CHEMISTRY A European Journal



Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201705208

Link to VoR: http://dx.doi.org/10.1002/chem.201705208

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Ru-catalyzed Completely Deoxygenative Coupling of 2-Arylethanols through Base-induced Net Decarbonylation

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Abstract: Substituted arylethanols can be coupled using a readily available Ru-catalyst in a fully deoxygenative manner to produce hydrocarbon chains in one step. Control experiments indicate that the first deoxygenation occurs through an aldol condensation whereas the second occurs through a base-induced net decarbonylation. This double deoxygenation enables further development in the use of alcohols as versatile and green alkylating reagents, as well as in other fields such as deoxygenation and upgrading of overfunctionalized biomass to produce hydrocarbons.

As a functional group and starting material, alcohols are easily accessible, highly versatile, widely abundant and often related to renewable sources and green chemistry. Catalytic alkylation reactions using alcohols as the alkylating reagent, have become a desirable and important method to avoid traditional toxic electrophilic reagents.^[11] The so-called hydrogen-borrowing method is frequently used in α -alkylation of carbonyls^[2], and in N-alkylation reactions.^[3] The typical mechanistic pathway involves dehydrogenation, nucleophilic attack at the carbonyl through either aldol reaction/condensation or imine formation depending on substrate, and rehydrogenation to eliminate the product, in addition to water. The majority of methods employ iridium or ruthenium metal centers that are well known for their ability to reversibly perform hydrogen transfer reactions.^[4] Not least due to its relevance to biomass conversion, this field of chemistry has experienced a remarkable development over the last decades.

Given the abundance and diversity of alcohols, a general and fully deoxygenative coupling to produce a carbon chain directly would be desirable. In comparison to traditional hydrogen borrowing alkylation chemistry where the heteroatoms are not removed, the challenge in such a reaction lies in the double deoxygenation. Several examples of nondeoxygenative cross-alkylation of alcohols are known, primarily involving ruthenium catalysis. For example, Cho and Shim^[5], Ramón and Yus^[6], Peris^[7], Lau^[8], Crabtree^[9], Jia^[10] and Kundu^[11] have reported the betaalkylation of secondary alcohols with primary alcohols to generate the Guerbet-products in good yields, and Beller^[12] reported the methylation of 2-arylethanols with methanol. Madsen^[13] and Achard^[14] reported the alkylation of secondary alcohols to form ketones. Wass^[15] and Szymczak^[16] have reported on the upgrading of ethanol to butanol. To the best of our knowledge, the fully deoxygenative reaction has not previously been reported with ruthenium, and only on two occasions with iridium and with varying success. Ishii, Obora and coworkers reported the iridium-catalyzed coupling of ω -arylalkanols to produce α -, ω -diarylalkanes in good yields.^[17] A related transformation was found as a side-reaction by Ramón and coworkers, to produce similar products, in ≤12% yields with an iridiummagnetite heterogeneous catalyst.^[18] To this background, we herein report a Ru-catalyzed method to couple substituted ethyl alcohols to produce hydrocarbon products in high yield.

Based on this recent progress in the field, we anticipated that significantly simpler and cheaper ruthenium-based metal centers should also be competent of performing a fully deoxygenative coupling and

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Scheme 1. Overview of Ru-catalyzed alkylation of alcohols using alcohols.

we investigated various conditions for this reaction, Table 1.^[19] When exploring the coupling of 2-phenylethanol **1a** to produce 1,3-diphenylpropene **2a** as a standard reaction, we found that $Ru(PPh_3)_3Cl_2$ was advantageous amongst a variety of different commercially available Ru-

Scheme 2. Screening of conditions for the standard reaction.

Table 1. Ruthenium(II)-catalyzed deoxygenative coupling of 2-arylethanols.^[a]

Entry	Catalvst	Base	Time	Yield [%] ^[a]
1	Ru(PPha)aCla	NaO ^t Bu	16	69
2	RuH(CO)(PPh ₃) ₃	NaO ^t Bu	16	59
3	[Ru(bpy) ₃]Cl ₂ .6H ₂ O	NaO ^t Bu	16	<1 ^[b]
4	$RuCl(PPh_3)_2(C_5H_5)$	NaO ^t Bu	16	64
5	Fe(acac) ₃	NaO ^t Bu	24	NR
6	Co(acac) ₂	NaO ^t Bu	24	NR
7	Ru(PPh ₃) ₃ Cl ₂	КОН	24	18
8	Ru(PPh ₃) ₃ Cl ₂	NaOMe	24	11
9	Ru(PPh ₃) ₃ Cl ₂	Cs ₂ CO ₃	24	10
10	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu (0.2)	24	36
11	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu (0.5)	24	81
12	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu	24	84
13	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu (1.2)	24	<1 ^[b]
14	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu	24	61 ^[c]
15	Ru(PPh ₃) ₃ Cl ₂	NaO ^t Bu	24	86 ^[d]
16	-	_	24	NR
17	Ru(PPh ₃) ₃ Cl ₂	-	24	NR
18	-	NaO ^t Bu	24	NR

[a] See table S1 for the full optimization table. Standard reaction conditions, unless otherwise noted: **1a** (0.41 mmol), [Ru] (1 mol%), base (0.6 eq to **1a**), toluene (3 ml), 111°C. Isolated yields after column chromatography. [b] Trace product observed in GC though not successfully isolated. [c] Reaction performed in 1,4-dioxane solvent (3 ml). [d] With dppp additive (1.2 mol%). NR; no reaction

10.1002/chem.201705208

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salts, entries 1-4. Of the different investigated bases, NaOtBu was found to be significantly better compared to KOH, NaOMe and carbonates, entries 7-9. Investigation of the effect of base loading revealed that 0.6 equivalents of NaOtBu relative to 1a was optimal, with higher or lower loading leading to a remarkable decrease in product formation, entries 10-13. Addition of a cocatalytic amount of dppp led to a slight increase in product formation, entry 15 vs 12. In all entries, the indicated product was the only isolated material, as no other intermediates were observed. Potential direct decarbonylation/dehydrogenation of 2-phenylethanol leading to toluene was not established, given the use of toluene as a solvent. Further, in the presence of dppp, the olefin was always obtained as the exclusive product whereas otherwise the corresponding 1,3-diarylpropane often formed as a side product, vide infra. Performing the reaction in a closed vessel where eliminated hydrogen could not escape, a ratio of up to 21% of 1,3-diphenylpropane vs 2a resulted, with lower overall conversion. In total, the optimization experiments showed that 1 mol% RuCl₂(PPh₃)₃ in combination with 1.2 mol% dppp and 60 mol% of NaOtBu was the optimal combination of Ru-catalyst, ligand and base.

Having optimized the conditions, we next explored the substrate scope and functional group tolerance of the reaction. The substrates **1a-11** with substituents like Me, OMe, Br and Cl, all underwent the deoxygenative coupling to afford the corresponding propene derivatives **2a-21** in moderate to good yields, scheme 3. Although conversion of **1a** always led to the olefin product **2a**, with substituted aryl substrates, a mixture of alkenyl and alkane products were obtained in the absence of the dppp ligand (**2b**, **2c** and **2e**). This observation may be explained by that the dppp ligand may irreversibly induce dihydrogen elimination to specifically produce the olefin, following the general trend that more facile reductive elimination occurs with larger bite angle ligands.^[20]

Increased steric bulk on the aryl group impeded the reaction, as expected. For instance, 2-(*p*-tolyl)ethanol **1b** reacted to produce the propene derivative **2b** in 81% yield whereas the ortho-isomer 2-(o-tolyl)ethanol **1d** resulted in **2d** in 60% yield. Both chloride- and bromide-substituted aryl ethanols in ortho-, meta- or para-positions could successfully be converted to the corresponding diarylpropene derivatives (**2g-2j**). The more electron-poor 3,4-dichlorophenyl-2-ethanol **1j** was more challenging and resulted in a **3**1% yield of **2j**. Despite that sulfur-containing substrates often act as catalyst poisons, product **2k** was obtained in 56% yield, indicating that the thiophene group was tolerated under these reaction conditions. More problematic was 2-(2-hydroxyethyl)naphthalene **1l**, resulting in only 26% yield. However with 5 mol% of Ru(PPh₃)₃Cl₂ catalyst, the yield of **2l** was increased to 82%, indicating that the obstacle is kinetic in nature.



Scheme 3. Deoxygenative coupling of 2-arylethanol substrates. Isolated yields after column chromatography. [a] Yields in parentheses indicate the distribution of 1,3-diarylpropene:1,3-diarylpropane when the reaction is performed in the absence of dppp ligand. [b] With 5 mol% catalyst.

Regarding naphtyl-substituted ethanols, the substitution pattern was found to be important for the reaction outcome. As observed in scheme 4, 1naphthalene ethan-2-ol **1m** underwent Ru-catalysed net dehydrogenation and decarbonylation to give 1-methylnaphthalene in 42% yield along with 12% of the expected propene derivate under the standard reaction conditions, compare **2l**, scheme 3. Upon reaction with 2-(pyridin-2-yl)ethanol **1n**, dehydration occurred to produce 2-vinylpyridine **4** in 41% yield. It is at this point not clear what causes the different reaction outcomes in these two specific cases.



Scheme 4. Experiments with hydrogen and hydrogen acceptor, respectively, and alcohols with differing reactivity outcome. Isolated yields after column chromatography.

In order to gain some mechanistic insight, a series of control reactions were carried out. First, the standard reaction was tested under a hydrogen atmosphere and with a hydrogen acceptor, respectively, scheme 4. Under an atmosphere of hydrogen, the total yield was not significantly affected, though the amount of 1,3-diphenylpropane increased dramatically even in the presence of dppp ligand. In presence of the hydrogen acceptor 1,7-octadiene, no other difference was observed other than that the yield was reduced. We initially hypothesized that the hydrogen acceptor may facilitate hydrogen transfer and elimination and thus shorten the reaction time, which turned out not to be the case. The reduced yield is likely due to competitive coordination between the substrate and the olefin. Further, anticipating that the first step in a catalytic cycle is the alcohol dehydrogenation, we investigated the reactivity of the corresponding aldehyde under a variety of conditions, scheme 5.



Scheme 5. Reactivity of phenylacetaldehyde under a variety of conditions. Isolated yields after column chromatography.

Under standard reaction conditions, phenylacetaldehyde was converted to product 2a in only 25% isolated yield. Under identical conditions except for the exclusion of base, the non-decarbonylated coupled aldol condensation product was obtained in 56% yield. This led us to believe that the base has an important role in the net decarbonylation step. When performing the same reaction exclusively with base and no Ru-precatalyst, we indeed observed both aldol coupling, condensation and decarbonylation albeit in only 22% yield. We then considered the possibility that after performing dehydrogenation of the alcohol, the Ru-catalyst could be facilitating the aldol chemistry through its Lewis acidic properties. A Lewis acid pathway was tested through performing the reaction in the presence of Cu(OTf)₂ with and without base, respectively. In the presence of base, the same product was obtained in a similar yield as without the Lewis acid, and without base 2phenylnaphthalene was obtained.^[21] No reaction occurred with 2phenylethanol with only 5 mol% Cu(OTf)₂. From these reactions, we cannot completely exclude the possibility of ruthenium promoting the coupling through Lewis acid-type participation, though it is clear that its presence is required for the overall reaction to occur. This is further indicated by the significant reduction in aldol-coupling yield in the absence of ruthenium precatalyst. On this basis, we consider three mechanistic possibilities for the coupling and net decarbonylation reaction, scheme 6.



Scheme 6. Possible mechanistic pathways for the net decarbonylation.

The first step involves dehydrogenation by ruthenium, followed by a catalytic aldol coupling to generate the β-hydroxyaldehyde. Typically in hydrogen-borrowing chemistry, the base is generally thought to be responsible for catalyzing the aldol reaction and condensation, though it is clear in this work that the aldol reaction from the aldehyde intermediate can also occur in the absence of base as shown in scheme 5. The synthesis of 1,3-diphenylpropene has on several occasions been reported to be achieved quantitatively through self-condensation of phenylacetaldehyde in ethanol solvent in the presence of KOH. $^{\left[22\right]}$ The β -hydroxyaldehyde could as in path A proceed through nucleophilic attack of hydroxide at the carbonyl, to eliminate formate in the form of CO2 and H2, in addition to regenerating the base. This reaction was, in a basic ethanol solution without transition metal catalysis, proposed by Stoermer.^[22c] Decarbonylation involving a carbanion intermediate as in path B has been proposed with 1,3-dihalosubstituted benzaldehydes^[23], and compared to aryl anions, benzylic anions should be significantly more accessible from an energetic perspective. Although transition metal-catalyzed decarbonylation is considerably more common with rhodium complexes, ruthenium complexes are also known to catalyze this transformation as in path C.^[24] In an early attempt to get further insight into the mechanism, we attempted to characterize the gaseous byproduct by

 13 C-NMR, by performing the reaction in a sealed J. Young NMR-tube, though neither CO₂ nor CO was observed.

Concerning the active catalyst speciation, we followed the reaction by GC analysis of aliquots taken during the course of the reaction and plotted a a kinetic trace of yield versus time. An induction period is observed, figure S2, indicating formation of a new catalytically active species likely involving formation of nanoparticles. Following this trace, the reaction mixture was commonly observed by visual inspection to gradually darken during this time and turn black, though we still cannot fully exclude the possibility of formation of another active homogeneous catalyst species. Although the mercury test is not necessarily applicable to ruthenium catalysis, in a separate experiment we added a drop of mercury to the reaction mixture without any observable decrease in activity. While the kinetic trace is highly supportive of that RuCl₂(PPh₃)₃ is only a pre-catalyst, the negative mercury test should most likely only be considered as an indication of its non-applicability in this catalytic system.^[25] In the kinetic experiments only the starting material and product were observed, no intermediates could be detected.

In summary, the fully deoxygenative coupling of arylethanols is herein reported to produce 1,3-diarylpropenes in good yields. The reaction is performed by the use of versatile and commercially available $RuCl_2(PPh_3)_3$. The observed dark reaction mixture combined with that the kinetic trace, which shows a sigmoidal curvature is indicative of that the Ru-complex is only a pre-catalyst. Control experiments further indicate that the base has an important role in the second deoxygenation or net decarbonylation to produce the hydrocarbon product. To the best of our knowledge, this is the first report of a Ru-catalyzed fully deoxygenative coupling of alcohols. We believe that these results could enable further development in the field of alcohol alkylation reactions and other deoxygenation reactions as for example relevant to biomass upgrading. Further and more detailed mechanistic studies are currently in progress in our laboratories.

Acknowledgements

Financial support by the Olle Engkvist Byggmästare foundation, the Royal Swedish Academy of Forestry and Agriculture, the Magnus Bergvall Foundation and the Royal Physiographic Society in Lund and the Science and Engineering Research Board, India, SB/OS/PDF-004/2015-16 (SM) is gratefully acknowledged.

Keywords: dehydrogenation; hydrogen-borrowing catalysis; ruthenium complexes; metal hydrides; decarbonylation

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Double deoxygenation: A fully deoxygenative coupling of primary 2-arylethanols was achieved by combining aldol condensation with a net decarbonylation. Control experiments indicate that the base and its loading, has an important cooperative role in the second deoxygenation. The reaction is achieved using cheap and commercially available $RuCl_2(PPh_3)_3$ as a precatalyst.

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Page No. – Page No.

Title

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