly the *tert*-butyl carbamates (Boc) proved to be optimal for the reaction, providing excellent reactivity, selectivity, and product stability (Table 1). Methallyl

Received: November 20, 2014
Published: December 30, 2014

DOI: 10.1021/ja511911b
J. Am. Chem. Soc. 2015, 137, 620–623

Table 1. Substrate Scope for Alkene Partner[a]

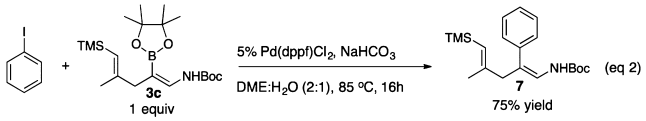


Entry	Ru%	Alkene	Product	Yield[b]
1	3% 1%	 1a	 3a	95 % 98 %
2	6%	 1b	 3b	61%
3	6%	 1c	 3c	83%
4	6%	 1d	 3d	58%(91%[c])
5	3%	 1e	 3e	52%
6	6%	 1f	 3f	70%(94%[c])
7	6%	 1g	 3g	55%(90%[c])
8	3%	 1h	 3h	82%

[a]One olefin isomer detected by NMR. Heating to 80 °C required to eliminate rotamers. [b]Yields are of isolated material. [c]Yield is based on recovered alkene (brsm).

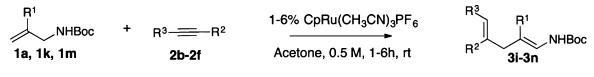
Boc amine **1a** could be coupled with alkyne **2** using either 3% or 1% catalyst to give enecarbamate **3a** in excellent yield. Carboxybenzyl (Cbz) (**1b**) was also effective, however, it was less reactive, presumably due to the sensitivity of the ruthenium catalyst to aromatic rings.

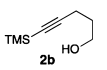
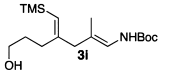
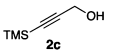
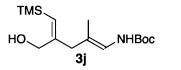
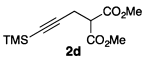
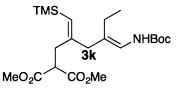
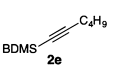
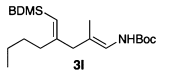
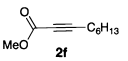
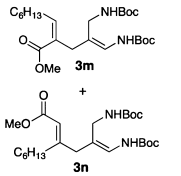
Varying the R group on the alkene was possible, as a number of different functional groups were tolerated (**1c**−**1h**)(Table 1). Heteroatoms, including oxygen (**1e**), sulfur (**1f**), and silicon (**1h**), electron-deficient aromatic rings (**1f**), branching at the allyl position (**1d**), and additional Lewis basic sites (**1g**) all gave good reactivity and only one olefin isomer. Of particular interest was the reaction of boronic ester **1c** to give **3c** in excellent yield. Under standard Suzuki coupling conditions the coupling of iodobenzene and enecarbamate **3c** proceeded smoothly to give compound **7** (eq 2).



In addition to TMS propyne more highly functionalized TMS alkynes and alkynoates[17] proved to be excellent substrates in the reaction (Table 2). Free alcohols (**2b** and **2c**) were tolerated without the need for any protecting groups. Our group has previously shown that benzyldimethylsilyl (BDMS) alkynes are also effective substrates for the ruthenium catalyzed alkene−alkyne coupling reaction,[18] and this proved to be true in our case as well (**2e**). The vinyl BDMS functional group represents an excellent substrate for Hiyama couplings and Tamao−Fleming

Table 2. Screening of Alkyne Partners[a]



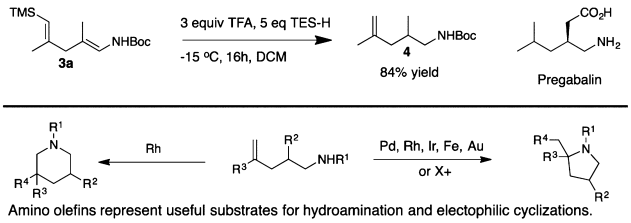
Entry	Ru%	Alkene	Alkyne	Product	Yield[b]
1	3%	R=Me **1a**	 2b	 3i	93%
2	6%	R=Me **1a** 2 equiv	 2c	 3j	72%
3	3%	R=Et **1k**	 2d	 3k	82%
4	6%	R=Me **1a** 5 equiv	 2e	 3l	77%
5	6%	R=CH2NHBoc **1m**	 2f	 3m + 3n	69% 3:1 **3m:3n**

[a]One olefin isomer detected by NMR. Heating to 80 °C required to eliminate rotamers. [b]Yields are of isolated material.

oxidations and is more stable than most activated silicon cross coupling reagents.

Satisfied that the method allowed for the synthesis of a diverse range of highly functionalized trisubstituted enecarbamates, we turned our attention to the functionalization of the products. We envisioned chemoselective activation of the enecarbamate being possible and were pleased to find that we could reduce the enecarbamate selectively by employing TFA and TES-H at low temperatures (Scheme 1). Compound **4** is a γ-amino olefin,

Scheme 1. Chemoselective Reduction



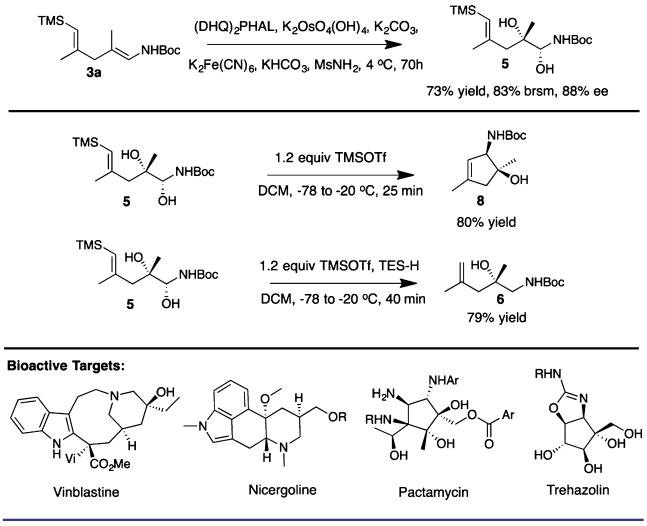
which are useful substrates for intramolecular electrophilic cyclization[19] and hydroamination reactions.[20] Additionally the product contains the substructure found in a number of $\alpha2\delta$-ligands known to modulate voltage-gated calcium channels, with the best-known example being the drug pregabalin.[21]

Given the stereoselectivity of the coupling reaction we were also interested in employing the enecarbamates as substrates for asymmetric transformations. Lam has shown that enecarbamates can be asymmetrically dihydroxylated with excellent ee's to form α-hydroxy aldehydes.[5] Inspired by this we attempted the Sharpless dihydroxylation of **3a**. The enecarbamate was dihydroxylated selectively to give **5** in good yield and enantioselectivity (Scheme 2).

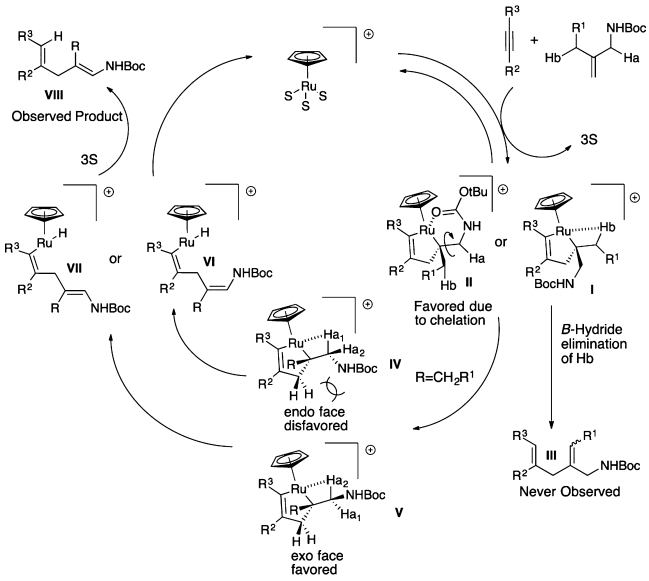
Surprisingly the product did not fragment to the aldehyde as seen by Lam. Lam used 2-oxazolidone as the nitrogen protecting

DOI: 10.1021/ja511911b
J. Am. Chem. Soc. 2015, 137, 620−623

Scheme 2. Asymmetric Synthesis of Cylopentanols and 1,2 Amino Alcohols



Scheme 3. Mechanistic Rationale



group, and this difference may account for the difference in stability of the N-acyl aminal products. The resulting N-acyl aminal **5** was stable to column chromatography and could be stored in the freezer without noticeable decomposition. Looking to take advantage of the aminal we reduced it to give the 1,2 amino alcohol **6**. 1,2 Amino alcohols are common in a number of bioactive molecules, including the drugs vinblastine and nicergoline, and have led to a number of synthetic methodologies.[22] In addition to reducing the aminal we hoped that we could use it as an imine surrogate. We hypothesized that the pendant vinyl silane of **5** could be used as a tethered nucleophile to attack the imine generated by addition of a Lewis acid. After some optimization it was shown that TMSOTf was the most effective Lewis acid. The reaction gave compound **8** as a single diastereomer in excellent yield. The method allows for the synthesis of highly substituted aminocyclopentitols. Aminocyclopentitols are structures of significant synthetic and biological interest,[23] with examples including the antibiotic pactamycin and insecticide trehazolin.

Our proposed mechanism for the alkene−alkyne coupling is depicted in Scheme 3. Assuming that the reaction proceeds through a ruthenacyclopentene intermediate, we believe that the observed stereo- and chemoselectivity can be accounted for based on two discriminating events in the mechanistic cycle. The first is chelation, which leads to preferential formation of intermediate **II** vs intermediate **I**. Compound **III**, formed by β-hydride elimination from intermediate **I**, was never observed. Additionally, intermediate **II** places the C−H_a bond available for β-hydride elimination following bond rotation, but places the C−H_b bond unable to acquire the necessary geometry to undergo β-hydride elimination. The second discriminating event occurs from intermediate **II**, where there are then two possible diastereotopic agostic interactions (**IV** or **V**), leading to either intermediate **VI** or intermediate **VII** after β-hydride elimination. Intermediate **V** experiences less detrimental steric interactions by placing the Boc-amido group on the convex-like face of the bicyclo[3.2.0]heptane-like system compared to intermediate **IV** where this group is on the concave-like face. Such differences account for formation of intermediate **VII** in preference to intermediate **VI**. After reductive elimination intermediate **VII** leads to the observed product **VIII**.

In summary we report the first general application of disubstituted olefins in the ruthenium catalyzed alkene−alkyne coupling, and its application to the synthesis of β,β-trisusbstituted enecarbamates with complete control of geometry. The application of such substrates to the synthesis of highly complex biologically relevant structural motifs has been illustrated. Mechanistic understanding from this endeavor should enable the continued expansion of the ruthenium catalyzed alkene−alkyne coupling reaction to additional disubstituted olefins.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bmtrost@stanford.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSF for their generous support of our programs (NSF CHE-1360634).

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DOI: 10.1021/ja511911b
J. Am. Chem. Soc. 2015, 137, 620−623

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DOI: 10.1021/ja511911b
J. Am. Chem. Soc. 2015, 137, 620−623