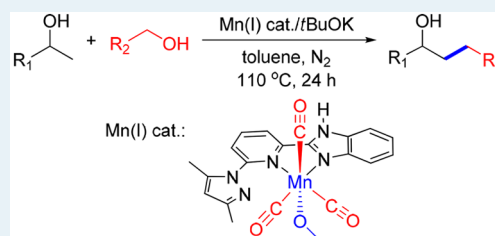


Manganese-Catalyzed β -Alkylation of Secondary Alcohols with Primary Alcohols under Phosphine-Free ConditionsTingting Liu,^{†,‡} Liandi Wang,[†] Kaikai Wu,[†] and Zhengkun Yu^{*,†,§}[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, P. R. China[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

Supporting Information

ABSTRACT: Manganese(I) complexes bearing a pyridyl-supported pyrazolyl-imidazolyl ligand efficiently catalyzed the direct β -alkylation of secondary alcohols with primary alcohols under phosphine-free conditions. The β -alkylated secondary alcohols were obtained in moderate to good yields with water formed as the byproduct through a borrowing hydrogen pathway. β -Alkylation of cholesterol was also effectively achieved. The present protocol provides a concise atom-economical method for C–C bond formation from primary and secondary alcohols.

KEYWORDS: manganese, alcohols, alkylation, borrowing hydrogen, cholesterol

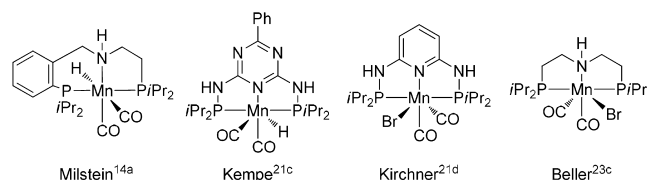


Construction of carbon–carbon bonds is of great importance in organic synthesis.¹ More and more concern on the consequence of climate change and dwindling crude oil reserves results in the search for alternative carbon resources for the formation of C–C bonds.² Thus, readily available alcohols have recently been paid much attention to be utilized as the electrophiles or alkylating agents to establish C–C bonds.³ The traditional method to prepare β -alkylated alcohols from secondary alcohols usually requires a multistep process that involves oxidation of the secondary alcohols, alkylation with alkyl halides, and reduction of the β -alkylated ketones. The drawbacks of such a protocol include waste generation, expensive and toxic noble-metal catalyst, and limited availability of the starting materials. β -Alkylation of secondary alcohols can also be realized by means of hydrogen autotransfer or borrowing hydrogen, which has become an important synthetic strategy in organic chemistry due to its high efficiency, low cost, and versatility.⁴ The operational simplicity, ready availability of the starting materials from renewable resources, and generation of water as the only stoichiometric byproduct make the borrowing hydrogen strategy be atom-economical, sustainable, and environmentally benign.⁵ Direct β -alkylation of secondary alcohols with primary alcohols has been documented under ruthenium,⁶ iridium,⁷ palladium,⁸ and copper⁹ catalysis or under metal-free conditions¹⁰ through a borrowing hydrogen strategy.

It has been desired to apply non-noble metal catalysis in organic synthesis due to the economic and ecological benefits as well as different reactivities of the metals. In this regard, base metals such as iron, cobalt, and nickel have achieved much progress in hydrogenation and dehydrogenation reactions.^{11–13} Manganese is the third most abundant metal in the earth's crust, which offers an attractive alternative to noble

metals. In particular, it is capable of existing in several oxidation states. Milstein and co-workers reported α -olefination of nitriles,^{14a} dehydrogenative cross-coupling of alcohols with amines,^{14b} N-formylation of amines with methanol,¹⁵ and deoxygenation of alcohols¹⁶ catalyzed by pincer-type Mn–PNP complexes. With a manganese complex as the catalyst, diverse alcohols underwent dehydrogenation-based processes such as N-alkylation of amines,¹⁷ C-alkylation of ketones,¹⁸ dehydrogenation of alcohols to esters¹⁹ and methanol to H₂ and CO₂,²⁰ and synthesis of pyrroles, quinolines, and pyrimidines.²¹ Hydrogenations of ketones, nitriles, esters, CO₂, and amides have also been realized with manganese complex catalysts.^{22,23} Very recently, Kempe et al. reported manganese-catalyzed dehydrogenative alkylation or α -olefination of alkyl-substituted N-heteroarenes with alcohols.²⁴ The typical phosphine-bearing amine-based PNP–MnH,^{14a} triazine-based PNP–MnH,^{21c} pyridine-based PNP–MnBr,^{21d} and amine-based PNP–MnBr^{23c} complex catalysts have been documented (Scheme 1).

Scheme 1. Selected Known Manganese Complex Catalysts



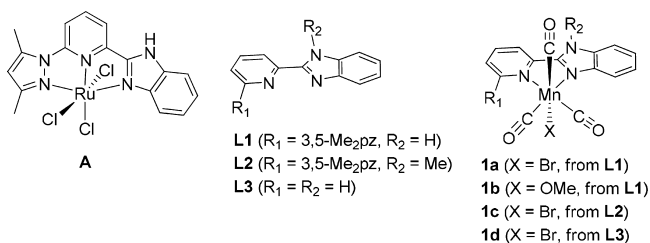
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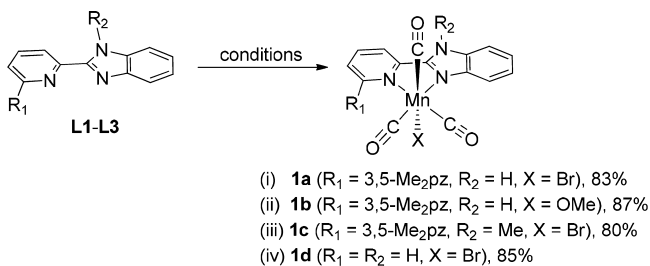
Recently, we reported versatile pyridyl-based NNN, CNN, and NNP ligands for the construction of ruthenium complex catalysts for transfer hydrogenation of ketones, dehydrogenation of N-heterocyclic compounds, synthesis of pyrrole derivatives, and Oppenauer-type oxidation of secondary alcohols.²⁵ Among these ruthenium complex catalysts, Ru(III) complex **A** exhibited a high catalytic activity in the β -alkylation of secondary alcohols.^{6b} During our continuous investigation of transition-metal complex catalysts bearing an unsymmetrical tridentate ligand, we found that the transition-metal complexes bearing a phosphine-free pyridyl-supported 2,6-(mixed N-heterocycles) ligand can usually exhibit enhanced catalytic activity and selectivity. Encouraged by these findings, we envisioned that these ligands might also be employed to construct manganese complex catalysts. Herein, we disclose the synthesis of Mn(I)-NN complexes **1** and their catalytic activities in β -alkylation of secondary alcohols with primary alcohols (Scheme 2).

Scheme 2. Relevant Ligands and Their Ru(III) and Mn(I) Complexes



Treatment of our previously reported pyridyl-supported pyrazolyl-imidazolyl ligand **L1**,^{25e} that is, 2-(3,5-dimethylpyrazol-1-yl)-6-(benzimidazol-2-yl)pyridine, with $\text{Mn}(\text{CO})_5\text{Br}$ (1 equiv) in tetrahydrofuran (THF) at 25 °C under a nitrogen atmosphere led to complex **1a** in 83% yield (Scheme 3). In a

Scheme 3. Synthesis of Manganese Complexes^a



^aConditions: **L1**–**L3** (0.5 mmol), $\text{Mn}(\text{CO})_5\text{Br}$ (0.5 mmol), solvent (25 mL), 0.1 MPa N_2 , 25 °C, 24 h. (i) Synthesis of **1a**: **L1**, THF, 83% yield. (ii) Synthesis of **1b**: **L1**, MeOH, 87% yield. (iii) Synthesis of **1c**: **L2**, MeOH, 80% yield. (iv) Synthesis of **1d**: **L3**, MeOH, 85% yield.

similar fashion, complex **1b** was obtained in 87% yield from the same reaction in methanol. The Mn–Br bond in **1a** was transformed to Mn–OMe in **1b**. Reacting $\text{Mn}(\text{CO})_5\text{Br}$ with the N-methylated ligand **L2** in methanol only afforded complex **1c** (80%), and the reaction exhibited no solvent effect. For the comparison study, bidentate ligand **L3** without bearing the 3,5-dimethylpyrazol-1-yl (Me_2pz) moiety was also applied in the reaction with $\text{Mn}(\text{CO})_5\text{Br}$ in methanol, giving complex **1d** in 85% yield. It is noteworthy that stirring a solution of complex **1a** in methanol at ambient temperature for

24 h quantitatively gave complex **1b**. The Mn–Br bond in **1a** was transformed to Mn–OMe in **1b** by reacting with methanol and release of hydrogen bromide under the stated conditions, while complexes **1c** and **1d** could not undergo the same type of reactions.

Complexes **1** were fully characterized by NMR, Fourier transform infrared (FT-IR), and elemental analyses, which are consistent with their compositions. The proton NMR signals of complex **1a** was shifted 0.1–2.1 ppm downfield as compared with those of the free ligand **L1**, suggesting that coordination of the ligand to manganese diminishes the electron density on the ligand. Three coordinating carbonyl groups in $\text{Mn}(\text{CO})_3$ moiety of complex **1a** were confirmed by the $^{13}\text{C}\{^1\text{H}\}$ NMR signals at 225.4, 220.2, and 215.2 ppm. The proton NMR signals of complex **1b** were broadened, and its $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum could not be obtained due to the possibility of a dynamic process.²⁶ The proton NMR spectrum of complex **1c** exhibited one singlet at 4.40 ppm, corresponding to the proton resonance of N-methyl group, and other proton resonance signals were shifted 0.1–0.5 ppm downfield as compared with those of the free ligand **L2** due to its coordination with the manganese center. In the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **1c**, the singlets at 226.6, 221.0, 216.6, and 33.1 ppm revealed the presence of three coordinating carbonyl groups and N-methyl, respectively. The NMR spectra of complex **1d** were in accordance with its composition, and the carbonyl resonance signals appeared at 224.2, 221.3, and 220.8 ppm, respectively. As compared with the infrared spectrum of ligand **L1**, the stretching vibrations of the carbonyls in $\text{Mn}(\text{CO})_3$ of complex **1a** were assigned at 2025 and 1933 cm^{-1} , respectively, corresponding to two types of coordinating carbonyls. In a similar manner, two types of carbonyl stretching vibrations were observed at 2027 and 1909 cm^{-1} , 2024 and 1935 cm^{-1} , and 2025 and 1933 cm^{-1} for complexes **1b**–**1d**, respectively.

Single crystals of complex **1b** suitable for X-ray diffraction were obtained by slow vapor diffusion of *n*-pentane into a saturated solution of the complex in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v, 1/2) at 4 °C. The molecular structure of complex **1b** adopts an octahedral geometry with the metal center coordinated by the pyridyl and imidazolyl nitrogen atoms of ligand **L1** and three carbonyls, and bonded to the methoxy oxygen atom (Figure 1). The potentially terdentate ligand **L1** actually acts as a bidentate ligand in complex **1b**, forming two coordination bonds of Mn(1)–N(3) (2.13 Å) and Mn(1)–N(4) (2.02 Å).

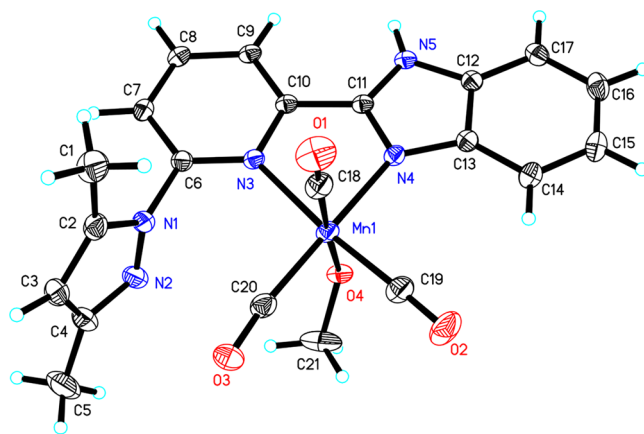
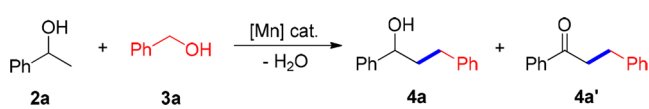


Figure 1. Perspective view of complex **1b** with thermal ellipsoids at the 30% probability level.

The unsymmetrical coordinating pyridyl–imidazolyl moiety occupies the two meridional sites with two carbonyls in a quasipolar disposition, and the manganese atom is nearly situated in such a plane. The methoxy oxygen atom is positioned *trans* to the third carbonyl with a C(18)–Mn(1)–O(4) angle of 176° and bond lengths of Mn(1)–O(4) (2.08 Å) and Mn(1)–C(18) (1.79 Å), suggesting that the axial carbonyl and methoxy oxygen atom are almost linearly positioned at the two sides of the quasipolar plane. The two coordinating nitrogen atoms are also nearly linearly arranged with the two equatorial carbonyls, exhibiting angles of N(3)–Mn(1)–C(19) (175°) and N(4)–Mn(1)–C(20) (176°), respectively.

The catalytic activities of complexes **1** were evaluated in the C-alkylation of 1-phenylethanol (**2a**) with benzyl alcohol (**3a**) (Table 1). With 2.1 mol % loading, complexes **1a–1d** were

Table 1. Screening of Reaction Conditions^a



entry	catalyst	base	conversion of 2a ^b (%)	4a : 4a' (molar ratio) ^b
1		<i>t</i> BuOK	83	40:60
2	1a	<i>t</i> BuOK	86	67:33
3	1b	<i>t</i> BuOK	96	94:6 (90) ^c
4	1c	<i>t</i> BuOK	84	53:47
5	1d	<i>t</i> BuOK	92	78:22
6	1b	<i>t</i> BuONa	87	92:8
7	1b	KOH	80	88:12
8	1b	NaOH	74	86:14
9	1b		<1	
10	1b ^d	<i>t</i> BuOK	91	65:35
11	1b	<i>t</i> BuOK ^e	90	90:10
12	1b	<i>t</i> BuOK ^f	84	91:9
13 ^g	1b	<i>t</i> BuOK	78	88:12
14 ^h	1b	<i>t</i> BuOK	66	89:11

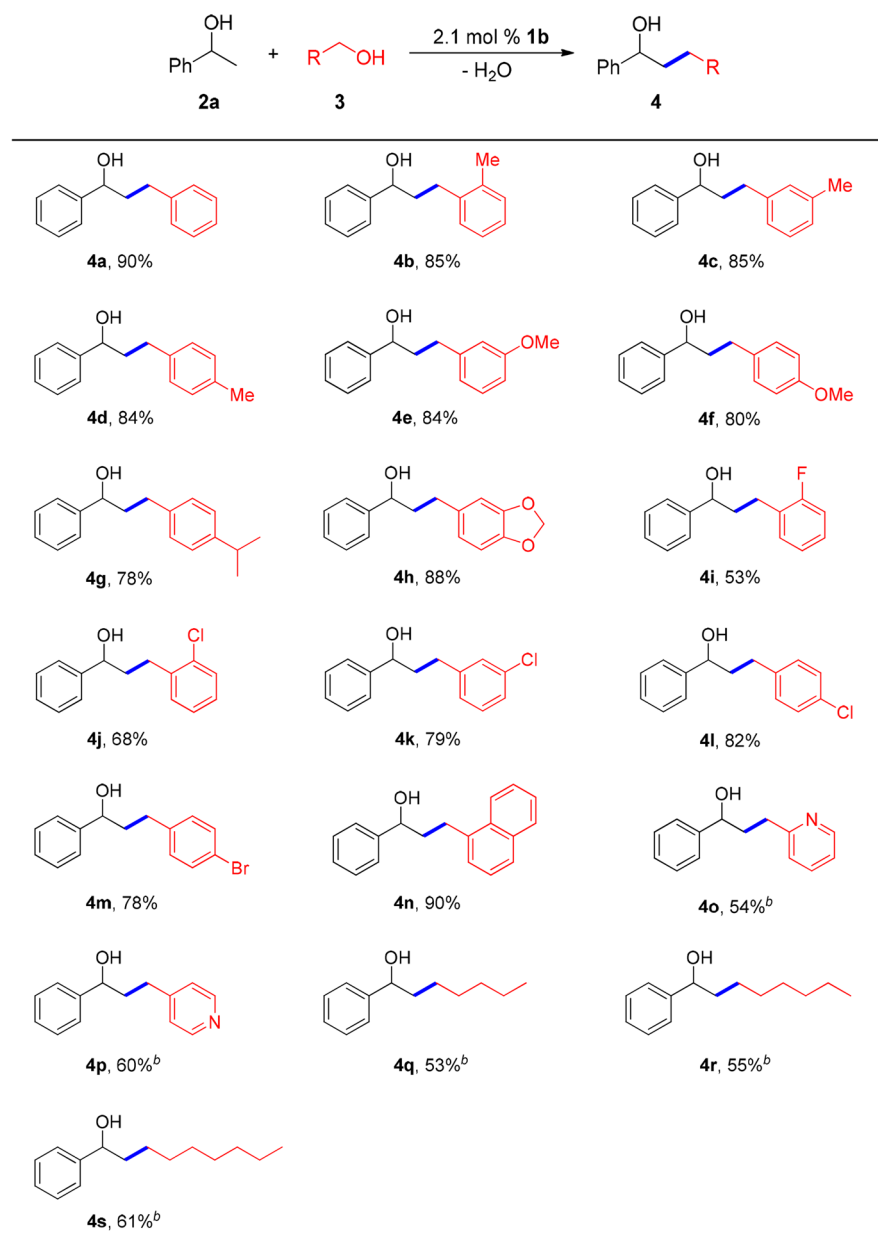
^aConditions: **2a** (2 mmol), **3a** (2 mmol), catalyst **1** (2.1 mol %), base (30 mol %), toluene (1 mL), 0.1 MPa N₂, 110 °C, 24 h. ^bDetermined by GC analysis. ^cIsolated yield of **4a** given in parentheses. ^d1.0 mol %. ^e20 mol %. ^f40 mol %. ^g100 °C. ^hSolvent-free conditions.

applied as the catalysts for the reaction in the presence of 30 mol % *t*BuOK as the base in refluxing toluene. In the case of using complex **1a**, 86% conversion was achieved for **2a** with a 67/33 selectivity for the target C-alkylation product **4a** and C-alkylation/dehydrogenation product **4a'** (Table 1, entry 2), while the reaction proceeded less efficiently without a catalyst (Table 1, entry 1). The reaction efficiency was remarkably improved with complex **1b** as the catalyst, reaching 96% conversion for **2a** and a 94/6 selectivity for **4a**/**4a'**, and the corresponding β -alkylation product **4a** was isolated in 90% yield (Table 1, entry 3). Under the same conditions, both complexes **1c** and **1d** behaved less efficiently to the reaction than complex **1b** as the catalyst (Table 1, entries 4 and 5). Presence of both the N–H functionality and 3,5-dimethylpyrazol-1-yl moiety in the ligand (**L1**) seems to be crucial to render the formation of complex **1b**. The order of the catalytic activities for these complexes was thus obtained as **1b** > **1d** > **1a** > **1c** (Table 1, entries 2–5). With **1b** as the catalyst, the reaction conditions were further optimized. An obvious base effect was observed on the alkylation efficiency with the order *t*BuOK > *t*BuONa > KOH > NaOH $\gg$ no base (Table 1,

entries 3 and 6–9). Lowering the catalyst loading to 1.0 mol %, varying the base loading to 20–40 mol %, or lowering the reaction temperature to 100 °C reduced the conversion of **2a** with deteriorated selectivities of **4a**/**4a'** (Table 1, entries 10–13). Equivalent base was needed in the hidden alkylation of alcohol reported by Kempe and co-workers.^{21b} Under the solventless conditions, the reaction could not efficiently occur (Table 1, entry 14). The high catalytic activity of complex **1b** is presumably attributed to the presence of an NH functionality in the ligand and the OMe ligand attached on the metal center. Methanol may be released to form a coordinatively unsaturated (16-electron) Mn(I) species, which thus enhances the interaction between the substrate and the catalytically active Mn(I) metal center, accelerating the reaction.

Under the optimized conditions, the protocol generality was explored by applying a variety of primary alcohols (Table 2). Benzyl alcohols (**3**) bearing an electron-donating methyl, methoxyl, isopropyl, or 3,4-methylenedioxy substituent reacted with **2a** to form the target products **4b–4h** in good yields (78–88%). Methyl group exhibited no obvious steric impact on the yields of **4b–4d** (84–85%), while methoxyl, isopropyl, and 3,4-methylenedioxy demonstrated various electronic/steric effects on the product yields of **4e–4h** (78–88%). The *ortho*-substituents such as 2-F and 2-Cl on the aryl group of the benzyl alcohol substrate showed negative electronic/steric effects, resulting in products **4i** (53%) and **4j** (68%), whereas the *m*- and *p*-Cl and *p*-Br-substituted benzyl alcohols reacted well with **2a** to afford the target products **4k–4m** in 78–82% yields. An obvious substituent effect was revealed on the reactivity of the chloro-substituted benzyl alcohols. 2-Naphthylmethanol efficiently underwent the reaction with **2a**, forming **4n** in 90% yield without showing a steric effect. With a higher catalyst loading (4.2 mol %) and longer reaction time (48 h) at a higher temperature (140 °C), 2- and 4-pyridylmethanols also reacted with **2a** to give **4o** and **4p** in 54–60% yields. In these cases, the catalyst might be partially deactivated by the coordination of the pyridyl atom to the metal center of the catalyst. Middle-chain aliphatic primary alcohols exhibited reactivities lower than those of the benzyl alcohols, and their reactions with **2a** were conducted under the relatively harsh conditions, forming the target products **4q–4s** in 53–61% yields. These results have revealed that benzyl alcohols are more reactive than aliphatic primary alcohols in the β -alkylation of secondary alcohols.

Then, the reactions of benzyl alcohol (**3a**) with structurally diverse secondary alcohols were investigated (Table 3). Various functional groups such as methyl, methoxyl, chloro, bromo, and trifluoromethyl could be tolerant on the aryl group of 1-arylethanol (**2**). The *o*-, *m*-, and *p*-methyls did not exhibit an obvious impact on the formation of **5a–5c** (81–84%). 2-OMe and 4-OMe diminished the yields of **5d** (62%) and **5e** (74%). 3-Chloro also led to a relatively low yield for **5f** (70%), while 4-chloro facilitated the production of **5g** (80%). Unexpectedly, 3- and 4-Br groups promoted the reactions to yield the target products **5h** and **5i** in good yields (83–93%). The strong electron-withdrawing trifluoromethyl did not favor the reactions to produce **5j** (60%) and **5k** (70%). In a similar fashion, 1-(2-naphthyl)ethanol efficiently reacted with **3a** to afford **5l** (82%), exhibiting no steric effect. 1-(2-Pyridyl)ethanol and aliphatic secondary alcohols reacted with **3a** less efficiently, giving **5m–5p** in 54–61% yields by means of 4.2 mol % **1b** as the catalyst under relatively harsh conditions.

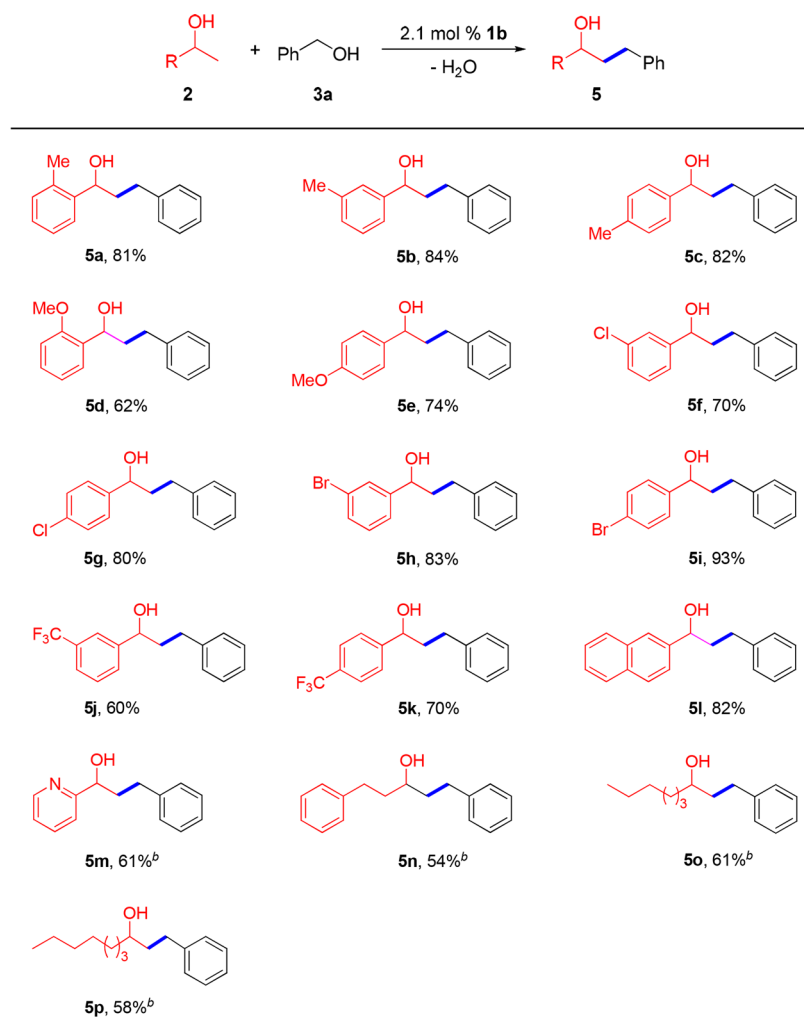
Table 2. Scope of Primary Alcohols (3)^a

^aConditions: **2a** (2 mmol), **3** (2 mmol), 2.1 mol % **1b**, 30 mol % *t*BuOK, 0.1 MPa N₂, toluene (1 mL), 110 °C, 24 h. ^b4.2 mol % **1b**, *o*-xylene (1 mL), 140 °C, 48 h.

Next, the substrate scope was extended to cyclic secondary alcohols. Thus, the reactions of cyclopentanol **6** with benzyl alcohols were explored (Scheme 4). To reach double C-alkylation, 2 equiv of benzyl alcohol was applied in the presence of 4.2 mol % catalyst. To our delight, cyclopentanol **6** efficiently reacted with benzyl alcohols, affording the di(β -alkylated) secondary alcohol products, that is, 2,5-dibenzylcyclopentanol **7**, in 77–83% yields. However, cyclohexanol, 1,2,3,4-tetrahydro-naphthalen-1-ol, and 2,3-dihydro-1*H*-inden-1-ol could not effectively react with benzyl alcohols under the stated conditions. The substrate scope was further extended to potentially useful cyclic secondary alcohols. In a similar manner, cholesterol and its derivative were employed to react with benzyl alcohols to access C-alkylated cholesterol derivatives (eqs 1 and 2). Unexpectedly, cholesterol (**8a**) reacted with excess of benzyl alcohol (3 equiv) afforded the

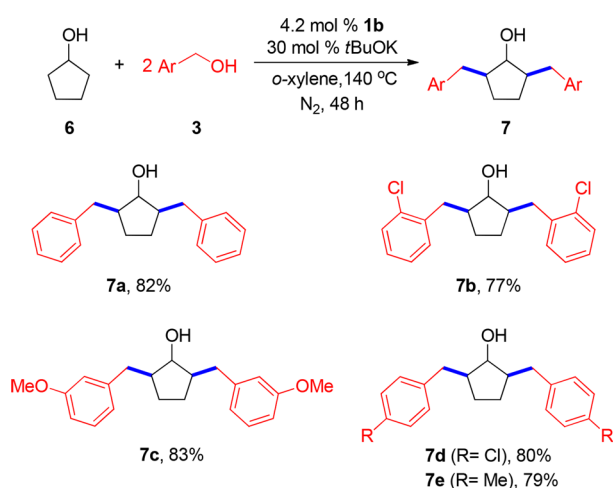
monoalkylation product **9a** (57%) with the olefinic C=C bond hydrogenated. The cholesterol derivative, that is, 5 α -cholestan-3 β -ol (**8b**), also reacted well with benzyl alcohol and 1-(2-methylphenyl)ethanol to form the corresponding C-monoalkylation products **9a** (60%) and **9b** (56%), respectively. Note that dialkylation did not occur to **8a** and **8b** under the stated conditions. The reactivity of the secondary carbon atoms of noncyclic alcohols was also investigated. 1-Phenylpropan-1-ol was reacted with benzyl alcohol to give no target product even under harsh reaction conditions (160 °C, 48 h). This result revealed that the reactivity of the secondary carbon atoms of noncyclic alcohols was much lower than that of cyclic alcohols.

This methodology was further applied for one-pot synthesis of flavan derivatives from simple alcohols.²⁷ Under the standard conditions, secondary alcohol **2a** was reacted with

Table 3. Scope of Secondary Alcohols (2)^a

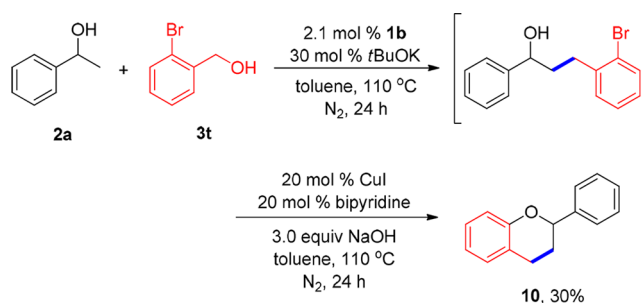
^aConditions: **2** (2 mmol), **3a** (2 mmol), 2.1 mol % **1b**, 30 mol % *t*BuOK, 0.1 MPa N₂, toluene (1 mL), 110 °C, 24 h. ^b4.2 mol % **1b**, *o*-xylene (1 mL), 140 °C, 48 h.

Scheme 4. Reactions of Cyclopentanol with Benzylic Alcohols

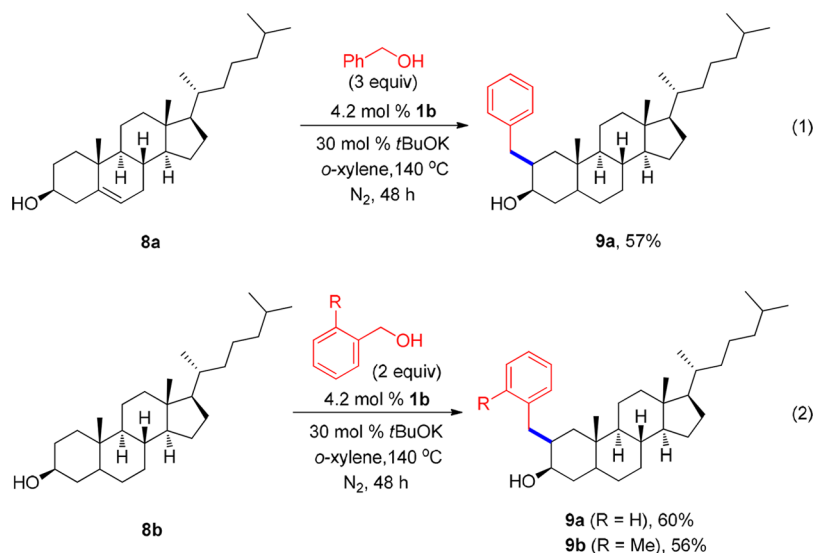


2-bromobenzyl alcohol (**3t**). The intermediate alcohol was not isolated, and then it was directly subjected to the copper(I)

catalysis, resulting in 2-phenylchroman (**10**) in 30% yield (Scheme 5).

Scheme 5. One-Pot Synthesis of Flavan Derivative **10**

In summary, we have developed efficient manganese-catalyzed direct β -alkylation of secondary alcohols with primary alcohols under phosphine-free conditions. The present protocol offers a concise strategy to construct transition-metal complex catalysts from readily available phosphine-free ligands, and it provides a useful alkylation method for secondary alcohols and cholesterol derivatives.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b01960.

Experimental materials and procedures, analytical data and NMR spectra of compounds and complexes, X-ray crystallographic analysis for **1b** (PDF)
X-ray crystallographic information (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zkylu@dicp.ac.cn.

ORCID

Tingting Liu: 0000-0002-0156-3054

Liandi Wang: 0000-0003-4996-3687

Kaikai Wu: 0000-0003-1950-5343

Zhengkun Yu: 0000-0002-9908-0017

Notes

The authors declare no competing financial interest.

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