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Cobalt-Mediated [3 + 2]-Annulation Reaction of Alkenes with α,β-Unsaturated Ketones and Imines

Jennifer M. Schomaker, F. Dean Toste,* and Robert G. Bergman*

Department of Chemistry, University of California, Berkeley, California 94720

rbergman@berkeley.edu; fdtoste@berkeley.edu

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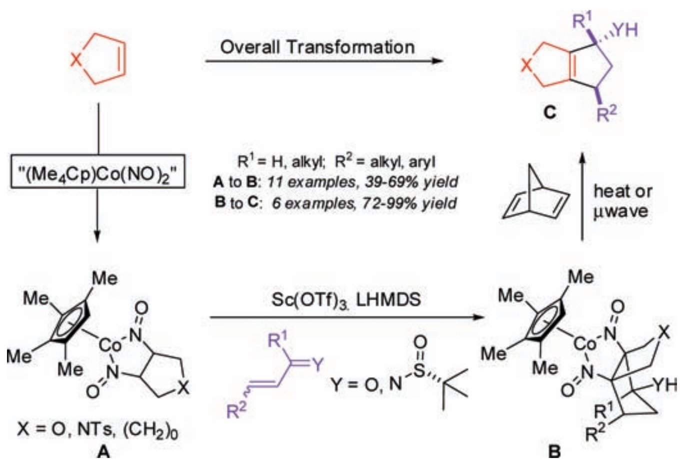
ABSTRACT



The utility of cobalt dinitrosyl complexes for the [3 + 2] annulation of alkenes with unsaturated enones and ketimines has been demonstrated. Reaction of a series of cobalt dinitrosyl/alkene adducts with conjugate acceptors in the presence of $Sc(OTf)_3$/LHMDS formed two new C−C bonds at the carbons α to the nitrosyl groups of the substrate, leading to unusual tri- and tetracycles. Retrocycloaddition of these products in the presence of norbornadiene yielded functionalized tetrasubstituted bicyclic olefins.

Vinyl anion synthons (e.g., **A** in eq 1) provide versatile partners for the formation of new carbon−carbon bonds at alkenyl centers.[1] In contrast, the generation of the corresponding dianion equivalent **B**, which would allow for the one-pot formation of two carbon−carbon bonds on adjacent carbons of the alkene substrate, is a much more challenging task.[2] We recently reported that in the presence of base, cobalt dinitrosyl/alkene adducts behaved as vinyl anion (**A**) equivalents and were capable of Lewis acid-mediated conjugate addition reactions to enones (eq 1).[3,4] Thermal retrocyclization of these alkylated intermediates produced organic products in which the unactivated alkene C−H bond had been functionalized. Herein, we report that sequential deprotonation of these cobalt complexes provides access to vinyl dianion equivalents (**B**, eq 2), allowing for the overall [3 + 2]-annulation reaction of alkenes with enones.

(1) For selected references, see: (a) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128* (17), 5604–5605. (c) Trost, B. M., Fleming, I., Eds.; *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 1, Part 1.

(2) For examples of metal-promoted 1,3-additions to enals see: Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030, and references therein. For other selected references on vinyl dianion equivalents, see: (a) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645. (b) Chambert, S.; Désiré, J.; Décout, J. *Synthesis* **2002**, *16*, 2319.

(3) Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777.

(4) First reported examples of cobalt dinitrosyl and dinitrosoalkane complexes: (a) Brunner, H. *J. Organomet. Chem.* **1968**, *12*, 517. (b) Brunner, H.; Loskot, S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 515. (c) Brunner, H.; Loskot, S. *J. Organomet. Chem.* **1973**, *61*, 401.

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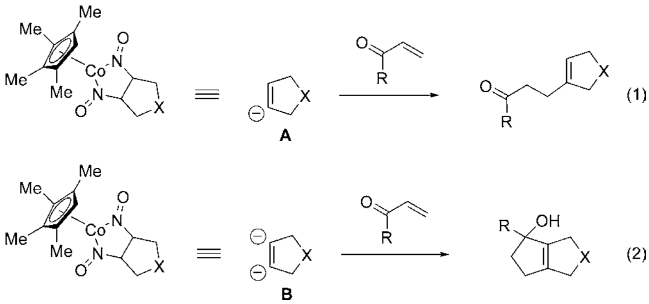
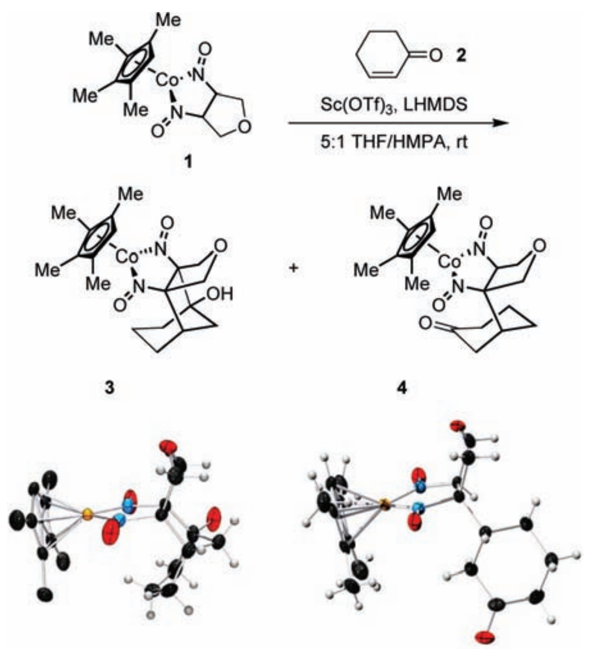
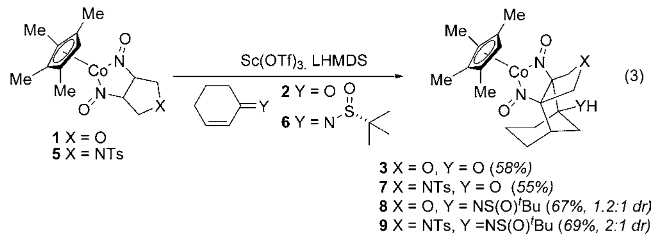


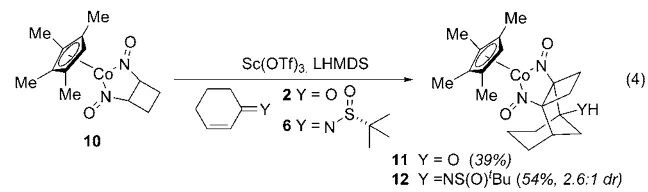
Treatment of the tetrahydrofuran-containing cobalt dinitrosoalkane adduct **1** with 2-cyclohexen-1-one **2** in the presence of 1.0 equiv of $Sc(OTf)_3$ and 2.1 equiv of LHMDS gave a 2.6:1 mixture of the polycyclic tertiary alcohol **3** and the Michael adduct **4**.[5] Both compounds were isolated and their structures confirmed by X-ray diffraction (Scheme 1).

Scheme 1. Annulation Reaction of Cobalt Complex **1**

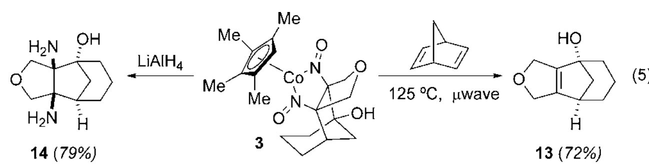


We were pleased to find that the annulation reaction was not limited to the tetrahydrofuran-containing complex **1**. Cobalt dinitrosopyrrolidine (**5**) and cyclobutane (**10**) complexes also underwent reaction with **2** to furnish the [3 + 2] annulated adducts **7**[6] and **11** respectively (eqs 3 and 4). We thus turned our attention to the use of α,β-unsaturated ketimines, which were not previously amenable to nucleophilic attack by anionic cobalt dinitrosoalkane species, as partners in the annulation reaction. Unsaturated *N-tert*-butylsulfinyl ketimines[7] **6** proved to be viable electrophiles in the annulation reaction, yielding tertiary amines **8**, **9**, and **12** in 54−69% yield and modest diastereoselectivity (up to 2.6:1 *dr*). An additional benefit imparted by the use of a chiral auxiliary was the ability to separate the product diastereomers.





The strained cobalt dinitrosoalkane complexes synthesized by this simple conjugate addition/aldol annulation reaction serve as useful precursors for a number of synthetic building blocks (eq 5). For example, treatment of the tricyclic fused-ring product **3** with norbornadiene under microwave conditions gave the expected tetrasubstituted bicyclic olefin **13** in 72% yield.[8] Alternatively, the *syn*-1,2-diamine **14** could be prepared by treatment of **3** with $LiAlH_4$. Since both nitrogen-bearing carbons are fully substituted, epimerization at these carbons is not possible and the stereochemistry installed by means of the [3 + 2] annulation reaction remains intact.



Given that cobalt complex **1** was prepared from 2,5-dihydrofuran, the sequence leading to **13** illustrated in eqs 2 and 5 constitutes the overall [3 + 2]-annulation of this alkene with 2-cyclohexen-1-one. Therefore, the cobalt dinitrosoalkane complex **1** was treated with several enones to determine the scope of the new cobalt-mediated annulation reaction (eq 6). Several acyclic conjugate acceptors underwent the first step of the sequence in 44−58% yield. In contrast to our previous work using cobalt dinitrosoalkanes, α,β-unsaturated aldehydes were now viable substrates for the annulation reaction, giving rise to secondary alcohols **15** and **16**. Unsaturated methyl ketones also underwent successful annulation with **1** to yield the tertiary alcohols **17** and **18**.[9] Moreover, the thermal retrocycloaddition liberated the newly

(5) 2-Cyclopenten-1-one afforded only the conjugate addition product, and 2-cyclohepten-1-one gave a 22% yield of fused-ring product and 48% of the acyclic product (see Supporting Information).

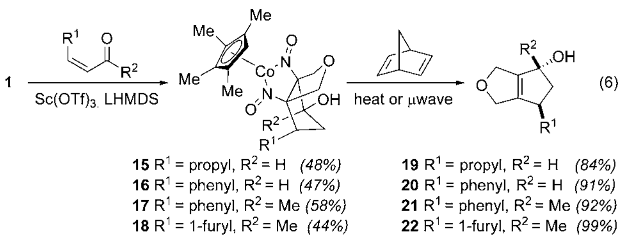
(6) Structure confirmed by X-ray structure analysis (see Supporting Information).

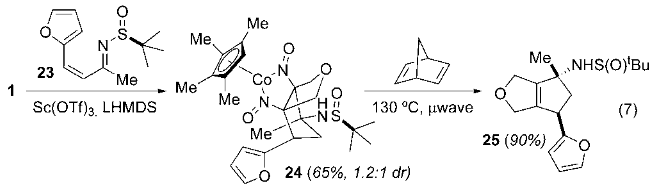
(7) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

(8) (a) Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787. (b) Becker, P. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 2985.

(9) Reaction of **18** with $LiAlH_4$ furnished the corresponding diamine in 66% yield (see Supporting Information for details).

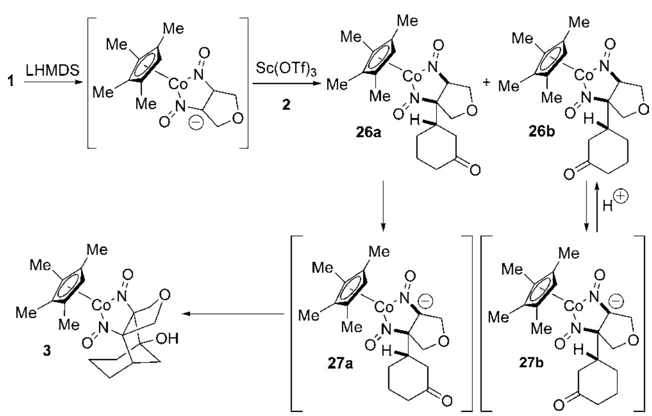
formed cyclopentenols (**19**−**22**) in greater than 90% yield in most cases. Notably, aliphatic enones and those conjugated to an aromatic or heteroaromatic group underwent the both steps of the sequence with equal efficiency.





Additionally, the two-step synthesis of aminated cyclopentenes can be achieved using α,*β*-unsaturated imines as electrophiles. For example, the use of the *N*-*tert*-butylsulfamide imine **23**, derived from *cis*-4-(2-furyl)-3-buten-2-one, allowed for the preparation of enantiomerically pure tertiary amine **25**, after separation of the diastereomers of **24** (eq 7).

Scheme 2. Proposed Mechanism for the Annulation Reaction



A proposed mechanistic pathway is outlined in Scheme 2 for the formation of annulated adduct **3**. We postulate that **3** is formed by a tandem reaction involving deprotonation of an α-nitrosyl hydrogen and formation of initial diastereomeric Michael adducts **26a** and **26b**. Both diastereomers are susceptible to further deprotonation at the remaining α-NO hydrogen leading to diastereomeric anions **27a** and **27b**. In **27a,** the carbanion is in close proximity to the carbonyl group; therefore, rapid ring closure ensues, affording **3** in 58% yield. In contrast, the anion of **27b** cannot readily approach the carbonyl moiety, and therefore **27b**[6] leads to **4** in 22% yield on protonation during workup. To explore this hypothesis, we subjected compound **26b** to further treatment with base and Lewis acid and found that it does not undergo cyclization.

In conclusion, we have demonstrated a facile [3 + 2]-annulation reaction of cobalt dinitrosoalkane complexes with α,*β*-unsaturated carbonyls and ketimines that leads to unusual tri- and tetracyclic ring systems. The cycloannulated tetrasubstituted olefins can be prepared by a thermally induced olefin exchange reaction of the fused-ring product with norbornadiene. Diamines are also accessible via a $LiAlH_4$ reduction of the aforementioned complexes. Future work will focus on the identification of other difunctionalized electrophiles that undergo the annulation reactions. Efforts to develop enantioselective, cobalt-catalyzed variants are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral information are available for all new compounds. X-ray crystal structure data are available for compounds **3**, **4** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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