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Atom- and Step-Economical Preparation of Reduced Knoevenagel Adducts Using CO as a Deoxygenative Agent

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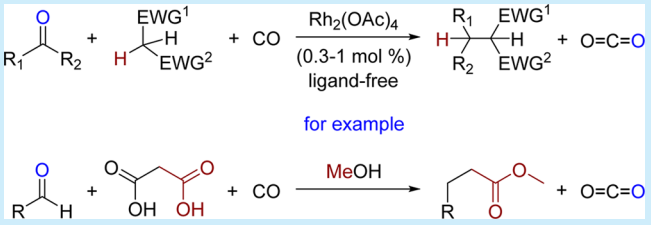
Supporting Information

ABSTRACT: A highly efficient one-step Rh-catalyzed preparation of reduced Knoevenagel adducts of various aldehydes and ketones with active methylene compounds has been developed. The protocol does not require an external hydrogen source and employs carbon monoxide as a deoxygenative agent. The use of malonic acid or cyanoacetamide enabled efficient formal deoxygenative addition of methyl acetate or acetonitrile to aldehydes. The developed methodology was applied to the synthesis of the precursors of biomedically important compounds.

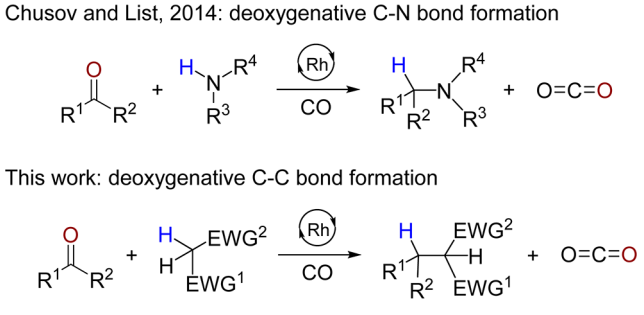


In light of growing environmental concerns, the concepts of atom,[1] step,[2] and redox[3] economies, introduced by Trost, Wender, and Baran respectively, are becoming increasingly influential on the design of novel chemical methodologies.[4] The atom economical approach seeks to maximize the incorporation of the reagents into the final product with concomitant minimization of side product formation. Whereas development of atom economical chemical methods has received considerable attention,[5,6] atom economical redox processes remain understudied.[7] Quite a few indispensable laboratory synthetic procedures, e.g. reduction with complex hydride agents, can hardly be used on the industrial scale due to the formation of substantial amounts of chemical waste. Certain redox transformations, e.g. hydrogenation of double bonds, seem to be almost perfectly atom economical at first glance. However, most hydrogen is industrially produced via steam reforming of natural gas;[8] the conventional technology involves a sequence of three high-temperature catalytic processes (conducted at 190−800 °C) followed by separation of the resulting gaseous products.[9] In order to accurately assess the economical and environmental profile of a given process, one should therefore consider the entire synthetic sequence starting from the natural sources.[10] Undoubtedly, development of novel atom-economical redox processes while keeping in mind a greater picture of environmental impact therefore represents an important goal for contemporary chemical methodology.

Knoevenagel condensation is one of the essential C−C bond forming reactions which is widely employed as a useful synthetic tool for the construction of α,β-unsaturated carbonyl compounds.[11] Notably, some reported synthetic strategies involve α,β-reduction immediately following the condensation,[12] which includes a number of industrially important processes, such as preparation of top-selling drugs pregabalin[13] and pioglitazone.[14] In this context, from the standpoint of step economy, it would be highly desirable to design a one-step protocol equivalent of the Knoevenagel condensation/reduction sequence.[15]

We recently reported a novel method of Rh-catalyzed reductive amination, which does not require an external hydrogen source: instead, carbon monoxide can be efficiently employed as the deoxygenative agent (Scheme 1).[16] Since carbon monoxide is formed in multiton quantities as a side product of steel production,[17] implementation thereof as a reagent in potentially scalable processes of high synthetic value is in compliance with the commitment to recycling and waste management optimization. In fact, purified carbon monoxide is employed in industrial processes of great importance (e.g., 75% of the worldwide production of acetic acid comes from the reaction of CO with methanol).[18] The use of CO in chemical synthesis is also becoming increasingly popular in the academic community.[19] Inspired by our success with the deoxygenative

Scheme 1. Use of Carbon Monoxide As a Deoxygenative Agent for the Formation of C−N and C−C Bonds



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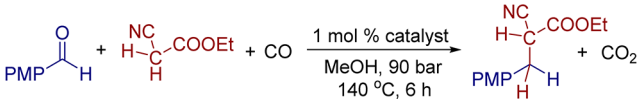
formation of a C−N bond, we decided to attempt implementation of CO as a reductant in deoxygenative C−C bond formation. Thus, herein we report the development of an atom-economical rhodium-catalyzed deoxygenative coupling of active methylene compounds with aldehydes and ketones, which results in efficient preparation of reduced Knoevenagel adducts.

We began our studies with the model reaction between ethyl cyanoacetate and *para*-methoxybenzaldehyde (Table 1).

Table 1. Catalyst and Solvent Optimization for the Preparation of Reduced Knoevenagel Adducts



entry	catalyst	solvent	yield[a] (%)
1[b]	$Pd(OAc)_2$	THF	trace
2[b]	$PdCl_2$	THF	trace
3[b]	$Pd(dppf)Cl_2$	THF	trace
4[b]	$CpRu(PPh_3)Cl_2$	THF	trace
5[b]	$[Pt(NH_3)_4Cl_2](NO_3)_2$	THF	trace
6	$[(cod)IrCl]_2$	THF	trace
7[b]	$CpRh(CO)I_2$	THF	trace
8	$[(cod)RhCl]_2$	THF	19
9	$[Rh(CO)_2Cl]_2$	THF	21
10	$Rh_2(OAc)_4$	THF	36
11	$Rh_2(OAc)_4$	dioxane	4
12	$Rh_2(OAc)_4$	Et_2O	12
13	$Rh_2(OAc)_4$	toluene	35
14	$Rh_2(OAc)_4$	MeCN	48
15	$Rh_2(OAc)_4$	CH_2Cl_2	13
16	$Rh_2(OAc)_4$	solvent free	19
17	$Rh_2(OAc)_4$	water	13
18	$Rh_2(OAc)_4$	ethanol	50
19	$Rh_2(OAc)_4$	methanol	64[c]

[a]Yields were determined by NMR with internal standard. [b]2 mol % of the catalyst was used. [c]Predominantly the product of transesterification (methyl ester).

Initially, a number of platinum group metal complexes were screened, among which rhodium(II) acetate showed the most promising catalytic activity (Table 1, entries 1−10); other rhodium complexes demonstrated inferior performance. We then tested a variety of reaction media (including solvent-free conditions; Table 1, entries 11−19); conducting the reaction in methanol furnished the product in 64% yield (predominantly transesterified). With these results in hand, we decided to test the optimized conditions (catalysis by rhodium(II) acetate in alcohols) for a representative range of substrates (Figure 1).

Good-to-excellent yields were observed for both electron-rich and -deficient aromatic aldehydes with various substitution patterns (**1a**−**1n**). The benzyloxy moiety was shown to be stable under reaction conditions; product **1n** was isolated in 60% yield. Aliphatic aldehydes efficiently furnished products **1o**−**1r** without any substantial competition from aldol condensation. The methodology could be successfully expanded to ketones, as exemplified by preparation of the cyclopentanone and cyclohexanone derivatives **1s** and **1t** respectively.

Altering the active methylene counterpart enabled one-step preparation of other types of synthetically useful products.

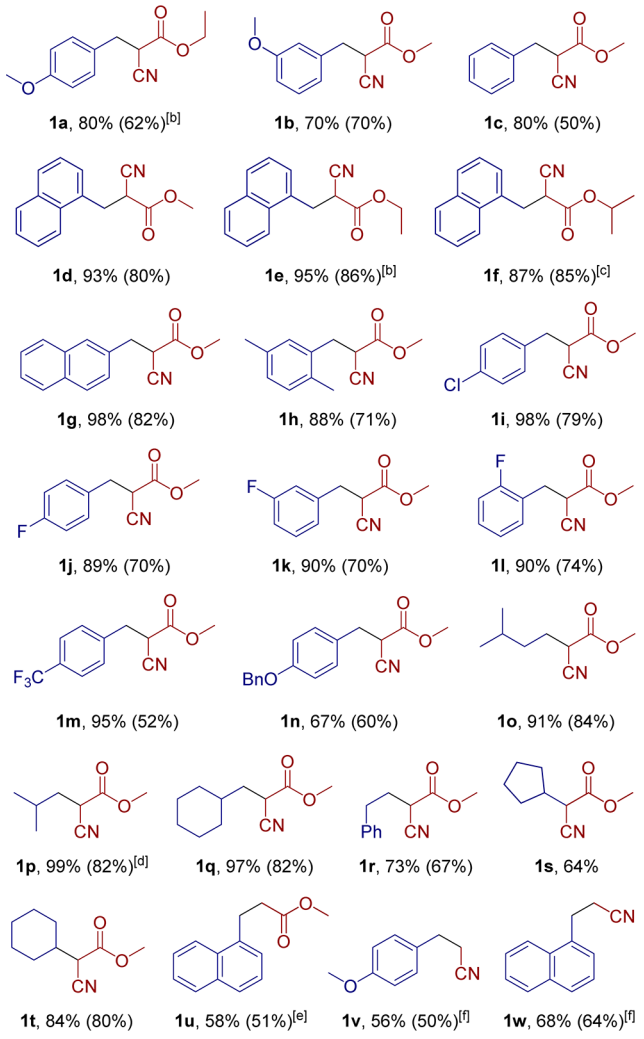


Figure 1. Investigation of the substrate scope for the Rh-catalyzed preparation of reduced Knoevenagel adducts with CO as a deoxygenative agent. [a] 0.4−1 mmol scale; 1:1 ratio of reactants, 1 mol % $Rh_2(OAc)_4$, methanol, 50 bar of CO, 110−140 °C, 22−44 h. Yields were determined by NMR with an internal standard. Isolated yields are shown in parentheses. [b] Ethanol was used as a solvent. [c] Isopropanol was used as a solvent. [d] 20 mmol scale: 99% NMR yield, 94% isolated yield. [e] Malonic acid was used as the active methylene component. [f] 1 equiv of water was added. Cyanoacetamide was used as the active methylene component.

Thus, methyl ester **1u** could be prepared in 51% yield from 1-naphthaldehyde by the use of malonic acid in methanol. Alternatively, formal deoxygenative addition of acetonitrile to aldehydes was successfully accomplished when cyanoacetamide was employed as the active methylene component in the presence of water: nitriles **1v** and **1w** were isolated in 50% and 64% yield, respectively.

Based on our previous mechanistic studies on reductive amination,[16] a plausible mechanism for this catalytic process can be speculated (Scheme 2). The catalytic cycle might involve oxidative insertion of the rhodium carbonyl species into the C−OH bond of the intermediate alcohol followed by intramolecular hydroxylation of the CO ligand; a rhodium hydride species formed after decarboxylation would then undergo reductive elimination to yield the reduced Knoevenagel adduct and reform the active catalytic species. Further investigation of

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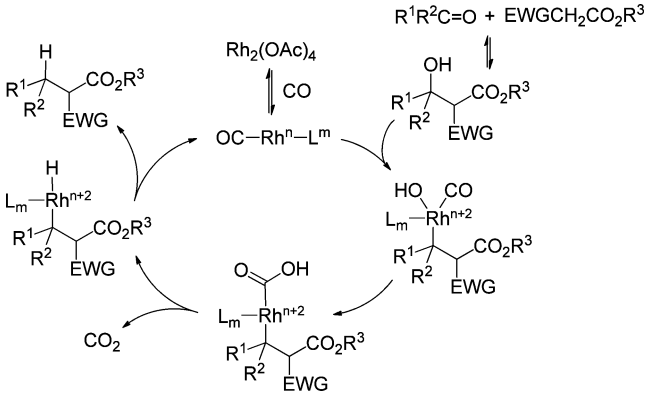
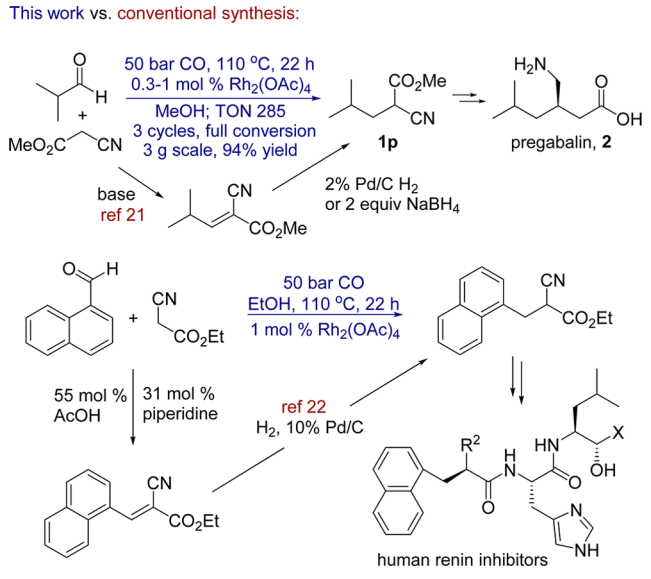
Scheme 2. Putative Mechanistic Scheme for the Developed Catalytic Process



the mechanistic details is currently underway in our group and is expected to be reported in due course.

We exemplified the practical significance of the developed methodology by implementation thereof into the synthesis of pharmaceutically important compounds. Pregabalin **2** is one of the leading anticonvulsant and neuropathic pain relieving drugs with 2013 sales exceeding $4.5 billion (Pfizer Inc.).[20] The manufacturing process involves synthetic intermediate **1p** prepared via a Knoevenagel condensation/catalytic hydrogenation sequence;[21] in contrast, our protocol allowed a single-step multigram preparation of compound **1p** in 94% yield after distillation (Scheme 3). The catalyst remained active after at

Scheme 3. Application of the Developed Methodology to the Synthesis of Precursors of Biomedically Important Compounds



least three reaction cycles carried out in the same autoclave without intermediate isolation of the product; each cycle led to full conversion. Likewise, the developed protocol could be successfully applied to the synthesis of a precursor of human renin inhibitory peptides[22] (Scheme 3 and Figure 1).

In summary, we have developed a highly efficient methodology for one-step preparation of reduced Knoevenagel adducts from a variety of aldehydes/ketones and active methylene compounds. The reaction does not require an external hydrogen source and employs carbon monoxide as a deoxygenative agent, which renders our methodology more atom economical in comparison to the existing synthetic alternatives. A wide range of aromatic and aliphatic aldehydes as well as ketones furnish the corresponding adducts with cyanoacetic esters in high yield; the use of malonic acid or cyanoacetamide as the active methylene counterpart enables efficient formal deoxygenative addition of methyl acetate and acetonitrile to aldehydes. The synthetic utility of the developed methodology was exemplified by the synthesis of precursors of biomedically important compounds, such as peptidic human renin inhibitors and pregabalin.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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