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Selective 1,4-reduction of unsaturated carbonyl compounds using $Co_2(CO)_8$–H_2O

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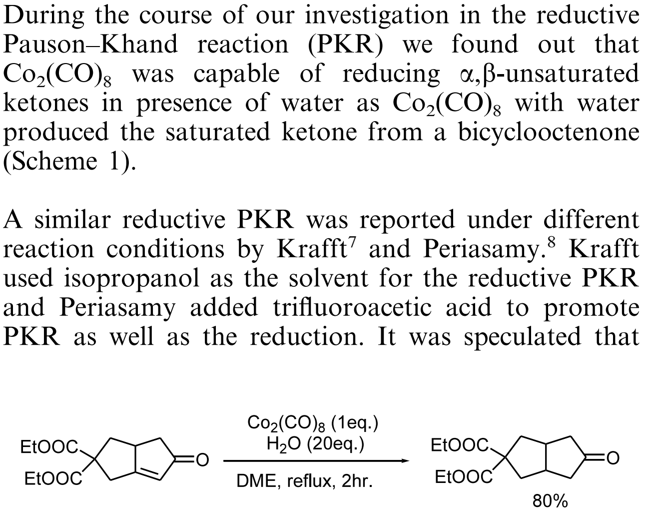
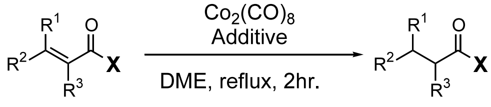
Abstract—α,β-Unsaturated ketones and aldehydes were selectively reduced to the corresponding saturated carbonyl compounds by $Co_2(CO)_8$–H_2O system. The current reducing system also offered a chemoselective reduction of less substituted unsaturated carbonyl groups.

Chemoselective reduction of conjugated carbonyl compounds[1] is a useful functional group transformation in organic synthesis. Many useful methodologies for selective 1,2-reduction of α,β-unsaturated carbonyl compounds have been developed through metal hydride mediated reduction[2] or hydrogenation reactions.[3] On the other hand, selective 1,4-reduction of α,β-unsaturated carbonyl compounds has not been developed as much.[4] Especially, 1,4-reduction of α,β-unsaturated aldehydes has been quite challenging and reduction of α,β-unsaturated aldehydes to the corresponding saturated aldehydes was achieved either through unusual reducing agents[4d,e] or indirectly through hydrosilation.[5] During the course of our investigation in the reductive Pauson–Khand reaction (PKR) we found out that $Co_2(CO)_8$ was capable of reducing α,β-unsaturated ketones in presence of water as $Co_2(CO)_8$ with water produced the saturated ketone from a bicyclooctenone (Scheme 1).

A similar reductive PKR was reported under different reaction conditions by Krafft[7] and Periasamy.[8] Krafft used isopropanol as the solvent for the reductive PKR and Periasamy added trifluoroacetic acid to promote PKR as well as the reduction. It was speculated that addition of a proton source to $Co_2(CO)_8$ generated a reducing species. Though the exact structure or nature of the reducing species under these conditions is not known, it is presumed that the reducing species would possess the similar properties to that of $CoH(CO)_4$ as both of them showed selective reduction of olefins of conjugated ketones. Though $CoH(CO)_4$ was reported to reduce unsaturated aldehydes as well as unsaturated ketones selectively to the corresponding saturated carbonyl compounds,[6] the reaction has not been developed for practical use partly due to the lack of reliable methodology for the preparation of $CoH(CO)_4$. We became interested in developing a synthetic methodology of selective reduction of unsaturated carbonyl compounds using $Co_2(CO)_8$.



Scheme 1.



Herein we report a selective reduction of unsaturated carbonyl compounds using $Co_2(CO)_8$ with water.

Reduction was tested on benzylideneacetone with all three different additives that were known to promote reductive PKR to select the best additive among them. Though the selective 1,4-reduction was achieved with all additives, isopropanol promoted the reduction with low conversion and addition of trifluoroacetic acid showed incomplete conversion and presence of unknown products other than the saturated ketone. When water was added as the additive, clean and complete reduction was observed (Scheme 2). The reactivity difference between $Co_2(CO)_8$–H_2O and

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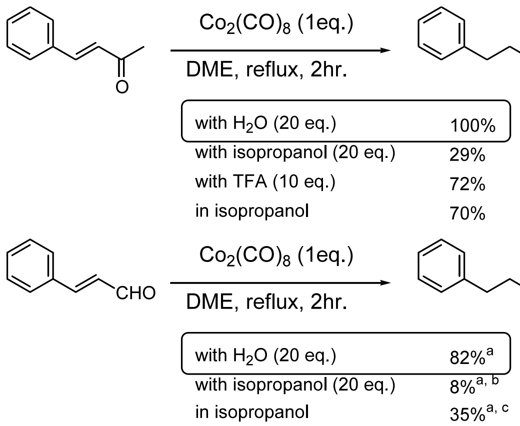
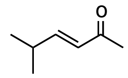
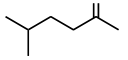
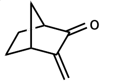
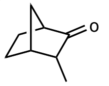
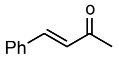
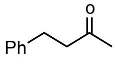
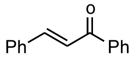
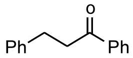
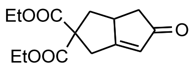
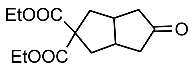
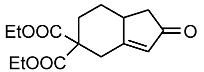
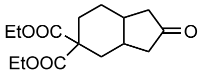
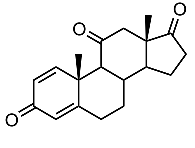
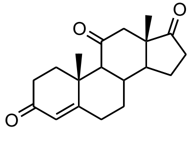
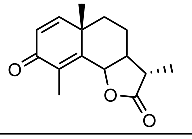
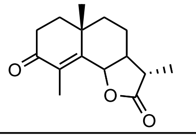


[a] GC yield, [b] major product was cinnamalcohol (89%), [c] major product was cinnamalcohol (59%)

Scheme 2.

Table 1. Reduction of unsaturated ketones

entry	substrate	product	yield[a]
1	2-pentenone	2-pentanone	80%[b]
2			91%[b]
3	cyclopentenone	cyclopentane	87%[b]
4	cyclohexenone	cyclohexane	98%[b]
5	cycloheptenone	cycloheptane	99%[b]
6			100%
7			100%
8			96%
9	pulegone	no reaction	--
10	carvone	no reaction	--
11	β–isophorone	no reaction	--
12			80%
13			10%
14			67%
15			81%

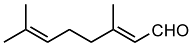
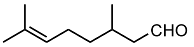
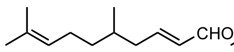
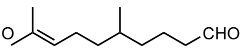
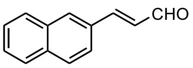
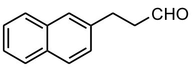
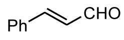
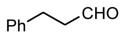
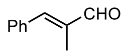
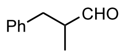
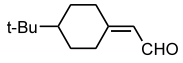
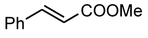
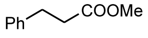
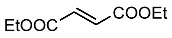
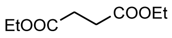
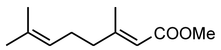
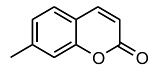
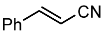
[a] isolated yield, [b] GC yield

$Co_2(CO)_8$–isopropanol was further tested with cinnamaldehyde. When isopropanol was used either as the additive or the solvent, the reaction produced cinnamalcohol as the major product. Based on this preliminary result, all the reactions for reduction study were carried out using $Co_2(CO)_8$ with H_2O in DME.

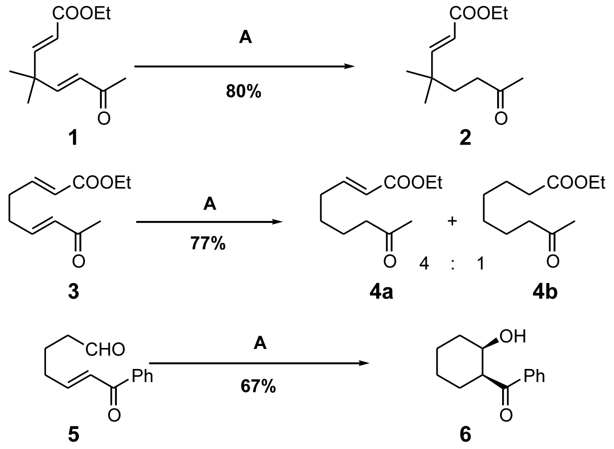
First, reduction of various α,β-unsaturated ketones was examined under this reaction condition and the result was summarized in Table 1.[9] Both acyclic and cyclic α,β-unsaturated ketones were reduced selectively to the corresponding saturated ketones in good yield (entries 1–8). However, sterically encumbered enones were not reactive under the reaction condition as evidenced by the fact that tri- or tetra-substituted enones did not react at all (entries 9–11). Only trisubstituted enones with ring strain were reduced (entries 12 and 13). These results prompted us to explore selective reduction between conjugated olefins in the same molecule with different substitution patterns. When there were two α,β-unsaturated ketones present in a molecule, only the disubstituted olefin was reduced while leaving the other olefin intact (entries 14 and 15). Encouraged by this fine selectivity for the enone reduction, we examined the reduction of α,β-unsaturated aldehydes, esters and nitriles (Table 2). A complete selectivity for the 1,4-reduction was observed with acyclic unsaturated aldehydes (entries 1–4) as no allylic alcohols or saturated alcohols were observed. 1,2-Reduction of unsaturated aldehydes was observed only with a cinnamoyl compound (entries 5 and 6). Contrary to unsaturated ketones, trisubstituted unsaturated aldehydes were reduced to the corresponding saturated aldehydes (entries 2 and 6). However cyclic unsaturated aldehyde was not reactive at all (entry 8). Unsaturated esters were less reactive than ketones or aldehyes as only unsaturated esters with extra activating groups were reduced to the corresponding saturated esters (entries 9 and 10). Entries 12 and 13 indicated that unsaturated lactones or unsaturated nitriles would not be reactive toward the current reducing system. Lack of the reactivity of unsaturated nitriles toward $Co_2(CO)_8$–water system was quite contrast to the report of successful reduction of unsaturated nitriles with $HCo(CO)_4$.[10]

Since this result also showed that the current reducing system might offer selective reduction among various conjugated functional groups, we next explored the chemoselective reduction between two sets of unsaturated carbonyls in the same molecule (Scheme 3). When a substrate with an unsaturated ketone and an unsaturated ester in the same molecule, **1** was treated with $Co_2(CO)_8$–water system, only the olefin of the unsaturated ketone of the molecule was reduced to afford **2** as the sole product. When compound **3** was treated with $Co_2(CO)_8$–water with anticipation of subsequent aldol type cyclization reaction, only the reduction products were obtained. In this case, over reduction product **4b** was also obtained as the minor product. On the other hand, the reductive aldol reaction was realized in the case of compound **5** that contained more reactive electrophile for aldol reaction than **3**. Reaction of **5** with $Co_2(CO)_8$–water system produced cyclohexyl com-

Table 2. Reduction of unsaturated aldehydes, esters, nitriles

entry	substrate	product	yield[a]
1	2-hexenal	hexanal	76%[b]
2			94%[b]
3			69%
4			70%
5			82%[b, c]
6			60%[c]
7	myrtenal	no reaction	--
8		no reaction	--
9			80%
10			91%
11		no reaction	--
12		no reaction	--
13		no reaction	--

[a] isolated yield, [b] GC yield, [c] cinnamalcohol was also produced (12%), [c]1,2-reduction product was also obtained (35%)



A: $Co_2(CO)_8$ (1eq.), H_2O(20 eq.), DME, reflux

Scheme 3.

pounds **6**[11] as a single diastereomer with *syn* stereochemistry. This result indicated that the intermediate from the reduction could react with electrophiles before being quenched by water presented in the reaction. This reductive aldol cyclization reaction produced the same result as the Krische's report of cobalt catalyzed reductive aldol reaction of **5**.[12] Krische reported that silane mediated reductive aldol cyclization with a cobalt catalyst produced β-hydroxyketones with complete selectivity for *syn*-diastereomers. Currently, we are investigating the scope of reductive aldol reaction using $Co_2(CO)_8$–water system.

In summary, we have developed a reagent not only for the selective 1,4-reduction of α,β-unsaturated carbonyl compounds but also the selective reduction of less substituted unsaturated carbonyl compounds. The exact nature and properties of the reducing agent will be the subject of future research since the understanding of the exact reducing species could lead to the catalytic use of $Co_2(CO)_8$.

Acknowledgements

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9. **General reduction procedure**: In a round bottom flask charged with Ar atmosphere, 0.5 M solution of $Co_2(CO)_8$ (1 equiv.) in DME was prepared. A 1.0 M solution of an unsaturated carbonyl compound (1 equiv.) in DME and water (20 equiv.) were added, and the mixture was refluxed for 2 h. Upon completion of the reaction, the

mixture was cooled to room temperature and concentrated in vacuo. Direct purification by flash chromatography (SiO_2, EtOAc/hexane) afforded the saturated carbonyl compound as a colorless oil.

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11. Spectroscopic data of **6**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.39–1.50 (m, 3H), 1.72–1.80 (m, 3H), 1.88–1.98 (m, 2H), 3.43 (ddd, 1H, $J=2$, 3.2, 9.2 Hz), 3.92 (brs, 1H), 4.26 (s, 1H), 7.45 (t, 2H, $J=8$ Hz), 7.56 (t, 1H, $J=8$ Hz), 7.90 (d, 2H, $J=8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 24.6, 25.6, 31.9, 48.1, 66.4, 128.4, 128.7, 133.4, 135.7, 205.9; IR (CH_2Cl_2) 3487, 2935, 2861, 1665, 1447, 1251, 1213, 978, 701 cm^{-1}; 300 MHz ^1H and ^{13}C NMR spectra of **6** overlaid exactly to the spectra reported in Ref. 12.
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