

Nonbifunctional Outer-Sphere Strategy Achieved Highly Active α -Alkylation of Ketones with Alcohols by *N*-Heterocyclic Carbene Manganese (NHC-Mn)

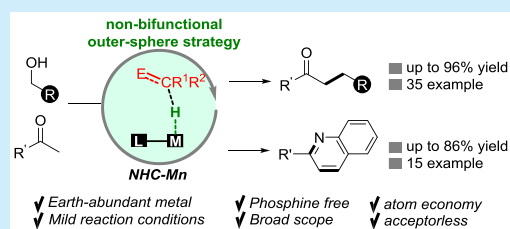
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S Supporting Information

ABSTRACT: The unusual nonbifunctional outer-sphere strategy was successfully utilized in developing an easily accessible *N*-heterocyclic carbene manganese (NHC-Mn) system for highly active α -alkylation of ketones with alcohols. This system was efficient for a wide range of ketones and alcohols under mild reaction conditions, and also for the green synthesis of quinoline derivatives. The direct outer-sphere mechanism and the high activity of the present system demonstrate the potential of nonbifunctional outer-sphere strategy in catalyst design for acceptorless dehydrogenative transformations.



The borrowing hydrogen/hydrogen autotransfer (BH/HA) has been emerging as a versatile method in synthesis. Using nonactivated renewable alcohols as starting materials, the BH/HA method dehydrogenates the alcohol for a subsequent reaction with a nucleophile, which is then followed by hydrogenation with the “borrowed” hydrogen, showing its merits in sustainability, atomic economy, and environmentally benign.¹

To ensure successful BH/HA, popular strategies (Figure 1) to develop transition-metal catalysts are (1) designing

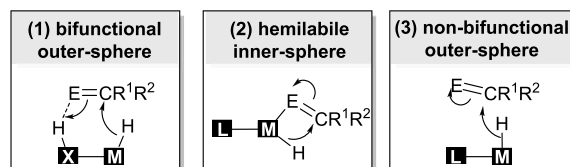


Figure 1. Design strategies for BH/HA catalysts.

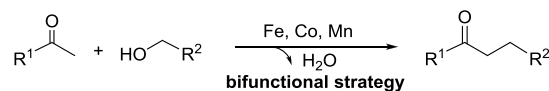
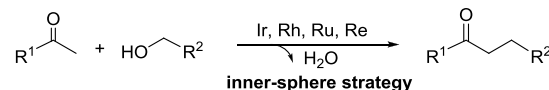
bifunctional ligands to achieve a bifunctional outer-sphere metal–ligand cooperation;² or (2) designing hemilabile ligands for inner-sphere mechanism.³ However, the incorporations of additional functional site(s) or hemilabile arm(s) to the ligands are usually expensive, air-sensitive, and difficult to synthesize at a large scale, thus impeding their application. Functional-site activation or ligand dissociation may also lead to reaction-conditions-sensitive systems with limited scope. In contrast, a (3) direct outer-sphere strategy with nonbifunctional ligands is rare in the development of BH/HA. With straightforward innocent ligands, the alternative direct outer-sphere strategy should enlarge the panel of BH/HA catalyst design and facilitate the combinational screening.

The α -alkylation of ketone via BH/HA has emerged as an attractive C–C bond formation protocol.^{1b,e,4,5} With green and sustainable alcohols as alkylating agents, α -alkylation of ketone via BH/HA provides advantages, compared to traditional procedures involving enolates and alkyl halides,⁶ avoiding the using of toxic halides and the formation of waste byproducts.^{1a–c}

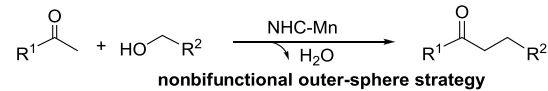
The inner-sphere strategy α -alkylation of ketones were widely studied with precious metals (Scheme 1a) such as Ru,^{4b,7} Ir,⁸ and Rh,⁹ bearing weak or hemilabile ligands. Later,

Scheme 1. General Strategies To Develop Transition-Metal Catalysts for α -Alkylation of Ketones with Alcohols

a) Previous systems for α -alkylation of ketones with alcohols via BH/HA



b) Present work: highly active NHC-Mn system



- non-bifunctional ligand
- non-noble metal
- highly active
- direct outer-sphere strategy
- phosphine-free
- broad scope

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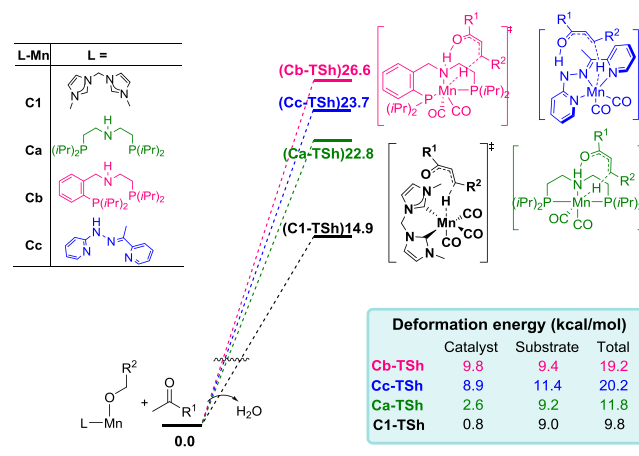
the bifunctional outer-sphere strategy was applied in α -alkylation of ketones with alcohols by Re systems using PNHP as a bifunctional ligand,¹⁰ and by Ru systems with 2-hydroxypyridine as the functional moiety.¹¹ Interestingly, a Pd system with nonbifunctional CN ligands was reported, which probably promoted the α -alkylation of ketones with alcohols via the outer-sphere mechanism.¹²

More recently, non-noble transition metals (such as Fe, Co, or Mn) have received increasing attention, because they are more eco-friendly and inexpensive, in addition to their different reactivity, compared with noble metals.¹³ Although encouraging developments have been reported very recently,¹⁴ the bifunctional outer-sphere strategy is popularly required to achieve a successful BH/HA C–C bond formation for non-noble transition metals (Scheme 1b), associated with sophisticated bifunctional ligands. In 2015, Darcel and co-workers reported Knölker-type Fe-catalyzed BH/HA alkylation of ketones with primary alcohols with the assistance of a carbonyl functional site.^{14g} In 2016, Beller and co-workers elegantly developed a manganese-catalyzed α -alkylation of ketones with primary alcohols, using bifunctional PNHP ligands.¹⁵ In 2017, Zhang and co-workers reported the cobalt-catalyzed α -alkylation using PNHP as bifunctional ligands.¹⁶ In 2018, the Milstein group reported an effective Mn(I) phosphorus pincer complexes for the α -alkylation of a range of ketones with alcohols, involving the (de)-aromatization bifunctional cooperation.¹⁷ A phosphine-free hydrazone-NNN ligand was developed by Maji and co-worker for bifunctional Mn-catalyzed alkylations of ketones using primary alcohols.^{14f} Despite the above developments, to the best of our knowledge, the nonbifunctional outer-sphere strategy has not yet been applied in the BH/HA C–C bond formation, although practical non-noble transition-metal systems with synthetically straightforward, highly tunable, innocent ligands are desired.¹⁸

Herein, we report the first implementation of the outer-sphere strategy in non-noble-metal catalyzed BH/HA C–C bond formation (Scheme 1c), using a very simple, inexpensive, tunable *bis*-NHC-Mn system, which not only promoted highly active α -alkylation of ketones with alcohols, but also the Friedländer annulation to form quinoline derivatives.

To begin our design, we investigated the possible advantage of the outer-sphere strategy by comparing the hydrogenation ability of the Mn–H species toward α,β -unsaturated ketone, which is suggested to be the key step in the BH/HA process.^{11,18,19} We are keenly interested in comparing the nonbifunctional *bis*-NHC-Mn system (C1) for the outer-sphere strategy¹⁸ with previously reported bifunctional systems, like PNHP-Mn (Ca),¹⁵ PNHP-Mn (Cb),¹⁷ and NNN-Mn (Cc)^{14f} for the bifunctional strategy (Scheme 2). Density functional theory (DFT) studies (for detailed information, see the Supporting Information (SI)) suggest a significant improvement in the hydrogenation of α,β -unsaturated ketone for the nonbifunctional outer-sphere strategy. Hydrogenation transition state C1-TSh in a non-bifunctional outer-sphere manner has a free energy of only 14.9 kcal mol⁻¹. The low transition-state free energy is mainly due to the small deformation energy, which indicates the superiority of the nonbifunctional outer mechanism. The bifunctional hydrogenation transition states all require one to overcome relatively higher activation free energies, 22.8, 23.7, and 26.6 kcal mol⁻¹ for the Ca, Cb, and Cc systems, respectively.

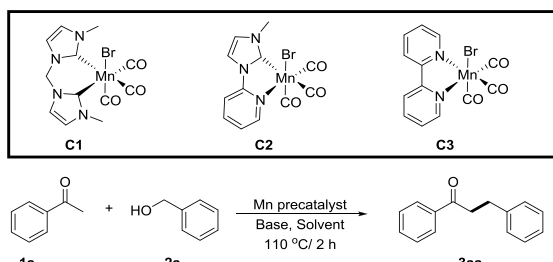
Scheme 2. Activation Free Energies of the Hydrogenation of α,β -Unsaturated Ketone for C1, Ca, Cb, and Cc



Encouraged by the theoretical prediction, precatalysts C1–C3 with nonbifunctional *bis*-NHC, NHC-pyridine, and bipyridine ligands, respectively, were prepared.²⁰ Screening and reaction optimization were performed, using acetophenone (1a) and benzyl alcohol (2a) as model substrates, as listed in Table 1. C1 with strong σ -donating *bis*-NHC was the most effective precatalyst (Table 1, entries 1–4) and NaOH was superior to other bases with 94% yield (Table 1, entries 5–11). Solvents other than toluene, such as 1,4-dioxane, dimethylsulfoxide (DMSO), dimethyl acetamide (DMAc), dimethyl formamide (DMF), and *tert*-amyl alcohol (*t*-AmOH), proved to be inferior (Table 1, entries 12–16). Other critical parameters, such as the base concentration, catalyst loading, and temperature, were also examined (see the SI). The optimal reaction conditions were demonstrated to be 4 mmol of C1 and 0.5 equiv of NaOH at 110 °C for 2 h (Table 1, entry 17). An inert atmosphere seemed to be important (Table 1, entry 18). Note that there was no reaction in the absence of a base, and a reaction in the absence of a manganese complex led to 3aa in only 14% yield (Table 1, entries 19 and 20). It is very exciting that the C1-catalyzed α -alkylation of ketone proceeds smoothly at 110 °C within 2 h. The reported bifunctional systems, such as Ca, Cb, and Cc, usually occurred at higher temperatures (125–140 °C) and over longer times (18–24 h).^{14f,15,17}

With the optimized reaction conditions, the substrate scope was next explored. As shown in Scheme 3, it was found that electron-rich (OMe, Me) and electron-deficient (Cl, F, CF₃) substituted primary alcohols are converted to corresponding products in good to excellent yields (3ab–3ae, 3ag–3ai). 4-Bromobenzyl alcohol furnished 3af in moderate yield (57%). 2-Methylbenzyl alcohol gave 3aj in 95%, but more hindered (2,6-dimethylphenyl)methanol made the transformation somewhat sluggish (3ak, 57%). 2-Naphthylmethanol and redox-active ferrocenylmethanol reacted with 1a to 3al–3am in high yields, 92% and 93%, respectively. Heteroaromatic substrates, such as thiophene and furan-containing alcohols, were also efficiently applied to the alkylation of 1a, although in moderate yields (3an–3ao). Aliphatic alcohols, such as 3-phenylpropanol and 1-hexanol, were also tolerated (3ap and 3aq).

Subsequently, various substituted ketones were studied with benzyl alcohol (2a) (Scheme 3). Electron-donating methyl or methoxy-substituted aryl ketones were well-tolerated, leading to desired products (3ba and 3ca) in yields of 85% and 93%,

Table 1. Optimization of the Reaction Conditions^a


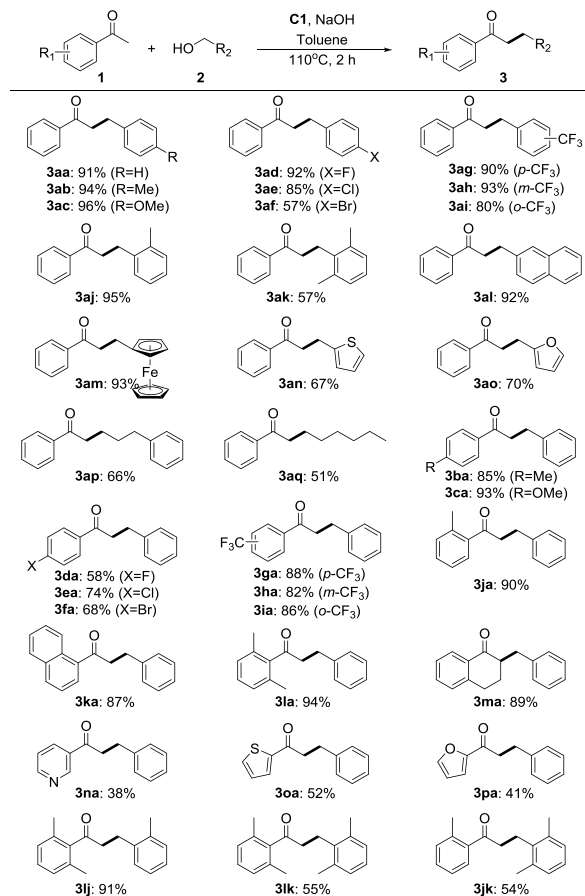
entry	catalyst (loading, mol %)	base (loading, equiv)	solvent	yield ^b (%)
1	C1 (5)	KO ^t Bu (0.5)	toluene	64
2	C2 (5)	KO ^t Bu (0.5)	toluene	27
3	C3 (5)	KO ^t Bu (0.5)	toluene	31
4	[MnBr(CO) ₃] (5)	KO ^t Bu (0.5)	toluene	27
5	C1 (5)	NaO ^t Bu (0.5)	toluene	75
6	C1 (5)	LiO ^t Bu (0.5)	toluene	trace
7	C1 (5)	KOH (0.5)	toluene	81
8	C1 (5)	HCsO·H ₂ O (0.5)	toluene	82
9	C1 (5)	NaOH (0.5)	toluene	94
10	C1 (5)	Cs ₂ CO ₃ (0.5)	toluene	49
11	C1 (5)	K ₂ CO ₃ (0.5)	toluene	4
12	C1 (5)	NaOH (0.5)	1,4-dioxane	62
13	C1 (5)	NaOH (0.5)	DMSO	8
14	C1 (5)	NaOH (0.5)	DMAc	25
15	C1 (5)	NaOH (0.5)	DMF	20
16	C1 (5)	NaOH (0.5)	<i>t</i> -AmOH	73
17	C1 (4)	NaOH (0.5)	toluene	95 (91)
18 ^c	C1 (4)	NaOH (0.5)	toluene	79
19	C1 (4)	—	toluene	trace
20	—	NaOH (0.5)	toluene	14

^aReaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), solvent (1.0 mL), at 110 °C for 2 h. ^bYield determined via gas chromatography (GC), with 1,4-di-*tert*-butylbenzene as an internal standard; isolated yield given in parentheses. ^cPerformed in air.

respectively. Electron-withdrawing substituted ketones, such as F, Cl, and Br, led to a slight decrease in efficiency (**3da**–**3fa**; see Scheme 3). Interestingly, the CF₃ substituted ketones gave corresponding products in high yields (82%–88%, **3ga**–**3ia**). Sterically hindered 2-methylacetophenone, 1-acetonaphthone, and 2,6-dimethylacetophenone were compatible, generating **3ja**, **3ka**, and **3la** in yields of 90%, 87%, and 94%, respectively. A cyclic substrate **3m** with a secondary α -carbon atom was also functionalized to afford product **3ma** in 89% yield.

Heterocyclic ketones containing pyridine, thiophene, and furyl moieties also showed reactivities (38%–52%, **3na**–**3pa**). More challenging bulky coupling partners were also compatible (**3lj**, **3lk**, and **3jk**; 91%, 55%, and 54%, respectively). The reactions are more sensitive to the steric hindrance of benzyl alcohols. For example, 2,6-dimethylacetophenone successfully coupled with benzyl alcohol and sterically demanding 2-methylbenzyl alcohol, leading to 94% and 91% yields, respectively (**3la**, **3lj**). However, moderate yields were obtained when (2,6-dimethylphenyl)methanol was used (**3ak**, **3lk**, and **3jk**).

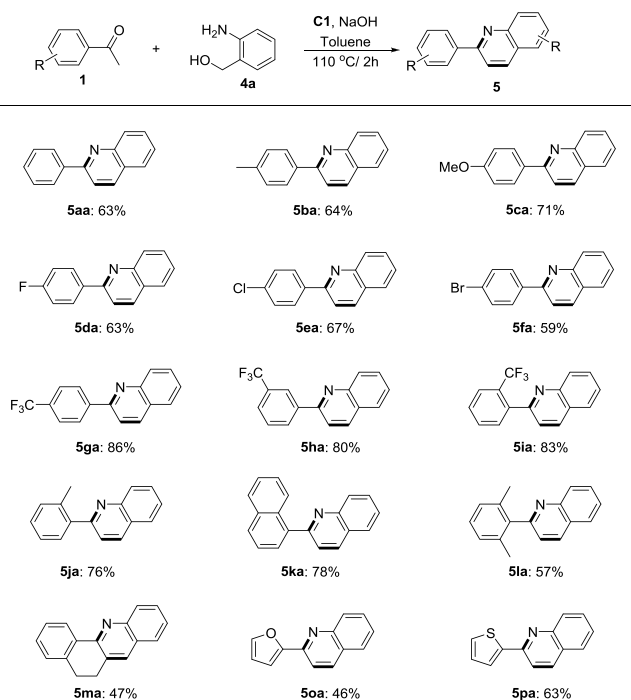
Subsequently, we were motivated to investigate the applicability of **C1** for the α -alkylation of ketones to the syntheses of quinoline derivatives via the Friedländer annulation reaction. As shown in Scheme 4, various aryl

Scheme 3. Scope of α -Alkylation of Ketones with Alcohols^a

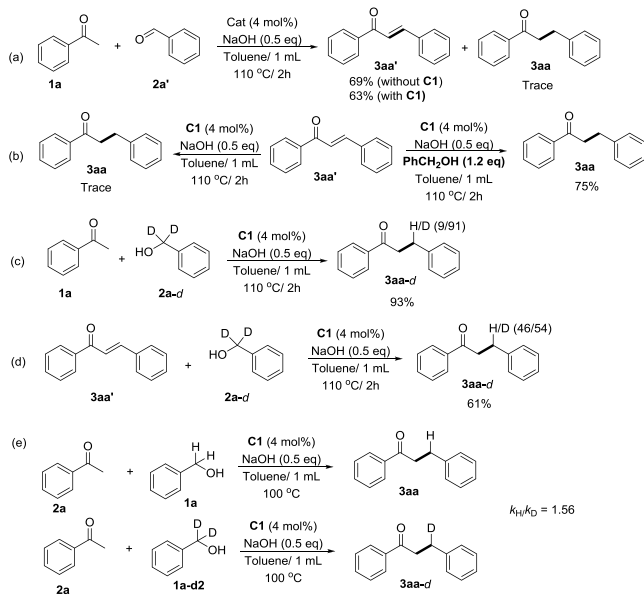
^aReaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **C1** (4 mol %), NaOH (50 mol %), toluene (1 mL), at 110 °C for 2 h, isolated yield.

ketones with different electronic substituents underwent smooth annulation reactions delivering the quinolines in yields of 59%–71% (**5aa**–**5fa**). Excitingly, excellent yields observed when CF₃-substituted ketones were utilized (80%–86% yields, **5ga**–**5ia**). These results, together with the results of **3ag**–**3ai**, **3ga**–**3ia** (Scheme 3), indicated that CF₃-substituted coupling partners were well-tolerated. The cross-coupling reactions of 2-aminobenzyl alcohol with sterically hindered 2-methylacetophenone and 1-acetonaphthone gave satisfactory yields (76% and 78%), while moderated yield was obtained when using 2,6-dimethylacetophenone as a substrate (**5ja**–**5la**). The use of α -tetralone as a coupling partner resulted in **5ma** in 47% yield. Heteroaromatic methylketones, such as 2-acetylthiophene and 2-acetylfuran, reacted with **4a** to yield quinolines **5oa** and **5pa** in 46% and 63% yields, respectively.

Control experiments were performed to shed light on the mechanism (Scheme 5). The acetophenone and benzaldehyde gave the α,β -unsaturated ketone smoothly with or without **C1** (Scheme 5a) under the optimal conditions, indicating the involvement of the aldol condensation in our protocol.²¹ This enone (**3aa'**) cannot be reduced without alcohols (Scheme 5b). However, transfer hydrogenation of α,β -unsaturated ketone could be achieved with **2a** or **2g** as the hydrogen sources (see Scheme S2 in the SI). A deuterium labeling experiment using [α,α -D₂]benzyl alcohol (**2a**–**2d**) shows deuterium atoms almost completely distributed in the β -positions (91% D, Scheme 5c), instead of the α -position

Scheme 4. Scope of the Friedländer Quinoline Synthesis^a

^aReaction conditions: **1** (0.5 mmol), **4a** (0.6 mmol), **C1** (4 mol %), NaOH (50 mol %), toluene (1 mL), at 110 °C for 2 h, isolated yield.

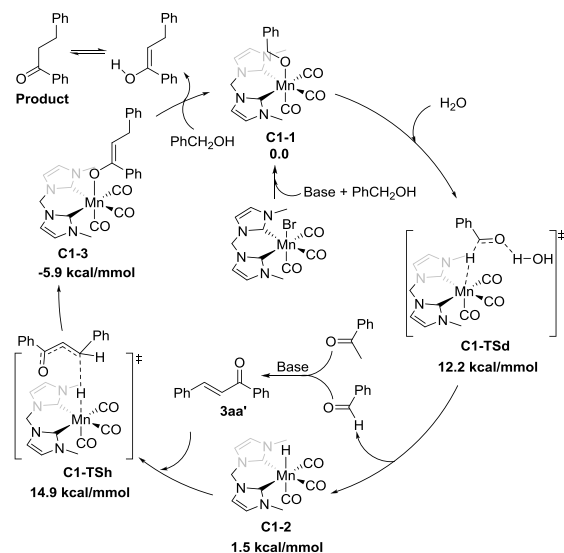
Scheme 5. Control Experiments^a

^aIsolated yields.

(Scheme 5d). These results imply the possibility of a different pathway from the previously observed prevalence of an NH-assisted bifunctional outer-sphere mechanism.¹⁵ It also indicates that the dehydrogenation of deuteride should be suppressed. A parallel experiment revealed a k_H/k_D value of 1.56 (see Scheme 5e), indicating that the dissociation of the α -C–H bond in benzylic alcohol may not be involved in the rate-determining step. The hydrogenation step or the aldol condensation step might be the slowest step in our reaction conditions.

Based on the above results and literature precedents,^{14f,18,21,22} a direct outer-sphere mechanism is presented in Scheme 6. The catalytic cycle involves three major stages:

Scheme 6. Plausible Reaction Mechanism



(1) the dehydrogenation of alcohol, (2) the aldol condensation, and (3) the hydrogenation of α,β -unsaturated ketone. Density functional theory (DFT) investigation (see Figure S1 in the SI) suggests that the reactive intermediate **C1-1** promotes the hydride elimination through transition state **C1-TSd** (12.2 kcal/mol) via an outer-sphere manner without the dissociation of CO ligands,¹⁸ liberating an aldehyde and the [Mn–H] species. The enone then could be reduced by the [Mn–H] species through transition state **C1-TSh** (14.9 kcal/mol). Note that the hydride elimination step could be facilitated by an extra protic molecule (byproduct H_2O).¹⁸ However, unlike the room-temperature *N*-alkylation, the *C*-alkylation required higher temperature, probably because of the weak coordination ability of ketones, compared to amines. We further evaluated the reaction in protic solvent *t*-AmOH (Table S1 in the SI), which is inferior to toluene. These results indicated that, besides the protic property, the solubility and dielectric constant of the solvent will also influence the kinetics and thermodynamics of the reaction. The formation of [Mn–H] species was confirmed by ¹H NMR spectroscopy (¹H NMR = –6.48 ppm; see the SI).

In summary, we have successfully utilized the unusual nonbifunctional outer-sphere strategy in developing an efficient manganese-catalyzed direct α -alkylation of ketones with alcohols through BH/HA method. This protocol is not only effective for the C–C bond formation between a variety of ketones and alcohols, but also is applicable in the catalytic Friedländer annulation reactions. This easily accessible and phosphine-free system shows advantages of the nonbifunctional outer-sphere strategy in catalyst design for acceptorless dehydrogenative transformations.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03030.

Detailed experimental procedures, characterization data, computational details and structures, copies of ^1H NMR and ^{13}C NMR spectra for all isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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