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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 $\text{Sc}(\text{OTf})_3/\text{LHMDS}$ 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 retrocyclozation 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 dianion equivalents (**B**, eq 2), allowing for the overall [3+2]-annulation reaction of alkenes with enones.

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 poly cyclic tertiary alcohol **3** and the Michael adduct **4**.⁵ Both compounds were isolated and their structures confirmed by X-ray diffraction (Scheme 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 (eq 3 and eq 4). We thus turned our attention to

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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 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-

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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 equation 2 and equation 5 constitutes the overall [3+2]-annulation of this alkene with 2-cyclohexen-1-one. Therefore, the cobalt dinitrosoalkane complex **1** was reacted 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 formed cyclopentenols (**19–22**) in greater than 90% yield in most cases. Notably, aliphatic enones and those conjugated to an aromatic or heteroaromatic underwent the both steps of the sequence with equal efficiency.

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(7)

Additionally, the two-step synthesis of aminated cyclopentenones 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).

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 work-up. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Scheme 1.
Annulation reaction of cobalt complex **1**

Scheme 2.
Proposed mechanism for the annulation reaction