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Ruthenium-Catalyzed Self-Coupling of Primary and Secondary Alcohols with the Liberation of Dihydrogen

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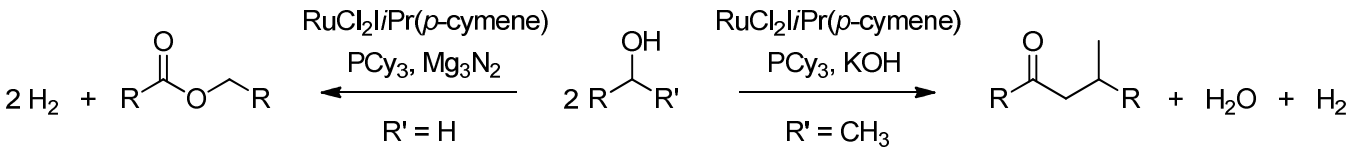

Abstract

The dehydrogenative self-condensation of primary and secondary alcohols has been studied in the presence of [$RuCl_2$(I*i*Pr)(*p*-cymene)]. The conversion of primary alcohols into esters has been further optimized by using magnesium nitride as an additive which allowed the reaction to take place at a lower temperature and catalyst loading than described previously. Secondary alcohols were dimerized into racemic ketones by a dehydrogenative Guerbet reaction with potassium hydroxide as the additive. The transformation gave good yields of the ketone dimers with a range of alkan-2-ols while more substituted secondary alcohols were unreactive. The reaction proceeds by dehydrogenation to the ketone followed by an aldol reaction and hydrogenation of the resulting enone.

INTRODUCTION

The metal-catalyzed dehydrogenative coupling of alcohols with carbon and heteroatom nucleophiles has received significant attention during the past decade.[1-3] The reaction proceeds by oxidation of the alcohol to the carbonyl compound followed by attack of the nucleophile to afford products such as amines, ketones, esters and amides. The most attractive protocol is to perform the transformation in the absence of hydrogen acceptors since only molecular hydrogen and/or water is then formed as the byproduct(s).

The self-coupling of an alcohol or the cross-coupling of two different alcohols constitutes a key transformation in this category to afford higher alcohols, ketones and esters.[1-3] In fact, the homodimerization of primary and secondary alcohols, the so-called Guerbet reaction, has been known for more than a century.[4] This transformation results in β-alkylated dimer alcohols where the new C-C bond is generated by an aldol condensation and a molecule of water is released.[5] In the original procedure the reaction was promoted by the corresponding sodium alkoxide at temperatures exceeding 200 °C[4] during which reversible hydrogen transfer occurs to form the carbonyl compounds.[6] More recently, late transition metal complexes based on iridium and rhodium have been shown to catalyze the Guerbet reaction at temperatures ranging from 120 to 140 °C.[7-9] The reaction has been extended to the selective β-alkylation of secondary alcohols with primary alcohols which has been achieved with metal catalysts based on iridium,[10-13] ruthenium,[13-18] palladium,[19] copper[20,21] and iron.[22] The cross-coupling is performed in the presence of a base at temperatures between 80 and 135 °C and often produces the corresponding ketone as a minor byproduct.[10-21] The ketone can also be obtained as the major product from the β-alkylation if the reaction is carried out with the heterogeneous catalysts Au-Pd/HT,[23]

Ag/Al_2O_3[24] or Pd/C[25] although only 1-phenylethanol and analogs have been employed as the secondary alcohol in these cases. Besides C-C bond formation the coupling of primary alcohols can also lead to esters as shown with several ruthenium,[26-31] iridium[32] and osmium[33,34] catalysts in the absence of hydrogen scavengers.

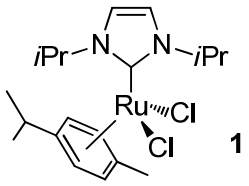

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Figure 1. Structure of ruthenium NHC complex **1**.

We have recently exploited the ruthenium N-heterocyclic carbene complex **1** (Figure 1) as a catalyst for dehydrogenative couplings with primary alcohols. In the presence of an amine and KO*t*Bu the coupling affords the amide[35,36] while in the absence of a base the corresponding imine is formed.[37] For the amidation the mechanism has been thoroughly investigated by a combination of experimental and theoretical methods.[38] If another nucleophile is not present primary alcohols will undergo homodimerization into esters and molecular hydrogen upon treatment with complex **1** (2.5 mol%), PCy_3 (4.5 mol%) and KOH (10 mol%).[39] Under these conditions, pentan-1-ol was fully converted into pentyl pentanoate upon reflux in mesitylene at 163 °C for 18 h.[39] However, for benzylic alcohols the esterification was accompanied by significant decarbonylation of the intermediate aldehyde which is presumably caused by the high reaction temperature. Therefore, we decided to reinvestigate the ester formation with complex **1** in an attempt to achieve the reaction at a lower temperature. During these studies we discovered a new dehydrogenative self-coupling of secondary alcohols which proceeds by alkylation in the

β-position and dehydrogenation to the ketone. Herein, we report the conditions for the improved ester synthesis from primary alcohols and the new synthesis of ketones from secondary alcohols.

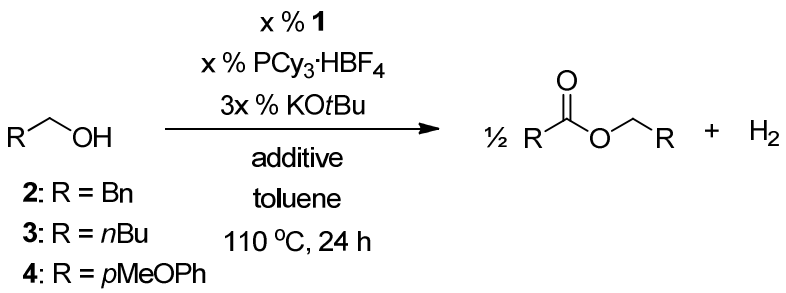
RESULTS AND DISCUSSION

The studies began with the same catalytic system that was used in our mechanistic investigation of the ruthenium-catalyzed amidation, *i.e.* complex **1** (5 mol%), PCy_3•HBF_4 (5 mol%) and KO*t*Bu (15 mol%) in refluxing toluene.[38] The HBF_4 salt of PCy_3 was selected since PCy_3 is easily oxidized by air and in our experience commercial samples of PCy_3 contain various amounts of impurities that are difficult to remove. Since a base is already required in the esterification it will also serve the purpose of deprotonating PCy_3•HBF_4.[40]

Our earlier studies had shown that PCy_3 and KO*t*Bu only gave a moderate yield of the ester[39] and this was confirmed with the PCy_3•HBF_4 salt (Table 1, entry 1). The previous optimization had only focused on various hydroxide and carbonate bases giving rise to KOH as the optimum choice.[39] However, in the development of the amidation reaction we investigated several ammonia equivalents in an attempt to prepare primary amides.[35] Surprisingly, exclusive ester formation was observed with Mg_3N_2[41] as the ammonia source (entry 2). This result prompted us to investigate the significance of Mg_3N_2 in closer detail since the esterification is now achieved in toluene in good yield and at a lower temperature of 110 °C. The phosphine and the base were still important components since very low conversion was observed in the absence of PCy_3 and with a lower amount of KO*t*Bu (entries 3 – 4). Changing the phosphine to PPh_3 or dppe also gave lower conversion (entries 5 – 6) which indicates that PCy_3 is still the optimum phosphine. At this moment, it was decided to change the alcohol to pentan-1-ol to achieve a better comparison with the earlier results.[39] To establish the optimum amount of Mg_3N_2 the catalyst

loading was lowered to 1.25% and the reaction stopped already after 2 h. This showed that the highest rate was observed with 16.7% of Mg_3N_2 (entries 7 – 11). This is an interesting number since 1 equiv. of Mg_3N_2 can theoretically react as a base with 6 equiv. of the alcohol. To determine whether other properties are important, Mg_3N_2 was replaced with similar additives (entries 12 – 18). No ester was formed with $MgBr_2$ and only a low yield was observed with the weaker bases MgO and Cs_2CO_3 (entries 12 – 14). On the contrary, high yields were achieved with the stronger bases Ca_3N_2, Li_3N and K_3PO_4 (entries 15 – 17) and it appears that the most important property of the additive is basicity. The amount of complex **1** could be lowered to 0.5% at the expense of a longer reaction time and a slightly lower yield (entries 18 – 20). Thus, the conversion of pentan-1-ol into pentyl pentanoate has now been achieved at a lower temperature and catalyst loading than in our previous study.[39] The conditions were also applied to *p*-methoxybenzyl alcohol which gave the lowest yield of all substrates in our earlier study due to extensive decarbonylation. With Mg_3N_2 as the additive the esterification of this alcohol was significantly improved and less decarbonylation observed (entries 21 – 24).

Table 1. Synthesis of Esters with Complex 1



Entry	alcohol	x (%)	additive	% additive	conversion (%)	yield (%)[a]
1	**2**	5	-	-	100	64

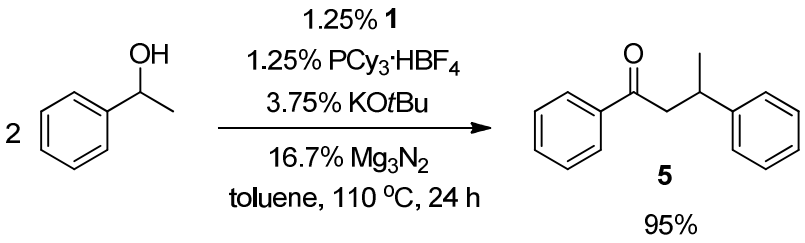
2	**2**	5	Mg_3N_2	100	100	84
3[b]	**2**	5	Mg_3N_2	100	23	14
4[c]	**2**	5	Mg_3N_2	100	21	1
5[d]	**2**	5	Mg_3N_2	100	89	66
6[e]	**2**	5	Mg_3N_2	100	82	65
7[f]	**3**	1.25	Mg_3N_2	4.2	-	36
8[f]	**3**	1.25	Mg_3N_2	8.3	-	61
9[f]	**3**	1.25	Mg_3N_2	16.7	-	78
10[f]	**3**	1.25	Mg_3N_2	27	-	61
11[f]	**3**	1.25	Mg_3N_2	100	-	49
12	**2**	1.25	$MgBr_2$	50	-	0
13	**2**	2.5	MgO	50	-	24
14	**3**	1.25	Cs_2CO_3	50	-	11
15	**3**	1.25	Ca_3N_2	16.7	-	95
16	**3**	1.25	Li_3N	33	-	80
17	**3**	1.25	K_3PO_4	33	-	98
18[g]	**3**	0.5	Mg_3N_2	16.7	-	70
19	**3**	1.25	Mg_3N_2	16.7	-	93
20[h]	**3**	5	Mg_3N_2	16.7	-	98
21	**4**	2.5	Mg_3N_2	16.7	65	33
22	**4**	5	Mg_3N_2	16.7	67	48
23	**4**	2.5	Mg_3N_2	100	80	44
24	**4**	5	Mg_3N_2	100	100	81

[a] GC yield. [b] Without PCy_3•HBF_4 and with 10% KO*t*Bu. [c] With 5% KO*t*Bu. [d] With PPh_3 instead of PCy_3•HBF_4 and 10% KO*t*Bu. [e] With dppe instead of PCy_3•HBF_4 and 10% KO*t*Bu. [f] Reaction time 2 h. [g] Reaction time 72 h. [h] Reaction time 3 h.

At this point, it was decided not to continue the investigations with other primary alcohols since the outcome most likely would be a rather predictable improvement of our previous substrate study. Instead, selective cross-esterifications were attempted which had not been possible so far with complex **1**. First, an equimolar mixture of benzyl alcohol and 2-phenylethanol were reacted under the optimized conditions, but this only resulted in a near equal mixture of all four possible esters. Then, the cross-esterification was attempted with 2-phenylethanol and 1-phenylethanol, but this only produced traces of the desired ester while 2-

phenylethanol was almost completely converted into the symmetrical ester and 1-phenylethanol to acetophenone. Since the latter seems to be easily dehydrogenated under the reaction conditions, an experiment was also performed with 1-phenylethanol in the absence of a primary alcohol. Surprisingly, this now produced a 95% GC yield of racemic ketone dimer **5** (Scheme 1). This transformation can be envisioned as a dehydrogenative Guerbet reaction with a secondary alcohol – a reaction that to the best of our knowledge has not been described previously with a homogeneous catalyst.

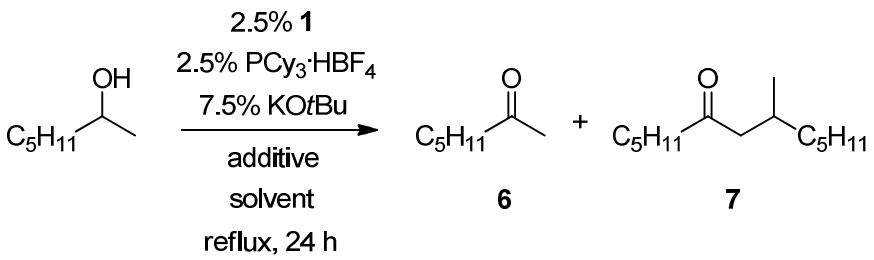
Scheme 1. Self-Condensation of 1-Phenylethanol



Therefore, we decided to investigate this transformation in further detail and began by optimizing the conditions (Table 2). Heptan-2-ol was selected for these studies since 1-phenylethanol is a relatively special substrate in this context. At first, heptan-2-ol only produced the corresponding ketone under the conditions in Scheme 1 and no dimerization was observed (entry 1). Apparently, Mg_3N_2 will not promote the subsequent aldol reaction with this ketone and other additives were therefore investigated. Similar results were observed with Ca_3N_2, K_3PO_4, K_2CO_3, $NaHCO_3$ and DBU where the reaction also stopped at the ketone stage (results not shown). Most likely, the lower acidity of the α protons in heptan-2-one as compared to acetophenone is responsible for hampering the aldol reaction. As a result, stronger bases were

included in the study and fortunately Li_3N, LDA, NaH, KO*t*Bu and KOH all gave ketone dimer **7** as the major product (entries 2 – 6). The importance of basicity was clearly illustrated when KOH, NaOH and LiOH were compared since the former gave dimer **7** as the major product while the latter only furnished heptan-2-one (entries 6 – 8). With Li_3N several other ligands and solvents were also investigated, but in all cases a lower yield of the desired ketone was obtained (entries 9 – 17). With KOH it was possible to leave out KO*t*Bu and even lower the amount of complex **1** without compromising the yield of **7** (entries 18 – 20). Only when lower amounts of KOH were employed did the yield of **7** decrease slightly (entry 21). Consequently, it was decided to use a small excess of KOH and catalytic amounts of complex **1** and PCy_3•HBF_4 in refluxing toluene as the general protocol for the dehydrogenative coupling.

Table 2. Dehydrogenation of Heptan-2-ol with Complex 1



Entry	additive	% additive	solvent	yield of **6** (%)[a]	yield of **7** (%)[a]
1	Mg_3N_2	16.7	toluene	38	0
2	Li_3N	33	toluene	12	86
3	LDA	100	toluene	6	56
4	NaH	100	toluene	2	92
5	KO*t*Bu	100	toluene	0	78
6	KOH	100	toluene	2	95
7	NaOH	100	toluene	44	55
8	LiOH	33	toluene	64	0
9[b]	Li_3N	33	toluene	1	50
10[c]	Li_3N	33	toluene	18	69

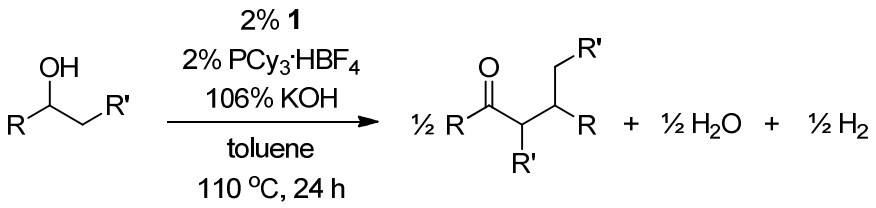
11[d]	Li_3N	33	toluene	10	34
12[e]	Li_3N	33	toluene	2	23
13	Li_3N	33	*o*-xylene	0	39
14	Li_3N	33	heptane	0	7
15	Li_3N	33	benzene	21	18
16	Li_3N	33	dioxane	10	36
17	Li_3N	33	water	14	0
18[f]	KOH	107.5	toluene	2	94
19[f,g]	KOH	115	toluene	1	97
20	KOH	185	toluene	2	92
21[f]	KOH	50	toluene	12	87

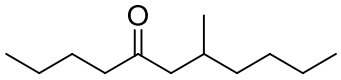
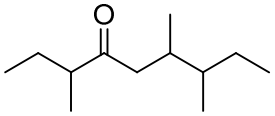
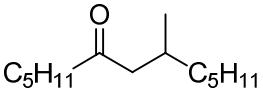
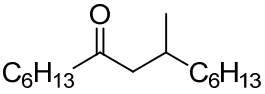
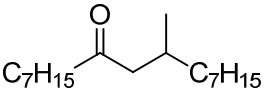
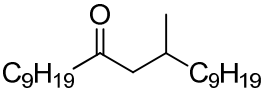
[a] GC yield. [b] Without PCy_3•HBF_4 and with 5% KO*t*Bu. [c] With PPh_3 instead of PCy_3•HBF_4 and with 5% KO*t*Bu. [d] With dppe instead of PCy_3•HBF_4 and with 5% KO*t*Bu. [e] With pyridine instead of PCy_3•HBF_4 and with 5% KO*t*Bu. [f] Without KO*t*Bu. [g] With 1.25% **1** and PCy_3•HBF_4.

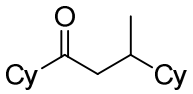
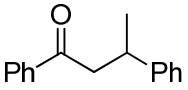
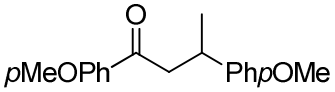
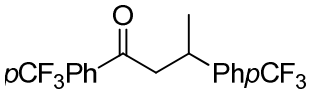
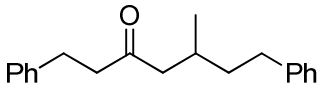
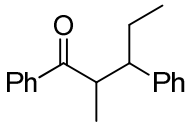
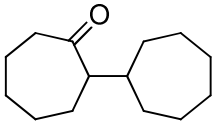
These conditions were then applied to a variety of other secondary alcohols (Table 3). Alkan-2-ols ranging from hexan-2-ol to nonan-2-ol were converted into the corresponding ketone dimers in high yields (entries 1 – 5). A further increase in the length of the aliphatic chain resulted in a lower reactivity as shown with undecan-2-ol and tetradecan-2-ol (entries 6 – 7). The former required a longer reaction time in order to give a good yield while the latter was only oxidized to the ketone and no aldol reaction was observed. Methyl carbinols containing a cyclohexyl or a phenyl group were also converted in good yield (entries 8 – 12) while the halogenated substrates 1-(*p*-chlorophenyl)- and 1-(*p*-bromophenyl)ethanol gave mixtures of several ketones due to partial dehalogenation (results not shown). Attempts to convert alkan-3-ols failed and the same was observed with nonan-5-ol (entries 13 – 16). Even the more easily oxidized propiophenone only gave a very low yield of the coupling product (entry 17). Cycloalkanols, on the other hand, were completely transformed into the α-alkylated ketones. Unfortunately, cyclopentanol and cyclohexanol both gave a mixture of the monoalkylated and

the α,α'-dialkylated ketone where the ratio was 1:7 with cyclopentanol and 1:1 with cyclohexanol. No attempts were made to separate these product mixtures. Cycloheptanol, on the other hand, afforded exclusively the monoalkylated product which was isolated in good yield (entry 18). In all, the dehydrogenative dimerization of secondary alcohols with complex **1** works well with a range of methyl carbinols while other acyclic secondary alcohols are not sufficiently reactive to undergo the coupling. Cycloalkanols are transformed in good yield, but only cycloheptanol gives complete regioselectivity for the monoalkylated product.

Table 3. Dehydrogenative Self-Coupling of Secondary Alcohols



Entry	R	R'	product	yield (%)[a]
1	*n*-C_4H_9	H		95
2	*sec*-C_4H_9	H		80
3	*n*-C_5H_{11}	H		92
4	*n*-C_6H_{13}	H		92
5	*n*-C_7H_{15}	H		94
6[b]	*n*-C_9H_{19}	H		87

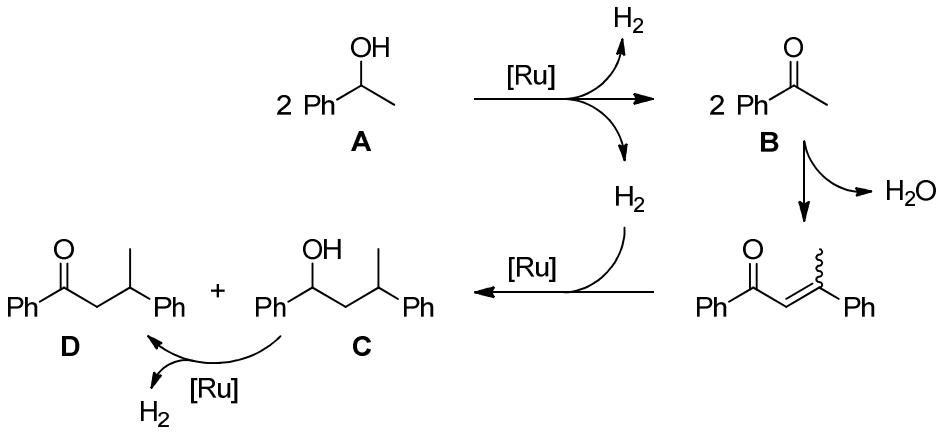
7	*n*-$C_{12}H_{25}$	H	-	0
8	Cy	H		92
9	Ph	H		95
10	*p*MeOPh	H		95
11	*p*CF_3Ph	H		80[c]
12	$BnCH_2$	H		88
13	C_2H_5	CH_3	-	0
14	*n*-C_3H_7	CH_3	-	0
15	*i*-C_3H_7	CH_3	-	0
16	*n*-C_4H_9	*n*-C_3H_7	-	0
17	Ph	CH_3		5[c]
18	-$(CH_2)_5$-			70

[a] Isolated yield. [b] Reaction time 65 h. [c] GC yield.

The reaction with 1-phenylethanol was monitored over time by GCMS where the corresponding ketone and β-alkylated alcohol were observed as intermediates (Scheme 2 and Figure 2). None of the α,β-unsaturated enone could be detected, but this compound is most likely hydrogenated rapidly and serves as an in situ hydrogen scavenger at the beginning of the reaction. To gain more information about the ruthenium species involved in the catalytic cycle the self-condensation of 1-phenylethanol was also monitored by NMR in toluene-d_8. After one

hour several signals in the hydride region of the ^{1}H NMR spectrum were detected. This includes doublets at –22.13 (J_{PH} = 40 Hz) and –22.24 ppm (J_{PH} = 35 Hz) which can be assigned to ruthenium monohydride species with PCy_3 trans to the N-heterocyclic carbene ligand.[42] In addition, signals at –6.47, –6.63 and –6.93 ppm were observed which can be ascribed to ruthenium dihydride species.[43,44] The dehydrogenative coupling was also performed with the monodeuterated alcohol, *i.e.* 1-deutero-1-phenylethanol, where rapid scrambling of deuterium and hydrogen in the α-position was observed under the reaction conditions. This shows that the dehydrogenation of the alcohol is a reversible process and that the ruthenium species thus formed is a dihydride. The same rapid scrambling was observed in the esterification, imination and amidation with complex **1** and primary alcohols.[37-39] The *p*-cymene ligand on complex **1** was quickly displaced during the reaction which was shown by an additional NMR experiment with octan-2-ol as the substrate where complete release of *p*-cymene was observed after 20 min.

Scheme 2. Mechanism for Dehydrogenative Self-Coupling



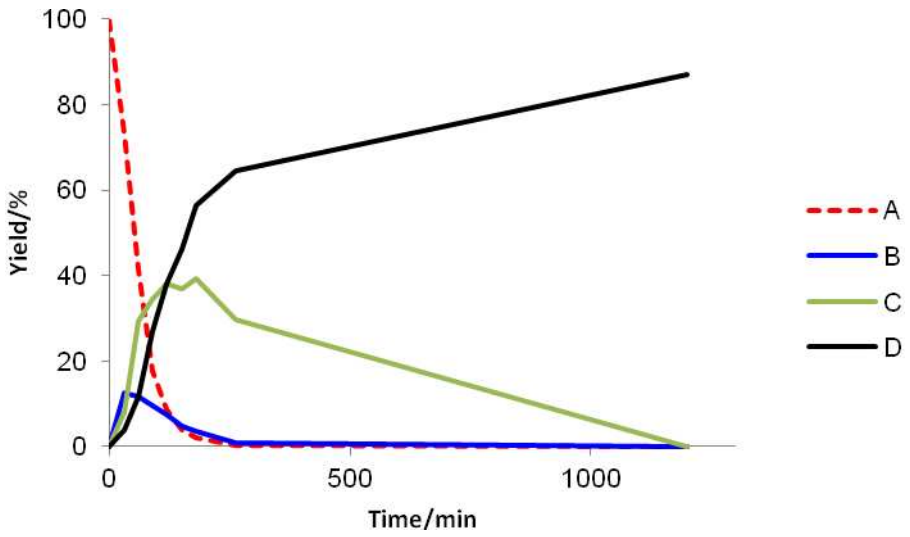


Figure 2. Composition of Reaction Mixture as a Function of Time.

In conclusion, we have described an improved procedure for the formation of esters from primary alcohols and a new protocol for the self-coupling of secondary alcohols. Both transformations are catalyzed by the ruthenium NHC complex **1** and occur with the liberation of molecular hydrogen.

EXPERIMENTAL SECTION

General Information. All solvents were of HPLC grade and were not further purified. Column chromatography separations were performed on silica gel (220 – 440 mesh). NMR chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H 7.26 ppm) and $CDCl_3$ (δ_C 77.16 ppm). HRMS measurements were made using ESI with TOF detection. 1-Deutero-1-phenylethanol[45] and 1-(4-(trifluoromethyl)phenyl)ethanol[46] were prepared according the reported procedures.

General Procedure for Esterification of Primary Alcohols. A Schlenk tube was charged with [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**1**)[35] (23 mg, 0.05 mmol), PCy_3•HBF_4 (18.4 mg, 0.05 mmol), KO*t*Bu (16.8 mg, 0.15 mmol), Mg_3N_2 (16.9 mg, 0.17 mmol) and a stir bar. A cold finger was attached and the tube was evacuated and refilled with argon three times. The primary alcohol (4 mmol) and nonane (257 mg, 2 mmol) were dissolved in toluene to give a 1 M solution of the alcohol (total volume 4 mL). This solution was transferred to the Schlenk tube which was then placed in a preheated oil bath (T = 120 °C). Samples for GCMS analysis were withdrawn after the indicated time periods.

General Procedure for Self-Coupling of Secondary Alcohols. A Schlenk tube was charged with **1**[35] (46 mg, 0.1 mmol), PCy_3•HBF_4 (36.8 mg, 0.1 mmol), KOH (298 mg, 5.3 mmol) and a stir bar. A cold finger was attached and the tube was evacuated and refilled with argon three times. The secondary alcohol (5 mmol) and nonane (321 mg, 2.5 mmol) were dissolved in toluene to give a 1 M solution of the alcohol (total volume 5 mL). This solution was transferred to the Schlenk tube which was then placed in a preheated oil bath (T = 120 °C). After 24 h the reaction mixture was cooled to room temperature and filtered through a pad of Celite which was washed with pentane. The collected solution was evaporated *in vacuo* and the resulting liquid purified either by vacuum distillation or column chromatography (EtOAc/pentane 50/1 → 15/1).

7-Methylundecan-5-one (Table 3, Entry 1). Distilled *in vacuo* to give a colorless liquid. Yield 437 mg (95%). bp 91 °C/5 mmHg (lit.[47] bp 103–105 °C/9 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.92 (m, 9H), 1.18–1.36 (m, 8H), 1.88 (p, J = 7.5 Hz, 2H), 1.92–2.03 (m, 1H), 2.14–2.22 (m, 1H), 2.31–2.40 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.2, 20.0, 22.5, 23.0, 26.0, 29.3, 29.4, 36.8, 43.3, 50.5, 211.6. IR (neat) 1712 cm^{-1}. HRMS *m*/*z* calcd for $C_{12}H_{25}O$ 185.1905 $[M + H]^+$, found 185.1899.

3,6,7-Trimethylnonan-4-one (Table 3, Entry 2). Distilled *in vacuo* to give a colorless liquid. Yield 367 mg (80%). bp 70 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74–0.89 (m, 9H), 1.03 (d, J = 6.0 Hz, 3H), 1.07–1.41 (m, 3H), 1.59–1.73 (m, 1H), 2.01–2.48 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 11.8, 11.9, 12.2, 12.2, 14.5, 14.5, 14.8, 14.9, 15.9, 15.9, 16.0, 16.0, 16.1, 16.1, 17.3, 17.3, 19.9, 25.9, 25.9, 26.0, 26.1, 26.1, 26.5, 27.4, 32.2, 32.9, 33.0, 34.6, 35.9, 38.9, 38.9, 39.5, 45.0, 45.0, 46.0, 46.9, 48.2, 48.2, 48.3, 48.4, 214.9, 214.9, 215.1, 215.1. IR (neat) 1708 cm^{-1}. HRMS *m*/*z* calcd for $C_{12}H_{25}O$ 185.1905 $[M + H]^+$, found 185.1900.

8-Methyltridecan-6-one (Table 3, Entry 3). Distilled *in vacuo* to give a colorless liquid. Yield 488 mg (92%). bp 111–112 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.90 (m, 9H), 1.19–1.34 (m, 12H), 1.55 (p, J = 7.5 Hz, 2H), 1.92–2.04 (m, 1H), 2.14–2.22 (m, 1H), 2.33–2.40 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.2, 20.0, 22.6, 22.8, 23.6, 26.8, 29.4, 31.6, 32.1, 37.1, 43.5, 50.5, 211.7. IR (neat) 1712 cm^{-1}. HRMS *m*/*z* calcd for $C_{14}H_{29}O$ 213.2218 $[M + H]^+$, found 213.2212.

9-Methylpentadecan-7-one (Table 3, Entry 4). Distilled *in vacuo* to give a colorless liquid. Yield 552 mg (92%). bp 130–131 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.89 (m, 9H), 1.16–1.34 (m, 16H), 1.50–1.59 (m, 2H), 1.92–2.03 (m, 1H), 2.14–2.22 (m, 1H), 2.32–2.39 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.2, 20.0, 22.6, 22.8, 23.9, 27.1, 29.1, 29.4, 29.6, 31.8, 32.0, 37.1, 43.6, 50.5, 211.7. IR (neat) 1713 cm^{-1}. NMR data are in accordance with literature values.[48]

10-Methylheptadecan-8-one (Table 3, Entry 5). Distilled *in vacuo* to give a colorless liquid. Yield 630 mg (94%). bp 154 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.89 (m, 9H), 1.18–1.31 (m, 20H), 1.50–1.59 (m, 2H), 1.92–2.03 (m, 1H), 2.14–2.21 (m, 1H), 2.31–2.39 (m,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.2, 20.0, 22.8, 22.8, 24.0, 27.1, 29.2, 29.4, 29.4, 29.5, 29.9, 31.8, 32.0, 37.1, 43.5, 50.5, 211.6. IR (neat) 1713 cm^{-1}. HRMS *m*/*z* calcd for $C_{18}H_{36}O$ 269.2839 $[M + H]^+$, found 269.2844.

12-Methylheneicosan-10-one (Table 3, Entry 6). Distilled *in vacuo* to give a colorless liquid which crystallized upon standing. Yield 705 mg (87%). bp 197 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.89 (m, 9H), 1.25 (br s, 28H), 1.50–1.59 (m, 2H), 1.94–2.03 (m, 1H), 2.14–2.22 (m, 1H), 2.33–2.40 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.3, 20.1, 22.8, 22.8, 24.0, 27.1, 29.4, 29.5, 29.6, 29.7, 29.8, 29.8, 29.9, 29.9, 32.0, 32.1, 37.1, 43.6, 50.5, 211.7. IR (neat) 1714 cm^{-1}. HRMS *m*/*z* calcd for $C_{22}H_{44}O$ 325.3465 $[M + H]^+$, found 325.3467.

1,3-Dicyclohexylbutan-1-one (Table 3, Entry 8). Distilled *in vacuo* to give a colorless liquid. Yield 543 mg (92%). bp 146 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.7 Hz, 3H), 0.92–1.39 (m, 11H), 1.59–1.96 (m, 11H), 2.17–2.34 (m, 2H), 2.44 (dd, J = 4.8, 16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 25.8, 25.9, 26.0, 26.8, 26.8, 26.9, 28.5, 28.7, 29.2, 30.5, 33.9, 42.9, 45.6, 51.3, 214.7. IR (neat) 1705 cm^{-1}. HRMS *m*/*z* calcd for $C_{16}H_{29}O$ 237.2218 $[M + H]^+$, found 237.2213.

1,3-Diphenylbutan-1-one (Table 3, Entry 9). Purified by column chromatography to give a yellow solid. Yield 532 mg (95%). NMR data are in accordance with literature values.[49]

1,3-Bis(4-methoxyphenyl)butan-1-one (Table 3, Entry 10). Purified by column chromatography to give a colorless liquid. Yield 675 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.9 Hz, 3H), 3.05–3.24 (m, 2H), 3.39–3.50 (m, 1H), 3.78 (s, 3H), 3.85 (s, 3H), 6.84 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 35.1, 47.1, 55.4, 55.6, 113.8, 114.0, 127.9, 130.4, 130.5, 130.7,

138.9, 158.0, 163.5, 197.9. IR (neat) 1672 cm^{-1}. HRMS *m/z* calcd for $C_{18}H_{21}O_3$ 285.1481 $[M + H]^+$, found 285.1488.

1,3-Bis(4-(trifluoromethyl)phenyl)butan-1-one (Table 3, Entry 11). After 24 h the reaction mixture was passed through a plug of Celite which was washed with pentane. The resulting solution was evaporated *in vacuo* to give 701 mg of a red liquid. The NMR spectrum showed approx. 85% of the desired product and GCMS also revealed the desired ketone as the major product. However, attempts to isolate the product quantitatively by column chromatography failed due to partial decomposition of the compound. Eluted twice through a column with silica gel (pentane/EtOAc 50/1 → 15/1) to give a reddish liquid. Yield 198 mg (22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 3H), 3.11–3.30 (m, 2H), 3.45–3.56 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 35.3, 46.9, 125.5–125.9 (m), 127.4, 128.3, 128.5, 129.4, 139.7, 150.3, 197.5. ^{19}F NMR (75 MHz, $CDCl_3$) δ −62.8, −62.0. IR (neat) 1692 cm^{-1}. HRMS *m/z* calcd for $C_{18}H_{15}F_6O$ 361.1027 $[M + H]^+$, found 361.1028.

5-Methyl-1,7-diphenylheptan-3-one (Table 3, Entry 12). Purified by column chromatography to give a slightly yellow liquid. Yield 308 mg (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.4 Hz, 3H), 1.32–1.58 (m, 2H), 1.90–2.03 (m, 1H), 2.13–2.21 (m, 1H), 2.30–2.37 (m, 1H), 2.41–2.64 (m, 4H), 2.78–2.83 (m, 2H), 7.07–7.22 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 29.1, 29.9, 33.5, 38.8, 44.9, 50.6, 125.9, 126.2, 128.5, 128.6, 141.6, 142.5, 209.9. IR (neat) 1712 cm^{-1}. HRMS *m/z* calcd for $C_{20}H_{25}O$ 281.1905 $[M + H]^+$, found 281.1902.

2-Cycloheptylcycloheptanone (Table 3, Entry 19). Distilled *in vacuo* to give a colorless liquid. Yield 364 mg (70%). bp 136 °C/5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16–1.63 (m, 16H),

1.76–1.91 (m, 5H), 2.21–2.38 (m, 2H), 2.43–2.53 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ25.5, 26.8, 26.9, 27.6, 28.2, 28.3, 28.6, 30.3, 30.9, 32.9, 42.2, 43.4, 59.5, 217.4. IR (neat) 1696 cm^{-1}. HRMS *m*/*z* calcd for $C_{14}H_{25}O$ 209.1905 $[M + H]^+$, found 209.1895.

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Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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