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CuI/L-Proline-Catalyzed Coupling Reactions of Aryl Halides with Activated Methylene Compounds

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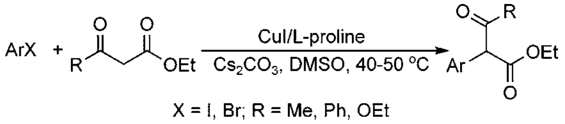
ABSTRACT



The arylation of ethyl acetoacetate, ethyl benzoyl acetate, and diethyl malonate under the catalysis of CuI/L-proline in DMSO proceeds smoothly at 40–50 °C in the presence of Cs_2CO_3 to provide the 2-aryl-1,3-dicarbonyl compounds in good yields. Both aryl iodides and aryl bromides are compatible with these reaction conditions.

In recent years, great advances have been achieved on the modification of copper-catalyzed Ullmann-type coupling reactions.[1] By using some special ligands such as *N*,*N*- and *N*,*O*-bidentate compounds, many CuI-catalyzed C−N,[2] C−O,[3] C−S,[4] and C−C[5] bond formation reactions could be carried out at relatively low temperatures. Although the detailed function for these ligands awaits further exploration,[1c] discovery of new transformations using these ligands is still actively pursued.[6] This campaign would not only provide useful synthetic processes but also shed light on mechanism investigations.

The arylation of activated methylene compounds in the presence of copper or copper salts, namely, the Hurtley reaction,[7] is an applicable transformation with a long history. The scope of this reaction is very narrow, as only *o*-bromobenzoic acid and its closely related bromides are reactive.[7] To overcome this drawback, numerous efforts have

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[1] For reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, *15*, 2428. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

[2] (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (d) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (e) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (f) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (g) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (h) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (i) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (j) Ma, D.; Cai, Q. *Synlett* **2004**, *1*, 128. (k) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (m) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888. (n) Deng, W.; Wang, Y.; Zou, W.; Liu, L.; Guo, Q. *Tetrahedron Lett.* **2004**, *45*, 2311. (o) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496. (p) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

[3] (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623. (b) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (c) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978. (d) Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *44*, 8257. (e) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913. (f) Ma, D.; Cai, Q.; Xie, X. *Synlett* **2005**, 1767.

[4] (a) Kwong, F.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (b) Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423. (c) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (d) Deng, W.; Zou, Y.; Wang, Y. F.; Liu, F.; Guo, Q. X. *Synlett* **2004**, 1254. (e) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696.

[5] (a) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312. (b) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269. (c) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (d) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934. (e) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441.

[6] For selected references, see: (a) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (b) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (c) Wang, Z.; Bao, W.; Jiang, Y. *Chem. Commun.* **2005**, 2849. (d) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (e) Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997.

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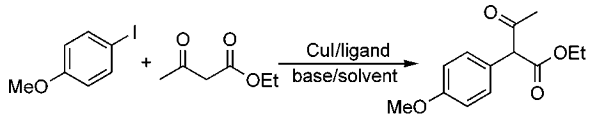
been devoted to develop new reaction conditions during the past decades.[4a,8,9] However, initial success for arylation starting from aryl halides relies on using stoichiometic or even excess amounts of copper salts.[8a−d] The first breakthrough for this arylation to use catalytic amounts of CuI was made by Miura and co-workers in 1993, in which the coupling reaction was carried out at 120 °C in DMSO.[8e] Under these conditions the products were readily decomposed, and therefore good yields were not obtained in some cases. In addition, only aryl iodides were suitable for this process and aryl bromides was found to afford poor conversion under the described conditions. A milder protocol was developed by Buchwald and Hennessy in 2002 to employ CuI/2-phenylphenol as a catalytic system to perform the arylation of diethyl malonate.[4a] Unfortunately, their substrates are still limited to aryl iodides. Furthermore, in the above two processes, 2 equiv of activated methylene compounds were required to ensure good yields, which would become problematic when some expensive activated methylene compounds were employed. Consequently, more efficient catalytic systems for these coupling reactions are required. Recently, we found that under the catalysis of CuI/L-proline, both aryl iodides and aryl bromides could couple with excess amounts of β-keto esters and diethyl malonate to provide the corresponding arylation products in good yields. Herein, we wish to report these results.

Table 1. Coupling Reaction of 4-Iodoanisole with Ethyl Acetoacetate under the Catalysis of CuI/Ligand[a]



entry	base	solvent	ligand[b]	temp (°C)	yield (%)[c]
1	Cs_2CO_3	DMSO	A	70	33[d]
2	Cs_2CO_3	DMSO	A	70	47
3	Cs_2CO_3	DMSO	A	40	83
4	Cs_2CO_3	DMSO	A	25	81
5	Cs_2CO_3	DMSO	A	40	84
6	Cs_2CO_3	dioxane	A	70	30
7	Cs_2CO_3	dioxane	A	50	0
8	Cs_2CO_3	toluene	A	70	20
9	Cs_2CO_3	toluene	A	50	0
10	K_2CO_3	DMSO	A	50	0
11	K_3PO_4	DMSO	A	50	0
12	NaH	DMSO	A	50	0
13	Cs_2CO_3	DMSO	B	40	54
14	Cs_2CO_3	DMSO	C	40	31
15	Cs_2CO_3	DMSO		40	0

[a] Reaction conditions: CuI (0.1 mmol), amino acid (0.2 mmol), 4-iodoanisole (0.5 mmol), ethyl acetoacetate (1.0 mmol), base (2 mmol), DMSO (1 mL), under Ar atmosphere, 24 h. [b] ligand: (A) L-proline; (B) *N*,*N*-dimethylglycine; (C) *N*-methylglycine. [c] Isolated yield. [d] 0.75 mmol of base was added. [e] Reaction time was 72 h. [f] 0.6 mmol of ethyl acetoacetate was used.

As indicated in Table 1, our experiments were first conducted by coupling 4-iodoanisole (1 equiv) with ethyl acetoacetate (2 equiv) catalyzed by 20 mol % of CuI and 40 mol % of L-proline. This reaction proceeded at 70 °C in DMSO in the presence of 1.5 equiv of Cs_2CO_3 to produce the desired coupling product in 33% yield (entry 1). Increasing the amounts of the base to 4 equiv gave higher yields (compare entries 1 and 2). Under these conditions it was determined that starting materials disappeared and some decomposed products formed. Accordingly, we decided to lower the reaction temperatures to improve the reaction yields further. To our delight, when this coupling reaction was carried out at 40 °C, a satisfactory yield was obtained (entry 3). By prolonging the reaction time the coupling could be completed at room temperature (entry 4). Reducing the amounts of ethyl acetoacetate to 1.2 equiv still afforded a good yield (entry 5). Thus, in the following studies we always used a slight excess of activated methylene compounds as the coupling agents. For other solvents, although 1,4-dioxane or toluene gave the coupled product at 70 °C (entries 6 and 8), no conversion was seen at 50 °C in these solvents (entries 7 and 9). In addition, a switch in the base to K_2CO_3, K_3PO_4, or NaH did not give any coupled product (entries 10−12), which indicated that using Cs_2CO_3 as a base was very critical for this reaction. For other ligands, *N*,*N*-dimethylglycine gave a moderate yield (entry 13), whereas *N*-methylglycine was even worse (entry 14). Without the addition of the ligands, no coupling reaction occurred (entry 15), which clearly showed that the presence of amino acids was necessary for this reaction.

On the basis of the above studies, we concluded that using L-proline as the ligand, DMSO as the solvent, and 4 equiv of Cs_2CO_3 as the base and carrying out the reaction at 40 °C are optimized conditions. The reaction scope was next explored with different aryl iodides and activated methylene compounds. As summarized in Table 2, other electron-rich aryl iodides were also compatible with these conditions, delivering arylation products in good yields by coupling with ethyl acetoacetate, ethyl benzoylactate, and diethyl malonate (entries 1−7). Sterically hindered aryl iodides were less reactive but still gave good yields by prolonging the reaction time (entries 8 and 9). The electron-deficient aryl iodides were generally superior to electron-rich ones, as evidenced by completion of the coupling reaction in shorter time and affording better yields. This trend is consistent with that observed in our aryl amination reactions[2p] but is opposite to that noticed in the coupling reactions of aryl iodides with sodium azide[2m] and sodium methanesulfinate.[4d] These differences implied that the mechanisms for these coupling reactions might not be analogous.

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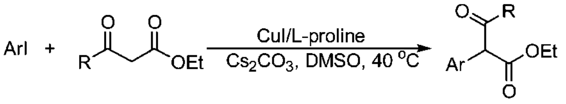
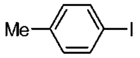
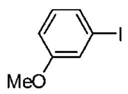
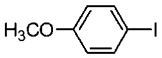
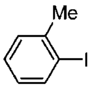
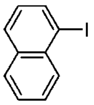
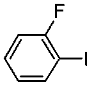
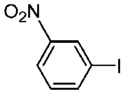
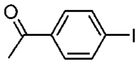
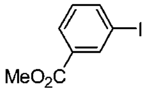
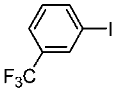
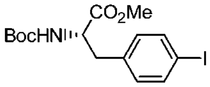
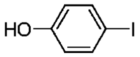
(7) (a) Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870. (b) Bruggink, A.; Ray, S. J.; McKillop, A. *Org. Synth.* **1978**, *58*, 52. For related studies, see: (c) Cirigottis, Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1974**, *27*, 2209. (d) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607. (e) Shinkwin, A. E.; Whish, W. J. D.; Threadgill, M. D. *Bioorg. Med. Chem.* **1999**, *7*, 297. (f) Bryson, T. A.; Stewart, J. J.; Gibson, J. M.; Thomas, P. S.; Berch, J. K. *Green Chem.* **2003**, *5*, 174.

(8) (a) Setsune, J.; Matsukawa, K.; Wakemoto, H.; Kaito, T. *Chem. Lett.* **1981**, 367. (b) Setsune, J.; Matsukawa, K.; Kaito, T. *Tetrahedron Lett.* **1982**, *23*, 663. (c) Suzuki, H.; Kobayashi, T.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1983**, 193. (d) Suzuki, H.; Yi, Q.; Inoue, J.; Kusume, K.; Ogawa, T. *Chem. Lett.* **1987**, 887. (e) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606. (f) Pivsa-Art, S.; Fukui, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2039.

(9) (a) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z. *Synlett* **1996**, 609. (b) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398. In their cases the substrates were limited to *o*-bromophenols.

Table 2. Coupling Reaction of Aryl Iodides with Activated Methylene Compounds under the Catalysis of CuI/L-Proline[a]



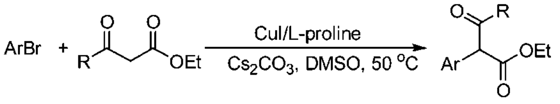
entry	ArI	R	time (h)	yield (%)[b]
1		Me	24	80
2		OEt	12	83
3		Me	24	85
4		OEt	12	84
5		Ph	24	81
6		OEt	12	84
7		OEt	24	80
8		OEt	24	77
9		Me	24	75
10		OEt	6	77
11		Me	16	71
12		OEt	4	94
13		Me	16	82
14		OEt	4	83
15		Me	16	82
16		Ph	12	86
17		OEt	4	90
18		Me	16	78
19		OEt	4	92
20		OEt	12	87
21		OEt	24	0

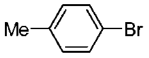
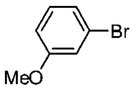
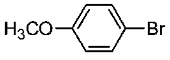
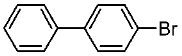
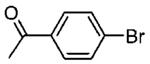
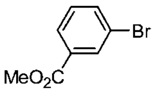
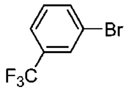
[a] Reaction conditions: aryl iodide (0.5 mmol), activated methylene compound (0.6 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (2 mmol), DMSO (1 mL), 40 °C, under Ar atmosphere. [b] Isolated yield.

Of the three activated methylene compounds we employed, diethyl malonate displayed the best reactivity as shown by shorter reaction time (compare entries 15−17), presumably as a result of its lowest acidity. Noteworthy is that an L-phenylalanine-derived iodide was also tolerated in this reaction, giving the corresponding coupling product in 87% yield (entry 20). This result indicated that the present method would be useful for modifying aromatic amino acids. Although in Buchwald's case,[4a] excellent conversion was obtained using 4-iodophenol as a substrate, no desired coupling product was determined in our reaction system (entry 21). The reason for this drawback is not clear yet.

We next examined aryl bromides as the substrates for our catalytic system and were pleased to find that coupling of 4-methylphenyl bromide with ethyl acetoacetate and ethyl malonate took place at 50 °C, producing the desired arylation products in good yields (Table 3, entries 1 and 2). Other bromides, whether electron-rich or electron-deficient, all worked well under these conditions. In these cases, good conversions were observed, although longer reaction times were required compared with aryl iodides. Attempts to shorten the reaction times by raising the reaction temperature gave slightly lower yield. Like aryl iodides, aryl bromides with electron-withdrawing groups showed better reactivity compared with those bearing electron-donating groups.

Table 3. Coupling Reaction of Aryl Bromides with Activated Methylene Compounds under the Catalysis of CuI/L-Proline[a]



entry	ArBr	R	time (h)	yield (%)[b]
1		Me	48	76
2		OEt	36	81
3		Me	48	75
4		OEt	36	79
5		Ph	48	78
6		Me	48	72
7		OEt	36	85
8		OEt	54	71
9		Me	24	83
10		OEt	24	86
11		Ph	36	81
12		Me	24	81
13		OEt	24	81
14		Me	32	76
15		OEt	32	76

[a] Reaction conditions: aryl bromide (0.5 mmol), activated methylene compound (0.6 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (2 mmol), DMSO (1 mL), 50 °C, under Ar atmosphere. [b] Isolated yield.

In summary, we have discovered that CuI/L-proline is a useful catalytic system for arylation of activated methylene compounds that delivered 2-aryl-1,3-dicarbonyl compounds in great diversity. In contrast with the previous processes,[4a,8e] excellent conversions were obtained when aryl bromides were employed. This advantage would prompt the synthetic applications of this CuI-catalyzed C−C bond formation reaction.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR spectrum for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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