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Synthesis of *α*,*β*-Unsaturated Aldehydes Based on a One-Pot Phase-Switch Dehydrogenative Cross-Coupling of Primary Alcohols

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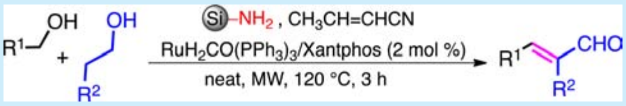
S *Supporting Information*

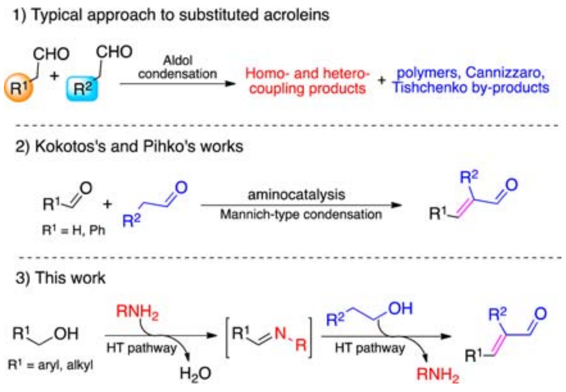


ABSTRACT: An efficient *one-pot* ruthenium-catalyzed hydrogen-transfer strategy for a direct access to *α*,*β*-unsaturated aldehydes has been developed. The employment of enolates prepared in situ from alcohols avoided handling unstable aldehydes and provided a very appealing route to different cinnamaldehydes substituted in position 2. A silica-grafted amine was used as phase-switch tag leading to a selective one-pot process in favor of cross-dehydrogenative coupling products.

Today, the forging of new carbon−carbon (C−C) bonds through the addition of active C−H nucleophiles to C-heteroatom double bonds is widely recognized as one of the most important topics in organic chemistry.[1] In this area, the aldol[2] and Mannich[3] reactions are highly efficient synthetic strategies that allow expedient access to versatile molecules such as *α*,*β*-unsaturated aldehydes, among others.[4] Because of their bifunctionality, substituted *α*,*β*-unsaturated aldehydes are used in the manufacture of a wide range of products including detergents, plasticizers, fragrances, pharmaceuticals, and cosmetics.[5]

Typical approaches to the preparation of these compounds involve condensation reactions between two aldehydes over basic or acidic catalysts (Scheme 1, eq 1). Although aldol reactions provide an attractive synthetic route to *α*,*β*-unsaturated aldehydes, the cross-aldol condensation between two different enolizable aldehydes continues to be a challenge that has found no general solution.[6] To prevent or reduce any unwanted side reactions, the Mannich-type reaction between aliphatic aldehydes and nonenolizable aldehydes in the presence of an amine represents a very useful approach to *α*,*β*-unsaturated aldehydes (Scheme 1, eq 2).[7] In this regard, the development of a synthetic process that employs enolates prepared in situ with high effectiveness and in low concentrations from a noncarbonyl precursor would avoid the handling of sensitive aldehydes.[8]

Scheme 1. Different Approaches to *α*,*β*-Unsaturated Aldehydes



Following our previous interest in hydrogen transfer (HT) and borrowing hydrogen strategies,[9] we now focused our attention on the development of a rapid access to *α*,*β*-unsaturated aldehydes, through the cross-dehydrogenative coupling of two different primary alcohols behaving as latent aldehydes (Scheme 1, eq 3). We designed a cascade reaction where a nonenolizable aldehyde is first generated in situ by the removal of a "hydrogen molecule" from an alcohol and then temporarily trapped as an imine. The following Mannich-type condensation between the imine species and the other transient aldehyde should give us the target compounds.[10]

In order to establish the optimal reaction conditions for imine synthesis, benzyl alcohol **1** and methylamine[11] **2** were chosen as model substrates and reacted with various ruthenium-based catalysts[12] in the presence of crotononitrile, used as a hydrogen trap (Table S1, Supporting Information). Among various Ru catalysts screened, we found that RuH$_2$CO(PPh$_3$)$_3$ (4 mol %) in combination with Xantphos ligand (4 mol %) gave an almost complete conversion of alcohol **1** into imine **3** (Scheme 2).

In the absence of an added hydrogen scavenger molecule, the imine intermediate **3** was reduced to *N*-methylbenzylamine as the major product. Interestingly, microwave (MW) dielectric heating cut down the reaction times from 24 h to a mere 1 h, highlighting the beneficial effect of MW in this process (Table S1, Supporting Information, compare entries 12 and 13).

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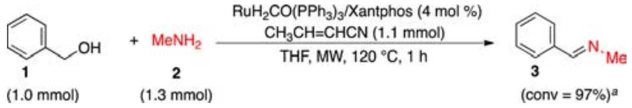
Scheme 2. Synthesis of Imine 3: An Assessment of the Reaction Conditions[a]



[a]Conversion into imine **3** determined by ^{1}H NMR analysis.

With an efficient procedure for preparing imines in hand, we investigated whether the same catalytic system could also promote the synthesis of *α*,*β*-unsaturated aldehydes by reacting in situ generated imines with aliphatic primary alcohols. To test our hypothesis, once the formation of **3** was completed, 1 equiv of heptanol **6** and 1.1 equiv of crotononitrile were added into the previously prepared imine solution containing the ruthenium catalyst, which was then heated in a MW oven at 120 °C for 2 h (Scheme 3). To our delight, the ruthenium–Xantphos system was indeed able to carry out both the transient oxidation of the alcohols **1** and **6** to the corresponding aldehydes and the subsequent Mannich-type reaction.

Scheme 3. Chemoselective Dehydrogenative Cross-Coupling Reaction of the Benzyl Alcohol with Heptanol via a Cascade Catalytic Sequence[a,b]

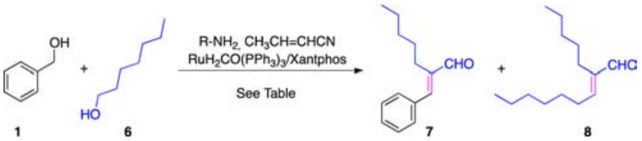
entry	ratio imine, **3**/alcohol, **6**	cross-coupling product, **7**/self-coupling product, **8**[a]
1	1:1	60:40
2	2:1	75:25
3	3:1	77:23
4	**2:1**	**85:15**[b]

[a]Ratio determined by ^{1}H NMR spectroscopy analysis. [b]Reaction performed by adding 100 mg of silica gel, particle size 40–63 *μ*m.

However, despite the complete conversion of heptanol **6**, we recovered a 6:4 mixture of the expected *α*,*β*-unsaturated aldehyde **7** and byproduct **8** derived from homocondensation (Scheme 3, entry 1). Improved selectivity was obtained doubling the imine to 1-heptanol ratio (Scheme 3, entry 2). Further increasing this molar ratio had no significant impact on either conversion or selectivity (Scheme 3, entry 3). Interestingly, the addition of 100 mg of silica gel exerted a beneficial effect on chemoselectivity (Scheme 3, entry 4), with up to 85% improvement toward the heterocoupling product **7** (see Table S2, Supporting Information, for acid catalyst screening). It must also be pointed out that the presence of a sacrificial hydrogen acceptor in this second step was mandatory both to promote hydrogen extraction from heptanol (RCH_2OH) and to avoid the over-reduction of the *α*,*β*-unsaturated aldehydes formed.

The combination of imine synthesis and Mannich condensation was then attempted in a one-pot reaction sequence. The desired product **7** was obtained, but a very low conversion (<10%) of alcohol **6** was observed (Table 1, entry 1), even after prolonged reaction time. However, reducing the amount of methylamine from 2 down to 0.5 mmol yielded 40% of *α*,*β*-unsaturated aldehyde **7** (Table 1, entry 2). Any attempt to reduce $MeNH_2$ below this threshold resulted in a slower reaction rates (see Table S3, Supporting Information, for a fine-tuning of the reaction conditions). We hypothesized that amine excess might inhibit or reduce the catalytic activity of the one-pot process. Thus, the use of an amine in heterogeneous phase[13] would allow us to perform a more efficient transformation.

Table 1. Dehydrogenative Cross-Coupling of Benzyl Alcohol 1 with Heptanol 6 via a One-Pot Reaction Sequence[a]



entry	amine	1/6[b]	conv 6[c] (%)	7/8[c]	7[d] (%)
1	$MeNH_2$ (2.0 mmol)	2:1	<10		
2	$MeNH_2$ (0.5 mmol)	2:1	100	76:24	40
3	(Si)-NH_2[e] (0.9 mmol)	2:1	>90	83:17	60
4	(Si)-NH_2[e] (0.9 mmol)	3:1	100	90:10	75

[a]Reaction performed under MWI at 120 °C using $RuH_2CO(PPh_3)_3$/Xantphos (4 mol %) as catalyst and crotononitrile (5.0 mmol) as hydrogen acceptor. [b]Heptanol (1.0 mmol). [c]Determined by ^{1}H NMR spectroscopy analysis. [d]Yields of isolated product **7** after column chromatography. [e]Reaction performed by using amine-grafted silica gel with particle size 40–63 *μ*m.

In order to achieve this goal, a new phase-switching strategy[14] was designed using a silica-grafted primary amine (Table S3, Supporting Information, entries 5–16) as phase-switch tag. This brought a noteworthy change in the outcome of the one-pot reaction, leading to the preparation of compound **7** in acceptable 60% yields (Table 1, entry 3).

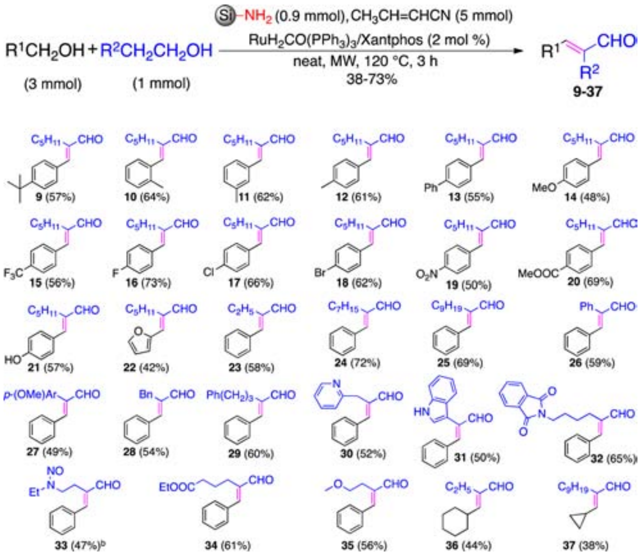
Optimization of the reaction parameters showed that mixing benzyl alcohol **1** and heptanol **2** in the ratio 3:1 with $RuH_2CO(PPh_3)_3$ (4 mol %) and Xantphos (4 mol %) in the presence of silica-immobilized amine (0.9 mmol), at 120 °C under MW dielectric heating for 3 h without solvent, afforded a 75% yield of the desired cross-coupling product **7** (Table 1, entry 4). Interestingly, when catalyst loading was halved (2 mol %), the activity and selectivity of the catalyst system remained unchanged (Table S3, Supporting Information, entry 11). Notably, silica-immobilized amine can be recovered by simple filtration, and it remained active, even after the fifth use (Table S4, Supporting Information). Several analyses showed the absence of any residual unsaturated aldehyde **7** on the solid support at the end of the cross-coupling reactions (see section 7, Supporting Information).

To better understand the substrate scope and limitations of this procedure, different aromatic alcohols and heptanol were reacted under the optimized reaction conditions (Scheme 4, products **9–22**). In general, substituents at different positions on the phenyl ring did not have a significant effect on the efficiency and selectivity of this procedure (Scheme 4, products **10–12**). Electron-withdrawing groups on the aromatic ring provided slightly better results than electron-donating substituents (Scheme 4, compare, for example, products **14** and **16**).

The reaction proceeded successfully even with benzylic alcohols bearing halogen moieties on the aromatic ring, leading to good yields of halogenated cinnamaldehydes **16–18** (65–73%, Scheme 4). *p*-Nitrobenzylic alcohol afforded the corresponding aldehyde **19** in a still acceptable yield (50%, Scheme 4). We were delighted to notice that base-sensitive residues as carboxymethyl ester or phenol were well tolerated under these conditions (Scheme 4, products **20** and **21**).

To assess the versatility of the reaction, the cascade catalytic sequence between benzyl alcohol **1** and a broad range of

Scheme 4. Catalyzed Dehydrogenative Cross-Coupling Reactions of Primary Alcohols under Solvent-Free MWI Conditions[a]

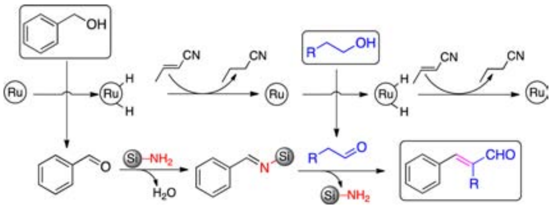


[a]Yield of isolated product. [b]Mixture of E/Z isomers: 65/35.

aliphatic alcohol partners was also investigated (Scheme 4, products **23**−**35**). The reaction proceeded smoothly to give the corresponding products **23**−**35** in 47−72% yields. This protocol has also proven fruitful with various primary alcohols containing pyridyl and indolyl motifs, thus allowing the introduction of different heterocyclic rings into the α,β-unsaturated aldehydes skeleton (Scheme 4, products **30** and **31**). In addition, a variety of functional moieties offering versatile synthetic functionality for further transformations were successfully incorporated (Scheme 4, products **32**−**35**). We were pleased to find that this catalytic system could also be extended to a few examples of reaction between α-branched and linear aliphatic alcohols (Scheme 4, products **36** and **37**). All the products, with the only exception of aldehyde **33**, were isolated as E-isomers (>98%), showing an excellent selectivity for the reaction. We were pleasantly surprised by the high rate of unknown compounds prepared (Scheme 4, products **9**, **10**, **12**, **13**, **16**, **17**, **20**−**22**, **25**, and **29**−**37**) using this method, suggesting that our approach could help in solving a synthetic problems still opened for α,β-unsaturated aldehyde synthesis. As expected, although this reaction may be applicable to the coupling between two linear aliphatic alcohols, a mixture of inseparable unsaturated aldehydes was recovered. In particular, if both reaction partners are enolizable and have a similar steric environment the most abundant products comes from the self-condensation.

A plausible mechanism that accounts for this ruthenium-promoted transfer-hydrogenation/Mannich-type domino reaction is proposed in Scheme 5. More reactive benzyl alcohol is first oxidized by the ruthenium-mediated hydrogen transfer from the substrate to crotononitrile. The formed benzaldehyde is probably caught by the supported amine leaving the restored catalyst to oxidize the aliphatic alcohol via a second hydrogen transfer with crotononitrile. Finally, the Mannich-type reaction between the grafted imine species and the second aldehyde gives the α,β-unsaturated coupling product.[15] To gain further insight into this catalytic mechanism, we checked the same reaction without the hydrogen acceptor. No reaction occurred in the absence of crotononitrile. These results highlight the key role of hydrogen transfer and how crotononitrile was able to intercept the dihydrogen molecule much more strongly than other unsaturated species (imine and α,β-unsaturated aldehyde) involved in the mechanism.

Scheme 5. Plausible Reaction Mechanism



In summary, we have developed an efficient *one-pot* synthesis of α,β-unsaturated aldehydes by a ruthenium-catalyzed procedure, which uses alcohols instead of aldehydes as starting material. The employment of enolates derived from a noncarbonyl precursors avoided handling unstable aldehydes and provided a very appealing and interesting alternative route to α,β-unsaturated aldehydes. The addition of a silica-grafted primary amine led to a selective one-pot process in favor of cross-dehydrogenative coupling products, which were obtained in good yields and with high chemoselectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(15) While we cannot exclude a priori an alternative mechanism via an aldol pathway, we assume the route shown in Scheme 5 (Mannich pathway) as the main mechanism by which the reaction occurs. The reaction mechanism postulated in Scheme 5 takes into account (a) the greater stability of Schiff bases compared to aldimines, (b) the use of an excess of aromatic alcohol (3 equiv) with respect to aliphatic one (mass effect), and (c) the driving force resulting from the release of an unstable intermediate carbinolamine from the solid support generating the final unsaturated aldehyde.