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Cobalt-Catalyzed Diastereoselective Reductive [3 + 2] Cycloaddition of Allenes and Enones

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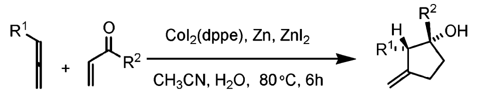
The [3 + 2] cycloaddition reaction is one of the primary methods to construct five-membered carbocycles, which are common structural cores of a large number of biologically important natural products and target molecules for numerous synthetic studies.[1] Among the many impressive methods available, transition-metal-catalyzed cycloadditions provide great opportunities for mild and highly selective cycloadditions since the complexation of the π-component to the metal significantly activates as well as polarizes the otherwise unreactive species.[2] Although a variety of approaches are available, most examples require a specialized substrate class that cannot be carried through routine synthetic sequences and that are sometimes difficult to install in complex organic molecules.[3] Thus, a more atom-economical, mild, highly stereoselective processes involving readily accessible starting materials would be of great potential in synthetic organic chemistry. Development toward this end has been made available via the participation of α,β-unsaturated carbonyl compounds as a three-carbon group in metal-catalyzed reductive [3 + 2] cycloaddition reactions. Sato et al. reported the stoichiometric titanium-promoted addition of tethered alkynes and enolates.[4] Montgomery's pioneering work on stoichiometric nickel-promoted addition of tethered alkynes and enals showed that the cyclization process can be achieved using enolate metallacycles.[5] The challenge in the above reductive cycloaddition process is the need for a metal catalyst/reducing agent combination that can propagate the catalytic cycle and a proton source if the ring formation is accompanied by a reduction. Very recently, the same group disclosed a catalytic, intermolecular version of this class of [3 + 2] cycloaddition using triethylborane as reducing agent in protic cosolvent.[6]

We have earlier reported a catalytic, intermolecular reductive coupling of alkynes and acrylates by employing zinc as reducing agent and water as a proton source.[7] During the course of our investigation in related reductive coupling reactions, we noticed that allenes and enones effectively cyclized to form cyclopentanols with very high diastereoselectivity. Thus, treatment of phenyl allene with methyl vinyl ketone in the presence of $CoI_2(dppe)$, Zn, ZnI_2, and water in CH_3CN gave 3-methylenecyclopentanol derivative **3a** in a very good yield of 88%. The reaction exhibited excellent chemo- and regioselectivity. The cycloaddition took place exclusively at the internal double bond of allene with the exocyclic double bond placed at the 3-position of cyclopentanol. The stereochemistry with the phenyl and the methyl substituents being trans to each other was thoroughly confirmed by NOE experiments. The use of ZnI_2 was crucial for the success of the reaction, without which no cycloaddition occurred.

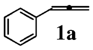
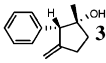
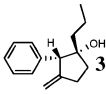
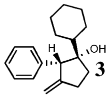
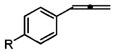
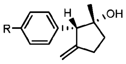
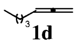
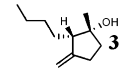
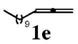
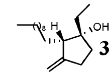
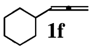
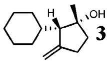
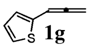
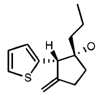
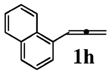
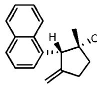
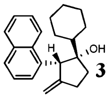
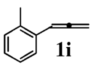
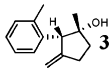
Both *n*-propyl vinyl ketone and cyclohexyl vinyl ketone reacted with phenyl allene to give the corresponding cyclopentanols in 80 and 74% yields, respectively (Table 1, entries 2 and 3). Both electron-withdrawing groups and electron-donating groups substituted in phenyl allenes gave cycloaddition products (entries 4 and 5).

Alkyl allenes also worked well for this reaction. For example, when *n*-butyl allene was employed, the [3 + 2] cycloaddition product was obtained in good yields (entry 6). Similarly, cyclohexyl allene reacted with methyl vinyl ketone under the standard conditions to give the cyclopentanol **3h** in 55% yield (entry 8). Heteroaromatic allenes are also compatible for the present reaction (entry 9). It is noteworthy here that all the above products were obtained as a single diastereomer. However, when phenyl allene was replaced by 1-napthyl allene, a mixture of diastereomers of cyclopentanol was obtained in 68% yield with 86% de (entry 10). The same allene also reacted with cyclohexyl vinyl ketone to yield

Table 1. Results of Cobalt-Catalyzed Reductive [3 + 2] Cycloaddition of Allenes and Enones[a]



1 2 3

entry	1	2^b	3	yield (%)^c
1	 **1a**	**2a**	 **3a**	88
2	**1a**	**2c**	 **3b**	80
3	**1a**	**2d**	 **3c**	74
4	 **1b** R = COMe	**2a**	 **3d**	91
5	**1c** R = OMe		**3e**	62
6	 **1d**	**2a**	 **3f**	61
7	 **1e**	**2b**	 **3g**	77
8	 **1f**	**2a**	 **3h**	55
9	 **1g**	**2c**	 **3i**	65
10	 **1h**	**2a**	 **3j**	68 (93:7)^d
11	**1h**	**2d**	 **3k**	58 (89:11)^d
12	 **1i**	**2a**	 **3l**	71 (92:8)^d

[a] Reaction conditions: 1.00 mmol of allene, 1.20 mmol of enone, 0.0500 mmol of $CoI_2(dppe)$, 2.75 mmol of Zn, and 0.050 mmol of ZnI_2, 2.00 mmol of water in 2 mL of CH_3CN at 80 °C for 6 h. [b] R^2: **2a** = methyl, **2b** = ethyl, **2c** = propyl, **2d** = cyclohexyl. [c] Isolated yields. [d] Structures of major isomer are represented.

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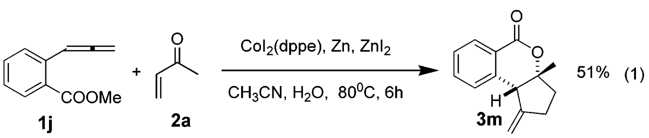
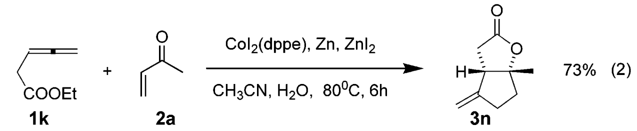
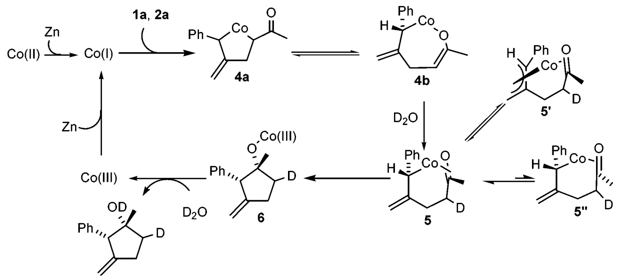
similar results (entry 11). Treatment of sterically hindered *o*-tolyl allene **1i** with methyl vinyl ketone also gave a mixture of the corresponding diastereomers of cyclopentanol **3l** in 71% yield (entry 12). Interestingly, when 2-allenyl benzoate was employed, the formation of cyclopentanol was accompanied by lactonization to yield benzopyranone derivative **3m** (eq 1).[8] The utility of this methodology was further realized by the synthesis of bicyclic-γ-lactone **3n** from very simple starting materials (eq 2).



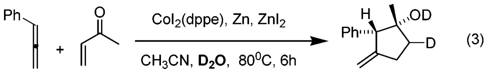


To understand the role of water and to elucidate the mechanism of the present catalytic reaction, an isotope labeling using D_2O to replace H_2O for the reductive [3 + 2] cycloaddition of methyl vinyl ketone and phenyl allene was carried out (eq 3). The results showed that the 5 position in the cyclopentanol ring and the alcohol were deuterated. A mechanism of the present reductive [3 + 2] cycloaddition would be very interesting in view of the ability of the catalyst to assemble an allene and an enone for cycloaddition and hydrogenation in one pot in a highly regio-, chemo-, and diastereoselective manner (Scheme 1). The catalytic cycle is likely initiated by the reduction of Co(II) to Co(I) by zinc dust. This is followed by the chemoselective cyclometalation of Co(I) with allene and enone to form cobaltacyclopentane intermediate **4a** which could be in equilibrium with the O-enolate **4b**. Selective protonation of **4b** to generate **5** followed by carbonyl insertion into the cobalt−carbon bond forms cobaltalkoxide **6**. Protonation of alkoxide **6** leads to the observed product. A similar chemo- and regioselectivity for allene was also observed in ruthenium-catalyzed coupling of allenes and enones, although the product is different.[9] The mechanistic basis for the outstanding diastereoselectivity observed in almost all cases described above is unclear at this stage. The addition of the Co−C bond to the carbonyl group to form **6** is likely to be an irreversible step. Assuming that there might exist an equilibrating mixture of diastereomers of **5**, it can be suggested that the equilibrium and kinetic preference for the addition across the carbonyl bond of **5** is responsible for the selectivity obtained in these reactions. It can also be inferred here that a sterically hindered substituent such as naphthyl or *o*-tolyl on the allene slightly affects the equilibrium and rates of carbonyl insertion of one isomer over the other.

Scheme 1. Proposed Mechanistic Pathway



In comparison with the previously known [3 + 2] cycloaddition methods to construct five-membered ring compounds, this method offers a very interesting advancement in that it offers the ability to combine two simple, stable π-systems.[2,3] Further, it is interesting to note that a phosphine-based organocatalytic [3 + 2] cycloaddition of allenes and enones is known.[10] In this case, allene acts as a three-carbon group and adds to the double bond of enone to yield cyclopentenes, whereas, in the present Co-catalyzed cycloaddition, enones act as the three-carbon group adding to the internal double bond of allene leading to cyclopentanols, thus providing a good complement to the above cycloaddition. Catalytic reductive couplings and cycloadditions are usually hampered by the need for a suitable proton source/electrophile and reducing agent to propel the catalytic cycle, while the use of Zn as reducing agent and water as a proton source in the present cobalt-catalyzed reactions effectively circumvents this problem.[11]



In conclusion, we have demonstrated a mild, highly diastereoselective catalytic intermolecular reductive [3 + 2] cycloaddition of allenes and enones. This is the first report of cobalt-catalyzed cycloaddition of this type. This new reductive cycloaddition reaction underlines the potential of using cobalt as a very user-friendly, inexpensive, and efficient catalyst for the formation of a carbon−carbon bond as well as synthesis of carbocycles. Further studies toward uncovering the immense potential of this chemistry including an asymmetric variation are underway in our laboratories.

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Supporting Information Available: General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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