JOC The Journal of Organic Chemistry

Article

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

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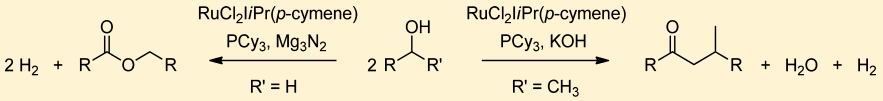
Supporting Information



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 allows the reaction to take place at a temperature and catalyst loading lower than those 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, whereas 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 the 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 because only molecular hydrogen or water is formed as the byproduct.

The self-coupling of an alcohol or the cross-coupling of two different alcohols constitutes a key transformation in the category aiming to afford higher yields of 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 (hydrotalcite supported),[23] Ag/Al_2O_3,[24] and Pd/C,[25] although only 1-phenylethanol and analogs have been employed as the secondary alcohol in these cases. Besides, C−C bond formation in 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.

We have recently exploited ruthenium N-heterocyclic carbene complex **1** (Figure 1) as a catalyst for dehydrogenative

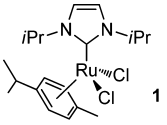


Figure 1. Structure of ruthenium NHC complex **1**.

couplings with primary alcohols. In the presence of an amine and KO*t*Bu, the coupling affords the amide,[35,36] whereas 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

Received: April 27, 2013
Revised: June 2, 2013
Accepted: June 3, 2013
Published: June 3, 2013

dx.doi.org/10.1021/jo4008699 | J. Org. Chem. 2013, 78, 6593−6598

attempt to achieve the reaction at a lower temperature. During these studies, we discovered a new dehydrogenative self-coupling of secondary alcohols that 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

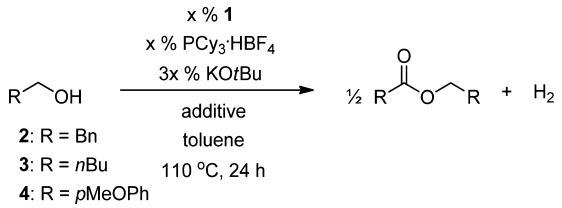
The studies began with the same catalytic system that was used in our mechanistic investigation of the ruthenium-catalyzed amidation, that is, complex **1** (5 mol %), $PCy_3{\cdot}HBF_4$ (5 mol %), and KO*t*Bu (15 mol %) in refluxing toluene.[38] The HBF_4 salt of PCy_3 was selected because PCy_3 is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

Our earlier studies had shown that PCy_3 and KO*t*Bu gave only a moderate yield of the ester,[39] and this was confirmed with the $PCy_3{\cdot}HBF_4$ salt (Table 1, entry 1). The previous optimization had focused on only 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 because 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 because very low conversion was observed in the absence of PCy_3 and with a smaller amount of KO*t*Bu (entries 3 and 4). Changing the phosphine to PPh_3 or 1,2-bis(diphenylphosphino)ethane (dppe) also gave a lower conversion (entries 5 and 6), which indicates that PCy_3 is still the optimum phosphine. Therefore, it was decided to change the alcohol to pentan-1-ol to achieve a better comparison between the current results and 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 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 because 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 temperature and catalyst loading lower than those in our previous study.[39] The conditions were also applied to *p*-methoxybenzyl alcohol, which gave the lowest yield of all the 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 was observed (entries 21−24).

The investigations with other primary alcohols were discontinued at this point because the most likely outcome would be a predictable improvement of our previous substrate study. Instead, selective cross-esterifications that had not been possible so far with complex **1** were attempted. First, an equimolar mixture of benzyl alcohol and 2-phenylethanol were reacted under the optimized conditions, but this resulted only in a nearly equal mixture of all four possible esters. Then, the cross-esterification was attempted with 2-phenylethanol and 1-phenylethanol, but this produced only traces of the desired ester. 2-Phenylethanol was almost completely converted into the symmetrical ester, and 1-phenylethanol was converted to acetophenone. Because 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.

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 because 1-

Table 1. Synthesis of Esters with Complex 1



entry	alcohol	catalyst loading (%)	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 $PCy_3{\cdot}HBF_4$ and with 10% KO*t*Bu. [c]With 5% KO*t*Bu. [d]With PPh_3 instead of $PCy_3{\cdot}HBF_4$ and 10% KO*t*Bu. [e]With dppe instead of $PCy_3{\cdot}HBF_4$ and 10% KO*t*Bu. [f]Reaction time is 2 h. [g]Reaction time is 72 h. [h]Reaction time is 3 h.

dx.doi.org/10.1021/jo4008699 | J. Org. Chem. 2013, 78, 6593−6598

Scheme 1. Self-Condensation of 1-Phenylethanol

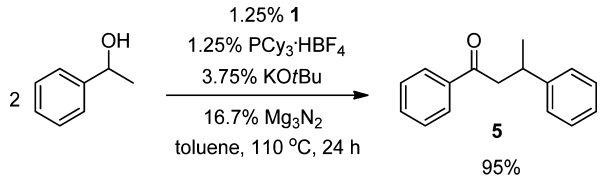
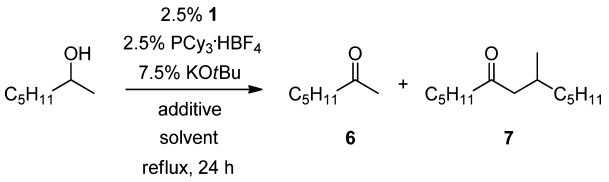


Table 2. Dehydrogenation of Heptan-2-ol with Complex 1



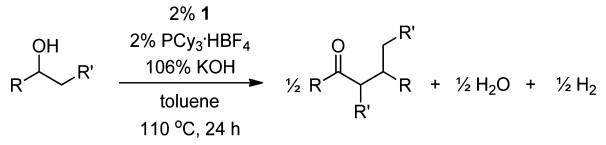
entry	additive	% additive	solvent	yield of **6** (%)[a]	yield of 7 (%)[a]
1	Mg_3N_2	16.7	toluene	38	0
2	Li_3N	33	toluene	12	86
3	LDA	100	toluene	6	56
4	NaH	100	toluene	2	92
5	KO*t*Bu	100	toluene	0	78
6	KOH	100	toluene	2	95
7	NaOH	100	toluene	44	55
8	LiOH	33	toluene	64	0
9[b]	Li_3N	33	toluene	1	50
10[c]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

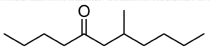
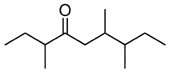
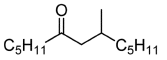
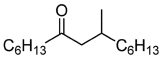
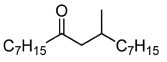
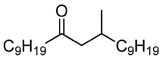
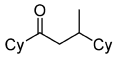
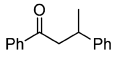
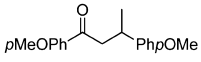
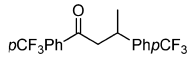
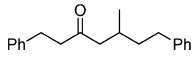
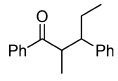
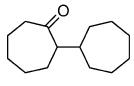
[a]GC yield. [b]Without $PCy_3·HBF_4$ and with 5% KO*t*Bu. [c]With PPh_3 instead of $PCy_3·HBF_4$ and with 5% KO*t*Bu. [d]With dppe instead of $PCy_3·HBF_4$ and with 5% KO*t*Bu. [e]With pyridine instead of $PCy_3·HBF_4$ and with 5% KO*t*Bu. [f]Without KO*t*Bu. [g]With 1.25% **1** and $PCy_3·HBF_4$.

phenylethanol is a relatively special substrate in this context. At first, heptan-2-ol produced only 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 that of 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 products were compared because the former gave dimer **7** as the major product, whereas the latter furnished only 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 to lower the amount of complex **1** without compromising the yield of **7** (entries 18–20). Only when smaller 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.

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

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

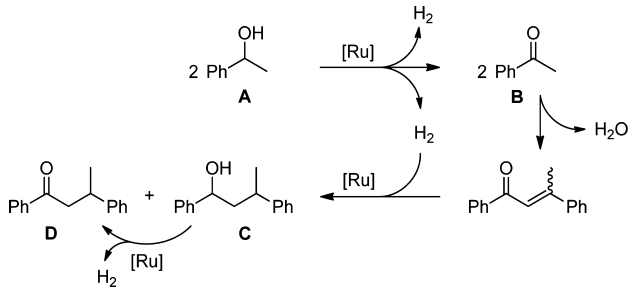
[a]Isolated yield. [b]Reaction time is 65 h. [c]GC yield.

dx.doi.org/10.1021/jo4008699 | J. Org. Chem. 2013, 78, 6593–6598

in the length of the aliphatic chain resulted in a lower reactivity, as shown with undecan-2-ol and tetradecan-2-ol (entries 6 and 7). The former required a longer reaction time in order to give a good yield. 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), whereas 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 failure was observed with nonan-5-ol (entries 13−16). Even the more easily oxidized propiophenone gave only 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 that 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, whereas 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.

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 most likely hydrogenates 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 of the self-condensation of 1-phenylethanol, this alcohol's reaction was also monitored by NMR in toluene-d_8. After 1 h, 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 the 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 the complete release of *p*-cymene was observed after 20 min.

Scheme 2. Mechanism for Dehydrogenative Self-Coupling



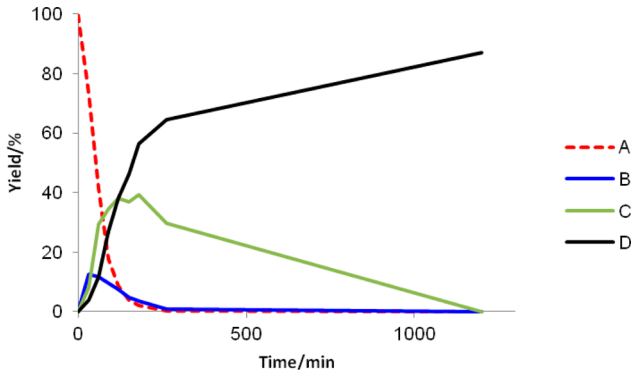


Figure 2. Composition of reaction mixture as a function of time.

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 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 to 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 coldfinger 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 coldfinger 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 rt and filtered through a pad of Celite, which was washed with pentane. The collected solution was evaporated in vacuo and the resulting liquid purified by either vacuum distillation or column chromatography (50/1 → 15/1 EtOAc/pentane).

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,

dx.doi.org/10.1021/jo4008699 | J. Org. Chem. 2013, 78, 6593−6598

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. ^1H 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. ^1H 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. ^1H 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. ^1H 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 that crystallized upon standing. Yield: 705 mg (87%). Bp: 197 °C/5 mmHg. ^1H 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. ^1H 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%). ^1H 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 approximately 85% purity 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. The red liquid residue was eluted twice through a column with silica gel (50/1 → 15/1 pentane/EtOAc) to give a reddish oil. Yield: 198 mg (22%). ^1H 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%). ^1H 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. ^1H 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, $CDCl_3$): δ 25.5, 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Danish Council for Independent Research—Technology and Production Sciences for financial support.

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