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Room Temperature, Reductive Alkylation of Activated Methylene Compounds: Carbon−Carbon Bond Formation Driven by the Rhodium-Catalyzed Water−Gas Shift Reaction

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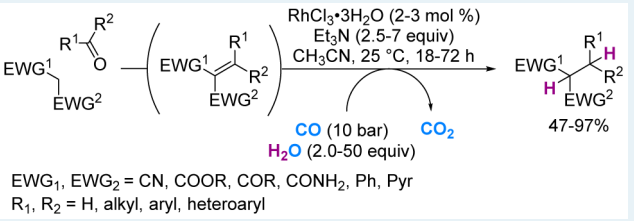
Supporting Information

ABSTRACT: The rhodium-catalyzed water−gas shift reaction has been demonstrated to drive the reductive alkylation of several classes of activated methylene compounds at room temperature. Under catalysis by rhodium trichloride (2−3 mol %), carbon monoxide (10 bar), water (2−50 equiv), and triethylamine (2.5−7 equiv), the scope has been successfully expanded to cover a wide range of alkylating agents, including aliphatic and aromatic aldehydes, as well as cyclic ketones, in moderate to high yields. This method is comparable to, and for certain aspects, surpasses the established reductive alkylation protocols.



KEYWORDS: *Reductive alkylation, Water−gas shift, Rhodium catalysis, Knoevenagel, Carbon−carbon bond formation, Conjugated alkene reduction*

1. INTRODUCTION

Since its original discovery over a century ago, the water−gas shift reaction (WGSR) has played a crucial role in industrial chemistry, providing a source of hydrogen to feed fundamental industrial transformations such as the Haber−Bosch synthesis of ammonia. Although the production of hydrogen remains nowadays the major application of the WGSR, the advent of homogeneous catalysis in the 1970s marked the beginning of a synergy between WGSR and organic chemistry.[1] The reducing power provided by the CO/H_2O couple has been exploited in the synthesis of fine chemicals, mainly in hydrogenation-type reactions (nitro reduction, reductive amination, hydrogenation of alkenes and carbonyls, etc.). On the other hand, the use of the WGSR to drive C−C bond forming processes remains underdeveloped.

Following the serendipitous discovery that the ruthenium-catalyzed allylation reaction of aldehydes can be driven by CO/H_2O as the terminal reductant,[2] our group became interested in expanding the range of applicability of the WGSR to the catalysis of other fundamental reductive C−C bond forming reactions. One of the simplest approaches to engage the WGSR in a reductive C−C bond formation relies on the well-established capacity of CO/H_2O to act as a H_2 surrogate (Figure 1). In this approach, an independent C−X bond forming event (where X can be C or N) leads to a functional group that can be reduced (hydrogenated) by CO/H_2O. The metal catalyst for the WGSR is not involved in the formation of the C−X bond, but only in the generation of a metal-hydride species that will reduce the substrate. The outcome is an overall reductive, tandem transformation that combines two steps in one, therefore enhancing step- and redox economy.[3]

Tandem, WGSR-based approaches have been described for reductive amination,[4] a C−N bond forming process that entails formation of an imine and its reduction by CO/H_2O. As early as 1978, Watanabe et al. employed WGSR conditions to carry out the methylation or benzylation of amines with aldehydes.[5] More recently, the scope and applicability of the reductive amination reaction under WGSR conditions have been significantly expanded by the independent contributions of List, Chusov, Chung, and co-workers.[6]

A similar strategy has been adopted in the formation of C−C bonds via tandem aldol condensation/WGSR-mediated alkene reduction. In this context, Watanabe et al. reported the methylation of ketones and methylpyridines with formaldehyde.[7] In addition, expanding on their studies of reductive amination, Chusov et al. disclosed two protocols for the reductive alkylation of active methylene compounds (reductive Knoevenagel alkylation, Figure 2). The transformation was achieved using either homogeneous $(Rh_2(OAc)_4)$[8] or heterogeneous (Rh/C)[6d] catalysis and allowed for the successful alkylation of methyl cyanoacetate with aldehydes and ketones. However, the reported protocols are plagued by a number of drawbacks. First, the reaction requires impractically high temperatures (110−160 °C) and pressures of CO (50−90 bar). Second, the forcing conditions cause unwanted side reactions, such as transesterification, hydrolysis and decarboxylation of esters (Figure 2c). Third, the protocol seems to be

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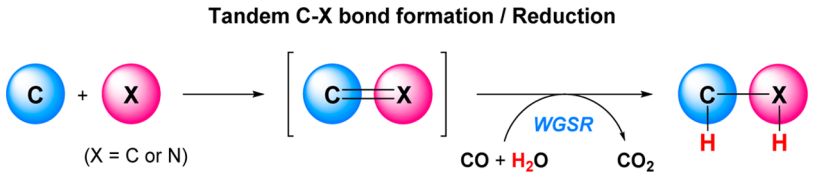


Figure 1. WGSR in C−X bond forming reactions.

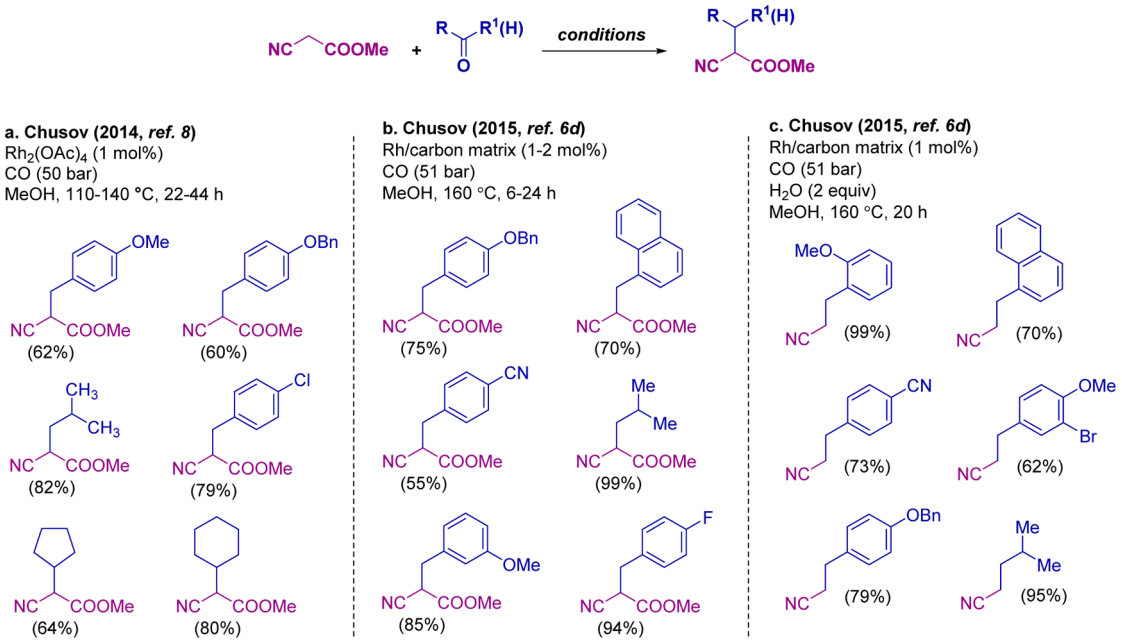
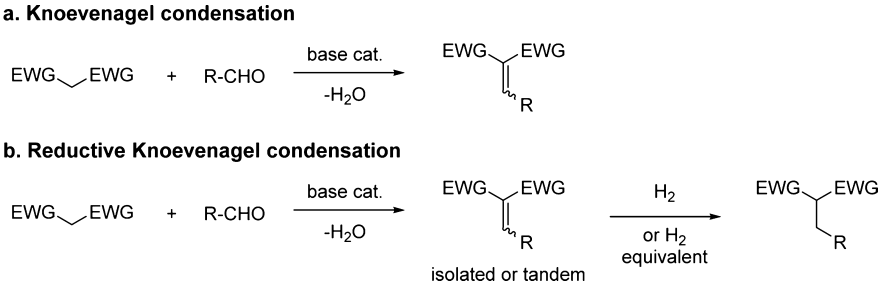


Figure 2. Reductive Knoevenagel alkylation under WGSR conditions.

Scheme 1. Knoevenagel Condensation and Its Reductive Variant



only applicable to cyanoacetates as the Knoevenagel nucleophiles.

The reductive variant of the Knoevenagel condensation represents an alternative to the direct alkylation of active methylene compounds with alkyl halides. This traditional method suffers from the need for a (super)stoichiometric amount of base (usually inorganic), as well as the occurrence of over alkylation and O-alkylation.[9] Key benefits of a reductive alkylation approach include the smooth C-monoalkylation, the greater availability of aldehydes and ketones compared to halides, their lower cost ($4/mol for benzaldehyde, $38/mol for benzyl bromide, for example)[10] and toxicity. Moreover, the use of WGSR conditions is more mass-efficient than regular alkylation reactions (CO_2 vs M^+Br^- as the byproducts), and it allows for a chemoselective reduction of the intermediate alkene that is compatible with a variety of other reduction-susceptible functional groups. Yet, the protocols developed by Chusov et al. are far from being synthetically useful because of the harshness of the reaction conditions. The identification of milder reaction conditions and the expansion of the substrate scope are essential for the further development of this strategic WGSR-driven, C−C bond forming reaction.

2. BACKGROUND

2.1. Knoevenagel Condensation and Its Reductive Variants. With over 120 years worth of history and applications in synthetic endeavors, the Knoevenagel condensation reaction represents an indispensible tool in organic synthesis.[11] The reaction entails the addition of an active methylene compound to an aldehyde or ketone followed by the elimination of water (Scheme 1a). The addition step requires bases such as amines, or inorganic basic salts including ammonium salts or potassium fluoride in organic solvents. Amino acids such as L-proline, glycine, β-alanine, and L-tyrosine have also been employed. The pK_a of the active methylene compound must be sufficiently low to allow for deprotonation

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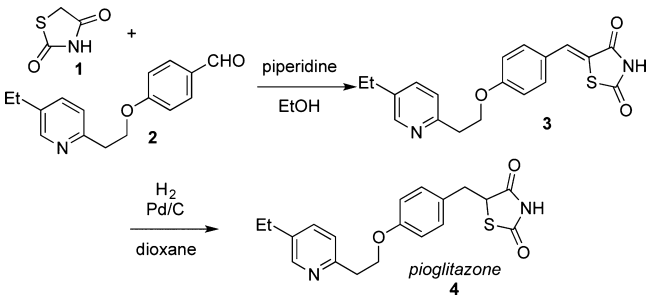
by a weak base. Thus, cyclic and acyclic 1,3-dicarbonyl compounds (and their equivalents) are a privileged class of substrates in Knoevenagel condensations, although reactions with heteroatom-, aryl-, or nitro-stabilized enol equivalents are not uncommon.

Because of its operational simplicity and expedited access to α,β-unsaturated motifs, the Knoevenagel condensation has found multiple applications in organic synthesis, including in industrial settings.[12] One of its key features is the possibility to engage the resulting alkene in tandem processes, such as Michael, Diels–Alder, or sigmatropic reactions.[11] In this context, the reductive variant of the Knoevenagel reaction, in which the alkene is hydrogenated immediately following the condensation (Scheme 1b), has also received significant attention. For example, the synthesis of the top-selling antidiabetic drug pioglitazone (**4**, Scheme 2) involves the

Scheme 2. Synthesis of Pioglitazone



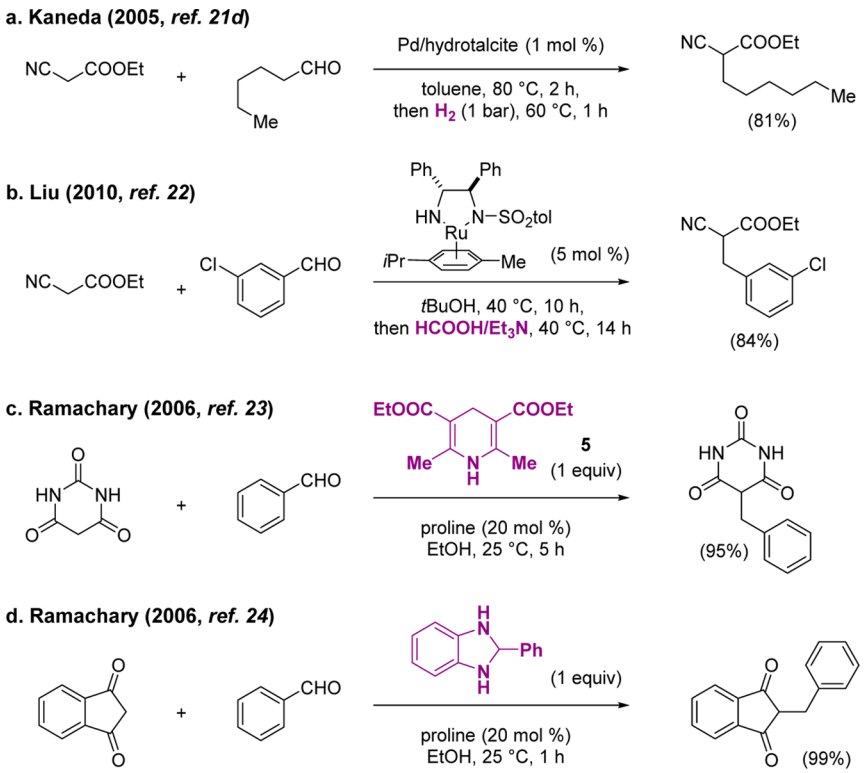
Knoevenagel condensation of 2,4-thiazolidinedione (**1**) with aldehyde **2**. The resulting Knoevenagel adduct **3** affords pioglitazone after a standard hydrogenation over Pd/C.[13]

Reductive Knoevenagel protocols of this kind, consisting of the reduction of a preformed Knoevenagel adduct in a separate step, are numerous. In addition to the widespread use of H_2, several other hydrogen sources have been employed in the reduction step, including sodium borohydride,[14] borane,[15] formic acid/triethylamine,[16] formate,[17] the Hantzsch ester,[18] 2-phenylbenzimidazoline,[19] and 2-phenylbenzothiazoline.[20] However, the need for a two-step process is impractical and limits the step-economy.

Consequently, efforts have been made to combine the condensation and reduction steps into a tandem (one-pot) process, using mutually compatible reagents and reaction conditions. Tandem protocols have been developed with several reducing agents (Scheme 3): H_2,[21] formic acid/triethylamine,[22] the Hantzsch ester (**5**),[23] 2-phenylbenzimidazoline,[24] and, of course, the CO/H_2O-based systems discussed above (Figure 2).[6d,8] Both aldehydes and ketones can be engaged as the electrophiles.

Although these methods are efficient from a step-economy standpoint, the use of reducing agents other than the simple H_2, H_2O/CO, or $HCOOH/Et_3N$ is highly wasteful and atom-uneconomic. However, the range of applicability of H_2 is limited because of its incompatibility with functional groups such as alkenes, alkynes, carbonyls, halides, nitro groups, and S-bearing functionalities. On the other hand, CO/H_2O and $HCOOH/Et_3N$ have fewer compatibility issues but are still unpractical because of the harsh conditions needed, or the long incubation time for the condensation to take place, respectively. Therefore, it is not surprising that, for applications of the reductive Knoevenagel alkylation with sensitive substrates in a total synthesis context, the use of the mild (yet wasteful) Hantzsch ester has been preferred (Scheme 4).[25]

Scheme 3. Selected Examples of One-Pot, Reductive Knoevenagel Alkylation



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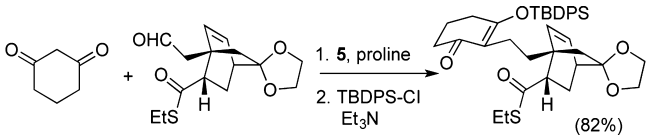
Scheme 4. Reductive Knoevenagel Alkylation in the Total Synthesis of Atropurpuran



2.2. Reductive Alkylation Methods Based on Hydrogen Transfer. An alternative to the use of external reducing agents is represented by the hydrogen-transfer technology.[26] In methods relying on hydrogen-transfer, the electrophile (aldehyde) is replaced by a primary alcohol, which acts both as the reactant and the source of reducing equivalents. A suitable metal catalyst allows for the in situ oxidation of the alcohol to the carbonyl, as well as the reduction of the alkene after the Knoevenagel condensation has taken place (hence the term hydrogen-transfer or hydrogen-borrowing). Although known since 1955,[27] the hydrogen-transfer alkylation of active methylene compounds has been considerably developed only in the past decade. Recent reports have described protocols for the alkylation of several classes of active methylene precursors, including arylacetonitriles,[28] barbituric acids,[29] cyano acetates,[30] oxindoles,[31] 1,3-diketones,[32] keto nitriles,[33] and malonates,[34] using Group 8 and 9 transition metal catalysts (Scheme 5a–e). The alkylation of unactivated ketones has also been reported (Scheme 5f).[35]

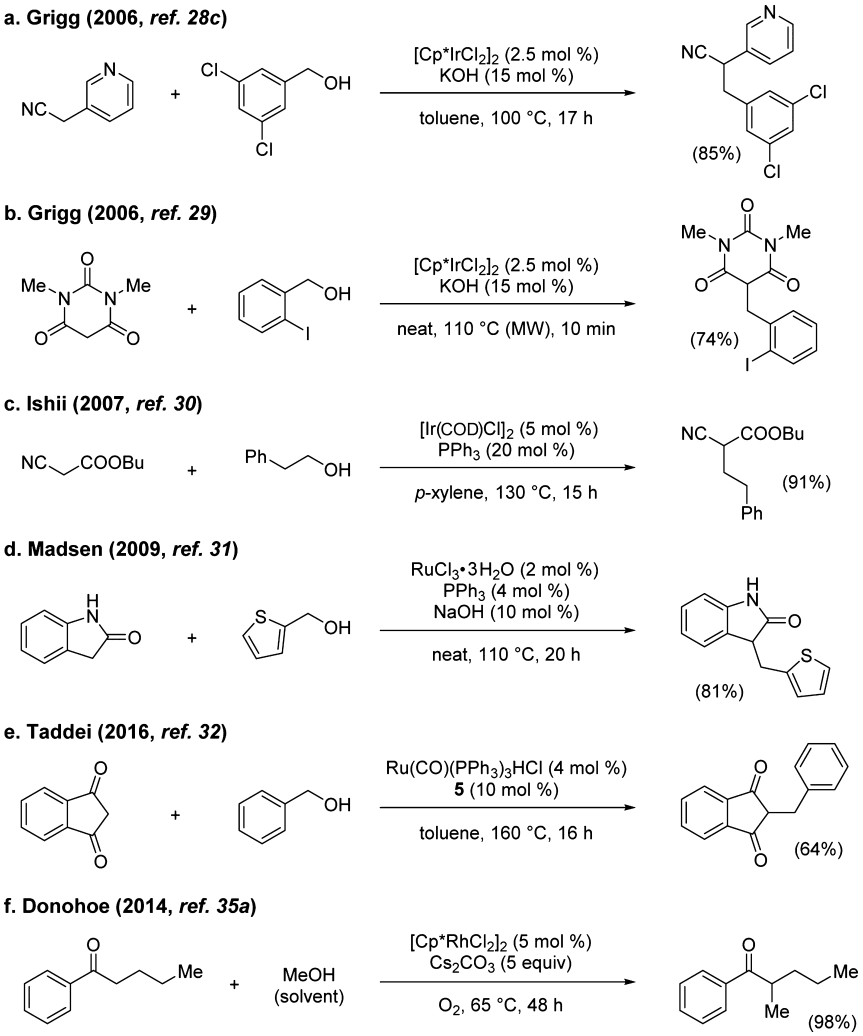
Despite the benefit of their catalytic nature, hydrogen-transfer alkylation protocols are still limited by the need for high temperatures (which, in conjunction with basic conditions, may cause transesterification or decarboxylation of esters),[30,34] and by the fact that only primary alcohols (mostly benzylic) are compatible. Therefore, the reductive alkylation with ketone electrophiles (from secondary alcohols) cannot be achieved under these conditions.

3. GOALS OF THIS STUDY

Within the context of our overarching goal to expand the applications of the WGSR in organic synthesis,[1] the present investigation intended to provide a robust and general protocol for the reductive Knoevenagel alkylation using CO/H_2O as the reducing agent. The development of our synthetic method involved the following steps:

(a) identification of milder and more practical reaction conditions than previously reported;
(b) application of the optimized reaction conditions to a wide range of electrophiles and nucleophiles, thus

Scheme 5. Selected Examples of Hydrogen-Transfer, Reductive Knoevenagel Alkylation



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demonstrating the generality and versatility of the approach;

(c) clarification of the observed reactivity trends through a mechanistic proposal, which may guide further optimization.

4. RESULTS

The alkylation of active methylene compounds was attempted using different aldehydes and ketones at room temperature under carbon monoxide atmosphere (Figure S1). To help both condensation and WGSR to proceed, basic reaction conditions and additional water were applied, aiming at achieving appreciable yields. Detailed optimization of each of the process parameters was performed based on the alkylation product yield measured by GC versus an internal standard (Table S1), and then the optimized conditions were extended to other substrates.

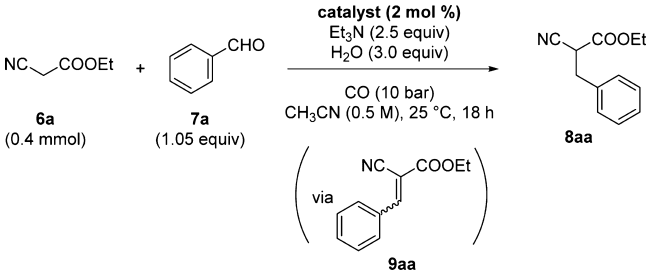
4.1. WGSR Reactivity of Different Transition Metals.

The reductive alkylation of ethyl cyanoacetate (**6a**) with benzaldehyde (**7a**) to produce ethyl 2-cyano-3-phenylpropionate (**8aa**) via **9aa** was investigated as a model reaction for the proposed WGSR-assisted, C−C bond formation. Ruthenium, iron, cobalt, manganese, iridium, and rhodium are among the transition metals complexes known to effectively catalyze the WGSR[36] and hence their carbonyl complexes were tested as catalysts under carbon monoxide atmosphere in the presence of water (Table 1). Only rhodium was found to be active for the reductive alkylation at room temperature (entries 1−6). In addition to $Rh_4(CO)_{12}$, other sources of rhodium including $RhCl_3·3H_2O$, $[Rh(COD)Cl]_2$, $Rh_2(OAc)_4$, and Rh nanoparticles supported on titanium oxide (Rh/TiO_2) were all effective catalysts (entries 7−10).

4.2. Reductive Alkylation Conditions Optimization.

Supported transition metal nanoparticles are preferred to their homogeneous analogs due to their ease of separation and reuse. However, upon testing the reusability of Rh/TiO_2, it was found out that excessive leaching of rhodium occurred and hence the heterogeneous catalyst could not be reused (Figure S2). Among the other active catalysts, $RhCl_3·3H_2O$ is the most common and inexpensive source of soluble rhodium and thus it was used for the optimization of conditions and investigation of scope.

Table 1. Transition Metals Reductive Alkylation Reactivity

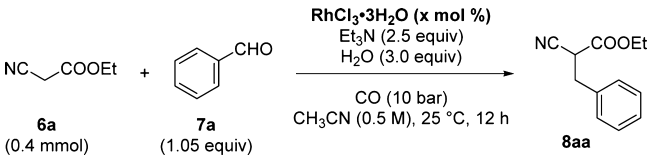


entry	catalyst	yield (%)[a]
1	$Ru_3(CO)_{12}$	<1
2	$Fe_2(CO)_9$	<1
3	$Co_2(CO)_8$	0
4	$Mn_2(CO)_{10}$	0
5	$[Ir(COD)Cl]_2$	0
6	$Rh_4(CO)_{12}$	98
7	$[Rh(COD)Cl]_2$	95
8	$Rh_2(OAc)_4$	96
9	$RhCl_3·3H_2O$	97
10	Rh/TiO_2	98

[a]Measured by GC with an internal standard.

4.2.1. Catalyst Loading. The catalytic activity can potentially be limited by the catalyst solubility in the reaction medium. In this case, only a small fraction of the catalyst would be actively participating in the reaction. To test for this limitation, the $RhCl_3$ loading was increased from 1 to 3 mol % and the product yield was measured after 12 h. The product yield increased as the catalyst loading was increased, indicating that there is no solubility limitation on the catalyst concentration in the specified range of metal loading (Table 2).

Table 2. Effect of Catalyst Loading on Product Yield



entry	Rh mole (%)	yield (%)[a]
1	1	12
2	1.5	24
3	2	67
4	3	96

[a]Measured by GC with an internal standard.

4.2.2. Effect of Solvent. The reductive alkylation was attempted in a number of solvents to test the effect of solvent properties on both condensation and reduction (Figure 3). Best results were obtained when acetonitrile was used as a solvent followed by butyronitrile, DMF, DMSO, and then 1,4-dioxane. No product was formed when protic solvents such as methanol, ethanol, 2-propanol, or water were used. Less polar solvents such as THF, triethylamine, and toluene were found not to be suitable for this reaction either. The Knoevenagel condensation step proceeded to completion in all the tested solvents except in methanol, water, and toluene. Complete conversion of the aldehyde to the dimethyl acetal and of the ethyl cyanoacetate to the methyl cyanoacetate occurred when methanol was used. Water limits the condensation by shifting the thermodynamic equilibrium toward the starting material and thus, condensation did not proceed to completion in water, whereas toluene is nonpolar and does not favor the enolization of the cyano ester for condensation to proceed.

Water, carbon monoxide, and Rh catalyst all need to be soluble in the solvent to effect reduction. The incompatibility of alcohols as solvents cannot be explained by their limited ability to dissolve water or carbon monoxide. Moreover, when $RhCl_3$ was replaced by $Rh_4(CO)_{12}$, a more soluble form of catalyst, reduction still did not proceed in alcohols indicating that they negatively affect the turnover of the catalytic cycle leading to reduction.

4.2.3. Effect of CO Pressure. Since the CO/H_2O couple is hypothesized to be the source of reducing equivalents, the CO pressure dependence of product yield was examined from 0 to 25 bar while keeping the water loading constant (Figure 4). A control experiment clearly established that no reaction takes place in the absence of carbon monoxide and increasing carbon monoxide pressure was found to have a positive impact on the

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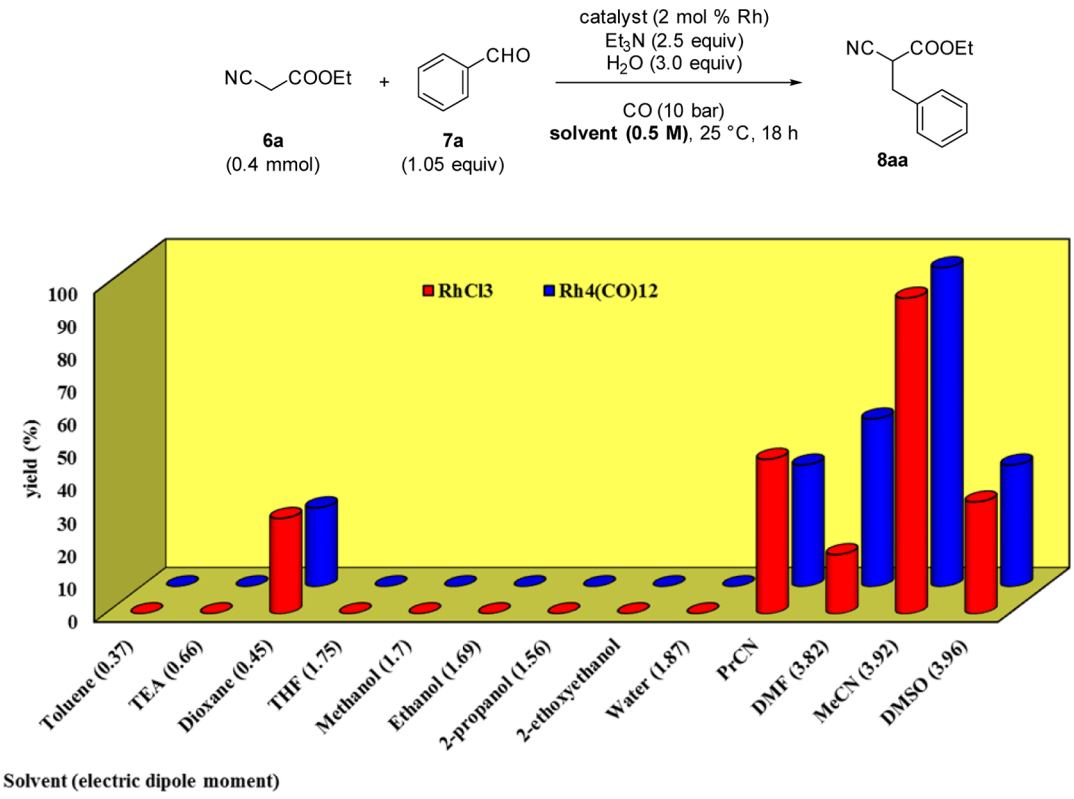

Figure 3. Effect of solvent on product yield (measured by GC with an internal standard).

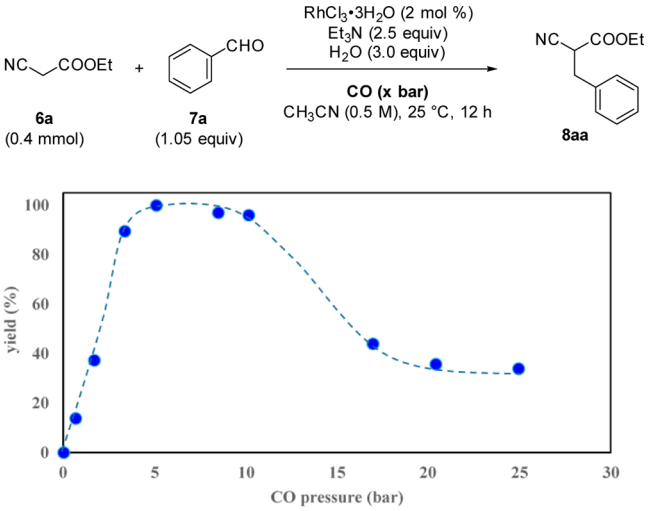

Figure 4. Effect of CO pressure on product yield (measured by GC with an internal standard).

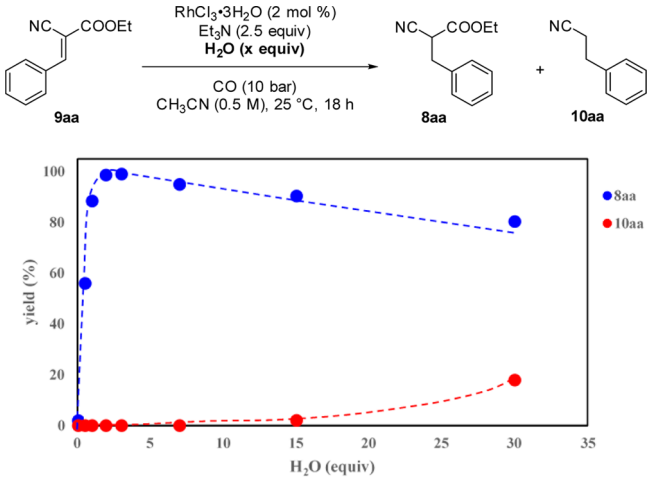

Figure 5. Effect of water on product yield (measured by GC with an internal standard).

desired product yield up to 10 bar. Further increase in carbon monoxide pressure resulted in an inverse response of the product yield.

4.2.4. Effect of Water Concentration. The effect of water concentration on the reduction step was studied on the preformed Knoevenagel condensation product **9aa** to eliminate the effect of water produced from the condensation step. Reduction does not proceed in the absence of water and the rate of reduction was found to be dependent on the water concentration. Increasing the amount of water beyond 3 equiv had a negative effect on the yield of the desired product because of an undesired hydrolysis and decarboxylation of **8aa** to **10aa** (Figure 5).

4.2.5. Effect of Base. Tertiary amines with different pK_a and structure were tested for the reduction of the Knoevenagel adduct **9aa** to **8aa** to study the effect of amine properties on reduction rate (Table 3). Aliphatic amines were the most suitable for reduction and higher reduction rate was observed as the amine alkyl chain became shorter (entries 7−9).

With the exception of 1,4 diazabicylo[2.2.2.]octane (DABCO), reduction did not proceed in amines that are less basic than triethylamine (entries 1−5), whereas more basic amines were found to inhibit reduction and catalyze the addition of the reduction product to the alkene intermediate leading to the unproductive consumption of the reactant (entries 11−13). Slow reductions were also observed when the highly hindered 1,2,2,6,6-pentamethylpiperidine (PMP) and

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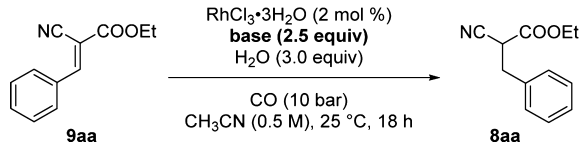
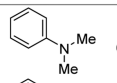
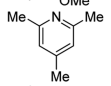
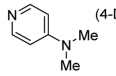
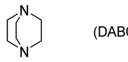
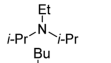
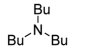
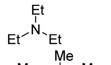
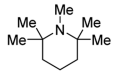
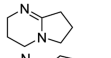
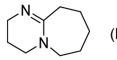
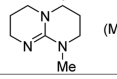
Table 3. Effect of Base Properties on Product Yield



9aa 8aa

entry	base	pKa MeCN	pKa THF[c]	consumption (%) 9aa[d]	yield (%) 8aa[d]
1	 (DMA)	11.43[a]	6.5	<5	<1
2		12.53[a]	7.4	<5	<1
3		14.23[a]	9.1	<5	<1
4		14.98[a]	9.6	<5	<1
5	 (4-DMAP)	17.95[a]	13	<5	<1
6	 (DABCO)	18.29[b]	--	73	60
7		--	--	60	55
8		18.09[b]	--	45	38
9		18.46[a]	14.1	100	97
10	 (PMP)	18.62[b]	--	5	4
11	 (DBN)	23.89[b]	--	87	5
12	 (DBU)	24.33[a]	18	73	7
13	 (MTBD)	25.44[a]	18.6	70	2

[a]pK_a values obtained from ref 37. [b]pK_a values obtained from ref 38. [c]pK_a values obtained from ref 39. [d]Measured by GC with an internal standard.

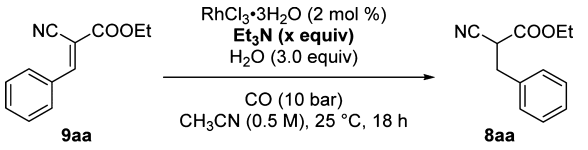
strongly binding 4-DMAP were used despite having basicities similar to triethylamine (entries 5 and 10).

In addition to base properties, the effect of base loading on reduction rate was also studied using triethylamine as a model base (Table 4). Superstoichiometric amount of triethylamine (2−4 equiv) were needed to drive reduction to completion whereas higher loading of amine did not affect the product yield (entries 1−9). It is worth mentioning here that only 0.1 equiv of triethylamine was enough to drive condensation to completion in 30 min which indicates that the super-stoichiometric loading of the amine is required for the reduction step to proceed.

4.3. Reductive Alkylation of Ethyl Cyanoacetate.

4.3.1. Aldehyde Scope. With the optimized conditions in hand, the substrate scope with respect to the nucleophile and the electrophile was evaluated. Initially, ethyl cyanoacetate was combined with a number of aliphatic and aromatic aldehydes on a 2.0 mmol scale (Table 5). During the exploration of the aldehyde scope, it was observed that the condensation was rapid relative to the reduction and that the rate of the reduction (and therefore the product yield) was highly dependent on the electronic properties of the aldehyde. In general, aliphatic and electron-rich aromatic aldehydes reacted faster than the

Table 4. Effect of Base Loading on Product Yield



9aa 8aa

entry	Et_3N (equiv)	yield (%)[a]
1	0	0[b]
2	0.1	<1[c]
3	0.5	42
4	1	64
5	2	84
6	2.5	97
7	4	96
8	7	98
9	10	95

[a]Yield measured by GC with an internal standard. [b]No condensation occurs. [c]Complete condensation achieved.

electron-poor ones. Indeed, with slow-reacting aldehydes, significant amounts of alkene **9** were detected in the reaction mixtures. To account for the different reactivity of the electrophiles and facilitate the reduction of **9**, small adjustments of the optimized conditions had to be made.[40]

Thus, benzaldehyde and other nearly electron-neutral aromatic aldehydes were efficiently converted when the reactions were conducted with H_2O (3.0 equiv) for 24 h (entries 1−5). Ortho-substituted benzaldehydes (methyl, fluoro) were good substrates. A meta-vinyl substituent was not reduced over the course of the reaction; however, the product **8ad** rapidly polymerized after isolation. The Lewis-basic methylthio substituent in **7e** did not significantly inhibit the reaction, nor did it undergo hydrodesulfurization.

Reductive alkylation of electron-rich aromatic aldehydes was achieved with lower H_2O loading (2.0 equiv) and shorter reaction time (18 h, entries 6−9). 4-Methoxy, 4-allyloxy, 4-dimethylamino, and 2,4,6-trimethoxybenzaldehyde all afforded the desired products in high yield. The allyl group in **7h** did not undergo competitive reduction or deallylation. The same reaction conditions could also be applied to a number of heteroaromatic aldehydes (entries 10−12), which worked efficiently regardless of their π-rich (**7j**, **7k**) or π-deficient (**7l**) character.

On the contrary, electron-poor aromatic aldehydes and 2-naphthaldehyde performed poorly when exposed to the same conditions as benzaldehyde. To facilitate the reduction of the corresponding adducts **9**, the water loading and the reaction time were increased (5.0 equiv, 36 h, entries 13−15). Under those conditions, decarboxylation of the ester moiety became competitive, accounting for the lower isolated yields for **7n** and **7o**. Remarkably, the 4-bromo substituent in **7m** remained intact. However, the nitro group in **7p** underwent fast reduction to the corresponding aniline, such that only traces of product **8ap** were observed (entry 16). The reaction afforded alkene **9ap′** primarily, which did not undergo further reduction. The reluctance of **9ap′** toward rhodium-catalyzed hydrogenation has already been noted[21g] and might be due to the Lewis-basic character of the amino substituent and its affinity for the rhodium center. On the contrary, the less Lewis-basic dimethylamino group in **7i** did not inhibit the reaction.

Aliphatic aldehydes also reacted smoothly under the conditions used for electron-rich aromatic aldehydes (entries

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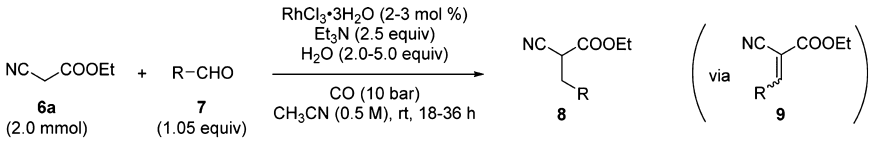
Table 5. Reductive Alkylation of Ethyl Cyanoacetate: Aldehyde Scope



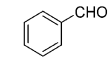
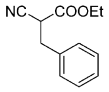
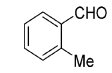
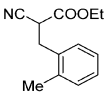
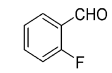
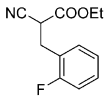
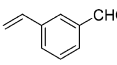
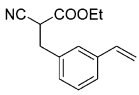
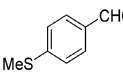
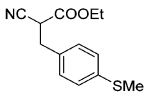
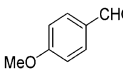
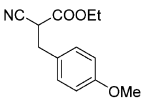
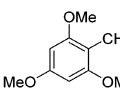
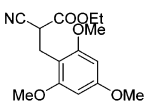
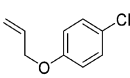
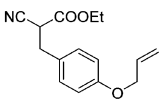
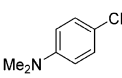
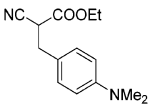
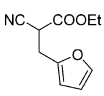
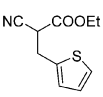
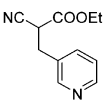
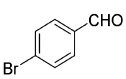
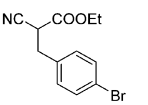
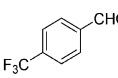
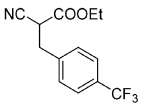
entry	aldehyde	$RhCl_3 \cdot 3H_2O$ (mol %)	H_2O (equiv)	time (h)	product	yield (%)[a]
1	 **7a**	2	3	24	 **8aa**	89
2	 **7b**	2	3	24	 **8ab**	88
3	 **7c**	2	3	24	 **8ac**	92
4	 **7d**	2	3	24	 **8ad**	92
5	 **7e**	2	3	24	 **8ae**	73
6	 **7f**	2	2	18	 **8af**	93
7	 **7g**	2	2	18	 **8ag**	91
8	 **7h**	2	2	18	 **8ah**	87
9	 **7i**	2	2	18	 **8ai**	90
10	 **7j**	2	2	18	 **8aj**	81
11	 **7k**	2	2	18	 **8ak**	95
12	 **7l**	2	2	18	 **8al**	87
13	 **7m**	3	5	36	 **8am**	82
14	 **7n**	3	5	36	 **8an**	54

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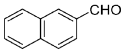
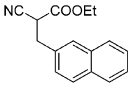
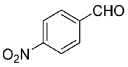
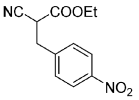
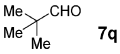
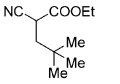
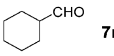
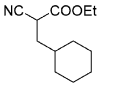
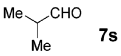
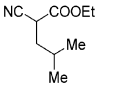
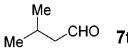
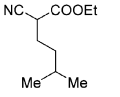
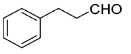
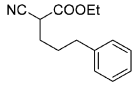
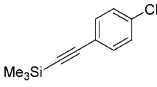
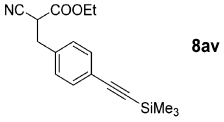
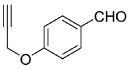
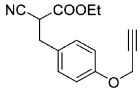
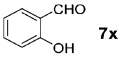
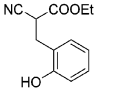
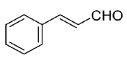
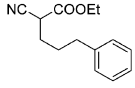
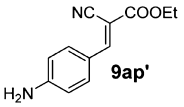
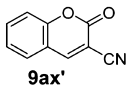
Table 5. continued

entry	aldehyde	$RhCl_3 \cdot 3H_2O$ (mol %)	H_2O (equiv)	time (h)	product	yield (%)[a]
15[b]	 **7o**	3	5	36	 **8ao**	69
16[c]	 **7p**	3	5	36	 **8ap**	traces
17	 **7q**	2	2	18	 **8aq**	90
18	 **7r**	2	2	18	 **8ar**	97
19	 **7s**	2	2	18	 **8as**	91
20	 **7t**	2	2	18	 **8at**	95
21	 **7u**	2	3	24	 **8au**	71
22[b]	 **7v**	3	5	24	 **8av**	19[d]
23	 **7w**	2	3	18	 **8aw**	0[d]
24[e]	 **7x**	3	3	24	 **8ax**	0[d]
25[f]	 **7y**	3	2	18	 **8au**	15[d]

[a]Yield of isolated, purified product. [b]1 M in CH_3CN. [c]The reaction afforded **9ap′** as the main product. [d]Determined by ^1H NMR spectroscopic analysis. [e]The reaction afforded **9ax′** as the main product. [f]The reaction afforded **8au** in addition to cis- and trans-isomers of the mono- and dienoates.



9ap'



9ax'

17−20). α-Trisubstituted (**7q**), α-disubstituted (**7r** and **7s**), and β-branched (**7t**) aldehydes afforded reductive alkylation products in nearly quantitative yield. The compatibility with **7q** is remarkable because the corresponding product **8aq** cannot be generated by simple alkylation of a neopentyl halide.[41] With the linear aldehyde **7u** (entry 21), self-condensation became competitive and a slightly diminished yield was obtained. Also, reaction of **7u** required a higher water loading and longer reaction time compared to other aliphatic aldehydes because of the slower rate of reduction of the intermediate alkene.

The compatibility with alkynyl moieties was also explored (entries 22−23). Trimethylsilylethynyl-substituted benzaldehyde **7v** reacted poorly due to the difficulty in reducing the corresponding Knoevenagel adduct **9av**. A propargyloxy substituent (**7w**) inhibited the reaction completely, and only **9aw** was observed in the reaction mixture. This observation is in contrast with the smooth reactivity of the similar, allyloxy-substituted benzaldehyde **7h**. Although the alkynyl groups themselves did not suffer from reduction under the reaction conditions, these data indicate that alkynes are incompatible because they may act as competitive ligands for the rhodium catalyst. In particular, the terminal alkyne in **7w**, in the presence of triethylamine, is prone to form a Rh-acetylide complex.[42]

The Knoevenagel condensation intermediate formed from the reaction of 2-hydroxybenzaldehdye with ethyl cyanoacetate underwent cyclization to form coumarin **9ax′**, which was not reduced under the reaction conditions (entry 24). Finally, when cinnamaldehyde was used as an alkylating agent, the dienoate

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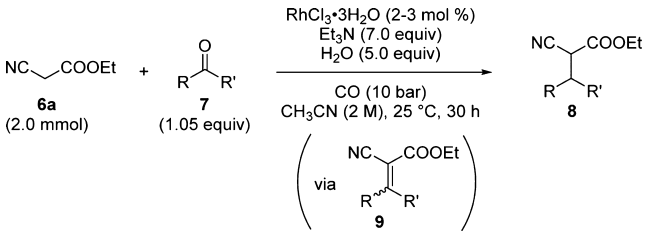
on the Knoevenagel intermediate **9ay** underwent unselective reduction leading to the formation of a mixture of *cis*- and *trans*-, mono- and dienoates, as well as the fully reduced product **8au** (entry 25).

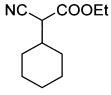
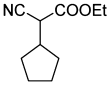
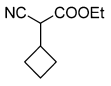
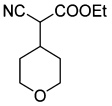
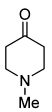
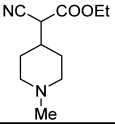
4.3.2. Ketone Scope. The promising results obtained with aldehydes prompted an investigation of ketones as a more challenging class of electrophiles. In general, the reactivity of ketones was limited by their slower rate of Knoevenagel condensation when compared to aldehydes. Condensation of cyclic ketones was more facile than that of acyclic ones possibly due to the coplanarity effect[43] and therefore adjustments of reaction conditions (H_2O and Et_3N loading) were needed for each category of ketones.

Cyclic ketones were successfully engaged in the reductive alkylation reaction by increasing the H_2O and Et_3N loading to 5.0 and 7.0 equiv, respectively (Table 6). However, the isolated yield decreased upon reducing the ring size from 6- to 5- and 4-membered ketones (entries 1−3). This trend reflects the higher propensity of cyclopentanone and cyclobutanone toward enolization and self-condensation,[44] thus depleting the electrophile. The tetrahydropyran-4-one (**7c′**) alkylation product **8ac′** was more prone to decarboxylation than that of cyclohexanone, which lead to lower isolated yield (entry 4). Alkylation of *N*-methylpiperdin-4-one (**7d′**) was slower, potentially due to competitive binding of its Lewis-basic site to the Rh catalyst relative to the more sterically hindered triethylamine. The loading of $RhCl_3$ had to be increased from 2 to 3 mol % for this ketone to achieve complete reduction of the Knoevenagel product. However, traces of the decarboxylation and demethylation side products were also observed accounting for the lower isolated yield compared to cyclohexanone (entry 5).

Condensation of acetone (**7e′**) and 3-pentanone (**7f′**) with ethyl cyanoacetate (**6a**) proceeded in triethylamine but not in acetonitrile. Reductive alkylation of ethyl cyanoacetate was attempted using these two ketones in triethylamine as the solvent and reaction time was extended to 72 h to allow enough time for the slow condensation (Table 7, entries 1−2). More than 50% loss in yield was observed due to the competing addition of the ketone to the Knoevenagel product and with itself under the basic reaction conditions. Extension of this protocol to other ketones such as 2,4-dimethyl-3-pentanone (**7g′**) and benzophenone (**7h′**) resulted in no condensation (entries 3−4).

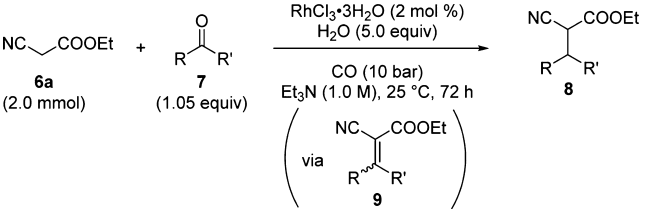
Table 6. Reductive Alkylation of Ethyl Cyanoacetate: Cyclic Ketone Scope

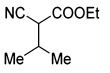
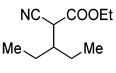
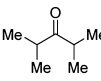
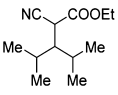
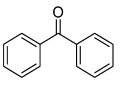
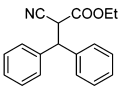


entry	ketone		$RhCl_3·3H_2O$ (mol %)	product		yield (%)[a]
1		**7z**	2		**8az**	93
2		**7a'**	2		**8aa'**	79
3		**7b'**	2		**8ab'**	47
4		**7c'**	2		**8ac'**	77
5		**7d'**	3		**8ad'**	88

[a]Yield of isolated, purified product.

Table 7. Reductive Alkylation of Ethyl Cyanoacetate: Acyclic Ketone Scope



entry	ketone		product		yield (%)
1		**7e'**		**8ae'**	47[a]
2		**7f'**		**8af'**	18[b]
3		**7g'**		**8ag'**	0[b]
4		**7h'**		**8ah'**	0[b]

[a]Yield of isolated, purified product. [b]Determined by ^1H NMR spectroscopic analysis.

4.4. Reductive Alkylation with Other Active Methylene Compounds. The final dimension of substrate scope of the reductive Knoevenagel reaction involved the investigation of other active methylene compounds. Not surprisingly, this task turned out to be particularly challenging, because of the different behavior of other carbon acids compared to **6a**.

The one-pot, tandem, condensation-reduction strategy was extended to benzoylacetonitrile (**6b**), cyanoacetamide (**6c**), and 2-pyridylacetonitrile (**6d**) (Table 8). Condensation of **6b** and **6c** with anisaldehyde (entries 1−2) was slower compared to ethyl cyanoacetate and hence the amount of triethylamine was increased to accelerate the condensation. Decomposition from hydrolysis was less problematic, such that the water content could be increased to accelerate reduction of the condensation product. The rate of condensation of **6d** with benzaldehyde was significantly slower owing to its lower carbon acidity (entry

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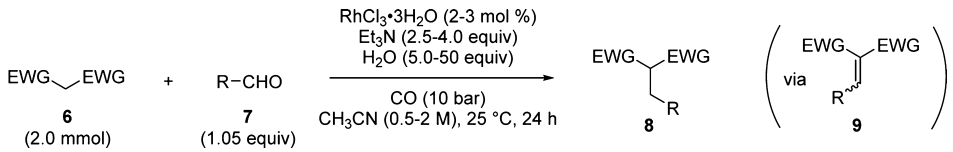
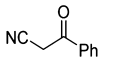
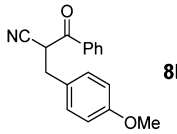
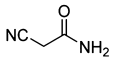
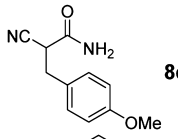
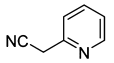
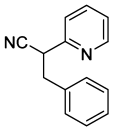
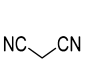
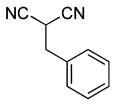
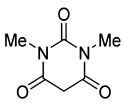
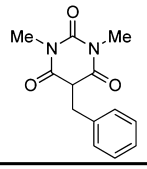
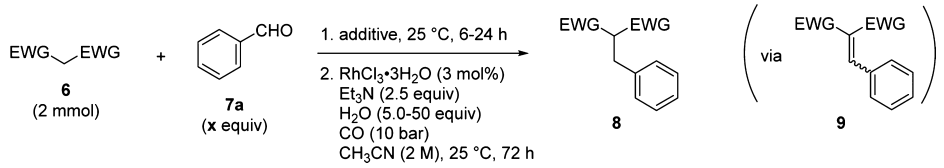
Table 8. Scope of Nucleophile in One-Step Reductive Alkylation

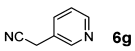
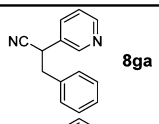
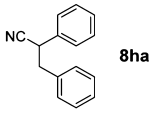
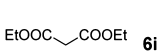
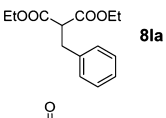
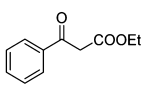
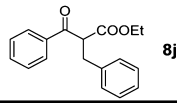


entry	nucleophile	electrophile	$RhCl_3 \cdot H_2O$ (mol %)	Et_3N (equiv)	H_2O (equiv)	CH_3CN (M)	product	yield (%)[a]
1	 **6b**	**7f**	3	4	5	1	 **8bf**	87
2	 **6c**	**7f**	2	4	5	0.5	 **8cf**	84
3[b]	 **6d**	**7a**	3	2.5	50	2	 **8da**	66
4	 **6e**	**7a**	3	2.5	25	0.5	 **8ea**	54[c]
5	 **6f**	**7a**	3	2.5	25	0.5	 **8fa**	23[c]

[a]Yield of isolated, purified product. [b]Run for 72 h. [c]Determined by ^{1}H NMR spectroscopic analysis.

Table 9. Scope of Nucleophile in Two-Step Reductive Alkylation



entry	nucleophile	7a (equiv)	step 1 (conditions)	total H_2O (equiv)	product	yield (%)[a]
1	 **6g**	1.05	DBN (0.05 equiv), 6 h	50	 **8ga**	78
2	 **6h**	1.05	DBN (0.05 equiv), 6 h	50	 **8ha**	63
3	 **6i**	2	L-proline (0.1 equiv), Et_3N (1.0 equiv), H_2O (5 equiv), 24 h	5[b]	 **8ia**	70
4	 **6j**	2	L-proline (0.1 equiv), Et_3N (1.0 equiv), H_2O (5 equiv), 24 h	5[b]	 **8ja**	33[c]

[a]Yield of isolated, purified product. [b]Step 2 was run for 48 h. [c]Determined by ^{1}H NMR spectroscopic analysis.

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3).[45] Reduction was also slower in this case. Thus, the amount of water was increased by 10-fold and the reaction was run for 72 h to allow complete reduction of the condensation product. The yield loss resulted from the competitive reduction of the aldehyde to the corresponding alcohol, a side reaction that is only observed in case of slow condensation. Alkylation of the strongly acidic malononitrile (**6e**) and *N*,*N*-dimethylbarbituric acid (**6f**) (entries 4−5) afforded complex reaction mixtures because of the tendency of the alkylated product to undergo 1,4-addition to Knoevenagel adducts **9** under basic conditions. Lowering the basicity of the medium by replacing triethylamine with weaker bases negatively affected reduction rate and did not shutdown the product-intermediate side reaction.

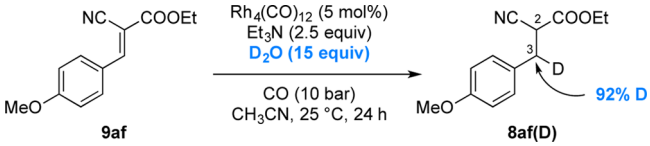
3-Pyridylacetonitrile (**6g**) and benzyl nitrile (**6f**) are expected to be less acidic compared to 2-pyridylacetonitrile.[45] Thus, their condensation with benzaldehyde had to be carried out in a separate precondensation step with 1,5-diazabicyclonon-5-ene (DBN, 0.05 equiv) in neat solution for 6 h prior to the addition of H_2O, CO, Rh catalyst, and solvent (Table 9, entries 1−2). This two-step, one-pot process does not involve any intermediate separation or migration from room temperature operation and thus, does not negatively affect the method efficiency. A similar approach was applied to alkylate diethyl malonate (**6i**) and ethyl benzoylacetate (**6j**) with aldehyde **7a** using L-proline (0.1 equiv) as a condensation catalyst in H_2O/Et_3N for 24 h (entries 3−4). DBN could not be used in this case as it catalyzed undesired 1,4-addition reactions, whereas the amount of benzaldehyde had to be increased to two equivalents to drive condensation closer to complete conversion.

4.5. Mechanistic Investigations. Control experiments have demonstrated that CO is essential for the reduction to proceed (section 4.2.3). It is reasonable to propose that CO undergoes WGSR to produce a Rh hydride species which reduces the condensation product. However, another possibility is that triethylamine may act as a hydride source through a Rh-catalyzed, β-hydride abstraction/hydrolysis mechanism.[46] Under this hypothesis, carbon monoxide could be needed to stabilize the low-valent Rh carbonyl clusters that act as catalyst for hydride formation from the amine.

The rate acceleration caused by triethylamine (compared to base-free conditions, or to the use of other bases, section 4.2.5) deserved further investigation. In addition to being a potential hydride source, triethylamine may be implicated in several other crucial steps along the reaction pathway. Triethylamine could (1) catalyze the Knoevenagel condensation; (2) act as a reducing agent for Rh(III) to a catalytically active, low-valent Rh species; (3) promote the WGSR by a base-catalyzed mechanism (generating hydroxide ions in the presence of water);[1,36] (4) act as a ligand for Rh, to help solubilize the Rh catalyst and disrupt the polynuclear Rh-CO clusters that are formed under CO atmosphere.[47] Consequently, several experiments were designed and executed to elucidate the reduction pathway and the role of the amine.

4.5.1. Role of Carbon Monoxide/Water. A deuteration experiment was performed to ascertain the involvement of CO/H_2O as the source of reducing equivalents. Thus, the preformed adduct **9af** was exposed to modified reaction conditions using $Rh_4(CO)_{12}$ and D_2O (Scheme 6). The choice of the starting material and the Rh catalyst was dictated by the need to remove potential H_2O sources (the condensation forms one equivalent of H_2O, and $RhCl_3$ is supplied as a trihydrate complex). Under these conditions, 92% deuterium

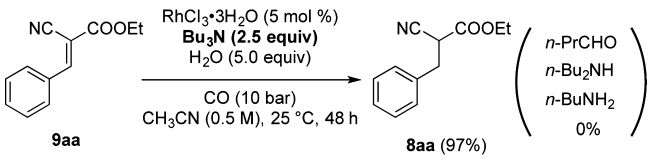
Scheme 6. Deuterium Incorporation Experiment



incorporation was measured at C(3) by mass spectrometry (Figure S3, Table S2). The incomplete incorporation might be due to the adventitious water in acetonitrile and/or CO. No deuterium incorporation was observed at C(2), presumably because of the fast D/H exchange upon exposure to moisture or silica gel.

4.5.2. Role of Base. Control experiments have shown that 0.1 equiv of triethylamine is sufficient to drive the Knoevenagel condensation of the ethyl cyanoacetate with aldehydes. However, higher triethylamine loading was necessary for reduction of the Knoevenagel product to proceed (Table 5). If a tertiary amine acts as a hydrogen source, the resulting iminium ion should be hydrolyzed to the corresponding secondary amine and aldehyde (diethylamine and acetaldehyde in the case of triethylamine).[46a] Because acetaldehyde and diethylamine are volatile and more difficult to detect, triethylamine was replaced with tributylamine, a base with similar pK_a and bulk in acetonitrile (Scheme 7). The reduction of **9aa** was slower with tributylamine likely because of its poor solubility in acetonitrile. Thus, the reaction time and water content had to be increased to achieve complete reduction. Under these conditions, no trace of butyraldehyde, dibutylamine, butylamine, or butyraldehyde self-condensation products was observed by GC analysis. These observations confirm that the amine does not act as a reducing agent, either for the hydrogenation of **9aa**, or for the reduction of Rh(III) to a lower oxidation state.

Scheme 7. Experiment with Tributylamine



Earlier studies showed that amines enhance the WGSR reactivity of Rh complexes by acting as ligands,[48] which could explain why a highly hindered amine such as PMP exhibits poor activity compared to the less hindered triethylamine (Table 10, entries 1−2). However, when a small quantity of triethylamine (0.05 equiv) was added to a reaction medium containing 2.45 equiv of PMP, a 10-fold increase in product yield was observed (entry 3). Since triethylamine and PMP have similar pK_as, the basicity of the medium (i.e., concentration of hydroxide ions) is expected to be similar for both bases, meaning that the WGSR is taking place at similar rates. Consequently, the increase in reduction rate observed in entry 3 must arise from the capacity of triethylamine to act as a ligand. However, in a separate control experiment, the addition of 0.1 equiv of triethylamine to a neutral reaction medium did not show any increase in the product yield (entry 4).

Similarly, if the amine is too strongly coordinating to the rhodium center, inhibition of the WGSR is observed. For example DMAP and triethylamine have similar pK_as but the

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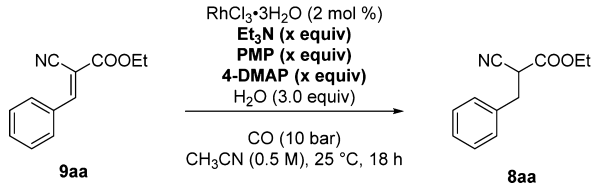
Table 10. Effect of Amine Coordination-Ability and Basicity of the Medium on Reduction Rate



pK_{BH+} (MeCN)	Et_3N (18.46)	PMP (18.26)	4-DMAP (17.95)	
entry	equiv	equiv	equiv	yield (%)[a]
1	2.5	0	0	97
2	0	2.5	0	4
3	0.05	2.45	0	45
4	0.1	0	0	<1
5	0	0	2.5	<1
6	2.5	0	0.1	67

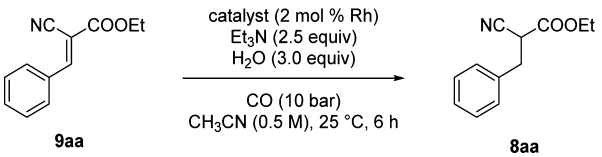
[a]Measured by GC with an internal standard.

former is unable to promote the reduction of **9aa** (Table 10, entry 5). The inhibitory effect of DMAP is manifest even in the presence of a 25-fold excess of triethylamine (c.f. entries 1 and 6).

On the basis of these observations, it appears that triethylamine is uniquely able to promote reduction of **9aa** by serving *both* as a ligand and as a source of hydroxide ions. A substoichiometric amount (0.1 to 0.3 equiv) of triethylamine is needed to coordinate the Rh catalyst, whereas the additional quantity (2.5 equiv total) is needed to provide the basic medium for the operation of the WGSR.

4.5.3. Catalytic Activity of Different Rh Precursors. The reactivity of Rh precursors with different oxidation states and nuclearity was compared at the 6-h time point (Table 11). Prior to carbon monoxide introduction, the reaction medium was stirred for 2 h to ensure complete dissolution of the catalyst. The $Rh_4(CO)_{12}$ cluster was found to be the most active form, followed by $RhCl_3{\cdot}3H_2O$ and $[Rh(COD)Cl]_2$, whereas the $Rh_2(OAc)_4$ was the least active. The high activity in the case of the low-valent $Rh_4(CO)_{12}$ (entry 1) suggests that a catalyst prereduction step is involved in all the other cases (entries 2–4). There is also an induction time associated with breaking the dimers, as indicated by the low reactivity of the dimeric $[Rh(COD)Cl]_2$ and $Rh_2(OAc)_4$ complexes compared to the monomeric $RhCl_3{\cdot}3H_2O$.

Table 11. Reductive Alkylation Reactivity of Different Rh Catalyst Precursors



entry	catalyst	Rh nuclearity	Rh oxid state	yield (%)[a]
1	$Rh_4(CO)_{12}$	4	0	85
2	$[Rh(COD)Cl]_2$	2	1	53
3	$Rh_2(OAc)_4$	2	2	3
4	$RhCl_3.3H_2O$	1	3	66

[a]Measured by GC with an internal standard.

5. DISCUSSION

5.1. Effect of Base on Substrate Scope. In the reductive alkylation of ethyl cyanoacetate (**6a**) with different aldehydes, the reduction of the alkene intermediate **9** is significantly slower than the condensation step, and requires a strong base (pK_a > 18 in CH_3CN) to proceed at an appreciable rate. In addition, the expansion of the scope with respect to the activated methylene compounds has demonstrated that the performance of the method highly depends on the carbon acidity of the activated methylene compound (Figure 6).[45]

Compounds with acidity similar to that of ethyl cyanoacetate ($pK_a \simeq 12-14$ in DMSO) were successfully alkylated in one step using triethylamine. Benzoylacetonitrile (**6b**) and cyanoacetamide (**6c**) afforded the corresponding alkylated products in high yield; 2-coumaranone should behave similarly, as expected based on its methylene acidity.

On the contrary, alkylation of strongly acidic activated methylene compounds (pK_a < 12 in DMSO), such as malononitrile (**6e**) and *N,N*-dimethylbarbituric acid (**6f**), was lower-yielding due to the competing Michael addition of the product to the condensation intermediate, an undesired reaction catalyzed by triethylamine. Replacing triethylamine with a weaker base to suppress the undesired reaction was found to shut down the reduction. Thus, this category of activated methylene compounds was determined to be incompatible with the proposed method.

The reductive alkylation of slightly less acidic active methylene compounds ($pK_a \simeq 14-18$ in DMSO) was limited by their condensation rate rather than the alkene reduction rate. For example, condensation of diethyl malonate (**6i**) and ethyl benzoylacetate (**6j**) required the addition of DBN, piperidine, or L-proline to proceed. However, DBN catalyzed an undesired 1,4-addition to the intermediate Knovenagel product, whereas piperidine underwent reductive amination with the aldehyde under the reaction conditions. Thus, the condensation was performed using L-proline in a separate step, followed by reduction under WGSR conditions in one pot.

Weakly acidic compounds (pK_a > 18 in DMSO) and their condensation intermediates did not undergo the undesired Michael addition. Therefore, their reductive alkylation was performed using DBN as a cocatalyst either in a single step (as in the case of 2-pyridylacetonitrile (**6d**)), or in two steps, if the condensation reaction was slower (3-pyridylacetonitrile (**6g**) and benzylnitrile (**6h**)). The two-step, one-pot approach minimized the reduction of the aldehyde to the alcohol.

5.2. Catalytic Cycle. The involvement of the WGSR, in which the CO/H_2O system serves as the hydride source, and not triethylamine, was clearly established on the basis of absence of amine oxidation products and deuterium incorporation when D_2O was used. Control experiments also clarified that the role of the base is threefold: (1) catalyst for the Knoevenagel condensation; (2) base for the WGSR; and (3) ligand for Rh.

The quest for optimum reaction conditions and the exploration of the substrate scope generated a wealth of mechanistic information that helped to formulate a plausible catalytic cycle (Figure 7) and revise a previous mechanistic proposal. Over the course of their studies of the Rh-catalyzed reductive Knoevenagel alkylation, Chusov et al. proposed a catalytic cycle that involves Rh insertion into the C–OH bond of an intermediate β-hydroxy ester (**11**).[8] The occurrence of the WGSR was not directly invoked, but the proposed

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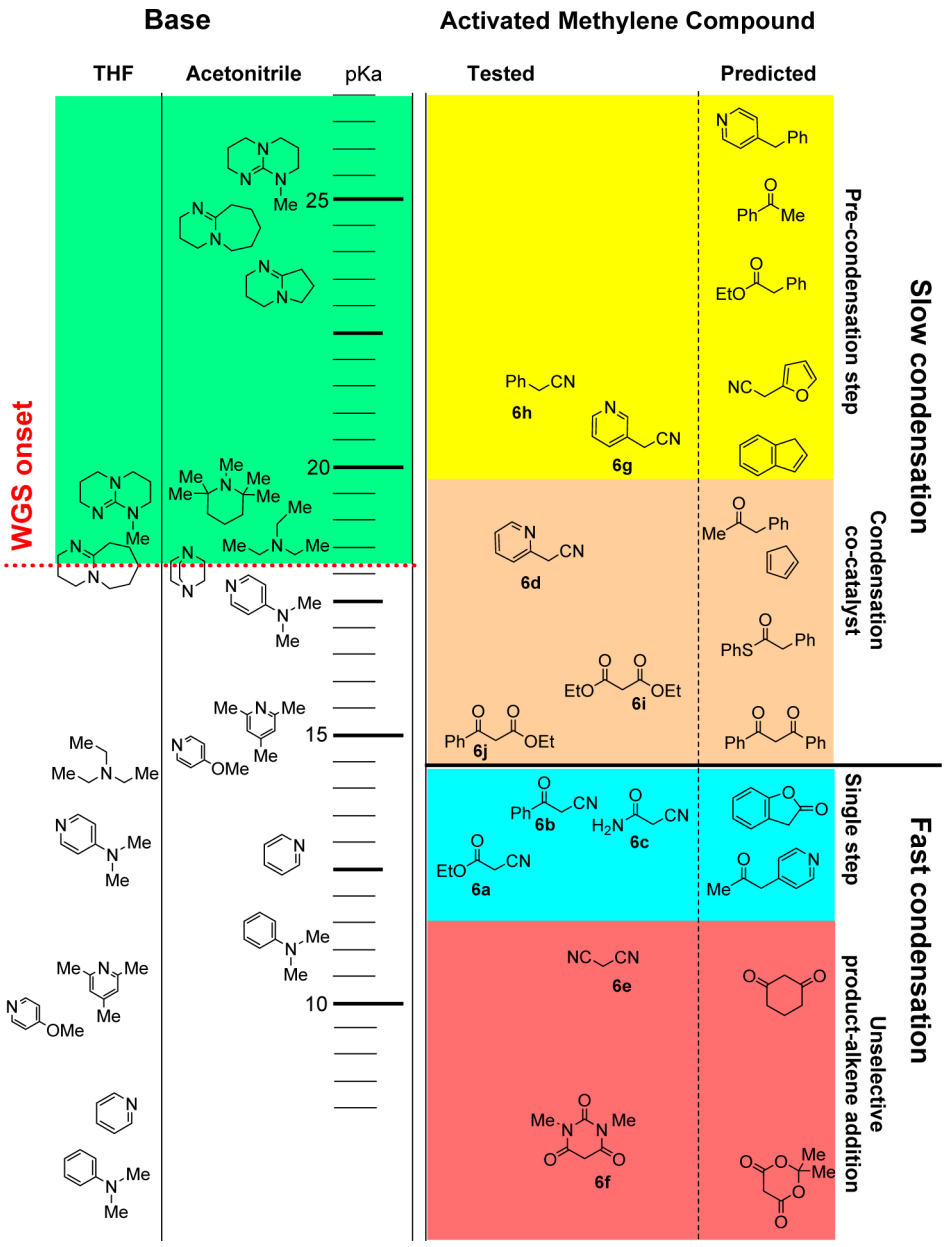

Figure 6. Reductive alkylation performance of different activated methylene compounds.

mechanism clearly shows intermediates (Rh-hydroxycarbonyls, Rh-hydrides) that would be expected for a WGSR-based process. Intermediates such as **11** are fleeting, and prone to dehydrate to form a Knoevenagel adduct (**9**). Indeed, our studies indicated that **9** rapidly accumulated in the reaction mixtures and was kinetically competent. Therefore, it is necessary to reformulate the mechanistic picture of the reductive Knoevenagel condensation as follows.

The catalytically active, low-valent Rh-carbonyl complex **i** (generated by WGSR-mediated reduction of $RhCl_3$) undergoes nucleophilic addition of hydroxide (from triethylamine and water) to a CO ligand. The resulting Rh-hydroxycarbonyl complex **ii** decarboxylates to form Rh-hydride **iii**. These steps are in agreement with those proposed for the WGSR under basic conditions.[36] The basicity of the amine must be sufficient to generate a suitable concentration of hydroxide ions to attack species **i** and form species **ii**. The inhibitory effect of alcohols when used as solvents could also be attributed to the competing formation of inactive alkoxycarbonyl complexes $[RhL_n(CO)_{m-1}(COOR)]^-$ instead of species **ii**.[49] The inability of carbonyl complexes of Fe, Co, and Mn to catalyze the WGSR at room temperature might arise from the lower propensity of these species to form the required metal hydroxycarbonyl complexes.[49]

In the next step, loss of a CO ligand from **iii** opens a coordination site (**iv**) that enables binding of substrate **9**. The need for ligand dissociation prior to olefin coordination can be kinetically relevant at high CO pressures, which explains the inhibitory effect of CO on reduction at pressures higher than 10 bar. Moreover, the strong inhibitory effect of Lewis-basic functional groups, such as primary anilines and terminal alkynes, reinforces the importance of coordinative unsaturation to enable olefin binding. From **v**, migratory insertion of the olefin and protonation of the anionic Rh complex **vi** affords **vii**. Reductive elimination generates the product **8** and the

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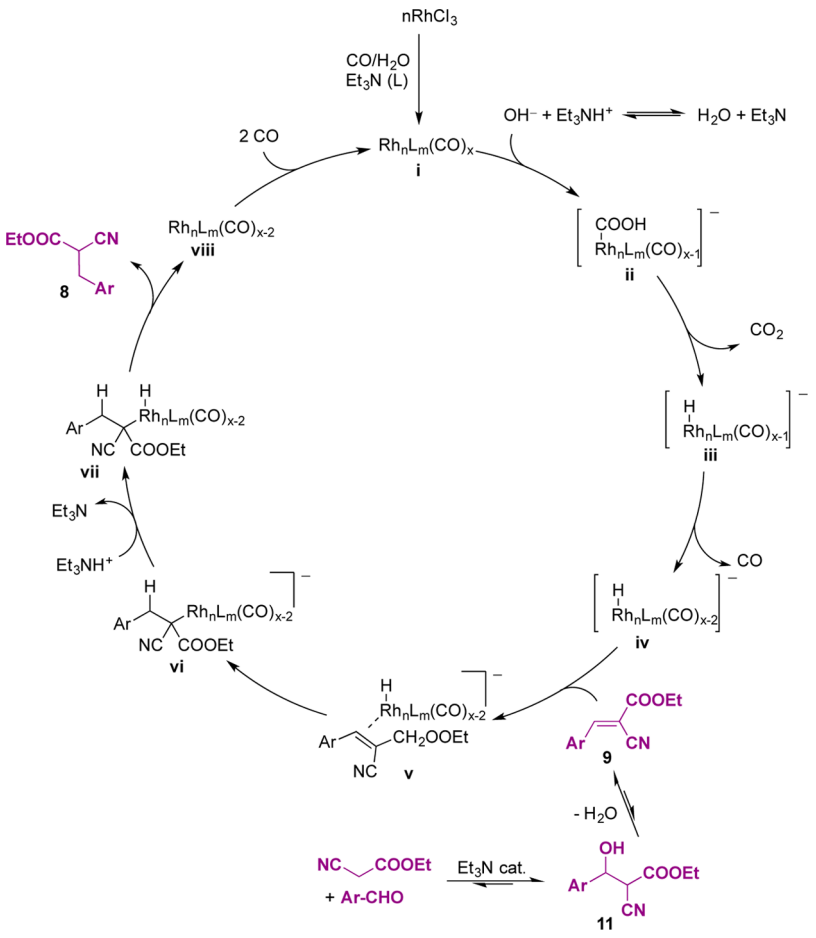


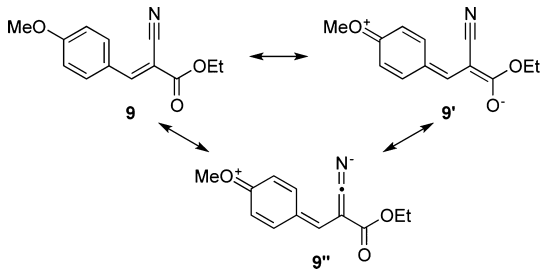
Figure 7. Proposed catalytic cycle.

coordinatively unsaturated complex **viii**, which can reenter the catalytic cycle upon CO coordination.

The exploration of the aldehyde substrate scope led to the puzzling observation that aromatic aldehydes bearing electron-donating groups reacted faster than those bearing electron-withdrawing groups. At a first glance, this observation is difficult to fit in the proposed mechanistic picture. Reasonably, an electron-poor arene should lower the LUMO of **9** and thus: (1) facilitate the coordination of **9** to the anionic complex **iv** (a metal-to-ligand interaction); and (2) promote hydride delivery (migratory insertion) to the electron-deficient π-system. These arguments are in agreement with Hammett studies performed on the hydrogenation and hydride reduction of styrene derivatives.[50] However, **9** already possesses a low-lying LUMO because of the strong conjugating effects of the ester and nitrile groups. Therefore, further lowering of the LUMO energy (and consequent acceleration) by an electron-poor aryl substituent is expected to be minimal.

Alternatively, the accelerating capacity of electron-rich arenes could be explained as a push–pull effect,[51] whereby the electron-donating substituent enhances the polarization of the alkene and lowers its bond order as represented by resonance structures **9′** and **9″** (Scheme 8). The resulting weakening of the double bond would account for a more facile hydride delivery in the formation of **vi** and explain the observed rates, if formation of **vi** were turnover-limiting. A similar manifestation of the push–pull effect has been documented in the Ni-catalyzed hydrogenation of styrene derivatives, for which the application of the Yukawa–Tsuno correlation furnished negative ρ values.[52]

Scheme 8. Resonance Structures of 9



5.3. Comparison with Existing Methods. The investigation of the rhodium-catalyzed, WGSR-driven, reductive Knoevenagel alkylation has identified triethylamine as a key component to allow for the reaction to proceed smoothly at room temperature. This is in sharp contrast with the base-free conditions developed by Chusov et al., which require temperatures in the range of 110–160 °C.[6d,8]

The mild conditions and the use of CO as the reducing agent brought about several improvements compared to traditional alkylation methods, and other reductive Knoevenagel alkylation protocols. In particular, the following improvements were achieved:

- use of an inexpensive, nonwasteful reducing agent, amenable to scale-up;

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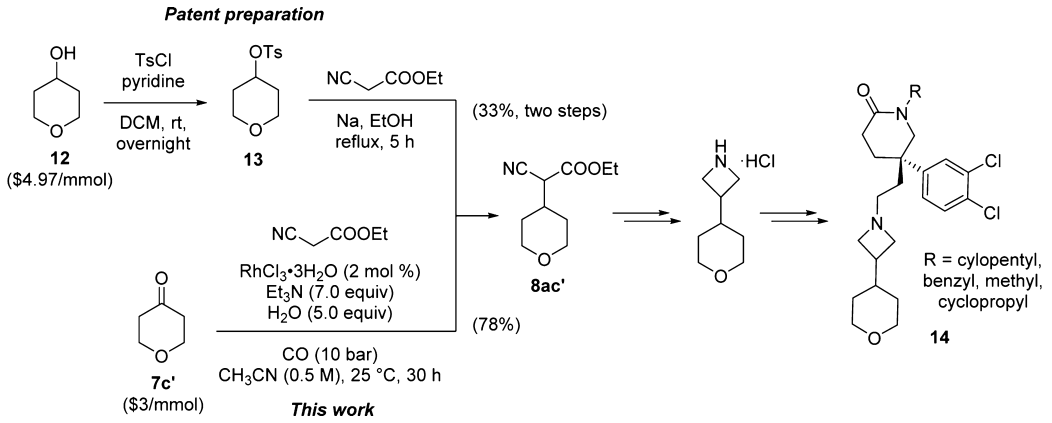
Scheme 9. Alkylation vs Reductive Alkylation for the Synthesis of 14



- the tandem, one-pot nature of the process, which does not require isolation of the intermediate alkene;
- suppression of dialkylation and O-alkylation, common issues when using alkyl halides;
- suppression of decarboxylation, which occurs with methods that require high temperature;
- compatibility with functional groups that are not tolerated when using H_2 (unactivated alkenes, allyl ethers, halides, thioethers);
- compatibility with electrophiles that are prone to self-condensation under basic conditions (linear aldehydes, cyclic ketones);
- possibility of installing a neopentyl group by alkylation.

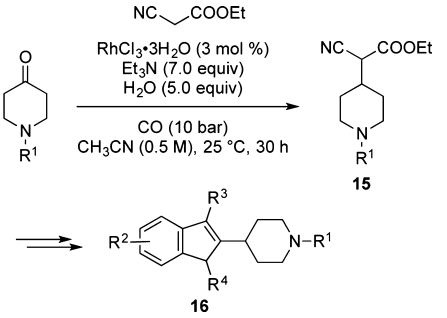
The ability to expand the scope of this work to include cyclic ketones affords a more economic route for the formation of important pharmaceutical intermediates. For example, reductive alkylation of ethyl cyanoacetate with tetrahydropyran-2-one yields an intermediate (**8ac′**) that can be transformed to tachykinin antagonist substances (**14**) with potential application as treatment for anxiety, depression, dementia and other types of central nervous system disorders in addition to inflammatory diseases such as arthritis, psoriasis and asthma (Scheme 9).[53] In comparison with the alkylation method of tosylate **13** employed in the original preparation, the present method has the advantages of starting from a less expensive alkylating agent, lower purification and separation cost, and higher yield of the desired intermediate. In addition, reductive alkylation of ethyl cyanoacetate with *N*-alkylpiperdin-2-one yields an intermediate (**15**) that can be converted to substituted indenes (**16**), which act as hypotensive agents (Scheme 10).[54]

Yet, some limitations of the reductive Knoevenagel alkylation under WGSR conditions also became apparent. First of all, the use of carbon monoxide, though desirable for its low cost and waste impact, poses severe safety concerns because of its toxicity and flammability. CO can certainly be handled safely by means of specialized techniques and equipment, but these handling restrictions limit its use in research laboratories.

Moreover, the following aspects also detract from the widespread application of our method:

- difficulty to optimize conditions for some classes of ketones that do not undergo condensation easily, and for active methylene precursors that are prone to conjugate addition;
- incompatibility of nitro groups, primary anilines, and alkynes;
- use of an expensive rhodium catalyst in high molar amount (2−3 mol %).

Scheme 10. Reductive Alkylation for the Synthesis of 16



6. CONCLUSION

The reductive power of the WGSR has been successfully harnessed to drive the alkylation of activated methylene compounds with carbonyl compounds at room temperature using rhodium catalysis. The proposed protocol was proven to be applicable to a wide range of alkylating agents, including aliphatic, aromatic and heteroaromatic aldehydes, as well as cyclic ketones. The method showed high tolerance toward halides, thioethers, allyl ethers and other functional groups that can be incompatible with other reduction methods.

Optimization studies have elucidated that the reaction proceeds through Knoevenagel condensation followed by reduction of the alkene, in which water is the source of hydrogen. The optimum amount of water varies from 2 to 50 equiv, depending on the rate of reduction of the alkene intermediate, and the vulnerability of the final product to hydrolysis.

Triethylamine was identified as a key component to allow for the reaction to proceed smoothly at room temperature Triethylamine is implicated in generating hydroxide ions to drive the WGSR catalytic cycle, in addition to its role as a ligand for rhodium and condensation catalyst. The reductive alkylation of the less acidic activated methylene compounds was rendered possible by increasing the amount of triethylamine or adding a stronger base to adjust the basicity of the reaction medium.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03183.

Additional optimization studies, full experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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