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Iridium-Catalyzed Alkylation of Secondary Alcohols with Primary Alcohols: A Route to Access Branched Ketones and Alcohols

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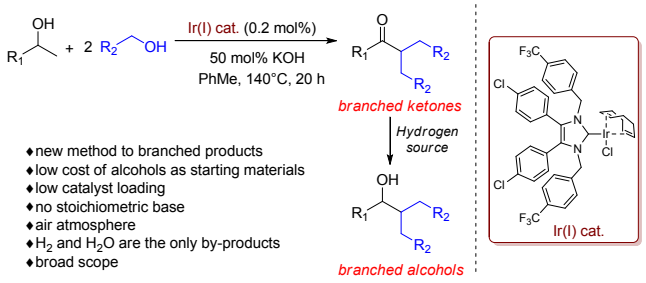
KEYWORDS: *N-heterocyclic carbene, iridium, borrowing hydrogen, alkylation, branched ketones and alcohols.*



ABSTRACT

Under borrowing hydrogen conditions, NHC–iridium(I) catalyzed the direct or one-pot sequential synthesis of α,α-disubstituted ketones *via* the alkylation of secondary alcohols with primary alcohols is reported. Notably, the present approach provides a new method for the facile synthesis of α,α-disubstituted ketones, and featured with several characteristics, including a broad substrate scope, using easy-to-handle alcohols as starting materials and performing the reactions under aerobic conditions. Moreover, the selective one-pot formation of β,β-

disubstituted alcohols was achieved by the addition of an external hydrogen source to the reaction mixture.

INTRODUCTION

The transition-metal (TM) catalyzed borrowing hydrogen (BH) strategy has become a valuable alternative for the construction of C–C bonds in organic chemistry to synthesize functionalized complex molecules.[1] The main advantage of this methodology is the utilization of readily available and easy-to-handle alcohols as greener alkylating agents over mutagenic alkyl halides.[1] α,α-Di-substituted ketones are important intermediates that have been widely used in organic synthesis and the pharmaceutical industry.[2] Therefore, the development of green and efficient catalytic systems for the synthesis of these products would be highly desirable. Over the past five years, application of Ru,[3] Rh,[4] Ir,[5] Pd,[6] Mn,[7] Fe[8] and Ni[9] catalysts for the monoalkylation of linear methylene ketones with primary alcohols providing α,α-di-substituted ketones is well established (Scheme 1a). There are also two reports on monoalkylation of secondary alcohols providing α,α-disubstituted ketones.[7d,8b] The main disadvantage of this monoalkylation approach is the preparation of linear methylene ketones or secondary alcohols as starting materials in advance. Direct access to α,α-disubstituted ketones *via* the alkylation of methyl ketones or secondary alcohols is also known but almost exclusively relies on the use of methanol as the alkylating agent (Scheme 1b).[3b,4,5a,7b,c,8a,9b,10]

A three-component direct or one-pot sequential double alkylation of methyl ketones with benzyl alcohol and methanol was also described by employing Ru,[3b] Rh,[4] Ir,[5a,b] Pd,[11] and Fe[12] catalysts for the formation of α,α-disubstituted ketones (Scheme 1c). After the early reports by the Donohoe and co-workers, a few groups extended this strategy by the sequential addition of

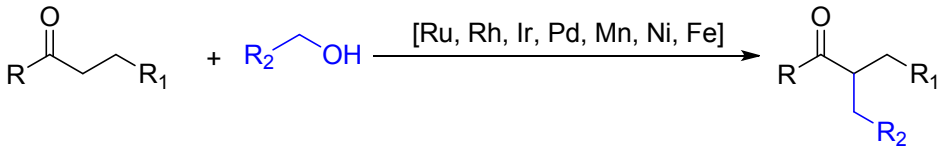
two different primary alcohols other than methanol (Scheme 1c).[3a,c,7a,8b,9a] The main disadvantages of these systems are the requirement of additional catalyst in the second step or their limited substrate scopes (2-8 examples). Very recently, Leitner,[13a] Maji,[13b] and co-workers have described the synthesis of α,α-disubstituted ketones from methyl ketones and diols by using manganese-based catalysts. Although considerable progress has been achieved in α-alkylation of carbonyl compounds to give α,α-disubstituted ketones, catalytic cross-coupling of secondary alcohols with primary alcohols remain unexplored. Thus, it is desirable to develop a new strategy for the synthesis of α,α-disubstituted ketones directly from secondary alcohols and primary alcohols.

Recently, we established a highly active catalytic system for the alkylation of secondary alcohols with primary alcohols to give α-alkylated ketones[14a] and β-alkylated alcohols[14b] using an iridium(I)–N-heterocyclic carbene (NHC) catalyst (**1a**) (Scheme 1d). On the bases of these reports, we further envisaged the cross-coupling of secondary alcohols with primary alcohols for the synthesis of α,α-disubstituted ketones. Herein, we describe the synthesis of three new NHC–Ir^{I} complexes (**1b-d**) (Scheme 2) with different backbones on the 4,5-position of imidazole. We then investigated the catalytic activities of NHC–Ir^{I} complexes (**1a-d**) in the direct double alkylation and one-pot sequential alkylation of secondary alcohols with primary alcohols to obtain a variety of α,α-di-substituted ketones under aerobic conditions (Scheme 1e). To the best of our knowledge, this study represents the first example of TM-catalyzed double alkylation of secondary alcohols with primary alcohols in the selective synthesis of α,α-di-substituted branched ketones. In addition, this catalytic system has also allowed the one-pot selective formation of β,β-disubstituted alcohols by the subsequent addition of an external hydrogen source to the reaction mixture.

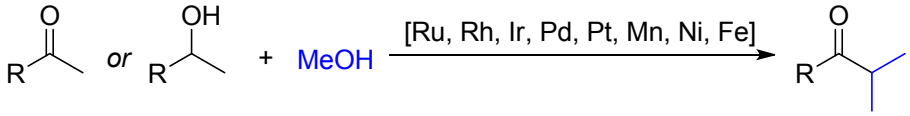
Scheme 1. Strategies for the TM-Catalyzed Formation of Branched Products

Previous work

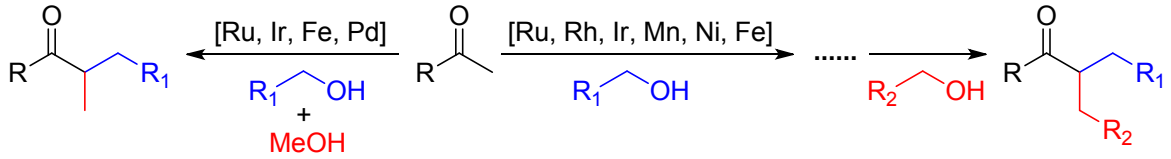
a) Monoalkylation of methylene ketones with alcohols to give branched ketones



b) Double methylation of ketones or secondary alcohols with methanol to give branched products

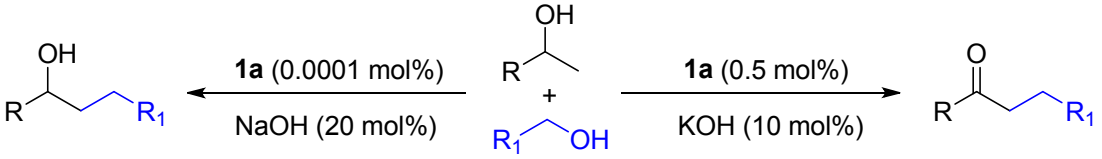


c) Direct or one-pot sequential alkylation of ketones with alcohols to give branched ketones



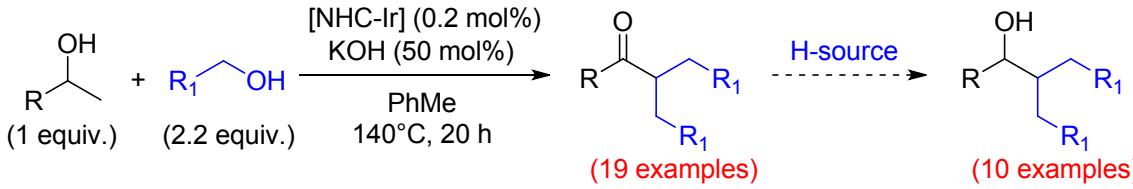
Our previous work

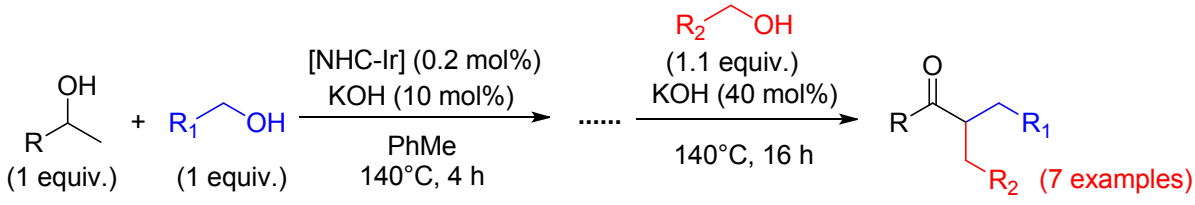
d) Alkylation of secondary alcohols with primary alcohols to give linear ketones or alcohols



This work

e) Direct or sequential alkylation of secondary alcohols with primary alcohols to give branched products

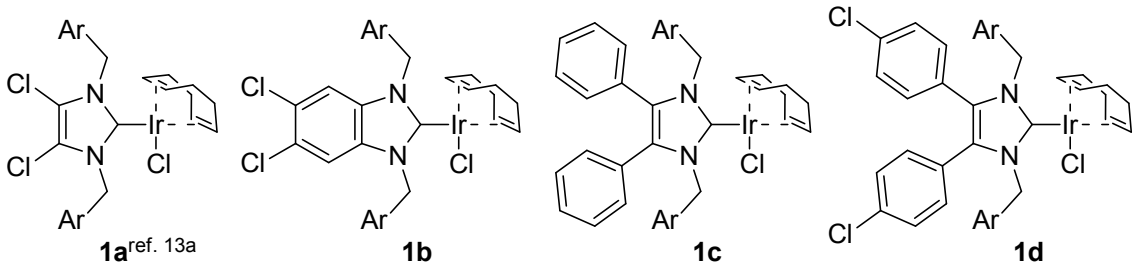




RESULTS and DISCUSSION

The electronic nature of the NHC ligand plays an important role for the catalytic activity of the related complexes.[15] For the classical NHCs, backbone modifications primarily change the electronic properties.[15a] Based on our experience on NHC–Ir^{I} catalyzed BH reactions,[14] we commenced to prepare a set of [IrCl(COD)(NHC)] complexes (**1a-d**) with potentially electron-withdrawing backbones on the 4,5-position of imidazole and 4-trifluorobenzyl substituents as the wingtip on the nitrogen atom of imidazole (Scheme 2). The synthesis of the ligand precursors and NHC–Ir^{I} complexes (**1a-d**) are summarized in Supporting Information (Scheme S1, S2). All the new ligands and complexes were prepared in high yields as air- and moisture-stable solids and were characterized by NMR spectroscopy and HRMS analysis.

Scheme 2. NHC–Ir^{I} Complexes (**1a-d**) Used in This Study

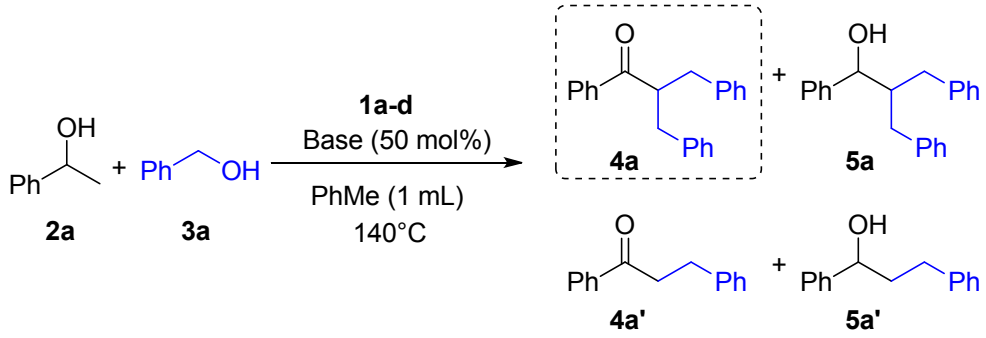


Reaction of 1-phenylethanol (**2a**) (0.5 mmol) with 2.0 equiv. benzyl alcohol (**3a**) (1.0 mmol), catalyst **1a-d** (0.5 mol%), and KOH (50 mol%) in toluene solution was heated to 140 °C (oil bath temperature) under air for an initial investigation (Table 1). Then, the reaction mixture was analyzed by gas chromatography (GC) and ^{1}H NMR spectroscopy. Conversions are based on ^{1}H NMR analysis of reaction mixtures by using 1,3,5-trimethoxybenzene as internal standard (Table 1). The GC analysis of reaction mixtures confirmed that conversion of 1-phenylethanol

(**2a**) in the presence of NHC–Ir^{I} catalysts (**1**) was complete. However, the product distribution showed that, along with the desired product **4a**, the double alkylation process was interrupted and unreacted monoalkylation intermediate **4a'** left over in appreciable amounts within 16 h (entries 1-4). Among all catalysts tested, the highest selectivity to **4a** was obtained with backbone substituted NHC–Ir^{I} complex **1d** (entry 4). Clearly, the electronic character of the NHC ligand is important for the reactivity[14] and it was observed that the catalytic activity of iridium complexes was enhanced by introducing electron-withdrawing 4-chlorophenyl group on the 4,5-position of imidazole. Increasing the reaction time to 20 h did not increase the formation of **4a** and similar product distribution was observed (entry 5). This is due to the formation of the side product potassium benzoate *via* dehydrogenation of benzyl alcohol under these conditions.[16] As a result, there was no benzyl alcohol left to react with **4a'** to form the final product **4a**. In order to suppress this side reaction, we first decreased the amount of catalyst to 0.2 mol%: here, amount of unreacted **4a'** decreased to 12% and along with desired product **4a** (72%) and reduced double alkylated byproduct **5a** (13%) (entry 6). Increasing the amount of benzyl alcohol to 2.2 equivalents resulted in a better outcome and formed the desired product **4a** in 81% along with the double alkylated alcohol **5a** in 18% conversion (entry 7). Here, double alkylated products **4a** and **5a** were isolated in 78 and 13% yields, respectively. Notably, unreacted intermediate **4a'** was not observed. Further increasing the amount of benzyl alcohol to 3.0 equivalents, led to lower selectivity to **4a** (entry 8). Replacing KOH with NaOH, KO^{t}Bu or NaO^{t}Bu did not improve the conversions (entries 9-11) where K-containing bases were found to be much more selective to double alkylated ketone product (**4a**) than their Na counterparts. It is worth noting that, an inert atmosphere seemed unnecessary (entry 12). When the reaction was carried out in a closed system 74% conversion of **4a** was achieved (entry 13) and the evolution of H_2 gas during the reaction

was detected by GC analysis (Figure S1). In the control experiments performed without catalyst or base, no double alkylated product was observed, indicating that catalyst and base are essential for the occurrence of the reaction (entries 14 and 15).

Table 1. Optimization of Reaction Conditions[a]



Entry	Cat. (mol%)	Base (mol%)	Time (h)	Conversion (%) [b]			
				4a	**4a'**	**5a**	**5a'**
1	**1a** (0.5)	KOH	16	61	21	13	5
2	**1b** (0.5)	KOH	16	53	22	21	4
3	**1c** (0.5)	KOH	16	67	31	-	-
4	**1d** (0.5)	KOH	16	71	27	-	-
5	**1d** (0.5)	KOH	20	73	26	-	-
6	**1d** (0.2)	KOH	20	72	12	13	-
7 [c]	**1d** (0.2)	KOH	20	81	-	18	-
8 [d]	**1d** (0.2)	KOH	20	45	10	30	8
9 [c]	**1d** (0.2)	NaOH	20	48	7	43	-
10 [c]	**1d** (0.2)	KO^{t}Bu	20	76	5	15	-
11 [c]	**1d** (0.2)	NaO^{t}Bu	20	31	14	36	17
12 [c,e]	**1d** (0.2)	KOH	20	79	3	17	-
13 [c,f]	**1d** (0.2)	KOH	20	74	8	18	-
14 [c]	-	KOH	20	-	-	-	19
15 [c]	**1d** (0.2)	-	20	-	-	-	-

[a]Reaction Conditions: **2a** (0.5 mmol), **3a** (1.0 mmol), **1a-d** (0.2-0.5 mol%), base (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, 16-20 h, under air. [b]Conversions were determined by ^{1}H

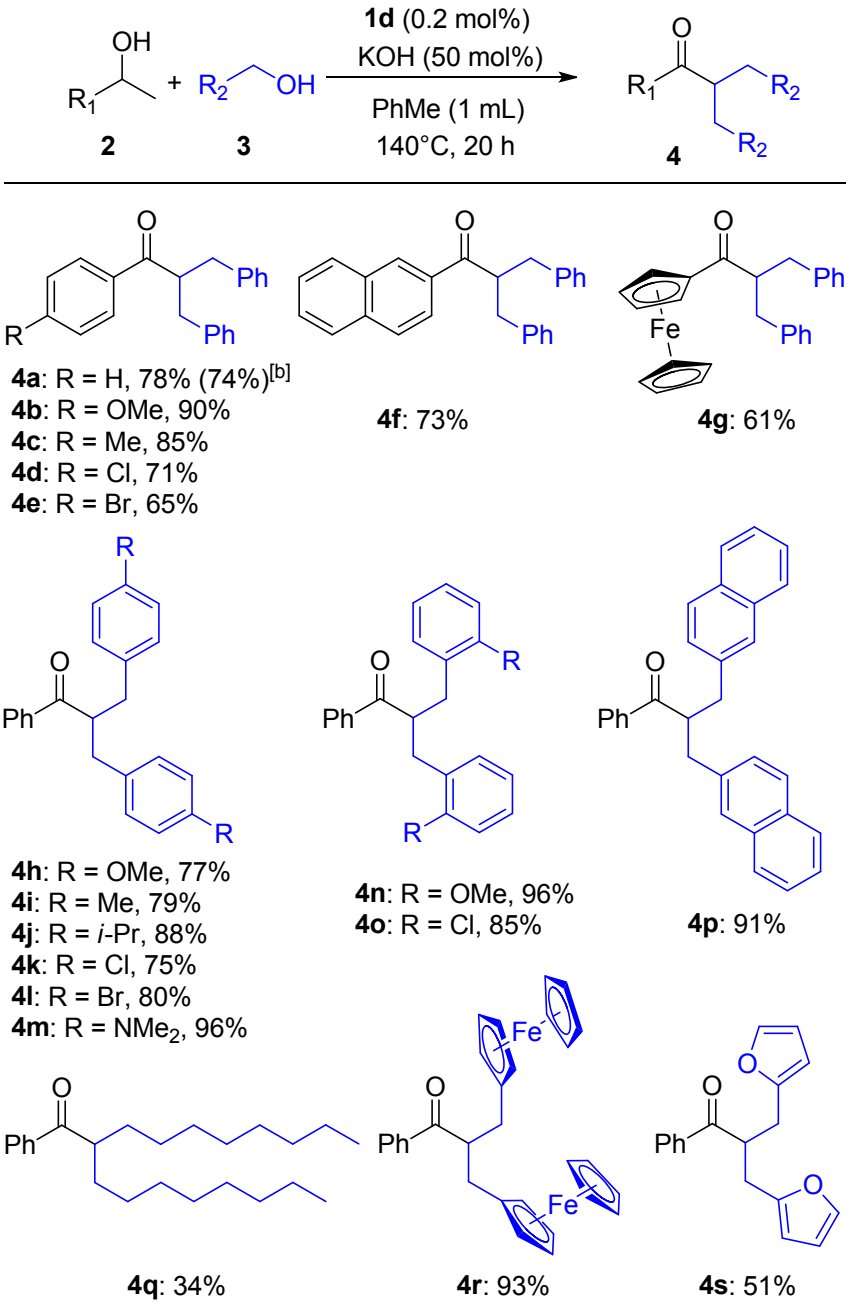
NMR analyses using 1,3,5-trimethoxybenzene as an internal standard. [c]**3a** (1.1 mmol). [d]**3a** (1.5 mmol). [e]Reaction was performed under an argon atmosphere. [f]Reaction was performed in a closed tube.

To examine the scope of the reaction, various secondary alcohols (**2**) were reacted with primary alcohols (**3**) under the optimized conditions (Table 1, entry 7) and the results are summarized in Scheme 3. Primarily, a range of *para*-substituted 1-phenylethanols decorated with –OMe, –Me, –Cl, or –Br substituents were benzylated to give α,α-disubstituted ketones (**4b-e**) in good yields (65-90%). When 1-phenylethanol (**2a**) was reacted with benzyl alcohol on 5.0 mmol scale, the corresponding product **4a** was isolated in 74% yield (1.10 g), highlighting the practicability of this reaction. Furthermore, 1-(2-naphthyl)ethanol (**2f**) and 1-(ferrocenyl)ethanol (**2g**) gave the corresponding products **4f** and **4g** in 73 and 61% yields, respectively. Nevertheless, application of electron deficient 1-(4-(trifluoromethyl)phenyl)ethanol did not result any desired product under standard catalytic conditions. Again, aliphatic secondary alcohol (2-heptanol) failed to give the desired product, and the number of undesired side products was observed, probably due to more than one reactive α-carbon exist in the molecule.

Next, we examined the scope of double alkylation reaction with respect to primary alcohols (**3**) (Scheme 3). The reaction of 1-phenylethanol (**2a**) with benzyl alcohols bearing 4–OMe, 4–Me, 4–*i*-Pr, 4–Cl, 4–Br, 4–NMe_2, 2–OMe, or 2–Cl substitution on the aryl ring and 2-naphthalenemethanol all resulted with high yields (75-96%) to give a series of disubstituted ketones (**4h-p**). In the case of 1-octanol as a primary alcohol, the corresponding ketone (**4q**) was isolated in 34% yield. This is due to conversion of 1-octanol to the Guerbet self-condensation product 2-octyl-1-octanol (observed by the NMR analysis of the crude reaction mixture) under the basic reaction conditions.[16b,17] Finally, the reaction of **2a** with ferrocenemethanol and 2-

furanmethanol afforded the desired products **4r** and **4s** in 93 and 51% isolated yields. However, applications of primary alcohols such as 4-(trifluoromethyl)benzyl alcohol, 2,4,6-trimethylbenzyl alcohol, 4-pyridinemethanol, 2-thiophenemethanol, 2-methoxyethanol, 2-phenoxyethanol, and cinnamyl alcohol were not successful and we observed only trace or no product conversion to the desired α,α-disubstituted ketones.

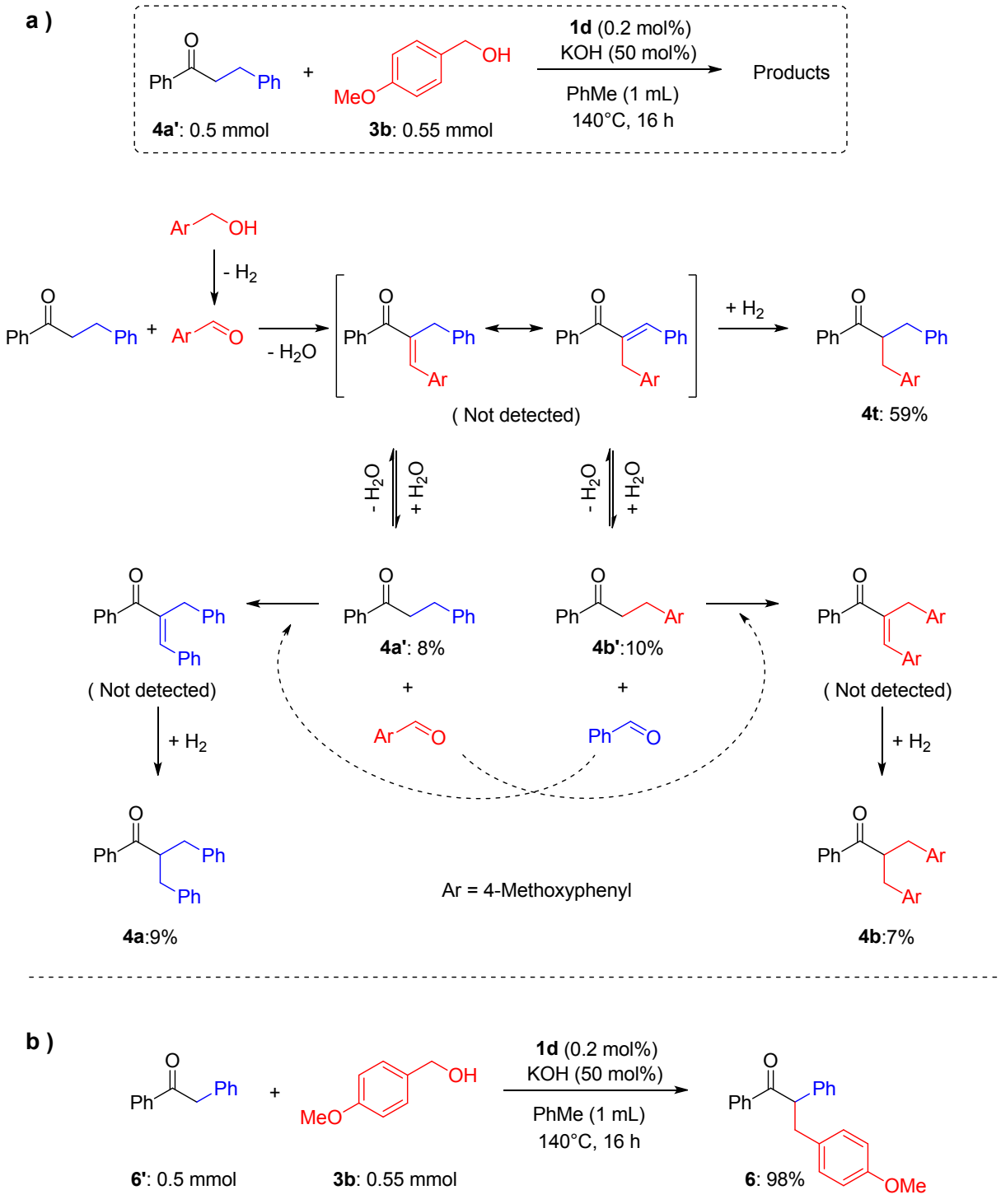
Scheme 3. Scope of Direct Synthesis of α,α-Disubstituted Ketones[a]



[a]Reaction Conditions: **2** (0.5 mmol), **3** (1.1 mmol), **1d** (0.2 mol%), KOH (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, 20 h, under air. Reported yields correspond to isolated pure compounds. [b]**2a** (5 mmol), **3a** (11 mmol), **1d** (0.2 mol%), KOH (1.25 mmol; 50 mol%), toluene (5 mL), 140 ºC, 20 h, under air.

Thereafter, we focused our studies on the one-pot sequential double alkylation of 1-phenylethanol using two different primary alcohols to obtain unsymmetrical dialkylated ketones (Scheme S3). When benzyl alcohol (1.0 equiv.) and 4-methoxybenzyl alcohol (**3b**) (1.1 equiv.) were introduced to 1-phenylethanol in sequence, unsymmetrical dialkylated product **4t** was obtained in 56% yield. Crucial to the success of this reaction is the selective monoalkylation in the first step and avoid the formation of dibenzylated ketone **4a**. In order to suppress this side reaction, we decreased the amount of KOH to 10 mol% in the first step and here, we were pleased to detect only the monoalkylated product **4a'** by means of NMR analysis after 4 h. A second addition of KOH (40 mol%), together with 4-methoxybenzyl alcohol, resulted with the formation **4t** in 56% isolated yield. Interestingly, when the other fractions of the column chromatography were analyzed by NMR, we also observed the formation of monoalkylated 3-(4-methoxyphenyl)-1-phenylpropan-1-one (**4b'**) (11%), symmetrical dialkylated **4a** (9%) and **4b** (6%) accompanied by **4a'** retrieved in 12% yield (Scheme S3). Similar product distributions were also observed when dihydrochalcone **4a'** (0.5 mmol) was reacted with 4-methoxybenzyl alcohol (**3b,** 0.55 mmol) in the presence of 0.2 mol% **1d** and 50 mol% KOH at 140 °C for 16 h (Scheme 4a). These interesting results can be explained by reversibility of the second aldol condensation of dihydrochalcone and 4-methoxybenzaldehyde in the presence of water generated in the reaction (Scheme 4a). Similar reversibility of the second aldol condensation product in the presence of water was previously reported by Renaud and co-workers in the case of benzyledene adduct.[12] To prove this observation, 1,2-diphenylethanone (**6'**) was reacted with **3b** under the same reaction conditions and the desired product 3-(4-methoxyphenyl)-1,2-diphenylpropan-1-one (**6**) was obtained in 98% yield as the sole product (Scheme 4b) where the isomerization of the aldol adduct is not possible.

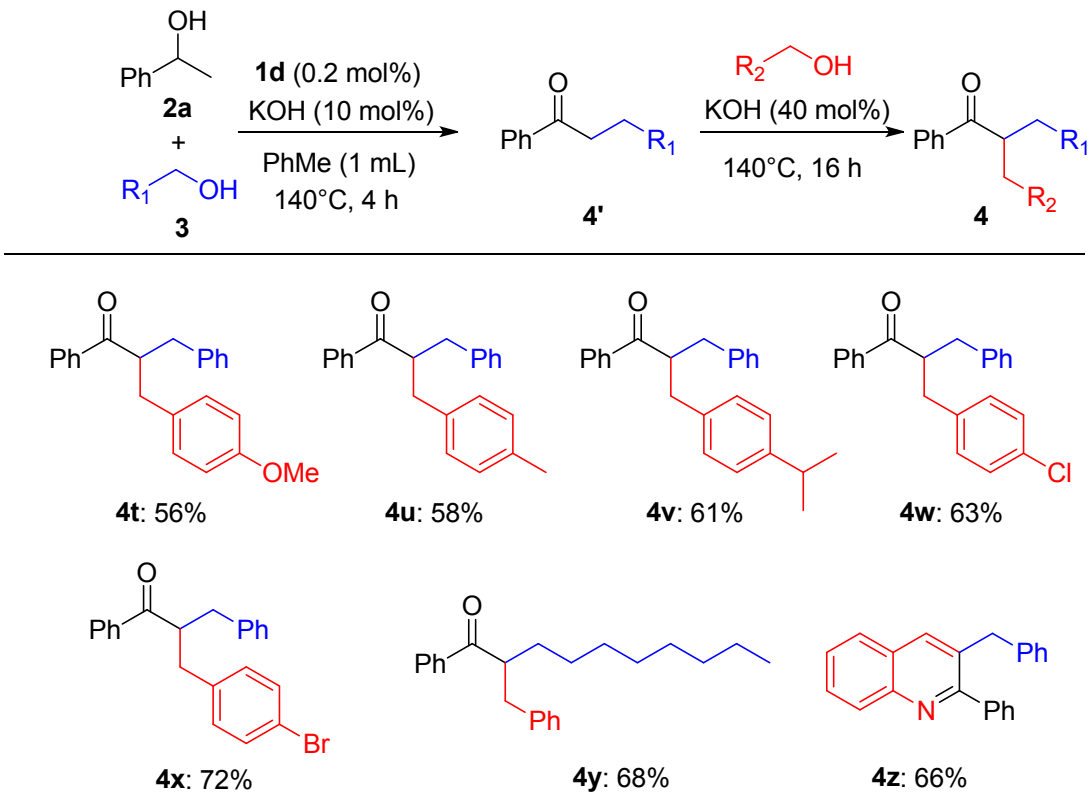
Scheme 4. Proposed Pathway for the Reversibility of the Second Aldol Condensation Step.



[a]Reaction Conditions: a) **4a'** (0.5 mmol), **3b** (0.55 mmol), **1d** (0.2 mol%), KOH (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, 16 h, under air. b) **6'** (0.5 mmol), **3b** (0.55 mmol), **1d** (0.2 mol%), KOH (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, 16 h, under air. Reported yields correspond to isolated pure compounds.

Other benzyl alcohols decorated with 4–Me, 4–*i*-Pr, 4–Cl, or 4–Br substitution on the aryl ring resulted in 58-72% yield to give corresponding unsymmetrical disubstituted ketones **4u-x** (Scheme 5). In the case of aliphatic alcohols, 1-octanol was subjected in the first step of the reaction, and then a sequential addition of benzyl alcohol resulted in the formation of **4y** in 68% isolated yield.[18] Finally, one-pot sequential addition of benzyl alcohol and 2-aminobenzyl alcohol to 1-phenylethanol afforded the quinoline derivative **4z** in 66% yield (Scheme 5).

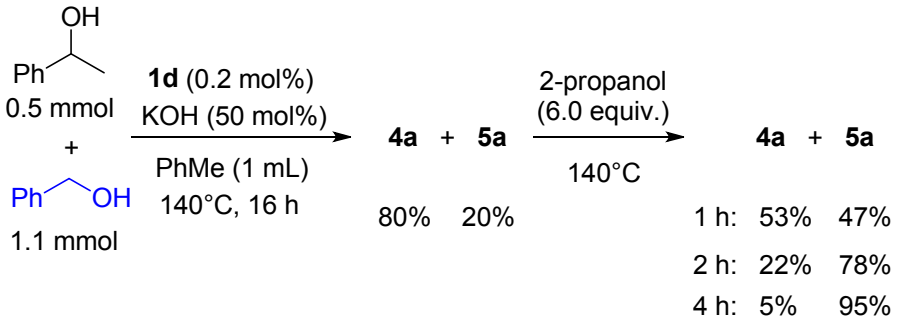
Scheme 5. Scope of One-Pot Sequential Synthesis of α,α-Disubstituted Ketones[a]



[a]Reaction Conditions: **2a** (0.5 mmol), **3** (0.5 mmol), **1d** (0.2 mol%), KOH (0.05 mmol; 10 mol%), toluene (1 mL), 140 ºC, 4 h, under air, then **3** (0.55 mmol), KOH (0.2 mmol; 40 mol%), 140 ºC, 16 h, under air. Reported yields correspond to isolated pure compounds.

Encouraged by our results, we envisioned that we could also improve the selectivity of the double alkylation reaction to the β,β-disubstituted alcohols (**5**) by adding an external hydrogen source at some point of the reaction. As an initial test reaction, 1-phenylethanol was reacted with benzyl alcohol under the optimized conditions (Table 1, entry 7) for 16 h and resulted with the formation of **4a** and **5a** with a ratio of 78:22. After addition of 2-propanol (6.0 equiv) into the reaction mixture, reduction of the keto group occurred due to hydrogen transfer from 2-propanol and the reaction resulted in the selective formation of **5a**[19] and the desired alcohol product could be isolated in 92% yield (Scheme 6). Ethanol and *n*-propanol as an external hydrogen sources led to lover selectivity to **5a** (ratio of **4a**:**5a**, ethanol, 60:40; *n*-propanol, 58:42).

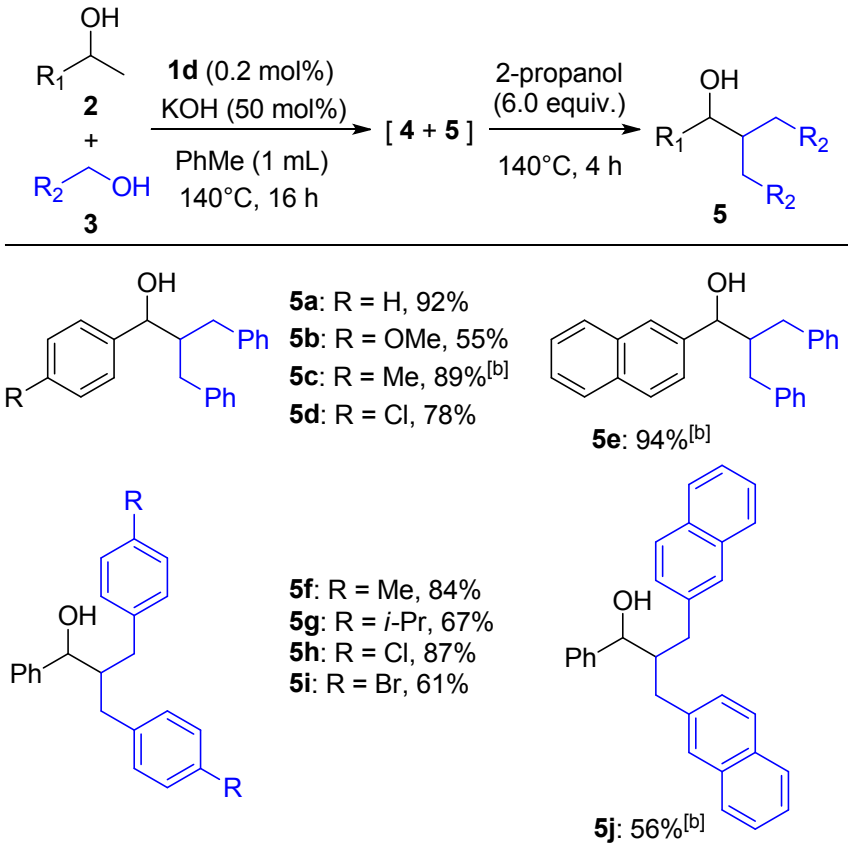
Scheme 6. Synthesis of β,β-Disubstituted Alcohols (^{1}H NMR conversions)



The one pot alkylation for the synthesis of β,β-disubstituted alcohols worked well when electronically different secondary alcohols (**2**) were employed with benzyl alcohol and resulted in **5a**-**e** in 55-92% isolated yields (Scheme 7). Next, applications of different benzyl alcohols (**3**) with 1-phenylethanol (**2a**) proceeded equally well, giving **5f-j** in 56-87% yields. Nevertheless, the addition of 2-propanol to the reaction mixture shown in Scheme S3, to obtain non-symmetrical β,β-disubstituted alcohol, resulted in an inseparable complex mixture where 14%

conversion to the desired product 2-benzyl-3-(4-methoxyphenyl)-1-phenylpropan-1-ol was detected via ^{1}H-NMR.

Scheme 7. Scope of β,β-Disubstituted Alcohols[a]



[a]Reaction Conditions: **2** (0.5 mmol), **3** (0.55 mmol), **1d** (0.2 mol%), KOH (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, 16 h, under air, then 2-propanol (3.0 mmol, 230 µL), 140 ºC, 4 h, under air. Reported yields correspond to isolated pure compounds [b]2-propanol was added after 12 h and the reaction was heated for additional 8 h.

Further, to investigate the reaction mechanism, initially we investigated the time profile of the model reaction between 1-phenyl ethanol (**2a**) with benzyl alcohol (**3a**) under the optimized conditions (Table 1, entry 7) (Figure 1). The results revealed that the reaction is very fast and resulted with the full consumption of 1-phenylethanol mainly into monoalkylated intermediates **4a'** (34%) and **5a'** (51%) along with a small amount of double alkylated **4a** (12%)

and **5a** (3%) within 30 min. These monoalkylated intermediates were consumed over time and led to the production of double alkylated products **4a** (68%) and **5a** (29%) within 6 h. After 6 h, the double alkylated alcohol **5a** slowly undergoes dehydrogenation to form **4a**. This final dehydrogenation step was also confirmed by independent experiments where the alcohol product **5a** gradually dehydrogenated to **4a** during the progress of the reaction and 94% conversion to **4a** was achieved within 8 h (Scheme 8). These observations are consistent with previous results.[8b,14]

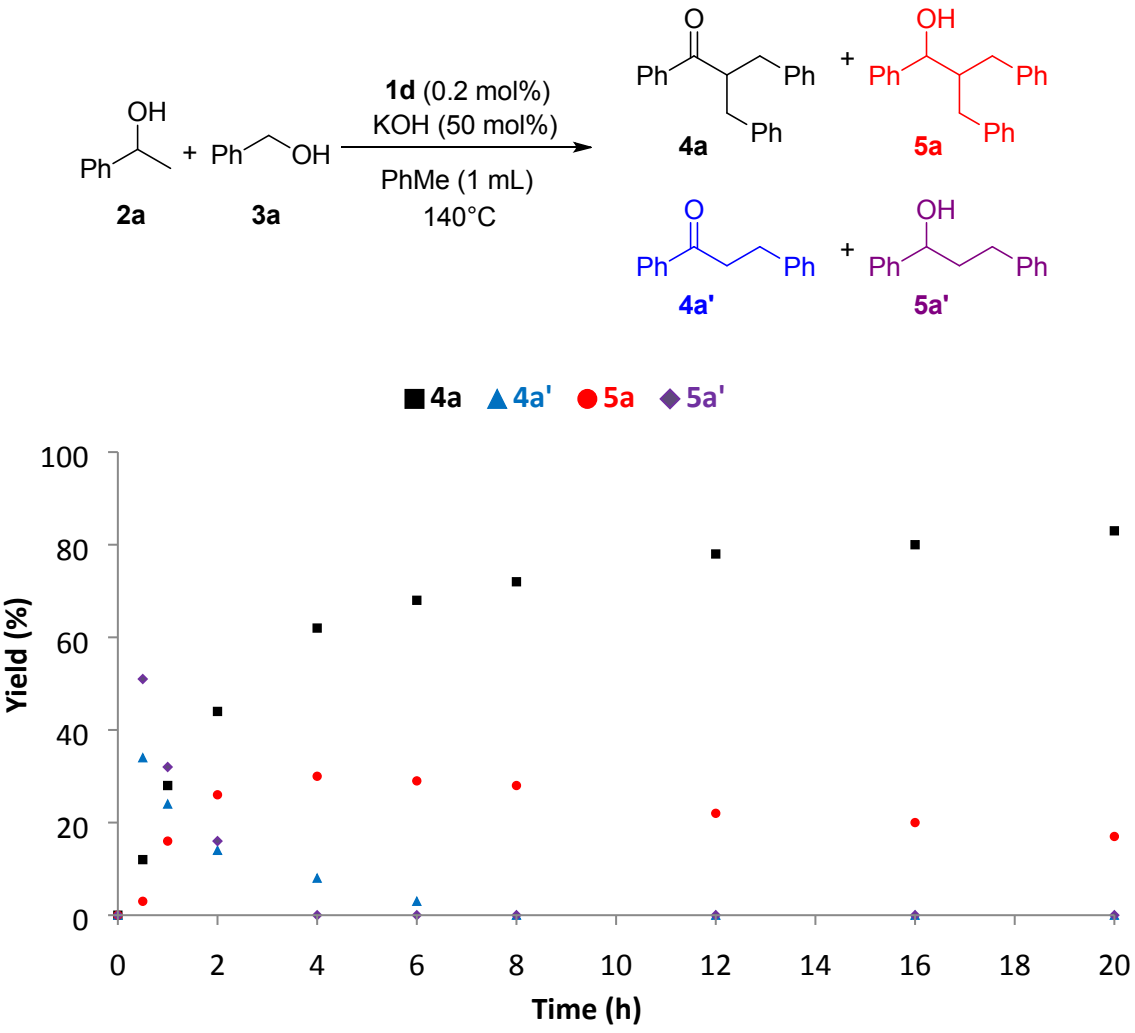
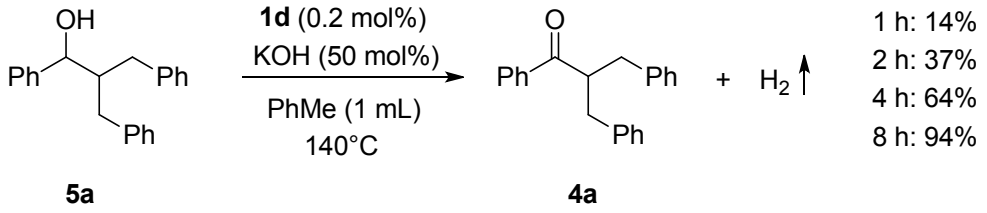


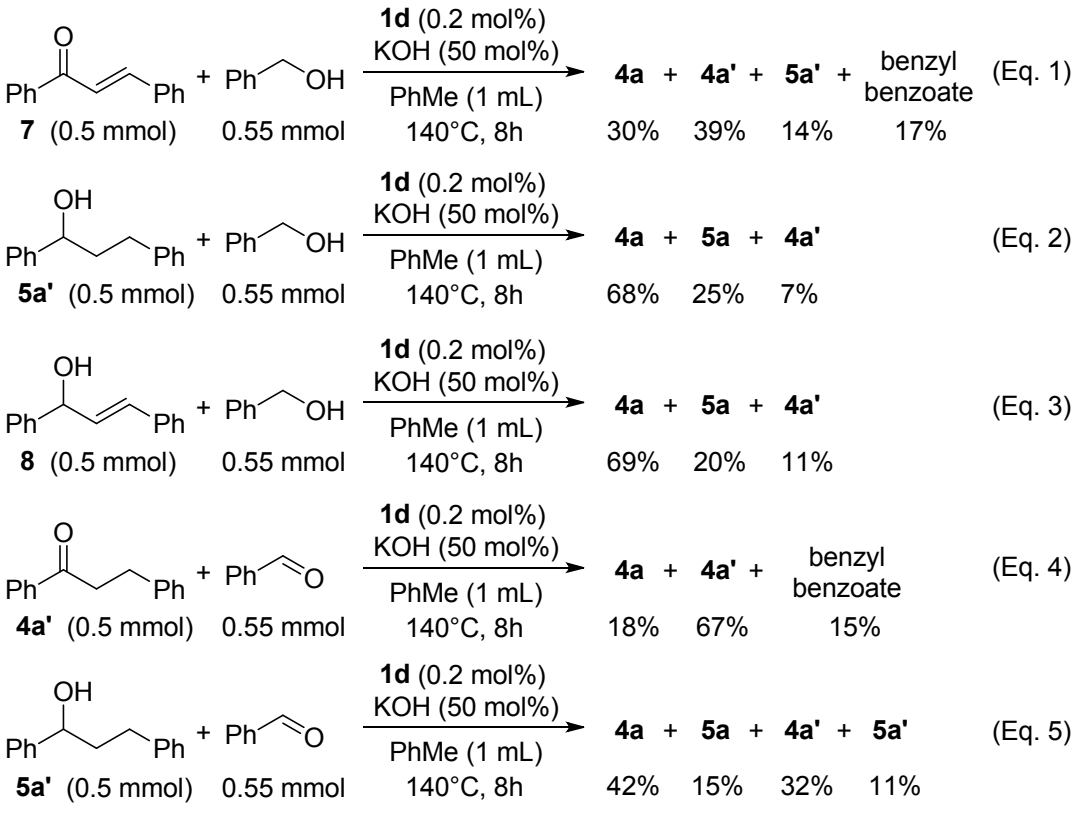
Figure 1. Time course of the reaction between **2a** and **3a**. Reaction Conditions: **2a** (0.5 mmol), **3a** (0.55 mmol), **1d** (0.2 mol%), KOH (0.25 mmol; 50 mol%), toluene (1 mL), 140 ºC, under air. Conversions were determined by ^{1}H NMR analyses of the independent reaction mixtures using 1,3,5-trimethoxybenzene as internal standard.

Scheme 8. Catalytic dehydrogenation of **5a** to **4a** (^{1}H NMR conversions)



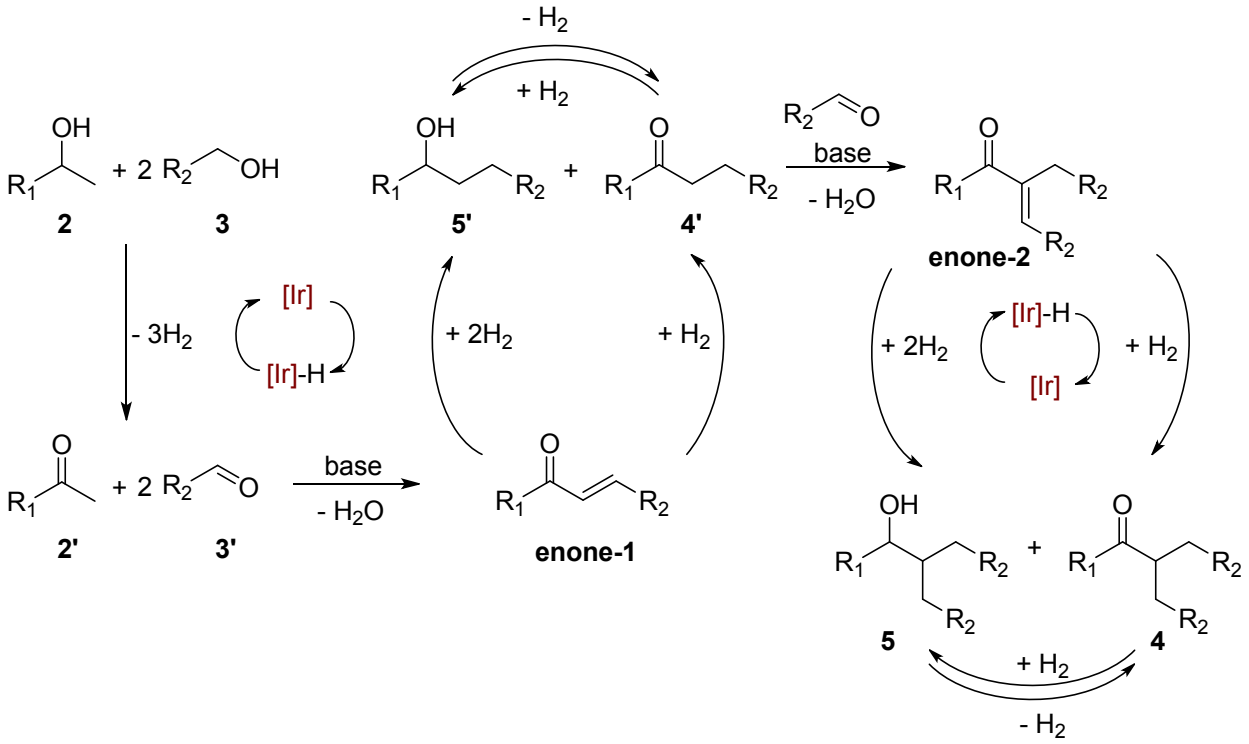
Next, we investigated the reaction of possible intermediates with benzyl alcohol or benzaldehyde under the optimized reaction conditions for 8 h (Scheme 9). When the chalcone (**7**) was reacted with benzyl alcohol, 30% conversion to **4a** was achieved (Eq. 1). Here, reduction of the **7** to **4a'** (39%) and **5a'** (14%) was also observed by using the hydrogen released from the dehydrogenation of benzyl alcohol along with the formation of 17% benzyl benzoate as a self-condensation product (Eq. 1). Reaction of 1,3-diphenylpropan-1-ol (**5a'**) with benzyl alcohol resulted with 68% **4a**, 25% **5a** and 11% **4a'** (Eq. 2). Similar product distribution was observed when 1,3-diphenylprop-2-en-1-ol (**8**) reacted with benzyl alcohol, possibly *via* the base promoted isomerization of the allylic alcohol **8** into **4a'**,[20] followed by the second alkylation of this intermediate in the presence of catalyst **1d** (Eq. 3). In addition, no accumulation of the second aldol condensation product between dihydrochalcone and benzaldehyde was observed where 18% conversion to **4a** was achieved and 67% dihydrochalcone was recovered (Eq. 4). Notably, the reaction of 1,3-diphenylpropan-1-ol with benzaldehyde also resulted in the formation of **4a** in 42%, also providing evidence for the participation of secondary alcohol as a hydrogen source (Eq. 5).

Scheme 9. Control Experiments



On the basis of these experimental evidences, a catalytic cycle for double alkylation of secondary alcohols with primary alcohols catalyzed by **1** is proposed in Scheme 10. The first part of the mechanism has been outlined in our reports[14] which involves the formation of **4'** *via* acceptorless dehydrogenative cross-coupling of **2** and **3** catalyzed by in situ generated transient iridium hydride.[14a] Then, a base mediated second cross-aldol condensation reaction between **4'** and **3'** may produces **enone-2**. No accumulation of this second α,β-unsaturated ketone was observed during the whole course of the reaction, which suggests that the hydrogenation of this intermediate to the final products **4** and **5** by iridium hydride was very fast. Finally, hydrogenation or dehydrogenation between **4** and **5** takes place in the presence of catalyst.

Scheme 10. Proposed Mechanism for the Ir-Catalyzed Synthesis of Branched Ketones and Alcohols



CONCLUSIONS

In conclusion, we have developed an efficient catalytic cross-coupling of secondary alcohols and primary alcohols under borrowing hydrogen conditions to give rise to a variety of branched ketones and alcohols. To the best of our knowledge, the present approach is the first example for the direct or one-pot sequential double alkylation of secondary alcohols with primary alcohols. Furthermore, selectivity of the reaction to branched ketones or alcohols can be controlled by a single catalyst with slightly modified reaction conditions. Use of easy-to-handle alcohols as starting materials and performing the reactions under aerobic conditions will be beneficial to broaden the scope of borrowing hydrogen catalysis.

EXPERIMENTAL SECTION

General Information. Experiments involving air or moisture sensitive reagents were performed under an atmosphere of dry argon using standard Schlenk techniques. Unless otherwise specified, all reagents were obtained commercially and used without further purification. Imidazolium salt $\mathbf{L_a}$ and complexes **1a** were synthesized according to published procedure and the physical properties and spectroscopic data of the obtained compound are in accordance with previous report.[14a] NMR spectra were recorded on Varian AS 400 Mercury NMR spectrometer at 25 ºC and reported in units of parts per million (ppm) relative to tetramethyl silane (δ = 0 ppm), $CDCl_3$ (δ = 7.26 ppm for ^1H and δ = 77.0 ppm for ^{13}C NMR) or DMSO-d_6 (δ = 2.50 ppm for ^1H and δ = 39.5 ppm for ^{13}C NMR). Melting points measured on Gallenkamp electrothermal melting point apparatus without correction. HRMS were carried out on Agilent 6530 Accurate-Mass Q-TOF mass spectrometer at Atatürk University East Anatolia High Technology Application and Research Center. Gas chromatography (GC) analyses were performed on an Agilent 6890N GC instrument with a HP-5 Agilent 19091J-413 column. GC analysis for H_2 evolution experiment was performed on an Agilent 7890A GC instrument and gas products were identified according to standard gas mixture (Agilent P/N 5190-0519).

Synthesis of imiazolium salts $\mathbf{L_b}$. A mixture of 5,6-dichloro-1*H*-benzimidazole (374 mg, 2 mmol) and K_2CO_3 (608 mg, 4.4 mmol) was suspended in CH_3CN (5 mL) and stirred at ambient temperature for 1 h. 4-(Trifluoromethyl)benzyl bromide (478 mg, 2 mmol) was then added to the suspension and the reaction mixture was stirred under reflux conditions for 12 h. The solution was filtered-off and the solvent was removed under reduced pressure. The resulting crude product was dissolved in toluene (5 mL), and a second portion of 4-(Trifluoromethyl)benzyl bromide (478 mg, 2 mmol) was added and stirred at reflux conditions for 12 h. The colorless

solid that separated out after cooling to room temperature was filtered off and washed with Et_2O (2×10 mL) and dried under reduced pressure (841 mg, 72%). M.p. = 268 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = 10.29 (s, 1 H), 8.57 (s, 2 H), 7.78 (s, 8 H), 5.92 (s, 4 H). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = 145.9, 138.6, 131.1, 129.8, 129.6 (q, J(C,F) = 31.4 Hz), 126.2 (q, J(C,F) = 3.8 Hz), 124.4 (q, J(C,F) = 272.4 Hz), 116.3, 50.1. ^{19}F NMR (376 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = – 61.2. HRMS (APCI) *m/z*: $[M–Br]^+$ calcd for $C_{23}H_{15}Cl_2F_6N_2$ 503.0516; found: 503.0523, Δ = + 1.4 ppm.

Synthesis of imiazolium salt L_c. A mixture of 4,5-diphenyl-1*H*-imidazole (441 mg, 2 mmol) and K_2CO_3 (608 mg, 4.4 mmol) was suspended in CH_3CN (5 mL) and stirred at ambient temperature for 1 h. 4-(Trifluoromethyl)benzyl chloride (389 mg, 2 mmol) was then added to the suspension and the reaction mixture was stirred under reflux conditions for 12 h. The solution was filtered-off and the solvent was removed under reduced pressure. The resulting crude product was dissolved in toluene (5 mL), and a second portion of 4-(Trifluoromethyl)benzyl chloride (389 mg, 2 mmol) was added and stirred at reflux conditions for 12 h. The colorless solid that separated out after cooling to room temperature was filtered off and washed with Et_2O (2×10 mL) and dried under reduced pressure (1.07 g, 93%). M.p. = 274 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = 9.79 (s, 1 H), 7.67 (d, J = 8.4 Hz, 4 H), 7.41-7.26 (m, 14 H), 5.55 (s, 4 H). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = 139.1, 137.8, 132.2, 131.2, 130.6, 129.2 (q, J(C,F) = 31.8 Hz), 129.2, 129.1, 125.9 (q, J(C,F) = 4.0 Hz), 125.8, 124.4 (q, J(C,F) = 272.6 Hz), 50.4. ^{19}F NMR (376 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = – 61.2. HRMS (APCI) *m/z*: $[M–Cl]^+$ calcd for $C_{31}H_{23}F_6N_2$ 537.1765; found: 537.1769, Δ = + 0.7 ppm.

Synthesis of imiazolium salt L_d. A mixture of 4,5-bis(4-chlorophenyl)-1*H*-imidazole (578 mg, 2 mmol) and K_2CO_3 (608 mg, 4.4 mmol) was suspended in CH_3CN (5 mL) and stirred at

ambient temperature for 1 h. 4-(Trifluoromethyl)benzyl bromide (478 mg, 2 mmol) was then added to the suspension and the reaction mixture was stirred under reflux conditions for 12 h. The solution was filtered-off and the solvent was removed under reduced pressure. The resulting crude product was dissolved in toluene (5 mL), and a second portion of 4-(Trifluoromethyl)benzyl bromide (478 mg, 2 mmol) was added and stirred at reflux conditions for 12 h. The colorless solid that separated out after cooling to room temperature was filtered off and washed with Et_2O (2×10 mL) and dried under reduced pressure (1.21 g, 88%). M.p. = 271 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = 9.70 (s, 1 H), 7.68 (d, J = 8.0 Hz, 4 H), 7.40 (t, J = 7.6 Hz, 8 H), 7.32 (d, J = 8.4 Hz, 4 H), 5.56 (s, 4 H). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6, TMS): δ = 138.9, 137.9, 135.7, 133.1, 131.5, 129.4, 129.2 (q, J(C,F) = 32.2 Hz), 129.2, 125.9 (q, J(C,F) = 4.0 Hz), 124.4 (q, J(C,F) = 272.6 Hz), 123.9, 50.5. ^{19}F NMR (376 MHz, DMSO-d_6, TMS, 25ºC, ppm): δ = – 61.2. HRMS (APCI) *m/z*: $[M–Br]^+$ calcd for $C_{31}H_{21}Cl_2F_6N_2$ 605.0986; found: 605.0988, Δ = + 0.3 ppm.

Synthesis of NHC–Ir^{I} complexes (1a-d). Under an argon atmosphere, a mixture of $\mathbf{L_{a-d}}$ (0.5 mmol) and Ag_2O (58 mg, 0.25 mmol) was suspended in degassed CH_2Cl_2 (10 mL) and stirred at ambient temperature for 1 h shielded from light. $[IrCl(COD)]_2$ (168 mg, 0.25 mmol) was then added to the suspension and the reaction mixture was stirred at ambient temperature for more 12 h. The resulting suspension was filtered over Celite®. The remaining solid was washed with CH_2Cl_2 (2×5 mL) and the solvent of the filtrate was evaporated. The residue was purified by column chromatography on silica gel using dichloromethane and hexane (6:4) mixture as eluent to give pure complex as a yellow solid.

1b. Following the general procedure, the title product was obtained as a yellow solid using silica gel column chromatography eluting with dichloromethane and hexane (6:4) mixture: yield 235

mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 7.66 (d, *J* = 8.4 Hz, 4 H), 7.55 (d, *J* = 8.4 Hz, 4 H), 7.05 (s, 2 H), 6.38 (d, *J* = 15.6 Hz, 2 H), 5.89 (d, *J* = 16.0 Hz, 2 H), 4.85 (t, *J* = 2.8 Hz, 2 H), 2.86 (t, *J* = 2.8 Hz, 2 H), 2.25-2.16 (m, 2 H), 2.12-2.03 (m, 2 H), 1.86-1.79 (m, 2 H), 1.67-1.61 (m, 2 H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 196.5, 138.7, 133.9, 130.6 (q, *J*(C,F) = 32.4 Hz), 127.9, 127.5, 126.5 (q, *J*(C,F) = 270.0 Hz), 126.1 (q, *J*(C,F) = 2.8 Hz), 112.1, 89.9, 53.6, 52.2, 33.3, 29.1. ^{19}F NMR (376 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = – 62.7. HRMS (APCI) *m/z*: $[M–Cl]^+$ calcd for $C_{31}H_{26}Cl_2F_6IrN_2$ 803.1006; found 803.0983, Δ = – 2.9 ppm.

1c. Following the general procedure, the title product was obtained as a yellow solid using silica gel column chromatography eluting with dichloromethane and hexane (6:4) mixture: yield 336 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 7.40 (d, *J* = 8.4 Hz, 4 H), 7.20-7.16 (m, 6 H), 7.09 (t, *J* = 7.8 Hz, 4 H), 6.88 (d, *J* = 8.0 Hz, 4 H), 6.20 (d, *J* = 15.2 Hz, 2 H), 5.59 (d, *J* = 15.2 Hz, 2 H), 4.70 (t, *J* = 2.8 Hz, 2 H), 2.92 (t, *J* = 2.8 Hz, 2 H), 2.21-2.12 (m, 2 H), 2.09-2.00 (m, 2 H), 1.76-1.70 (m, 2 H), 1.61-1.51 (m, 2 H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 181.7, 158.8, 140.6, 132.1, 130.4, 129.4 (q, *J*(C,F) = 32.4 Hz), 128.8, 128.3, 127.9, 127.9, 125.1 (q, *J*(C,F) = 2.8 Hz), 124.0 (d, *J*(C,F) = 270.0 Hz), 114.0, 85.9, 52.8, 52.3, 33.4, 29.3. ^{19}F NMR (376 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = – 62.6. HRMS (APCI) *m/z*: $[M–Cl]^+$ calcd for $C_{39}H_{34}F_6IrN_2$ 837.2255; found 837.2284, Δ = + 3.5 ppm.

1d. Following the general procedure, the title product was obtained as a yellow solid using silica gel column chromatography eluting with dichloromethane and hexane (6:4) mixture: yield 362 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 7.44 (d, *J* = 8.4 Hz, 4 H), 7.22 (d, *J* = 8.0 Hz, 4 H), 7.09 (d, *J* = 8.4 Hz, 4 H), 6.79 (d, *J* = 8.4 Hz, 4 H), 6.22 (d, *J* = 15.2 Hz, 2 H), 5.56 (d, *J* = 15.6 Hz, 2 H), 4.72 (t, *J* = 2.8 Hz, 2 H), 2.91 (t, *J* = 2.8 Hz, 2 H), 2.21-2.12 (m, 2 H),

2.09-2.01 (m, 2 H), 1.78-1.70 (m, 2 H), 1.62-1.56 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = 182.8, 140.3, 135.4, 131.5, 131.3, 129.8 (q, *J*(C,F) = 32.7 Hz), 128.8, 127.9, 126.0, 125.3 (q, *J*(C,F) = 3.8 Hz), 124.0 (d, *J*(C,F) = 280.0 Hz), 86.5, 52.9, 52.4, 33.4, 29.3. ^{19}F NMR (376 MHz, $CDCl_3$, TMS, 25ºC, ppm): δ = – 62.7. HRMS (APCI) *m/z*: $[M–Cl]^+$ calcd for $C_{39}H_{32}Cl_2F_6IrN_2$ 905.1476; found 905.1454, Δ = – 2.4 ppm.

General optimization procedure for the direct synthesis of α,α-disubstituted ketones. In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added base (0.25 mmol, 0.5 equiv.), 1-phenylethanol (0.5 mmol), benzyl alcohol (1.1 mmol) and a solution of **1** (0.001-0.0025 mmol, 0.2-0.5 mol%) in toluene (1 mL). The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 16-20 h. Then the reaction mixture was cooled to ambient temperature, 2 M HCl (2 mL) and ethyl acetate (4 mL) were added to it, and then the solution was extracted with ethyl acetate (2×5 mL), the combined organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was submitted for ^{1}H NMR analysis to calculate the yield by using 1,3,5-trimethoxybenzene as internal standard.

Procedure for the hydrogen evolution experiment. In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (0.25 mmol, 0.5 equiv.) 1-phenylethanol (0.5 mmol), benzyl alcohol (1.1 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL). The tube was then sealed with a septum and vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 20 h. It was then cooled to room temperature. Gas samples were taken with a gas-tight syringe, and analyzed on a Agilent 7890A GC instrument. Hydrogen gas was detected with a thermal conductivity detector referencing against standard gas with a known concentration of hydrogen (Figure S13). Then to the resulting reaction mixture 2 M HCl (2 mL) and ethyl acetate (4 mL) were added to it, and then the solution was extracted with ethyl acetate (2×5 mL),

the combined organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was submitted for ^1H NMR analysis to calculate the yield by using 1,3,5-trimethoxybenzene as internal standard.

General procedure for the direct synthesis of α,α-disubstituted ketones (4a-s). In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (14 mg, 0.25 mmol, 0.5 equiv.), secondary alcohol (0.5 mmol), primary alcohol (1.1 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL) under air atmosphere. The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 20 h. Then the reaction mixture was cooled to ambient temperature and purified by silica gel column chromatography using hexane and dichloromethane (6:4) mixture as eluent to afford the desired ketone.

2-Benzyl-1,3-diphenylpropan-1-one (4a).[3a,9a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 117 mg, 78%. Colorless solid (m.p.: 82 ^oC). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.76 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 4H), 7.19-7.14 (m, 6H), 4.15-4.03 (m, 1H), 3.18 (dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz, 2H), 2.85 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.3, 139.5, 137.4, 132.7, 129.0, 128.4, 128.4, 128.1, 126.3, 50.5, 38.3.

2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-one (4b).[7a,9a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 149 mg, 90%. Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.76 (d, J = 9.2 Hz, 2H), 7.25-7.21 (m, 5H), 7.16 (d, J = 7.6 Hz, 5H), 6.82 (d, J = 8.8 Hz, 2H), 4.03-3.96 (m, 1H), 3.80 (s, 3H), 3.15 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H),

2.82 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 201.6, 163.3, 139.7, 130.4, 130.4,129.0, 128.4, 126.2, 113.6, 55.4, 49.9, 38.4.

2-Benzyl-3-phenyl-1-(p-tolyl)propan-1-one (4c).[21] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 134 mg, 85%. Colorless solid (m.p.: 76 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.68 (d, J = 8.4 Hz, 2H), 7.26-7.22 (m, 5H), 7.18-7.14 (m, 7H), 4.07-4.00 (m, 1H), 3.16 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 2H), 2.82 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 2H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.8, 143.6, 139.6, 134.9, 129.2, 129.0, 128.4, 128.3, 126.2, 50.3, 38.2, 21.6.

2-Benzyl-1-(4-chlorophenyl)-3-phenylpropan-1-one (4d). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 119 mg, 71%. Colorless solid (m.p.: 56 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.60 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.22 (t, J = 7.2 Hz, 4H), 7.17-7.13 (m, 5H), 4.00-3.93 (m, 1H), 3.13 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H), 2.85 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.4, 139.3, 139.2, 135.9, 129.4, 128.9, 128.7, 128.5, 126.4, 50.7, 38.5. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{20}ClO$ 335.1203; found: 335.1198, Δ = – 1.5 ppm.

2-Benzyl-1-(4-bromophenyl)-3-phenylpropan-1-one (4e). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 123 mg, 65%. Colorless solid (m.p.: 70 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.51 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.21 (t, J = 7.0 Hz, 4H), 7.16-7.11 (m, 6H), 3.98-3.91 (m, 1H), 3.11 (dd, J_1 = 13.6 Hz, J_2 = 8.4 Hz, 2H), 2.83 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.6, 139.2,

136.3, 131.7, 129.5, 128.9, 128.5, 127.9, 126.4, 50.7, 38.5. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{20}BrO$ 379.0698; found: 379.0699, Δ = + 0.3 ppm.

2-Benzyl-1-(naphthalen-2-yl)-3-phenylpropan-1-one (4f). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 128 mg, 73%. Colorless solid (m.p.: 102 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.17 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.82 (q, *J* = 6.1 Hz, 3H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.27-7.22 (m, 8H), 7.18-7.14 (m, 2H), 4.26-4.19 (m, 1H), 3.26 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H), 2.95 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.3, 139.6, 135.4, 134.8, 132.4, 129.8, 129.6, 129.1, 128.5, 128.4, 128.3, 127.7, 126.6, 126.3, 124.0, 50.7, 38.6. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{26}H_{23}O$ 351.1749; found: 351.1746, Δ = – 0.9 ppm.

2-Benzyl-1-(ferrocenyl)-3-phenylpropan-1-one (4g). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 125 mg, 61%. Yellow solid (m.p.: 154 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.16 (m, 10H), 4.67 (t, *J* = 1.6 Hz, 2H), 4.41 (t, *J* = 1.6 Hz, 2H), 3.74 (s, 5H), 3.44-3.37 (m, 1H), 3.13 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 2H), 2.66 (dd, J_1 = 13.4 Hz, J_2 = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 205.4, 140.1, 129.3, 128.4, 126.4, 79.0, 72.1, 69.3, 69.2, 53.4, 37.7. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{26}H_{25}FeO$ 409.1255; found: 409.1259, Δ = + 1.0 ppm.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (4h). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 139 mg, 77%. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* =

7.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 4H), 6.76 (d, J = 8.8 Hz, 4H), 3.99-3.92 (m, 1H), 3.74 (s, 6H), 3.07 (dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz, 2H), 2.76 (dd, J_1 = 13.8 Hz, J_2 = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.6, 158.0, 137.5, 132.7, 131.6, 129.9, 128.4, 128.1, 113.8, 55.2, 50.9, 37.3. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}O_3$ 361.1804; found: 361.1800, Δ = – 1.1 ppm.

2-(4-Methylbenzyl)-1-phenyl-3-(p-tolyl)propan-1-one (4i). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 130 mg, 79%. Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.82 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 6.8 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.08 (q, J = 4.9 Hz, 8H), 4.09-4.02 (m, 1H), 3.16 (dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz, 2H), 2.82 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 2H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.4, 137.5, 136.5, 135.7, 132.7, 129.1, 128.9, 128.5, 128.2, 50.6, 37.7, 21.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}O$ 329.1905; found: 329.1900, Δ = – 1.5 ppm.

2-(4-Isopropylbenzyl)-3-(4-isopropylphenyl)-1-phenylpropan-1-one (4j). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 169 mg, 88%. Colorless solid (m.p.: 77 ^oC). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.09 (s, 8H), 4.06-3.99 (m, 1H), 3.13 (dd, J_1 = 13.8 Hz, J_2 = 8.0 Hz, 2H), 2.90-2.80 (m, 4H), 1.21 (d, J = 7.2 Hz, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.6, 146.7, 137.6, 136.9, 132.6, 128.9, 128.3, 128.2, 126.4, 50.5, 37.8, 33.7, 24.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{28}H_{33}O$ 385.2531; found: 385.2529, Δ = – 0.5 ppm.

2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-1-phenylpropan-1-one (4k). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with

hexane and dichloromethane (6:4) mixture: yield 139 mg, 75%. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.72 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 8.4 Hz, 4H), 7.06 (d, J = 8.0 Hz, 4H), 3.98-3.91 (m, 1H), 3.09 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H), 2.75 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.6, 137.7, 137.1, 133.1, 132.2, 130.3, 128.6, 128.5, 128.0, 50.2, 37.5. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{19}Cl_2O$ 369.0813; found: 369.0818, Δ = + 1.4 ppm.

2-(4-Bromobenzyl)-3-(4-bromophenyl)-1-phenylpropan-1-one (4l). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 183 mg, 80%. Colorless solid (m.p.: 72 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.72 (d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.38-7.31 (m, 6H), 7.00 (d, J = 8.4 Hz, 4H), 3.97-3.90 (m, 1H), 3.07 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H), 2.73 (dd, J_1 = 13.8 Hz, J_2 = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.5, 138.2, 137.0, 133.1, 131.5, 130.7, 128.6, 128.0, 120.2, 50.0, 37.5. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{19}Br_2O$ 456.9803; found: 456.9803, Δ = 0 ppm.

2-(4-(Dimethylamino)benzyl)-3-(4-(dimethylamino)phenyl)-1-phenylpropan-1-one (4m). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 186 mg, 96%. Yellow solid (m.p.: 118 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.77 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.01 (d, J = 8.8 Hz, 4H), 6.61 (d, J = 8.8 Hz, 4H), 3.96-3.89 (m, 1H), 3.02 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 2H), 2.87 (s, 12H), 2.71 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 204.0, 149.2, 137.6, 132.5, 129.6, 128.3, 128.2, 127.9, 112.9, 51.1, 40.8, 37.1. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{26}H_{31}N_2O$ 387.2436; found: 387.2437, Δ = + 0.3 ppm.

2-(2-Methoxybenzyl)-3-(2-methoxyphenyl)-1-phenylpropan-1-one (4n). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 173 mg, 96%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 4H), 6.81-6.74 (m, 4H), 4.30-4.23 (m, 1H), 3.72 (s, 6H), 3.12 (dd, J_1 = 13.2 Hz, J_2 = 7.6 Hz, 2H), 2.82 (dd, J_1 = 13.4 Hz, J_2 = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.8, 157.5, 132.4, 130.9, 128.4, 128.2, 128.1, 127.4, 120.3, 110.1, 55.0, 45.7, 33.5. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}O_3$ 361.1804; found: 361.1801, Δ = – 0.8 ppm.

2-(2-Chlorobenzyl)-3-(2-chlorophenyl)-1-phenylpropan-1-one (4o). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 157 mg, 85%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 7.30-7.26 (m, 4H), 7.17 (t, J = 4.6 Hz, 2H), 7.07-7.04 (m, 4H), 4.51-4.43 (m, 1H), 3.21 (dd, J_1 = 13.4 Hz, J_2 = 8.4 Hz, 2H), 3.03 (dd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.5, 137.4, 136.8, 134.1, 132.9, 131.8, 129.5, 128.3, 128.0, 127.9, 126.7, 45.1, 36.6. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{19}Cl_2O$ 369.0813; found: 369.0812, Δ = – 0.3 ppm.

3-(Naphthalen-2-yl)-2-(naphthalen-2-ylmethyl)-1-phenylpropan-1-one (4p). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 182 mg, 91%. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.82 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 8.8 Hz, 4H), 7.43 (t, J = 7.6 Hz, 4H), 7.35-7.26 (m, 7H), 7.14 (t, J = 7.8 Hz, 2H), 4.42-4.35 (m, 1H), 3.59 (dd, J_1 = 13.6 Hz, J_2 = 8.0 Hz, 2H), 3.40 (dd, J_1 = 14.0 Hz, J_2 = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6

MHz) δ (ppm): 204.3, 137.5, 135.4, 133.9, 132.7, 131.7, 128.9, 128.2, 127.9, 127.6, 127.2, 125.9, 125.4, 125.3, 123.3, 48.2, 35.7. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{30}H_{25}O$ 401.1905; found: 401.1904, Δ = – 0.3 ppm.

2-Octyl-1-phenyldecan-1-one (4q). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 57 mg, 34%. Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.95 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 3.44-4.37 (m, 1H), 1.79-1.71 (m, 2H), 1.53-1.45 (m, 2H), 1.36-1.22 (m, 24H), 0.86 (t, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 204.8, 137.8, 132.7, 128.5, 128.1, 46.2, 32.5, 31.8, 29.8, 29.4, 29.2, 27.6, 22.6, 14.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{24}H_{41}O$ 345.3157; found: 345.3158, Δ = + 0.3 ppm.

3-Ferrocenyl-2-(ferrocenylmethyl)-1-phenylpropan-1-one (4r). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 240 mg, 93%. Yellow solid (m.p.: 149 ^oC). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.78(d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 4.05 (s, 10H), 3.98 (t, *J* = 7.8 Hz, 6H), 3.62-3.56 (m, 1H), 2.86 (dd, J_1 = 14.2 Hz, J_2 = 7.6 Hz, 2H), 2.58 (dd, J_1 = 14.2 Hz, J_2 = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.6, 137.4, 132.7, 128.4, 128.2, 86.1, 68.9, 68.8, 68.6, 67.6, 67.4, 51.1, 33.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{30}H_{28}Fe_2O$ 516.0839; found: 516.0844, Δ = + 1.0 ppm.

3-(Furan-2-yl)-2-(furan-2-ylmethyl)-1-phenylpropan-1-one (4s). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 72 mg, 51%. Brown oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.87 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H) 7.24 (d,

J = 1.6 Hz, 2H), 6.19 (q, *J* = 1.2 Hz, 2H), 5.97 (d, *J* = 3.2 Hz, 2H), 4.23-4.16 (m, 1H), 3.12 (dd, J_1 = 15.2 Hz, J_2 = 7.6 Hz, 2H), 2.87 (dd, J_1 = 14.8 Hz, J_2 = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.2, 152.8, 141.3, 136.7, 132.9, 128.5, 128.2, 110.2, 106.8, 44.5, 30.3. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{18}H_{17}O_3$ 281.1178; found: 281.1174, Δ = – 1.4 ppm.

General procedure for the one-pot sequential synthesis of α,α-disubstituted ketones (4t-z). In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (2.8 mg, 0.05 mmol, 0.1 equiv.), secondary alcohol (0.5 mmol), primary alcohol (0.5 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL) under air atmosphere. The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 4 h. After 4 h, another primary alcohol (0.55 mmol) and KOH (11.2 mg, 0.2 mmol, 0.4 equiv.) was added, and the reaction mixture was heated at 140 ºC for 16 h. Then the reaction mixture was cooled to ambient temperature and purified by silica gel column chromatography using hexane and dichloromethane (6:4) mixture as eluent to afford the desired ketone.

2-Benzyl-3-(4-methoxyphenyl)-1-phenylpropan-1-one (4t).[3c,9a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 93 mg, 56%. Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.76 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.26-7.21 (m, 2H), 7.18-7.13 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.78 (d, *J* = 7.2 Hz, 2H), 4.05-3.98 (m, 1H), 3.75 (s, 3H), 3.18-3.08 (m, 2H), 2.86-2.76 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.5, 158.1, 139.6, 137.5, 132.7, 131.5, 129.9, 129.0, 128.4, 128.3, 128.1, 126.2, 113.8, 55.2, 50.7, 38.2, 37.4.

2-benzyl-1-phenyl-3-(p-tolyl)propan-1-one (4u). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and

dichloromethane (6:4) mixture: yield 91 mg, 58%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.78 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26-7.15 (m, 6H), 7.08-7.04 (m, 3H), 4.07-4.00 (m, 1H), 3.20-3.09 (m, 2H), 2.87-2.77 (m, 2H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.3, 139.6, 137.4, 136.4, 135.7, 132.7, 129.0, 129.1, 129.0, 128.9, 128.4, 128.3, 128.1, 126.2, 50.6, 38.1, 37.8, 21.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{23}O$ 315.1749; found: 315.1747, Δ = – 0.6 ppm.

2-Benzyl-3-(4-isopropylphenyl)-1-phenylpropan-1-one (4v). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 104 mg, 61%. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.72 (d, *J* = 6.8 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.23-7.18 (m, 2H), 7.15-7.13 (m, 3H), 7.09-7.06 (m, 4H), 4.05-3.98 (m, 1H), 3.17-3.08 (m, 2H), 2.86-2.77 (m, 3H), 1.20 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 203.4, 146.8, 139.6, 137.5, 136.7, 132.6, 129.0, 128.9, 128.4, 128.3, 128.1, 126.4, 126.2, 50.5, 38.1, 37.9, 33.7, 24.0. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{25}H_{27}O$ 343.2062; found: 343.2057, Δ = – 1.5 ppm.

2-benzyl-3-(4-chlorophenyl)-1-phenylpropan-1-one (4w). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 105 mg, 63%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.73 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.25-7.14 (m, 7H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.02-3.95 (m, 1H), 3.16-3.08 (m, 2H), 2.81-2.76 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.9, 139.2, 138.0, 137.2, 132.9, 132.0, 130.3, 128.9, 128.5, 128.4, 128.1, 126.4, 120.1, 50.3, 38.5, 37.3. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{20}ClO$ 335.1203; found: 335.1207, Δ = + 1.2 ppm.

2-Benzyl-3-(4-bromophenyl)-1-phenylpropan-1-one (4x). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 137 mg, 72%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.38-7.31 (m, 4H), 7.26-7.23 (m, 2H), 7.18-7.15 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.04-3.97 (m, 1H), 3.17-3.08 (m, 2H), 2.82-2.75 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 202.9, 139.2, 138.6, 137.2, 132.9, 131.4, 130.8, 129.0, 128.5, 128.4, 128.1, 126.4, 120.1, 50.3, 38.5, 37.3. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{22}H_{20}BrO$ 379.0698; found: 379.0703, Δ = + 1.3 ppm.

2-Benzyl-1-phenyldecan-1-one (4y). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 110 mg, 68%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H) 7.25-7.13 (m, 5H), 3.74-3.67 (m, 1H), 3.12 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 1H), 2.78 (dd, J_1 = 13.8 Hz, J_2 = 6.8 Hz, 1H), 1.85-1.76 (m, 1H), 1.59-1.51 (m, 1H) 1.28-1.21 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 204.0, 140.1, 137.6, 132.7, 129.0, 128.5, 128.3, 128.1, 126.1, 48.4, 38.2, 32.4, 31.8, 29.7, 29.3, 29.2, 27.3, 22.6, 14.1. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{23}H_{31}O$ 323.2375; found: 323.2372, Δ = – 0.9 ppm.

3-Benzyl-2-phenylquinoline (4z).[9a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture: yield 97.4 mg, 66%. Yellow solid (m.p.: 84-85 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.16 (d, *J* = 8.8 Hz, 1H), 7.93 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H) 7.54-7.43 (m, 6H), 7.27-7.18 (m, 3H), 7.01 (d, *J* = 6.8 Hz, 2H), 4.14 (s, 2H). ^{13}C{^{1}H} NMR

($CDCl_3$, 100.6 MHz) δ (ppm): 155.9, 141.8, 135.8, 135.2, 132.3, 127.8, 124.5, 124.4, 124.3, 124.1, 123.7, 123.6, 123.5, 122.8, 122.4, 121.7, 121.5, 34.3.

General procedure for the synthesis of β,β-disubstituted alcohols (5a-j). In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (14 mg, 0.25 mmol, 0.5 equiv.), secondary alcohol (0.5 mmol), primary alcohol (1.1 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL) under air atmosphere. The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 12-16 h. Then, 2-propanol (230 µL, 3.0 mmol, 6 equiv.) was added, and the reaction mixture was heated at 140 ºC for 4-8 h (in total 20 h). Then the reaction mixture was cooled to ambient temperature and purified by silica gel column chromatography using hexane and ethyl acetate (95:5) mixture as eluent to afford the desired alcohol.

2-Benzyl-1,3-diphenylpropan-1-ol (5a).[19] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 139 mg, 92%. Colorless solid (m.p.: 68 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39-7.11 (m, 15H), 4.73 (t, J = 3.6 Hz, 1H), 2.81-2.56 (m, 4H), 2.43-2.35 (m, 1H), 1.90 (d, J = 3.6 Hz, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 143.5, 141.0, 140.9, 129.2, 129.1, 128.4, 128.3, 128.2, 127.2, 126.1, 125.9, 125.8, 73.7, 49.5, 36.1, 34.1.

2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-ol (5b). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 91 mg, 55%. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.13 (m, 12H), 6.91 (d, J = 8.4 Hz, 2H), 4.68 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 2.80-2.63 (m, 3H), 2.54 (dd, J_1 = 13.8 Hz, J_2 = 6.8 Hz, 1H), 2.42-2.34 (m, 1H), 2.00 (br s, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 158.8, 141.0, 141.0, 135.5, 129.3, 129.2, 128.3,

128.3, 127.3, 125.9, 125.8, 113.7, 73.5, 55.3, 49.5, 36.0, 34.2. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{23}H_{23}O_2$ 331.1698; found: 331.1694, Δ = – 1.2 ppm.

2-Benzyl-3-phenyl-1-(p-tolyl)propan-1-ol (5c). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 141 mg, 89%. Colorless solid (m.p.: 96 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28-7.09 (m, 14H), 4.67 (t, *J* = 3.6 Hz, 1H), 2.77-2.58 (m, 3H), 2.51 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 2.39-2.33 (m, 1H), 2.35 (s, 3H), 1.75 (d, *J* = 3.6 Hz, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 141.0, 140.9, 140.4, 136.8, 129.2, 129.1, 128.9, 128.3, 128.2, 126.0, 125.8, 125.8, 73.7, 49.3, 35.9, 34.1, 21.1. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{23}H_{23}O$ 315.1749; found: 315.1746, Δ = – 1.0 ppm.

2-Benzyl-1-(4-chlorophenyl)-3-phenylpropan-1-ol (5d). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 131 mg, 78%. Yellow solid (m.p.: 101 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.17 (m, 10H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 4.68 (t, *J* = 3.8 Hz, 1H), 2.71 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.61-2.54 (m, 3H), 2.35-2.27 (m, 1H), 1.81 (d, *J* = 4.0 Hz, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 142.0, 140.7, 140.6, 132.8, 129.2, 129.1, 128.5, 128.4, 128.4, 127.4, 126.0, 126.0, 73.1, 49.5, 36.0, 34.0. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{22}H_{20}ClO$ 335.1203; found: 335.1190, Δ = – 3.9 ppm.

2-Benzyl-1-(naphthalen-2-yl)-3-phenylpropan-1-ol (5e). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 166 mg, 94%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85-7.80 (m, 4H), 7.51-7.46 (m, 2H), 7.36 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.30-7.15

(m, 8H), 7.08 (d, J = 8.0 Hz, 2H), 4.87 (t, J = 3.0 Hz, 1H), 2.82-2.58 (m, 4H), 2.50-2.42 (m, 1H), 1.94 (d, J = 3.2 Hz, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 141.0, 140.9, 140.8, 133.2, 132.8, 129.2, 129.1, 128.4, 128.2, 128.0, 127.9, 127.6, 126.1, 125.9, 125.8, 125.7, 124.8, 124.2, 73.8, 49.3, 36.1, 34.1. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{26}H_{23}O$ 351.1749; found: 351.1750, Δ = + 0.3 ppm.

2-(4-Methylbenzyl)-1-phenyl-3-(p-tolyl)propan-1-ol (5f). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 139 mg, 84%. Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40-7.27 (m, 5H), 7.13-7.06 (m 6H), 7.02 (d, J = 8.0 Hz, 2H), 4.73 (t, J = 3.6 Hz, 1H), 2.75-2.52 (m, 4H), 2.41-2.31 (m, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 1.89 (d, J = 3.6 Hz, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 143.6, 137.8, 137.8, 135.3, 135.2, 129.1, 129.1, 129.0, 129.0, 128.2, 127.1, 126.1, 73.7, 49.5, 35.5, 33.6, 21.0, 21.0. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{24}H_{25}O$ 329.1905; found: 329.1902, Δ = – 0.9 ppm.

2-(4-Isopropylbenzyl)-3-(4-isopropylphenyl)-1-phenylpropan-1-ol (5g). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 130 mg, 67%. Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.31 (m, 4H), 7.27-7.23 (m, 1H), 7.13-7.05 (m, 6H), 7.00 (d, J = 8.0 Hz, 2H), 4.72 (t, J = 3.8 Hz, 1H), 2.90-2.83 (m, 2H), 2.73-2.50 (m, 4H), 2.41-2.34 (m, 1H), 1.78 (d, J = 3.6 Hz, 1H, OH), 1.24 (d, J = 1.6 Hz, 6H), 1.22 (d, J = 2.0 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 146.3, 146.2, 143.5, 138.1, 138.0, 129.0, 128.9, 128.1, 127.1, 126.3, 126.2, 126.1, 73.9, 49.1, 35.6, 33.7, 33.7, 33.7, 24.0, 24.0. HRMS (APCI): *m/z*: $[M–H_2+H]^+$ calcd for $C_{28}H_{33}O$ 385.2531; found: 385.2538, Δ = + 1.8 ppm.

2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-1-phenylpropan-1-ol (5h). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 162 mg, 87%. Colorless solid (m.p.: 89 ^{o}C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.20 (m, 9H), 7.02 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 4.64 (t, J = 3.6 Hz, 1H), 2.72-2.53 (m, 3H), 2.46 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 1H), 2.28-2.20 (m, 1H), 1.82 (d, J = 3.6 Hz, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 143.2, 139.2, 139.1, 131.7, 131.6, 130.5, 130.4, 128.5, 128.4, 128.4, 127.4, 126.0, 73.6, 49.5, 35.4, 33.4. HRMS (APCI): *m/z*: $[M]^+$ calcd for $C_{22}H_{20}Cl_2O$ 370.0891; found: 370.0878, Δ = – 3.5 ppm.

2-(4-Bromobenzyl)-3-(4-bromophenyl)-1-phenylpropan-1-ol (5i). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 140 mg, 61%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39-7.33 (m, 6H), 7.29-7.26 (m, 3H), 6.97 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 4.63 (t, J = 3.4 Hz, 1H), 2.71-2.51 (m, 3H), 2.44 (dd, J_1 = 13.8 Hz, J_2 = 6.4 Hz, 1H), 2.28-2.20 (m, 1H), 1.84 (d, J = 3.2 Hz, 1H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 143.1, 139.7, 139.6, 131.4, 131.3, 130.9, 130.8, 128.4, 127.4, 126.0, 119.7, 119.7, 73.6, 49.3, 35.5, 33.5. HRMS (APCI): *m/z*: $[M]^+$ calcd for $C_{22}H_{20}Br_2O$ 457.9881; found: 457.9863, Δ = – 3.9 ppm.

3-(Naphthalen-2-yl)-2-(naphthalen-2-ylmethyl)-1-phenylpropan-1-ol (5j). Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and ethyl acetate (95:5) mixture: yield 113 mg, 56%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85 (d, J = 8.0 Hz, 1H), 7.79-7.74 (m, 2H), 7.69 (dd, J_1 = 7.0 Hz, J_2 = 2.4 Hz, 1H), 7.45-7.28 (m, 11H), 7.14-6.96 (m, 4H), 4.86 (s, 1H), 3.37-3.28 (m, 2H), 3.13

(dd, J_1 = 13.6 Hz, J_2 = 4.4 Hz, 1H), 3.00 (dd, J_1 = 14.0 Hz, J_2 = 10.0 Hz, 1H), 2.59-2.52 (m, 1H), 1.99 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 143.6, 137.0, 137.0, 134.0, 133.9, 132.1, 132.0, 128.6, 128.5, 128.2, 127.8, 127.5, 127.2, 127.0, 126.8, 126.0, 125.5, 125.5, 125.3, 125.2, 123.9, 123.8, 73.3, 48.0, 33.6, 31.4. HRMS (APCI): *m/z*: $[M]^+$ calcd for $C_{30}H_{26}O$ 402.1984; found: 402.1988, Δ = +1.0 ppm.

The observation of the reversibility/non-reversibility of the second aldol condensation step in the reaction of 4a'/6 and 3b. In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (14 mg, 0.25 mmol, 0.5 equiv.), **4a'** or **6** (0.5 mmol), **3b** (0.55 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL) under air atmosphere. The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 16 h. Then the reaction mixture was cooled to ambient temperature and purified by silica gel column chromatography using hexane and dichloromethane (6:4) mixture as eluent to afford the products (Scheme S4).

1,3-Diphenylpropan-1-one, (4a'). [14a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture. Colorless solid (m.p.: 70 ºC). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.98 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.34-7.21 (m, 5H), 3.32 (t, J = 7.6 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H).

3-(4-Methoxyphenyl)-1-phenylpropan-1-one (4b').[14a] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture. Colorless solid (m.p.: 64 ºC). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.97 (d, J = 8.0 Hz, 2H), 7.56 (tt, J_1 = 7.2 Hz, J_2 = 2.8 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H),

7.18 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 3.79 (s, 3H), 3.28 (t, J = 7.2 Hz, 2H), 3.03 (t, J = 8.0 Hz, 2H).

3-(4-Methoxyphenyl)-1,2-diphenylpropan-1-one (6).[3c] Following the general procedure, the title product was isolated by using silica gel column chromatography eluting with hexane and dichloromethane (6:4) mixture. Colorless solid (m.p.: 103 ^{o}C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90 (d, J = 8.4 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.29-7.17 (m, 5H), 7.00 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 4.78 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H), 3.52 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H), 3.02 (dd, J_1 = 13.6 Hz, J_2 = 6.8 Hz, 1H).

Procedure for the time profile of the reaction. Independent reactions were conducted for the following of the time profile of the reactions. In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (0.25 mmol, 0.5 equiv.), 1-phenylethanol (0.5 mmol), benzyl alcohol (1.1 mmol) and a solution of **1d** (0.001 mmol, 0.2 mol%) in toluene (1 mL). The reaction mixture was vigorously stirred (1200 rpm) under reflux in a preheated oil bath at 140 ºC for 30 min to 20 h. Then the reaction mixture was cooled to ambient temperature, 2 M HCl (2 mL) and ethyl acetate (4 mL) were added to it, and then the solution was extracted with ethyl acetate (2×5 mL), the combined organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was submitted for ^{1}H NMR analysis to calculate the yield by using 1,3,5-trimethoxybenzene as internal standard.

Procedure for the dehydrogenation of 5a to 4a. Independent reactions were conducted for the time dependent dehydrogenation of **5a** to **4a**. In a 20 mL reaction tube (1 cm × 20 cm) with a condenser were added KOH (0.125 mmol, 0.5 equiv.), **5a** (0.25 mmol), and a solution of **1d** (0.0005 mmol, 0.2 mol%) in toluene (1 mL). The reaction mixture was vigorously stirred (1200

rpm) under reflux in a preheated oil bath at 140 ºC for 1-8 h. Then the reaction mixture was cooled to ambient temperature, the solvent was evaporated and the crude product was submitted for ^{1}H NMR analysis to calculate the conversion.

ASSOCIATED CONTENT

The following files are available free of charge.

Traces of ^{1}H, ^{13}C NMR and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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