

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

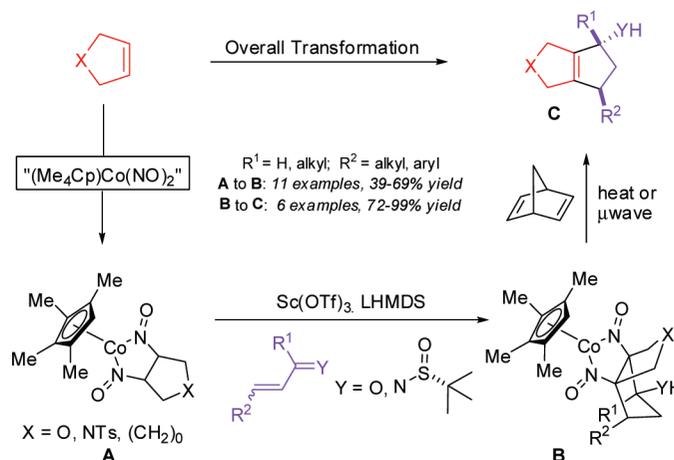
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ABSTRACT



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

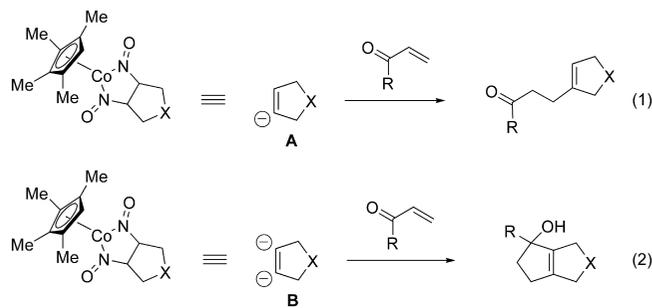
task.² We recently reported that in the presence of base, cobalt dinitrosyl/alkene adducts behaved as vinyl anion (**A**) equivalents and were capable of Lewis acid-mediated conjugate addition reactions to enones (eq 1).^{3,4} Thermal retrocyclization of these alkylated intermediates produced organic 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.

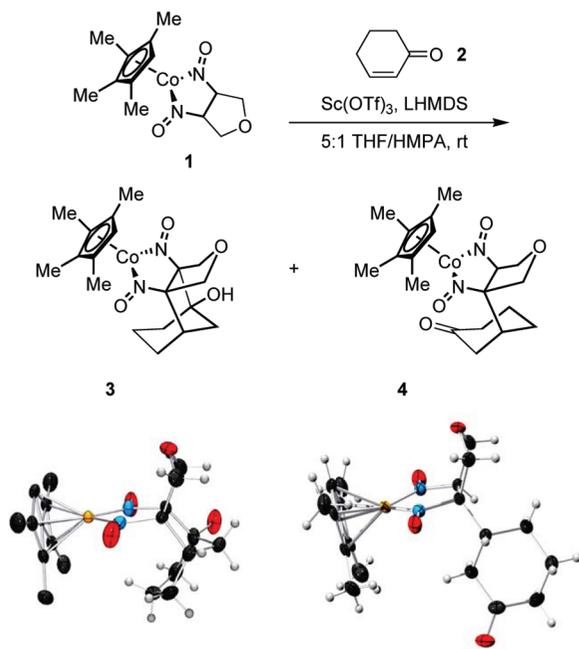
(3) Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777.

(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.



Treatment of the tetrahydrofuran-containing cobalt dinitrosoalkane adduct **1** with 2-cyclohexen-1-one **2** in the presence of 1.0 equiv of $\text{Sc}(\text{OTf})_3$ 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**



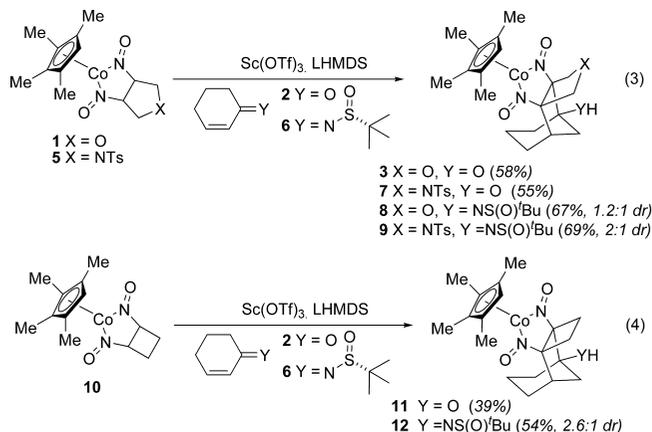
We were pleased to find that the annulation reaction was not limited to the tetrahydrofuran-containing complex **1**. Cobalt dinitrosopyrrolidine (**5**) and cyclobutane (**10**) complexes also underwent reaction with **2** to furnish the [3 + 2] annulated adducts **7**⁶ and **11** respectively (eqs 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*-

(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).

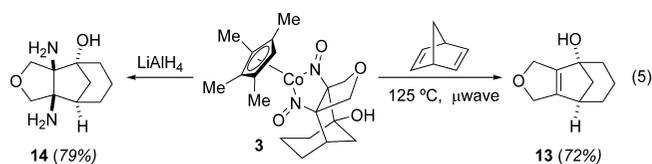
(6) Structure confirmed by X-ray structure analysis (see Supporting Information).

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

butylsulfinyl ketimines⁷ **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.

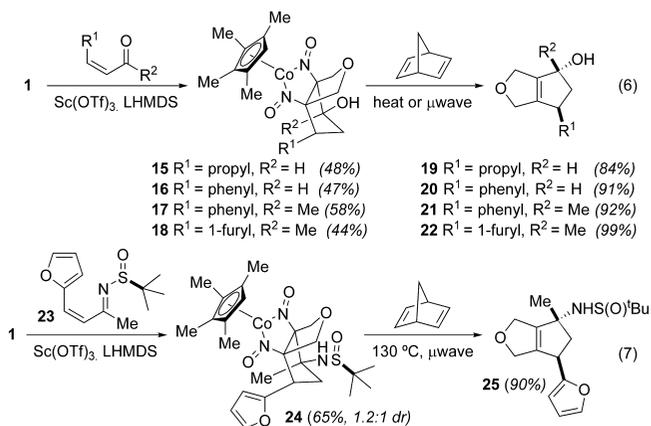


Given that cobalt complex **1** was prepared from 2,5-dihydrofuran, the sequence leading to **13** illustrated in eqs 2 and 5 constitutes the overall [3 + 2]-annulation of this alkene with 2-cyclohexen-1-one. Therefore, the cobalt dinitrosoalkane complex **1** was treated with several enones to determine 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

(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.

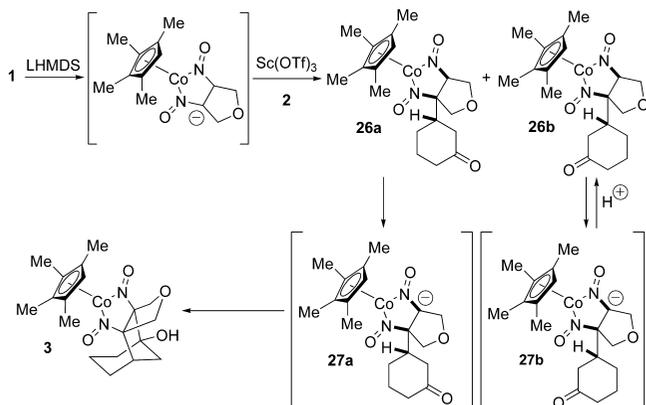
(9) Reaction of **18** with LiAlH_4 furnished the corresponding diamine in 66% yield (see Supporting Information for details).

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 cyclopentenols can be achieved using α,β -unsaturated imines as electrophiles. For example, the use of the *N-tert*-butylsul-

Scheme 2. Proposed Mechanism for the Annulation Reaction



famide 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).

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 LiAlH₄ 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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