

Catalytic Cross-Coupling of Secondary Alcohols

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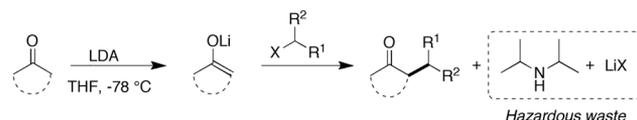
S Supporting Information

ABSTRACT: Herein, an unprecedented ruthenium(II) catalyzed direct cross-coupling of two different secondary alcohols to β -disubstituted ketones is reported. Cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β -disubstituted ketones to broaden the scope of this catalytic protocol. Number of bond activation and bond formation reactions occur in selective sequence via amine–amide metal–ligand cooperation operative in Ru-MACHO catalyst. The product-induced diastereoselectivity was also observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Reactions are sensitive to steric hindrance. This new C–C bond forming methodology requires low catalyst load and catalytic amount of base. Notably, the reaction produces H₂ and H₂O as the only byproducts making the protocol greener, atom economical and environmentally benign.

Alcohols and ketones are prevalent in nature and are highly promising industrial feedstock chemicals. Ketones are versatile building blocks for the construction of natural products, polymers, biological and pharmaceutical compounds and extensively used as industrial solvents.¹ Traditional synthesis of α - and β -substituted ketones involves reaction of carbonyl compounds under cryogenic conditions with strong bases (^tBuLi, LDA, etc.) followed by addition of toxic alkyl halides (Scheme 1a). This enolate alkylation approach suffers from serious drawbacks, which include (i) generation of stoichiometric metal halides as chemical waste (ii) over alkylation to di- or trisubstituted ketones, and (iii) homolytic coupling of carbonyl compounds curtailing the atom economy of the reactions.² In addition, organic halides and carbonyl compounds are expensive and they are not readily available substrates, which can be replaced by most abundant, cheap and environmentally benign alcohols for alkylation reactions. Moreover, alcohols can be obtained from renewable resources such as lignocellulosic biomass.³ The recent development in transition metal catalysis aims to develop sustainable, one-step, and atom economical efficient methodologies for the preparation of valuable synthetic building blocks by using easily available starting materials. In this regard, “borrowing hydrogen” methodology has become one of the most attractive

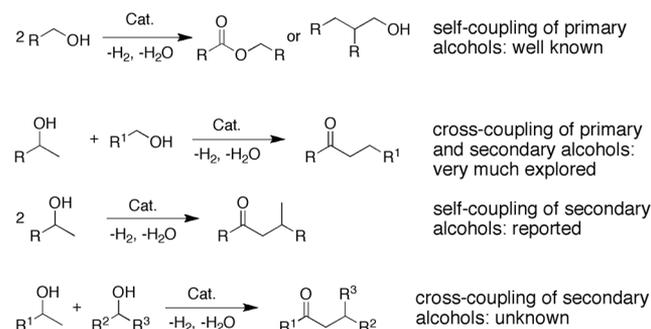
Scheme 1. Traditional and Selectivity Challenges in Synthesis of β -Disubstituted Ketones and Cross-Coupling of Secondary Alcohols

a) Traditional approach: synthesis of β -disubstituted ketones

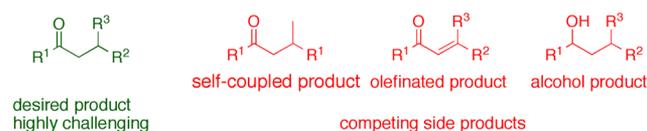


Drawbacks: (i) use of stoichiometric strong metallic base
(ii) stoichiometric metal halide as the waste
(iii) not environmentally benign and not atom economical reaction

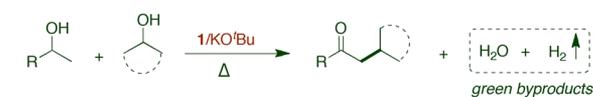
b) Catalytic coupling of alcohols



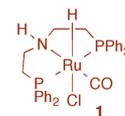
c) Selectivity challenges: direct cross-coupling of secondary alcohols



d) Our approach: direct cross-coupling of secondary alcohols



Advantages:
(i) alcohols: cheap industrial feedstock
(ii) no stoichiometric base required
(iii) only byproducts: H₂ and H₂O
(iv) direct synthesis of β -disubstituted ketones from two different secondary alcohols



transformation for C–C and C–N bond formation in organic synthesis.^{4,5}

Synthesis of α -substituted ketones from ketones and alcohols is well established.⁵ Direct cross-coupling of alcohols

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with hydrogen evolution via acceptorless dehydrogenation is one of the most atom economical and environmentally benign methods for constructing new C–C bonds (Scheme 1b).⁶ Catalytic self-coupling^{7,8} and cross-coupling⁹ of primary alcohols to esters and higher alcohols are reported. Cross-coupling of secondary alcohols with primary alcohols has been widely explored.^{10,11} There are two reports on self-coupling of secondary alcohols.¹² However, the catalytic cross-coupling of two different secondary alcohols remains unknown.

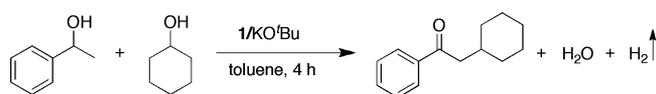
The major challenge in cross-coupling of secondary alcohols is to overcome the unwanted self-coupling from aldol reactions, which generates undesired byproducts and hence, diminishes the atom economy of the overall transformation (Scheme 1c). More importantly, synthesis of β -disubstituted ketones directly from two different secondary alcohols can usually be accomplished via four-step transformations (oxidation, aldol condensation, hydrogenation, and oxidation). Recently, Donohoe and co-workers reported the synthesis of β -disubstituted ketones via borrowing hydrogen methodology.¹³ However, the reaction requires stoichiometrically excess amount of base and the substrate scope is limited to bulky ketones (e.g., Ph*COCH₃, Ph* = pentamethyl phenyl). Thus, it is desirable to develop a new strategy for the synthesis of β -disubstituted ketones directly from two different secondary alcohols (Scheme 1d).

Recently, selective α -alkylation and α -olefination of nitrile compounds by alcohols were reported from our laboratory using a commercially available Ru-MACHO catalyst (**1**).¹⁴ On the basis of these reports, we further envisaged the cross-coupling of secondary alcohols. Herein, we describe the synthesis of β -disubstituted ketones directly from two different secondary alcohols. This catalytic method does not require stoichiometric oxidants; it only requires a catalyst and catalytic amount of base. Water and liberated H₂ are the only byproducts of this reaction.

Reaction of 1-phenylethanol (0.5 mmol) with cyclohexanol (0.5 mmol), catalyst **1** (1 mol %), and base (2 mol %) in toluene solution was heated to 135 °C for an initial investigation. Further, the reaction mixture was analyzed by ¹H NMR spectroscopy and gas chromatography (GC), which confirmed the complete conversion of 1-phenylethanol and high reactivity for cross-coupling reaction along with unreacted acetophenone (in situ generated intermediate) and trace amount of self-coupled aldol product were detected (entry 1, Table 1). Notably, overalkylation products and β -alkylated secondary alcohols were not observed (Scheme 1c). However, upon increasing base load to 5 mol % and lowering temperature to 125 °C, resulted in a better outcome and the cross-coupled product was isolated in 85% and 86% yields (entries 2, 3, Table 1). Use of 10 mol % of base, diminished the product formation presumably due to aldol side reactions (entry 4, Table 1). Further, upon increasing the amount of cyclohexanol no significant improvement in yield was observed (entry 5, Table 1). On decreasing catalyst load, use of lower temperature and replacing KO^tBu with NaO^tBu provided considerably lower yields (entries 6–8, Table 1). Other bases were not effective on the reaction (see SI). In control experiments performed by employing only base, and without catalyst and base, no cross-coupling product was observed, indicating that catalyst and base are essential for the success of the reaction (entries 9,10, Table 1).

Having optimal reaction conditions in hand, the scope of the various secondary alcohols on cross-coupling was investigated

Table 1. Optimization for Cross-Coupling of Secondary Alcohols Catalyzed by **1^a**

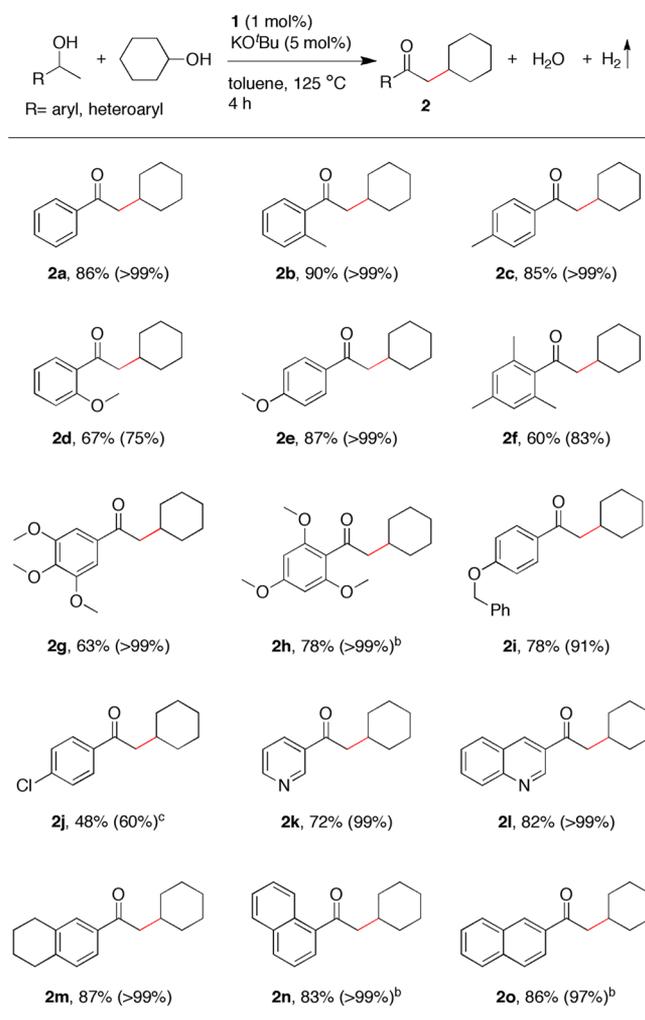


entry	cat. (mol %)	base (mol %)	temp. (°C)	conv. (%) ^b	yield (%) ^c
1	1	2	135	>99	69 (74)
2	1	5	135	>99	85 (90)
3	1	5	125	>99	86 (91)
4	1	10	125	>99	70 (76)
5 ^d	1	5	125	>99	87 (94)
6	1	5	115	94	63 (69)
7	0.5	5	125	>99	70 (72)
8 ^e	1	5	125	>99	79 (83)
9 ^f	–	5	125	5	–
10 ^f	–	–	125	–	–

^aReaction conditions: 1-phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 mL), catalyst **1** (1 mol %), and KO^tBu (5 mol %) were heated under argon flow. ^bConversion of 1-phenylethanol was determined by GC analysis using benzene as an internal standard. ^cYields were calculated for isolated products after column chromatography; yields calculated from GC analysis of the reaction mixtures are given within parentheses. ^d2 equiv of cyclohexanol was used. ^e5 mol % of NaO^tBu was used. ^fReaction was performed up to 24 h.

(Scheme 2). In general, methyl, methoxy and benzyloxy substituted 1-phenylethanols reacted well with cyclohexanol and provided the corresponding cross-coupled products **2b–2i** in good to high yields. The electron withdrawing group present in aromatic ring of secondary alcohol slightly diminished the reactivity as observed in 1-(4-chlorophenyl)ethan-1-ol to **2j**. Notably, heteroaryl and bicyclic aromatic secondary alcohols were tolerated well and the cross-coupling products **2k–2o** were obtained in good yields (Scheme 2).

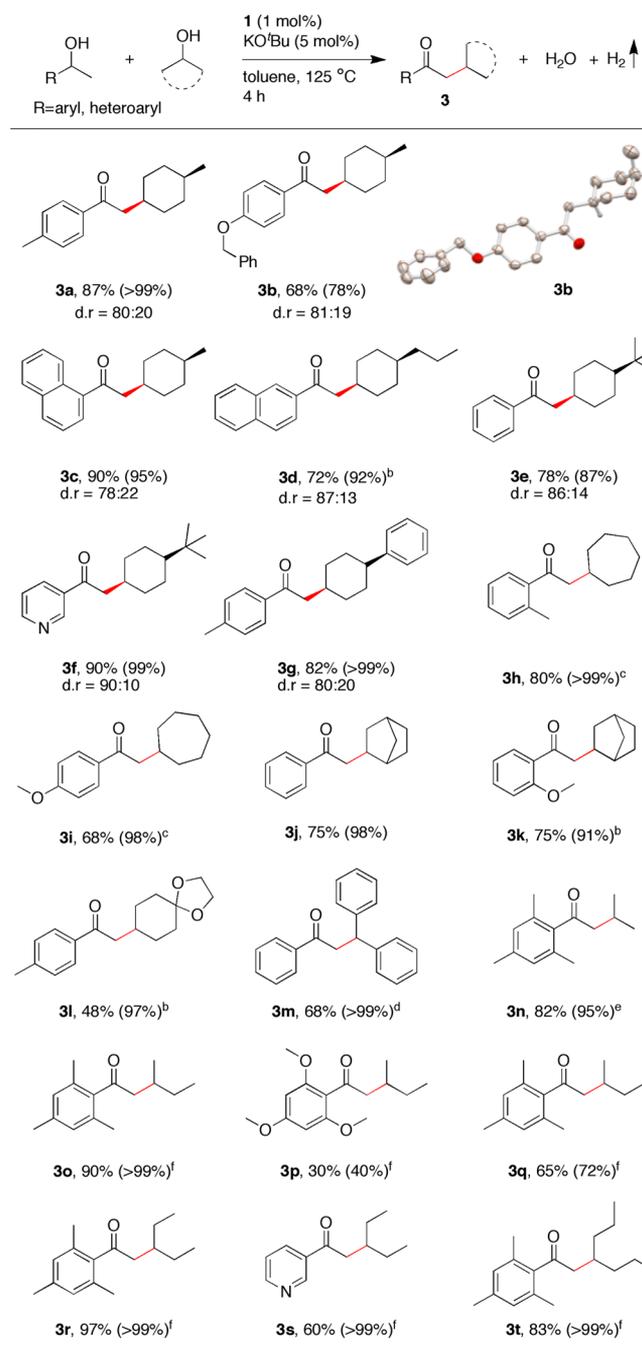
Encouraged by these results, a range of secondary alcohols was further explored for catalytic cross-coupling reaction. Both cyclic and acyclic secondary alcohols were directly coupled with benzylic secondary alcohols, which afforded cross-coupled ketone products in good to excellent yields (Scheme 3). Substitution on cyclohexyl ring provided products as a mixture of diastereoisomers and the diastereomeric ratios were obtained from ¹H NMR of crude reaction mixture. 4-Methylcyclohexanol was selectively coupled with various 1-arylethanol derivatives to provide the products **3a–3c** (d.r., 80:20, 81:19, 78:22, respectively) in very good yields as a mixture of diastereoisomers. Representatively, the single-crystal X-ray structure for major isomer of product **3b** is solved, which revealed the 1,4-cis conformation on cyclohexyl ring. Accordingly, similar 1,4-cis conformation is assigned for all major isomers of products **3a–3g**. Good yields with similar diastereoselectivities were also obtained for 4-propyl, 4-*tert*-butyl, and 4-phenyl-substituted cyclohexanol derivatives (**3d–3g**). Gratifyingly, 1-cycloheptanol and 2-norborneol were reacted with 1-phenylethanol derivatives and the corresponding products **3h–3k** were isolated in very good yields (Scheme 3). 4-Hydroxycyclohexanone ethyleneacetal with 1-(4-methylphenyl)ethanol provided product **3l** in moderate yield. A sterically hindered substrate, 1,1-diphenylmethanol delivered cross-coupled product **3m** in 68% yield. Finally, the highly challenging unactivated acyclic aliphatic secondary alcohols were subjected to catalysis with increased catalyst load of **1** (4

Scheme 2. Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols Using Cyclohexanol^a

^aReaction conditions: 1-arylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 mL), catalyst **1** (1 mol %), and KO^tBu (5 mol %) were heated at 125 °C under argon flow for 4 h. Conversion of 1-arylethanol determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to isolated pure compounds. ^bReaction was performed using 2 mol % catalyst **1** and 10 mol % base. ^c4 mol % of catalyst **1** and 20 mol % of base were used.

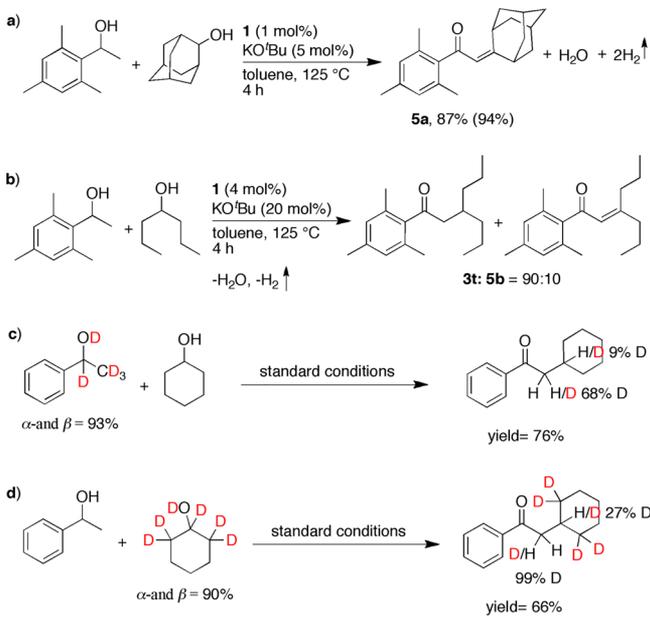
mol %) and base (20 mol %). A variety of secondary alcohols such as 2-propanol, 2-butanol, 2-pentanol, 3-pentanol, and 4-heptanol were well tolerated and selectively converted into β -disubstituted ketones (**3n–3t**).

Further, experiments aimed at deciphering the mechanistic insights were performed. When 1-mesitylethanol was reacted with sterically hindered 2-adamantanol, selective formation of olefin product **5a** was observed (Scheme 4a). GC analysis of this reaction mixture clearly indicated the absence of alkylated product. However, the reaction of 1-mesitylethanol with 4-heptanol under optimized conditions provided alkylated product **3t** and olefin product **5b** in 90:10 ratio (Scheme 4b). These results indicate the borrowing hydrogen pathway is interrupted due to sterically encumbered ruthenium on catalyst **1** and the reaction proceeds via α,β -unsaturated ketone intermediates. In addition to that deuterium-labeling experiments were conducted and the results imply that the liberated

Scheme 3. Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols^a

^aReaction conditions: A mixture of two secondary alcohols (each 0.5 mmol scale at 1:1 ratio), toluene (1.5 mL), catalyst **1** (1 mol %), and KO^tBu (5 mol %) were heated at 125 °C in open conditions under the argon flow. Diastereomeric ratios (d.r.) were determined by ¹H NMR analysis of crude reaction mixture; major isomer shown. was determined by GC analysis using benzene as an internal standard and given within parentheses. Reported yields correspond to isolated pure compounds. ^b2 mol % catalyst **1** and 10 mol % base were used. ^c3 mol % catalyst **1** and 15 mol % base and 3 equiv of cycloheptanol were used. ^d5 mol % of catalyst and 10 mol % base were used. ^e4 mol % catalyst **1** and 20 mol % base and 10 equiv of isopropyl alcohol were used. ^fReaction was performed using 5 equiv of aliphatic secondary alcohol, 4 mol % catalyst **1**, and 20 mol % base.

Scheme 4. Mechanistic Studies for the Cross-Coupling of Secondary Alcohols

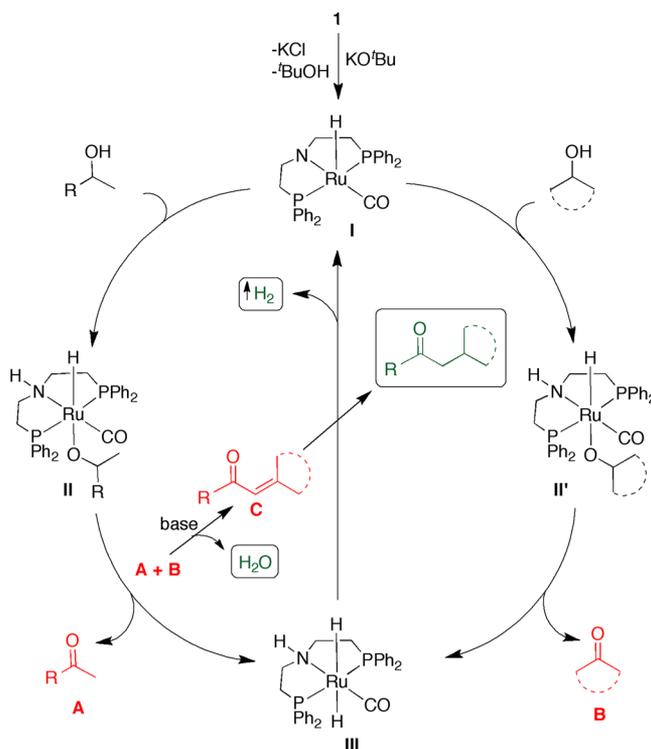


dideuterium/dihydrogen from cyclohexanol are predominantly reinstalled to unsaturated intermediate rather than dideuterium/dihydrogen liberated from 1-phenylethanol (Scheme 4c,d). These observations clearly indicate that the catalytic cross-coupling of secondary alcohols reactions are sensitive to steric hindrance. Thus, in addition to the faster dehydrogenation of aliphatic secondary alcohols by catalyst **1**, the higher reactivity of aliphatic cyclic ketones intermediates presumably due to the conformation strain and the steric compatibility also facilitates the formation of cross-coupling products by precluding the self-coupling reactions.

On the basis of these experimental evidence, the catalytic cycle for cross-coupling of secondary alcohols catalyzed by **1** is proposed in Scheme 5. Facile O–H, O–D, N–H, and spC–H bond activation reactions by catalyst **1** have been established in our previous reports.^{14,15} Catalyst **1** reacts with base to generate an unsaturated reactive intermediate **I**, which has been previously observed in mass spectrometry analysis.^{15b,16} The resulted reactive intermediate **I** further reacts with both secondary alcohols to provide an alkoxo coordinated ruthenium intermediates **II** and **II'** as already established.^{15d} β -Hydride elimination reaction from alkoxo ligands may result in formation of ketone intermediates **A** and **B** and both dehydrogenation reactions converge to provide the same ruthenium dihydride complex **III**. However, involvement of other mechanistic pathways cannot be ruled out.¹⁷ A base mediated cross-aldol condensation reaction between in situ formed ketones **A** and **B** produces α,β -unsaturated carbonyl compound **C**, which undergoes selective hydrogenation by complex **III** to provide desired β -disubstituted ketones. The amine–amide metal–ligand cooperation operative in these catalytic intermediates allow the regeneration of active intermediate **I** upon hydrogenation as well as liberation of a H₂ molecule by ruthenium dihydride **III**.

In summary, we have developed an efficient catalytic cross-coupling of secondary alcohols to provide β -branched ketones. This methodology provides broad substrate scope. Various aromatic, heteroaromatic, cyclic, linear, symmetrical, and

Scheme 5. Proposed Mechanism for Cross-Coupling of Secondary Alcohols



unsymmetrical secondary alcohols were well tolerated. The reaction proceeded by O–H bond activation of secondary alcohols by catalyst via amine–amide metal–ligand cooperation to provide corresponding carbonyl intermediates, which condensed and underwent catalytic hydrogenation to eventually deliver the products. Overall, two equivalent of molecular H₂ is obtained from oxidation of two different secondary alcohols. While one equivalent is used for the hydrogenation of the α,β -unsaturated carbonyl compound to provide the desired β -branched ketones, the other equivalent is liberated as H₂. Remarkably, H₂O and H₂ are the only byproducts. Use of readily available and challenging starting materials, broad scope, high selectivity and absence of any deleterious side reactions in this C–C bond formation will be beneficial and contribute to the development of new “green” and “sustainable” catalytic processes in future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b00025.

Experimental procedures, spectral data, and copies of ¹H and ¹³C NMR spectra of the products (PDF)

Crystal data of compound **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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