Efficient Copper(II)-Catalyzed Addition of Activated Methylene Compounds to Alkenes

Yu Li,[†] Zhengkun Yu,*[,†,‡] and Sizhong Wu[†]

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road,
Dalian, Liaoning 116023, PR China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

zkyu@dicp.ac.cn

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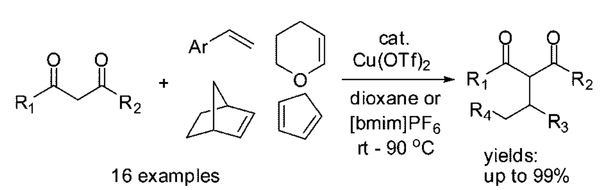

Efficient regioselective addition of β-diketones to styrenes, norbornene, cyclic enol ether, and diene has been realized by means of copper(II) triflate as the catalyst. The solvent effect is prominent on the reactions, and the desired addition products were obtained in good to excellent yields only in dioxane or ionic liquid [bmim]PF$_6$. The mechanism suggests that copper(II) triflate activates the enolic O−H bond of a β-diketone substrate to initiate the addition reaction.

Catalytic alkylation of 1,3-dicarbonyl compounds is considered as one of the most promising atom-economical organic processes for C−C bond formation because use of a stoichiometric amount of base and an organic halide can be avoided.[1] Catalytic addition to alkenes is extremely attractive for alkylation of 1,3-dicarbonyl compounds and has recently been paid considerable attention.[2] Highly efficient addition of activated methylene compounds to alkenes was reported by means of AuCl$_3$ catalyst in the presence of AgOTf in CH$_2$Cl$_2$.[3] In solvent CH$_3$NO$_2$ and at elevated temperature such as 100 °C, inter- and intramolecular alkylation of 1,3-dicarbonyl compounds by alkenes can be catalyzed by AgOTf.[4] Intramolecular hydroalkylation of alkenyl-1,3-dicarbonyl compounds was also documented with palladium(II) catalysts.[5] Lewis acidic indium triflate-catalyzed vinylation of β-ketoesters with acetylene gas occurred efficiently under atmospheric pressure.[6] Recently, inexpensive FeCl$_3$-catalyzed addition of 1,3-dicarbonyl compounds to styrenes has been developed.[7] Cationic ruthenium(II) is also effective to catalyze the addition of β-diketones to alcohols and styrenes.[8] Catalytic addition of 1,3-dicarbonyl compounds to alkynes was promoted with palladium,[9] rhenium,[10] or nickel/Yb.[11] Ni(II)-catalyzed addition of 1,3-dicarbonyl compounds to conjugated nitroalkenes[12] and base-mediated addition of β-diesters to allenes[13] have been explored. Copper(II) triflate has recently been documented to catalyze the addition of O−H bonds to norbornene[14] and N−H bonds to norbornene, vinyl arenes, and 1,3-cyclohexadiene.[15] Cu(OTf)$_2$-catalyzed intramolecular hydroamination of γ- and δ-alkenyl sulfonamides were reported by Takaki et al.[16] Very recently, Li's group reported Cu(OTf)$_2$-catalyzed hydroalkylation of alkenes in neat liquids (12 examples):[2] only in the reactions of dibenzoylmethane with styrene or 4-chlorostyrene the desired products were collected in 85% yields, and in other cases, the hydroalkylation products were obtained in 5−58% yields. In SnBr$_4$-catalyzed hydroalkylation of the same alkenes in ionic liquid [bmim]OTf (bmim = 1-butyl-3-methylimidazolium),[2] the products were usually formed in poor yields (0−41%), and only in the reactions of dibenzoylmethane with styrene or 4-chlorostyrene the desired products were afforded in 60−61% yields. Keeping this in mind, we became interested in copper(II) triflate-catalyzed reactions of alkenes and substrates with activated C−H bonds that are similar in acidity to the N−H bonds of amines,[17] that is, β-diketones, and found that Cu(OTf)$_2$-catalyzed addition reactions of β-diketones to alkenes are very sensitive to the reaction media. Herein, we wish to report Cu(OTf)$_2$-catalyzed intermolecular hydroalkylation of alkenes by activated methylene compounds (i.e., β-diketones) in dioxane and ionic liquid [bmim]PF$_6$.

[†] Dalian Institute of Chemical Physics.

[‡] Shanghai Institute of Organic Chemistry.

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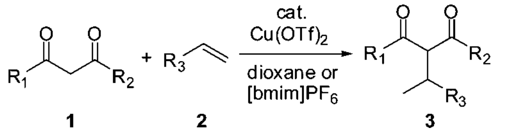
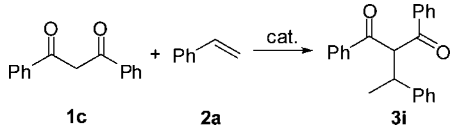


(1)

The catalytic efficiency of various copper reagents was initially tested in the addition of dibenzoylmethane to styrene (Table 1). Because styrene dimer can be easily formed as the side product in all the cases, excess of styrene (1.5 equiv) was used in the reactions. At 75 °C in dioxane, Cu(I) and Cu(II) halides such as CuI, CuBr, and $CuCl_2$ exhibited no catalytic activity to the alkylation of dibenzoylmethane (**1c**) by styrene (**2a**), while $CuBr_2$ showed low catalytic activity with a poor conversion of the β-diketone substrate (Table 1, entries 1−4). In the poor polar solvent, such as toluene, copper(II) triflate demonstrated negligible catalytic activity (entry 5). However, in refluxing THF (66 °C) or in DCE at 75 °C, $Cu(OTf)_2$ showed a better catalytic activity, and the desired product was isolated in 26−40% yields (entries 6 and 7). In dioxane at 75 °C, the catalytic activity of $Cu(OTf)_2$ was remarkably improved, promoting the formation of **3i** in 72% yield (entry 8). With a lower loading of the catalyst (i.e., 15 mol % $Cu(OTf)_2$), the desired product was isolated in 68% yield (entry 9). With 15 mol % of the catalyst and increasing the reaction temperature to 90 °C, the same reaction afforded **3i** in 76% yield (entry 10). Using ionic liquid [bmim]PF_6 as the reaction medium, $Cu(OTf)_2$-catalyzed alkylation of **1c** by **2a** also worked very well (entry 11). It is obvious that the reaction is very sensitive to the reaction media and temperature. The Cu(II) catalyst may be additionally stabilized by the oxygen or nitrogen donor atoms in dioxane or [bmim]PF_6 because it has showed very good catalytic activity in the addition of dibenzoylmethane to styrene in these solvents. The reaction can not be efficiently carried out at temperatures above 90 °C due to obvious dimerization or polymerization of styrene.

Subsequently, the optimized reaction conditions were applied in the alkylation of a variety of β-diketones by alkenes (Table 2). Most of the 1,3-dicarbonyl compounds were effectively added to styrenes, norbornene, cyclic enol ether, and diene, but no desired product was detected from the reactions of dimethyl malonate with alkenes (Table 2, entry 16), which might be attributed to the incapability of dimethyl malonate to be enolized during the reaction. The addition of 2,4-pentanedione (**1a**) to styrenes (**2a**−**c**) and norbornene (**2d**) in dioxane formed the desired products (**3a**−**d**) in 42−69% yields (Table 2, entries 1−4). Unexpectedly, the reaction of **1a** and norbornene in ionic liquid [bmim]PF_6 afforded product **3d** in 94% yield (entry 5). The reaction favors exclusive formation of the *exo*-isomer (coupling between the *endo*-proton and its adjacent bridgehead methane proton is conspicuously absent from the H−H COSY spectrum of **3d**).[15] The addition of a more reactive unsymmetrical β-diketone, such as 1-phenyl-1,3-butanedione (**1b**), to **2a**−**d** produced the desired products **3e**−**h** as two diastereomers in 72−82% yields (entries 6−9). The diastereoselectivity of the products is presumably attributed to the two enolizable forms of the 1,3-diketone substrate and introduction of two different chiral centers to the product molecules. In the same fashion, the reaction of **1b** with norbornene in [bmim]PF_6 afforded the desired product **3h** in 99% yield (entry 10). The reactions of symmetrical β-diketone **1c** and alkenes **2a**, **2c**, and **2d** formed products **3i**, **3k**, and **3l** in 76−79% yields, respectively, while its reaction with **2b** only produced **3j** in 29% yield (entries 11−14). The desired product **3l** was also formed in a high yield (96%) in the ionic liquid (entry 15). As discussed for the configuration of **3d**, the H−H COSY spectrum of **3l** also revealed exclusive formation of the *exo*-isomer. However, in other cases, ionic liquid [bmim]PF_6 or [bmim]BF_4 did not improve formation of the expected addition products. It should be noted that because 3,4-dihydro-2*H*-pyran (**2e**) and cyclopentadiene (**2f**) can be easily polymerized at elevated temperature, their reactions were carried out under rather mild conditions. At ambient temperature (25 °C), β-diketones **1a** and **1d** demonstrated no obvious reactivity to alkenes **2e** and **2f**, while the addition products **3n**−**q** were isolated in 27−73% yields from the reactions of **1b**,**c** with **2e**,**f** (entries 17−20), respectively.

TABLE 1. Catalytic Addition of Dibenzoylmethane to Styrene (Conditions: dibenzoylmethane, 1 mmol; styrene, 1.5 mmol; solvent, 5 mL; 20 h)

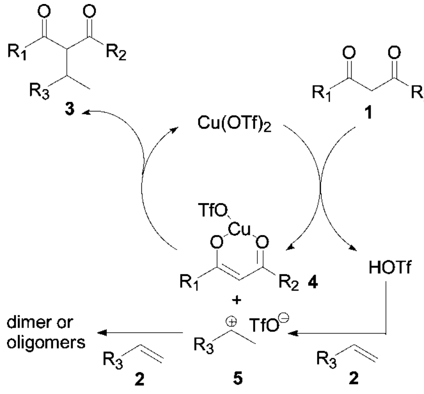


entry	catalyst (mol %)	solvent	temp (°C)	yield (%)[a]
1	CuI (25)	dioxane	75	0
2	CuBr (25)	dioxane	75	0
3	$CuCl_2 \cdot 2H_2O$ (25)	dioxane	75	0
4	$CuBr_2$ (25)	dioxane	75	18[b]
5	$Cu(OTf)_2$ (25)	toluene	75	<5
6	$Cu(OTf)_2$ (25)	THF	65	26
7	$Cu(OTf)_2$ (25)	DCE[c]	75	40
8	$Cu(OTf)_2$ (25)	dioxane	75	72
9	$Cu(OTf)_2$ (15)	dioxane	75	68
10	$Cu(OTf)_2$ (15)	dioxane	90	76
11	$Cu(OTf)_2$ (25)	[bmim]PF_6	90	52

[a] Isolated yields of **3i**. [b] 30% conversion for **1c**. [c] DCE = dichloroethane.

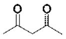
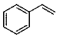
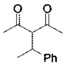
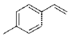
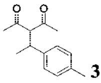
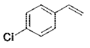
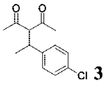
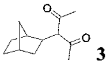
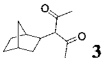
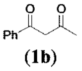
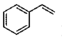
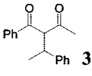
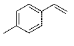
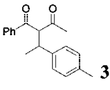
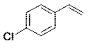
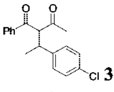
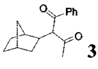
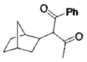
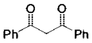
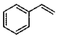
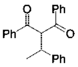
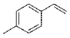
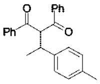
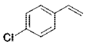
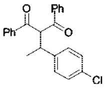
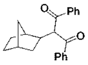
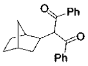
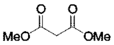
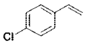
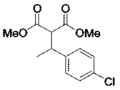
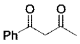
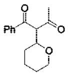
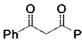
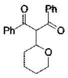
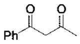
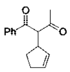
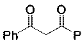
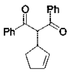
A mechanism for the present $Cu(OTf)_2$-catalyzed addition reactions is proposed in Scheme 1. The catalyst reacts with the enolized form of a β-diketone to generate copper(II) intermediate **4** and release of triflic acid (HOTf) which then protonates the alkene, furnishing a carbocation **5**. The carbocation reacts with intermediate **4** to yield the desired addition product **3** and/or it reacts with another molecule of alkene to form a dimer and/or higher oligomers as the side products.

SCHEME 1. A Proposed Mechanism for $Cu(OTf)_2$-Catalyzed Addition Reactions



In conclusion, efficient regioselective addition of β-diketones to styrenes, norbornene, cyclic enol ether, and diene has been

TABLE 2. Copper(II)-Catalyzed Addition of β-Diketones to Alkenes (Conditions: β-diketone, 1 mmol; alkene, 1.5 mmol; $Cu(OTf)_2$, 0.15 mmol; dioxane, 5 mL, 90 °C, 20 h)

entry	β-diketone	alkene	product	yield (%)[a]
1	 **(1a)**	 **2a**	 **3a**	63
2	**1a**	 **2b**	 **3b**	69
3	**1a**	 **2c**	 **3c**	42
4	**1a**	 **2d**	 **3d**	57[b]
5[c]	**1a**	 **2d**	 **3d**	94[b]
6	 **(1b)**	 **2a**	 **3e**	78 (1.1 : 1.0)
7	**1b**	 **2b**	 **3f**	72 (1.2 : 1.0)
8	**1b**	 **2c**	 **3g**	78 (1.3 : 1.0)
9	**1b**	 **2d**	 **3h**	82 (1.1 : 1.0)
10[c]	**1b**	 **2d**	 **3h**	99 (1.1 : 1.0)
11	 **(1c)**	 **2a**	 **3i**	76
12	**1c**	 **2b**	 **3j**	29[d]
13	**1c**	 **2c**	 **3k**	78
14	**1c**	 **2d**	 **3l**	79[b]
15[c]	**1c**	 **2d**	 **3l**	96[b]
16	 **(1d)**	 **2c**	 **3m**	0
17	 **1b**	 **2e**	 **3n**	73[e] (2.6 : 1.0)
18	 **1c**	 **2e**	 **3o**	28[e]
19	 **1b**	 **2f**	 **3p**	27[e] (2.6 : 1.0)
20	 **1c**	 **2f**	 **3q**	35[e]

[a] Isolated yields, isomer ratios (in parentheses) determined by ^1H NMR. [b] The *exo* product was determined by H−H COSY analysis. [c] 5 g of $[bmim]PF_6$ was used as the solvent. [d] 38% conversion for **1c**. [e] 25 °C, 20 h.

realized with a remarkable solvent effect by means of copper(II) triflate as the catalyst. The mechanism suggests that copper(II) triflate activates the enolic O−H bond of a β-diketone to initiate the reaction.

Experimental Section

Typical Procedure for $Cu(OTf)_2$-Catalyzed Addition Reactions in Dioxane: A mixture of the catalyst $Cu(OTf)_2$ (54 mg, 0.15 mmol) and 5 mL of dioxane was stirred under nitrogen at 90 °C for 10 min, and then a β-diketone **1** (1 mmol) and alkene **2** (1.5 mmol) were introduced. The resulting mixture was stirred at 90 °C for 20 h. After cooling to ambient temperature, all the volatiles were removed under reduced pressure. Purification of the resultant residue by flash silica gel column chromatography (petroleum ether (60−90 °C)/ethyl acetate, v/v = 50/1) afforded the desired product **3**. All the addition products were >98% pure by HPLC determination and identified by comparison of their ^1H NMR features with the reported authentic NMR data for the known compounds, and the new compounds **3f**, **3j**, and **3p**were further characterized by HRMS analysis.

Synthesis of 1-Phenyl-2-(1-*p*-tolylethyl)butane-1,3-dione (3f): A mixture of 1-phenyl-1,3-butanedione **1b** (0.162 g, 1 mmol), 4-methylstyrene **2b** (0.177 g, 1.5 mmol), and $Cu(OTf)_2$ (0.054 g, 0.15 mmol) in 5.0 mL of dioxane was stirred at 90 °C for 20 h. After quenching the reaction and workup, purification by silica gel column chromatography (petroleum ether (60−90 °C)/ethyl acetate, v/v = 50/1) afforded **3f** as a colorless oil (0.201 g, 72%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.4 Hz, 2H), 7.62−6.97 (m, 7H), 4.89 (d, J = 11.0 Hz, 1H), 3.87−3.81 (m, 1H), 2.38 (s, 3H), 1.92 (m, 3H), 1.20 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.5, 195.5, 140.2, 137.4, 136.7, 133.9, 129.6, 129.0, 128.6, 127.3, 71.2, 40.7, 27.9, 21.9, 21.0. The other diastereomer (from the mixture of two isomers and some peaks are difficult to be distinguished.): ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.4 Hz, 2H), 7.62−6.97 (m, 7H), 4.82 (d, J = 11.0 Hz, 1H), 3.87−3.81 (m, 1H), 2.23 (s, 3H), 2.21 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.0, 195.5, 140.6, 137.2, 136.2, 133.5, 129.3, 128.7, 128.5, 126.6, 71.8, 40.0, 27.6, 21.2, 20.5; HRMS (EI) m/z calcd for $C_{19}H_{20}O_2$ (M^+) 280.1463, found 280.1473.

Synthesis of 1,3-Diphenyl-2-(1-*p*-tolylethyl)propane-1,3-dione (3j): A mixture of dibenzoylmethane **1c** (0.224 g, 1 mmol), 4-methylstyrene **2b** (0.177 g, 1.5 mmol), and $Cu(OTf)_2$ (0.054 g, 0.15 mmol) in 5.0 mL of dioxane was stirred at 90 °C for 20 h. After quenching the reaction and workup, purification by silica gel column chromatography (petroleum ether (60−90 °C)/ethyl acetate, v/v = 50/1) afforded **3j** as a white solid (0.100 g, 29%): mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.44 Hz, 2H), 7.78 (d, J = 7.4 Hz, 2H), 7.58− 7.27 (m, 6H), 7.18 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 5.64 (d, J = 10.1 Hz, 1H), 4.10−4.06 (m, 1H), 2.22 (s, 3H), 1.36−1.34 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.2, 194.7, 140.9, 137.3, 137.0, 136.2, 133.6, 133.1, 129.2, 128.9, 128.6, 128.5, 127.6, 65.1, 40.9, 21.0, 20.5; HRMS (EI) m/z calcd for $C_{24}H_{22}O_2$ (M^+) 342.1620, found 342.1626.

Typical Procedure for $Cu(OTf)_2$-Catalyzed Addition Reactions in $[bmim]PF_6$—Synthesis of 3-Bicyclo[2.2.1]hept-2-yl-pentane-2,4-dione (3d): A mixture of 2,4-pentanedione **1a** (0.101 g, 1 mmol), norbornene **2d** (0.141 g, 1.5 mmol), and $Cu(OTf)_2$ (0.054 g, 0.15 mmol) in 5.0 g of $[bmim]PF_6$ was stirred at 90 °C for 20 h. After cooling to ambient temperature, the resulting mixture was extracted with diethyl ether (4 × 5 mL). The ether phase was concentrated under reduced pressure and further purified by silica gel column chromatography (petroleum ether (60−90 °C)/ethyl acetate, v/v = 50/1) to afford **3d** as a colorless oil (0.184 g, 94%). Compound **3d** was identified by comparison of its ^1H NMR features with the reported authentic NMR data,[16] and its configuration was determined by H−H COSY NMR analysis (see the Supporting Information).

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Supporting Information Available: Experimental details, spectroscopic data, and copies of ^{1}H, $^{13}C\{^{1}H\}$ NMR and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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