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Cu(I)-catalyzed α -alkylation of ketones with styrene derivatives

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Carbon-carbon bond forming reactions are used to construct main frameworks of organic molecules. α -Alkylation of carbonyl compounds is among the most important and widely used approaches for this purpose. Generally, α -alkylation of carbonyl compounds is accomplished through initial conversion to enolates using stoichiometric amounts of base, followed by nucleophilic attack of the thus-generated enolates to alkylating reagents, such as alkyl halides and tosylates. This method is reliable, but the use of more than 1 equiv of strong base limits compatible functional groups in the substrates. In addition, the use of alkylating reagents with leaving groups inevitably produces a stoichiometric amount of metal salt waste, which is not favorable in terms of atom economy.¹ Overalkylation is also problematic in some cases. Although, recent catalytic allylic alkylation reactions have overcome these drawbacks to some extent,² the use of enolates containing a single carbonyl group as a nucleophile in allylic alkylation reactions remains difficult. The Michael addition³ produces α-alkylated carbonyl compounds; however, the electrophiles require electronwithdrawing groups.

On the other hand, there have been several reports of catalytic α -alkylation or alkenylation of carbonyl compounds using unactivated alkenes and alkynes as electrophiles.⁴ These types of reactions do not require leaving groups or electron-withdrawing groups on the electrophiles. 1,3-Diketones, β -keto esters, and aldehydes have been used as common nucleophiles in these reactions.^{5,6} α -Alkylation of ketones using olefins as electrophiles

ABSTRACT

 α -Alkylation of ketones with styrene derivatives was developed using a mesitylcopper–dppp complex as a soft Brønsted base catalyst. No waste derived from the alkylating reagent was produced in this catalytic alkylation reaction. The bisphosphine ligand structure, as well as the reaction solvent, had profound effects on catalyst activity. The reaction proceeded under mild conditions from a range of ketones and styrene derivatives. The present catalysis is especially useful for the selective mono-alkylation of ketones. © 2012 Elsevier Ltd. All rights reserved.



Figure 1. Activation of ketones and olefins.

has been less explored, however, despite the fact that ketones are a common functional group in organic synthesis.⁷ The previously reported catalytic methods of α -alkylation of ketones with unactivated unsaturated C–C bonds can be classified into the following three types; (1) addition of α -carbon radicals derived from ketones to alkenes (Fig. 1a),⁸ (2) addition of enols or silyl enol ethers to alkenes or alkynes through the activation of π -bonds by π -acidic transition metals (Fig. 1b),⁹ and (3) addition of highly nucleophilic alkali metal enolates to alkenes or alkynes (Fig. 1c).¹⁰

We envisioned that the addition of ketone-derived enolates to unactivated alkenes in the third category is a potentially useful alkylation method because the ketone-derived enolates are rather stable and relatively easy to prepare using a Brønsted base catalyst. All of the previously reported enolate addition reactions to unactivated alkenes used potassium enolates as the active species. The reaction conditions are highly basic, however, so application to multifunctional substrates is difficult. In addition, overalkylation





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Table 1

Initial screening



Entry	Base	Additive	Solvent	Yield ^a (%)
1	CuO ⁱ Pr	None	DMSO	0
2	CuO ⁱ Pr	1,10-Phen	DMSO	0
3	CuO ⁱ Pr	rac-Binap	DMSO	0
4	CuO ⁱ Pr	Bu₃P ^b	DMSO	8
5	CuO ⁱ Pr	dppe	DMSO	21
6	CuO ⁱ Pr	dppp	DMSO	88 (85) ^c
7	CuO ⁱ Pr	dppb	DMSO	1<
8	CuO ⁱ Pr	dppp	DCE	0
9	CuO ⁱ Pr	dppp	THF	0
10	CuO ⁱ Pr	dppp	HMPA	0
11	CuO ⁱ Pr	dppp	DMF	90
12	MesCu	dppp	DMSO	91 (84) ^c

^a Yields were determined by ¹H NMR spectroscopy by using an internal standard.
^b 21 mol% of Bu₃P was added.

^c Isolated yields were shown in parentheses.

Table 2

Substrate scope^a

decreases the yield of the desired products. We hypothesized that the reaction would proceed under milder basic conditions with the use of a transition metal enolate due to the ability of transition metals to activate π -bonds (Fig. 1d), leading to higher functional group tolerance and the capacity for mono-alkylation.

Based on this idea, we began our investigation with the catalytic α -alkylation of propiophenone (1a) using styrene (2a). We first studied various catalytic combinations of transition metal triflates or halides (metal = nickel, rhodium, ruthenium, palladium, gold, silver, etc.) with potassium *tert*-butoxide, expecting the formation of transition metal enolates in situ. These combinations, however, did not improve the reactivity compared to the use of potassium tert-butoxide as a catalyst. Therefore, we next focused our attention on a copper(I) alkoxide¹¹ catalyst. We previously reported that a chiral copper alkoxide could be a Brønsted base catalyst for various asymmetric addition reactions.^{12,13} Thus, copper(I) alkoxides should deprotonate ketones, generating a copper enolate species. Furthermore, copper(I) could interact with olefins because copper(I) forms π -complexes with olefins.¹⁴ Together, we hypothesized that both enolate formation and π -activation of olefins would be possible with a copper(I) catalyst.¹⁵

We first investigated copper isopropoxide, generated from commercially available mesityl copper and 1 equiv of *i*PrOH,^{11,12} as a catalyst in the reaction of **1a** and **2a** (Table 1). In the absence of any ligands, copper isopropoxide formed a precipitate under the



Entry	Ketones	Olefins	Time (h)	Yield (%)
1	Ph Me 1a	≫ ^{Ph} 2a	24	85
2	Ph Et 1b	2a	24	70
3	MeO Me	2a	24	92
4	Fe Me 1d	2a	24	71
5	1e	2a	24	78 ^b
6	Me Me 1f	2a	48	35
7 8	1a 1a	Br 2b: 4-Br 2c: 2-Br	35 26	85 89

 Table 2 (continued)

Entry	Ketones	Olefins	Time (h)	Yield (%)
9	1a	2d	42	87
10	1a	CN 2e	42	61
11	1a	2f : 4-vinvl	37	81
12	1a	N 2g: 2-vinyl	35	92
13	1a	Ph 2h	24	67 ^c

^a Conditions: MesCu (10 mol%), dppp (11 mol%), DMSO (0.5 M), 45 °C. Yields are isolated yields.

^b Reaction temperature: 60 °C.

^c Yield was determined after hydrogenation by Pd/fibroin, H₂, MeOH.



Figure 2. Comparison experiments of mono-alkylation.

reaction conditions (entry 1). To stabilize the active copper species, we screened various ligands. Although, amine ligands and tri-aryl phosphine ligands did not produce any desired alkylation products (entries 2 and 3), 3aa was obtained in 8% yield when using tributylphosphine (entry 4). Use of a 1,2-bis(diphenylphosphino)ethane ligand significantly improved the reactivity, and the yield of 3aa was increased to 21% (entry 5). Encouraged by this result, we next studied the effects of the linker length between two phosphine moieties, and found that 1,3-bis(diphenylphosphino)propane was the best ligand for this reaction (85% yield, entry 6). Catalyst activity was sharply decreased, however, by increasing the linker by one carbon using 1,4-bis(diphenylphosphino)butane as the ligand (entry 7). These results suggest that both proper bite angle and flexibility of the ligand backbone are keys for high catalyst activity. The solvent effects were also large, and only DMSO and DMF were appropriate solvents (entries 6 and 11). The use of other solvents, such as THF, dichloroethane, and hexamethylphosphoramide resulted in negative effect on the product yields (entries 8-10). Finally, we found that mesitylcopper catalyzed the α -alkylation with efficiency comparable to copper isopropoxide (entry 12). Due to the easier manipulations, we considered the conditions of entry 12 to be optimal.

The substrate scope was investigated under the optimized conditions (Table 2). The reaction of butyrophenone (**1b**) produced a slightly lower yield than propiophenone, possibly due to the increased steric bulkiness (entry 2). Propiophenone derivative **1c** with an electron-donating *p*-methoxy substituent on the aromatic ring exhibited higher reactivity (entry 3) than propiophenone, while a propiophenone derivative with an electron-withdrawing *p*-chloro substituent produced only trace amounts of the product. This finding suggests that the addition of a copper enolate to alkenes, rather than the deprotonation of ketones, was the rate-determining step,¹⁶ which is consistent with the result using electron-rich ferrocene-substituted ketone **1d** (entry 4). α -Tetralone (**1e**) also had a high reactivity (entry 5). The product yield from aliphatic ketone **1f** was moderate because dialkylations proceeded as side reactions (entry 6).

The scope of olefin substrates was then investigated. Both o- and *p*-bromo styrene derivatives **2b** and **2c** afforded the corresponding products in high yield (entries 7 and 8). The reaction proceeded selectively at the C=C double bond, even when using olefins with polar electron-withdrawing functional groups, such as an ester or nitrile, on the aromatic ring (entries 9 and 10). However, the reaction of an olefin possessing an electron-donating *p*-methoxy group did not proceed at all under the optimized conditions. On the other hand, it is noteworthy that vinyl pyridines 2f and 2g, which potentially coordinate to the copper catalyst and deactivate its activity, were excellent olefin substrates in this reaction (entries 11 and 12). Diene 2h was a competent substrate with the reaction proceeding selectively at the terminal position of the diene (entry 13). Although, the present catalysis is limited to the aryl-substituted olefins, the requirement of just a 1:1 ratio of ketones and olefins for high product yields is significant. In contrast, under the previous conditions, excess amounts of ketones were always required.

An advantage of the current Cu(I)-catalyzed alkylation of ketones is its excellent selectivity for mono-alkylation in the case of aromatic ketones. Thus, we compared the current Cu(I)-catalyzed reaction to the previous KOtBu-catalyzed reaction¹⁰ under various conditions (Fig. 2). First, we performed the reaction between 1 equiv of 1a and 2 equiv of 2a (Fig. 2a). Using KOtBu as the catalyst, 55% of mono-alkylated product 3aa and 45% of dialkylated product 3aa' were obtained after 24 h. On the other hand, use of the Cu(I)-dppp catalyst produced mono-alkylated product **3aa** in 96% yield concomitant with only 4% of di-alkylated product 3aa'. In addition, a competitive experiment using 0.5 equiv of 1a and 0.5 equiv of 1g in the presence of 1 equiv of 2a showed excellent selectivity for mono-alkylation in the current catalysis (Fig. 2b). In the KOtBu catalysis, 3aa was obtained in 49% along with 3ga 29%. On the other hand, in the Cu(I)-dppp system, 3aa was obtained selectively in 48% along with only 2% of 3ga. Thus, the Cu(I)-catalyzed alkylation is especially suitable for selective mono-alkylation of aromatic ketones.

In summary, we have demonstrated a catalytic α -alkylation reaction of ketones with styrene derivatives using a mesitylcopper–dppp complex. The reaction proceeded under mild conditions from a range of ketones and styrenes. The present catalysis is especially suitable for mono-alkylation of ketones.

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