JOC*Article*

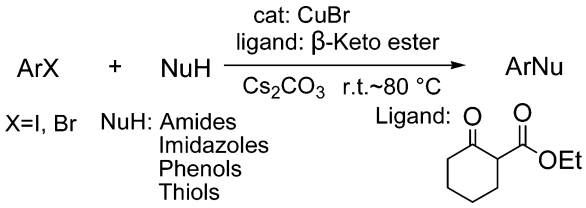
A β-Keto Ester as a Novel, Efficient, and Versatile Ligand for Copper(I)-Catalyzed C−N, C−O, and C−S Coupling Reactions

Xin Lv and Weiliang Bao*

Department of Chemistry, Xixi Campus, Zhejiang University, Hangzhou 310028, People's Republic of China

wlbao@css.zju.edu.cn

Received March 3, 2007



Employing ethyl 2-oxocyclohexanecarboxylate as a novel, efficient, and versatile ligand, the copper-catalyzed coupling reactions of various N/O/S nucleophilic reagents with aryl halides could be successfully carried out under mild conditions. A variety of products including *N*-arylamides, *N*-arylimidazoles, aryl ethers, and aryl thioethers were synthesized in good to excellent yields.

Introduction

N-Arylamides, *N*-arylimidazoles, aryl ethers, and aryl thioethers are valuable compounds widely employed in organic synthesis, pharmaceutical, or biological areas.[1] One of the most common synthetic protocols for their preparation is copper-catalyzed Ullmann coupling. However, classic Ullmann reactions are usually conducted under harsh conditions, and therefore, their applications would be restricted. Recently, much enthusiasm has been paid to the improvement of Ullmann coupling, and significant progress has been made.[2−4] In 2001, Taillefer et al. discovered that pyrazoles were successfully N-arylated when several oxime/imine-type ligands (Cristau−Taillefer ligands) were used.[2g] In 2002, Buchwald et al. found that several diamino-type ligands could greatly facilitate the reactions between aryl halides and amides at low temperatures.[2j] Recently, they reported the copper-catalyzed C−N coupling reactions of aliphatic amines with aryl iodides promoted by β-diketone at room temperature, and satisfying results were achieved in relatively shorter reaction times.[5] Very recently, BINOL was used as a new ligand for copper-catalyzed N-arylation of aliphatic amines at room temperature by Fu and co-workers.[6] Ma et al. reported a C−C bond formation at surprisingly low temperatures facilitated by *trans*-4-hydroxy-L-proline, and they extended the Ullmann coupling to the area of enantioselective synthesis.[7] The above reports revealed that proper ligands could obviously accelerate the reaction rates and substantially lower the reaction temperatures. However, the applications of these Ullmann methods might be limited in a certain degree by the high expense, unavailability, or specificity

* To whom correspondence should be addressed. Tel/Fax: +86 571 88273814. E-mail: wlbao@css.zju.edu.cn.

(1) For reviews, see: (a) Barchechath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409. (b) Zhong, C.; He, J.; Xue, C.; Li, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4009. (c) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345. (d) Buckingham, J. B. In *Dictionary of Natural Products*; CRC Press: Boca Raton, FL, 1994; Vol. 1.

(2) For recent copper-catalyzed C−N coupling reactions, see: (a) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem.* **2007**, *46*, 934. (b) Chen, Y-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609. (c) Buchwald, S. L.; Altman, R. A. *Org. Lett.* **2006**, *8*, 2779. (d) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435. (e) Zhang, H.; Cai, Q.; Ma, D. W. *J. Org. Chem.* **2005**, *70*, 5164. (f) Buchwald, S. L.; Antilla, J. C.; Baskin, J. M.; Barder, T. E. *J. Org. Chem.* **2004**, *69*, 5578. (g) Cristau, H.-J.; Cellier, P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695. The related applications were earlier reported in a patent in 2001 (FR 01 16547). (h) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (i) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (j) Buchwald, S. L.; Klapars, A.; Huang, X. H. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(3) For recent C−O coupling reactions, see: (a) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Organometallics* **2007**, *26*, 65. (b) Ouali, A.; Spindler, J.-F.; Cristau, H. J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499. (c) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913. (d) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (e) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 10770. (f) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.

(4) For recent C−S coupling reactions, see: (a) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.

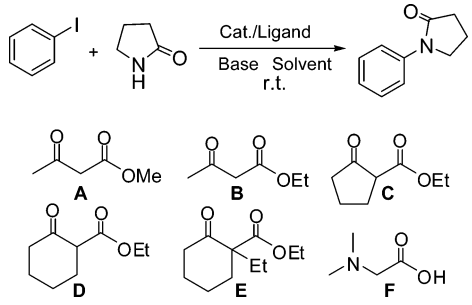
(5) Shafir, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(6) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672.

(7) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.

10.1021/jo070443m CCC: $37.00
Published on Web 04/14/2007

TABLE 1. N-Arylation of 2-Pyrrolidinone in Different Conditions[a]



entry	cat/L	base	solvent	yield %[b]
1	CuI/**A**	Cs_2CO_3	DMF	trace
2	CuI/**B**	Cs_2CO_3	DMF	36
3	CuI/**C**	Cs_2CO_3	DMF	30
4	CuI/**D**	Cs_2CO_3	DMF	78
5	CuI/**E**	Cs_2CO_3	DMF	trace
6	CuI/**F**	Cs_2CO_3	DMF	34
7	CuI/−	Cs_2CO_3	DMF	trace
8	CuI/**D**	K_2CO_3	DMF	16
9	CuI/**D**	K_3PO_4	DMF	55
10	CuI/**D**	Cs_2CO_3	CH_3CN	83
11	CuI/**D**	Cs_2CO_3	NMP	70
12	CuI/**D**	Cs_2CO_3	dioxane	22
13	CuI/**D**	Cs_2CO_3	[Bmim]BF_4	trace
14	CuI/**D**	Cs_2CO_3	DMSO	93
15	CuBr/**D**	Cs_2CO_3	DMSO	96
16	CuCl/**D**	Cs_2CO_3	DMSO	11
17	Cu_2O/**D**	Cs_2CO_3	DMSO	7

[a] Reaction conditions: iodobenzene (1.0 mmol), amide (1.2 mmol), Cu(I) catalyst (0.1 mmol), ligand (0.2 mmol), and Cs_2CO_3 (2.1 mmol) in indicated solvent (1.0 mL) at rt (~25 °C) under N_2 for 22 h. [b] Isolated yields.

of the ligands. Recently, several examples have been presented to apply the same ligands for various carbon−heteroatom coupling reactions, and their applications seem to be of more and more importance.[2d,e,3d,8] Therefore, more efficient, versatile, and facile ligands for facilitating these coupling reactions under relatively milder conditions are still in demand.

Inspired by Buchwald's active β-diketone-type ligands, we examined more commercially available and facile β-keto esters as ligands. Fortunately, we found one of them could facilitate various copper(I)-catalyzed carbon−heteroatom coupling reactions. Herein we report that, promoted by ethyl 2-oxocyclohexanecarboxylate, aryl halides could successfully couple with N/O/S nucleophilic reagents at relatively lower temperatures (no higher than 80 °C).

Results and Discussion

Optimization of the Coupling Condition. Initially, we tried to seek the optimal ligand from compounds **A**−**F** for Cu(I)-catalyzed C−N bond formation. Iodobenzene and 2-pyrrolidinone were chosen as the model substrates with CuI as the catalyst. The linear β-keto esters **A** and **B** were employed (Table 1, entries 1 and 2). However, there was only a trace amount of the product detected in the presence of **A**; the reaction promoted by **B** gave low yield. The cyclic β-keto ester **C** seemed to not be suitable for this coupling either (entry 3). Another cyclic β-keto ester **D** was tested, and moderate result was achieved (entry 4). Interestingly, an α-substituted cyclic β-keto ester **E** was introduced into the reaction to compare with ligand **D**, but it seemed to be inefficient (entry 5). Maybe the Et group blocked the formation of the enolate. An amino acid *N*,*N*-dimethyl glycine (ligand **F**), once reported as a good ligand for vinyl C−N coupling, was examined.[9] However, low yield revealed that **F** was inefficient in this reaction condition (entry 6). Finally, a blank test without any ligand was carried out, and almost no product was detected in the same condition (entry 7). The effects of these ligands on the reaction were clearly demonstrated by Figure 1.

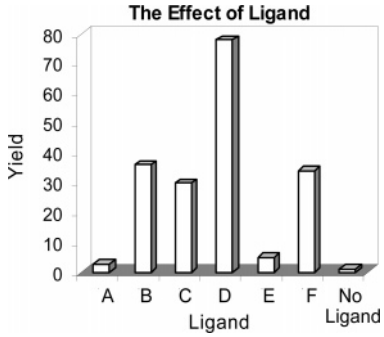


FIGURE 1. The effect of the ligand in the N-arylation of 2-pyrrolidinone.

A brief study of several other reaction conditions was carried out after the best ligand was determined. As shown in Table 1 (entries 4, 8, and 9), with their basicities increasing, K_2CO_3, K_3PO_4, and Cs_2CO_3 led to sharply ascending efficiencies in the arylation of pyrrolidin-2-one. Cs_2CO_3 was found to be the most appropriate base (entry 4). Then the effect of solvent was evaluated (Table 1, entries 4 and 10−14). Dioxane was not suitable as a solvent. To our surprise, the reaction in the RTIL (room-temperature ionic liquid) gave a disappointing result (entry 13). DMSO performed as the prime solvent; DMF, CH_3CN, and NMP were fairish, but were not as good as DMSO. The copper(I) resources also were proved to have remarkable effects on the reaction (entries 14−17). Both CuI and CuBr were satisfying, whereas CuBr was a little better than CuI. CuCl and Cu_2O performed improperly for the coupling reaction. Therefore, the optimized conditions employed 10 mol % of CuBr, 20 mol % of ligand **D**, and 2.1 equiv of Cs_2CO_3 in DMSO.

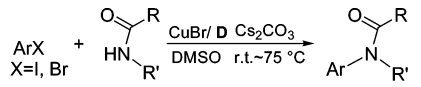
Coupling Reactions of Aryl Halides with Amides under the Catalysis of CuBr/Ethyl 2-Oxocyclohexanecarboxylate. After the best reaction condition was set, we screened different aryl halides and amides to explore the scope of the C−N coupling reactions. The *p*-Cl and *p*-Br groups on the aryl iodides were tolerated, and good results could be obtained at room temperature (Table 2, entries 2 and 3). Electron-donating groups on the aryl halides usually depressed the efficiencies of the reactions to a certain extent. Those halides with a *p*-Me group generally required higher temperatures (entries 4 and 10). Para-methoxy aryl halides gave the worst results and needed higher temperatures and longer reaction time (entries 5 and 11).

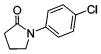
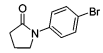
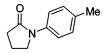
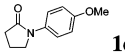
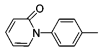
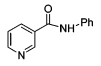
Coupling Reactions of Aryl Halides with Imidazoles under the Catalysis of CuBr/Ethyl 2-Oxocyclohexanecarboxylate. The C−N coupling reactions between aryl halides and imida-

(8) (a) Ouali, A.; Laurent, R.; Caminade, A.-M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990. (b) Ouali, A.; Renard, B.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2006**, *20*, 5301. (c) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (d) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (e) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803.

(9) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.

TABLE 2. CuBr/Ethyl 2-Oxocyclohexanecarboxylate-Catalyzed N-Arylation of Amide[a]



entry	ArX	amides	product	temp, time	yield %[b]
1			 **1a**	r.t., 22 h	96
2			 **1b**	r.t, 23 h	90
3			 **1c**	r.t., 22 h	85
4			 **1d**	60 °C, 24 h	86
5			 **1e**	75 °C, 25 h	85
6			 **1f**	60 °C, 22 h	95
7			 **1g**	60 °C, 24 h	84
8			 **1h**	60 °C, 24 h	83
9			 **1i**	75 °C, 28 h	84
10			**1d**	75 °C, 26 h	81
11			**1e**	75 °C, 30 h	76
12			 **1j**	60 °C, 22 h	95

[a] Reaction conditions: halide (1.0 mmol), amide (1.2 mmol), CuBr (0.1 mmol), ligand **D** (0.2 mmol), and Cs_2CO_3 (2.1 mmol) in DMSO (1.0 mL) under N_2. [b] Isolated yields.

zoles were examined. The CuBr/β-keto ester-catalyzed protocol could also facilitate this type of C−N coupling efficiently (Table 3). The reactions of imidazole with some aryl iodides successfully occurred at an especially low temperature (45 °C, entries 1 and 2). It was found that they could handle the electronic effects (entries 2, 6, and 8). Unfortunately, the reactions seemed to be sensitive to the steric hindrance on the nucleophilic reagents. 1*H*-Benzoimidazole seemed to be more difficult to react with aryl halides compared to imidazole, but once higher temperatures were provided, moderate to good results were achieved (entries 3 and 7).

Coupling Reactions of Aryl Halides with Phenols under the Catalysis of CuBr/Ethyl 2-Oxocyclohexanecarboxylate. We also applied this ligand to the copper-catalyzed C−O coupling reactions of phenols with aryl halides. Fortunately, the catalysis system was found to be efficient in the aryl C−O bond-forming reactions. The diaryl ether products from the coupling between phenols and aryl iodides were obtained in good to excellent yields (Table 4, entries 1−4 and 8). While higher temperature and longer reaction times were employed, three aryl bromides also gave good yields (entries 5−7).

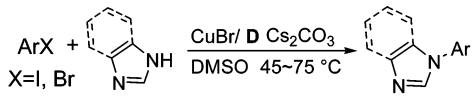
Coupling Reactions of Aryl Iodides with Thiols under the Catalysis of CuBr/Ethyl 2-Oxocyclohexanecarboxylate. The same catalytic system was applied for the last portion of our work: C−S bond formations via coupling of thiols with aryl iodides. The results showed that this ligand also could successfully promote these reactions, and the desired products were gained in good to excellent yields (Table 5).

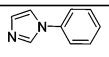
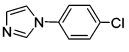
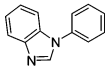
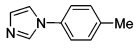
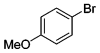
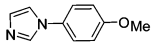
In summary, we found that the novel and commercially available ethyl 2-oxocyclohexanecarboxylate was an efficient and facile ligand. It could promote CuBr-catalyzed C−N, C−O, and C−S coupling reactions. Generally, good to excellent yields of the desired products could be successfully obtained. Noteworthy was that the readily available ligand would be versatilely used, and the coupling reactions promoted by this ligand occurred under mild conditions. Given these advantages, this method would have wilder implications for further development of Ullmann reactions.

Experimental Section

General Consideration. All reactions were carried out in Schlenk or test tubes, and run under an atmosphere of N_2. All of the copper sources, ligands, and bases were commercially available. Organic solvents, also were commercially available, were dried over 4 Å molecular sieves before being used. All amides, imidazoles, phenols, and thiols were used as received. Thin-layer chromatography (TLC) was carried out with 0.2 mm thick silica gel plates (GF 254) and visualized by UV light. The columns were packed

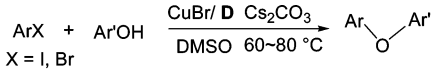
TABLE 3. CuBr/Ethyl 2-Oxocyclohexanecarboxylate-Catalyzed N-Arylation of Imidazole[a]

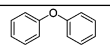
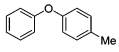
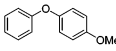
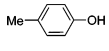


entry	ArX	imidazoles	product	temp, time	yield %[b]
1			 **2a**	45 °C, 22 h	96
2			 **2b**	45 °C, 23 h	91
3			 **2c**	60 °C, 25 h (45 °C, 28 h)	85 (55)
4			 **2d**	75 °C, 24 h	90
5			**2a**	75 °C, 22 h	87
6			**2b**	75 °C, 24 h	93
7			**2c**	75 °C, 28 h (45 °C, 24 h)	72 (23)
8			 **2e**	75 °C, 24 h	91

[a] Reaction conditions: halide (1.0 mmol), imidazole (1.2 mmol), CuBr (0.1 mmol), ligand **D** (0.2 mmol), and Cs_2CO_3 (2.1 mmol) in DMSO (1.0 mL) under N_2. [b] Isolated yields.

TABLE 4. CuBr/Ethyl 2-Oxocyclohexanecarboxylate-Catalyzed O-Arylation of Phenol[a]



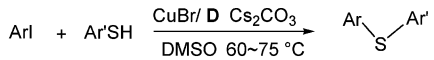
entry	ArX	phenols	product	temp, time	yield %[b]
1			 **3a**	60 °C, 20 h	97
2			 **3b**	80 °C, 22 h	85
3			 **3c**	75 °C, 26 h	82
4			**3b**	60 °C, 22 h	95
5			**3a**	80 °C, 26 h	81
6			**3b**	80 °C, 36 h	84
7			**3c**	80 °C, 36 h	72
8			**3d**	60 °C, 22 h	93

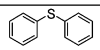
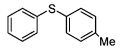
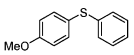
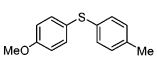
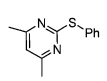
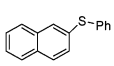
[a] Reaction conditions: halide (1.0 mmol), phenol (1.2 mmol), CuBr (0.1 mmol), ligand **D** (0.2 mmol), and Cs_2CO_3 (2.1 mmol) in DMSO (1.0 mL) under N_2. [b] Isolated yields.

with silica gel 60 (200−300). All products were confirmed by ^1H NMR and ^{13}C NMR. An unknown compound was additionally confirmed by IR and elemental analysis.

General Procedure. An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, Cs_2CO_3 (684 mg, 2.1 mmol), CuBr (15 mg, 0.10 mmol, 10 mol %), and ethyl 2-oxocyclohexanecarboxylate (34 mg, 0.20 mmol, 20 mol %). The tube was evacuated and backfilled with N_2 (this procedure was repeated three times). Under a counter flow of N_2, DMSO (0.5 mL) was added by syringe and pre-stirred for 0.5 h at room

TABLE 5. CuBr/Ethyl 2-Oxocyclohexanecarboxylate-Catalyzed S-Arylation of Thiol[a]



entry	ArX	thiols	product	Temp., Time	yield %[b]
1			 **4a**	60 °C, 20 h	97
2			 **4b**	60 °C, 20 h	94
3			 **4c**	60 °C, 24 h	85
4			 **4d**	75 °C, 22 h	93
5			 **4e**	75 °C, 24 h	81
6			 **4f**	60 °C, 22 h	92
7			 **4g**	60 °C, 22 h	90

[a] Reaction conditions: halide (1.2 mmol), thiol (1.0 mmol), CuBr (0.1 mmol), ligand **D** (0.2 mmol), and Cs_2CO_3 (2.1 mmol) in DMSO (1.0 mL) under N_2. [b] Isolated yields.

temperature. Then a solution of halide (1.0 mmol for C−N and C−O coupling; 1.2 mmol for C−S coupling) and nucleophilic reagent (1.2 mmol for C−N and C−O coupling; 1.0 mmol for C−S coupling) in DMSO (0.5 mL) was added via syringe under a counter flow of N_2. The tube was sealed, and the mixture was allowed to stir at the temperature indicated in Tables 2−5. The reaction was monitored by TLC. After the starting material was completely consumed, the reaction was stopped and the mixture was cooled to room temperature. The reaction mixture was directly passed through Celite. After being rinsed with another 60 mL of ethyl acetate, the combined filtrate was washed with saturated brine (10 mL × 2). After the organic layer was dried by Na_2SO_4, it was concentrated by rotatory evaporation. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give the pure product.

1-Phenylpyrrolidin-2-one (1a):[8d] The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as eluent to give a white solid of 1-phenylpyrrolidin-2-one (155 mg, 96%): white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2 H, d, J = 8.0 Hz), 7.36 (2 H, t, J = 7.8 Hz), 7.13 (1 H, t, J = 7.4 Hz), 3.82−3.86 (2 H, m), 2.57−2.61 (2 H, m), 2.10−2.17 (2 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.4, 139.6, 129.0, 124.7, 120.2, 49.0, 33.0, 18.3 ($CDCl_3$ δ 77.3).

Acknowledgment. This work was financially supported by the Natural Science Foundation of China (No. 20372058).

Supporting Information Available: Typical experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all of the coupling products with additional IR spectra for the unknown compound. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070443M