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Room-Temperature Copper-Catalyzed α-Arylation of Malonates

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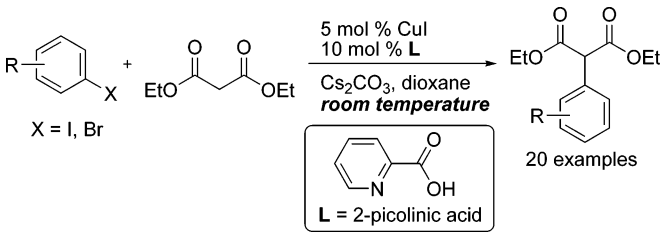
ABSTRACT



An effective method in targeting α-aryl malonates is reported. In the presence of a catalytic amount of 2-picolinic acid and CuI, the coupling of aryl iodides with diethyl malonate proceeds smoothly even at room temperature. The high levels of functional group compatibility and exceptionally mild reaction conditions offer this an attractive protocol in accessing a variety of arylated malonates.

Carboxylic acids and acid derivatives processing α-aryl substitutents comprise an important class of organic compound. They have been highlighed by their occurrence in a myriad of natural products and wide applications in pharmaceutical chemistry.[1] In fact, α-aryl malonates have a notable potential in the synthesis of α-aryl acids and have themselves recently been reported to be effective modulators in mammalian membranes.[2] Additionally, α-aryl acetic acids (e.g., indomethancin, sulindac, ibufenac, diclofenac) and α-aryl propionic acids (e.g., ibuprofen, naproxen, ketoprofen) are two main categories of nonsteroidal antiinflammatory drugs.[3] Therefore, the development of an effective protocol in accessing a variety of their derivatives is noteworthy. Among many methods available for the synthesis of α-aryl carbonyl compounds, palladium-catalyzed methodologies have received particular attention.[4] However, these are relatively expensive catalytic systems that are usually found to be less tolerant with some functional groups on the aromatic moiety.

Recently, great advances have been achieved on the conceptual evolution of copper-catalyzed Ullmann-type reactions.[5] With the application of structurally appropriate ligands (such as N,N-, N,O-, or O,O-bidentate ligands), a variety of Cu-catalyzed C−N,[6] C−O,[7] C−S,[8] and C−C[9] coupling reactions could be carried out at relatively mild reaction conditions.

In fact, the arylation of activated methylene compounds in the presence of copper metal or copper salts, called the Hurtley reaction, has been reported in pioneering studies.[10] The initial scope of this reaction is very narrow, as only *o*-bromobenzoic acid and its closely related halides are reactive.[10] Earlier examples of Cu-mediated arylation of malonates and their derivatives by nonchelating aryl halides

(1) For selected examples, see the following. Vancomycin: (a) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223. Lucuminic acid: (b) Takeda, T.; Gonda, R.; Hatano, K. *Chem. Pharm. Bull.* **1997**, *45*, 697. Polymastiamide A: (c) Kong, F.; Andersen, R. J. *J. Org. Chem.* **1993**, *58*, 6924. Chloropeptin I and II: (d) Hegde, V. R.; Dai, P.; Patel, M.; Gullo, V. P. *Tetrahedron Lett.* **1998**, *39*, 5683. Vulculic acid: (e) Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T. *Agric. Biol. Chem.* **1991**, *55*, 1137.

(2) Beyer, J.; Jensen, B. S.; Strøbæk, D.; Christophersen, P.; Teuber, L. WO Patent 00/37422, 2000.

(3) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(4) For a review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

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

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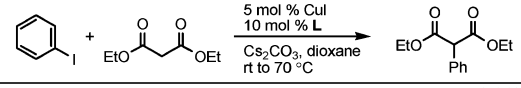
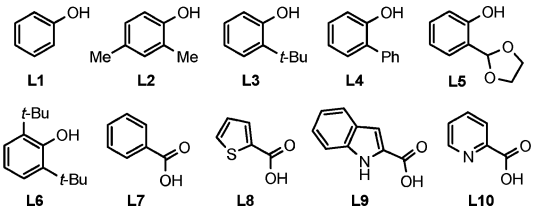
are well-known to share the common deficiencies of Ullmann chemistry (e.g., stoichiometric amount of Cu complex, high reaction temperature, polar solvent (e.g., DMSO, pyridine), poor reproducibility, good yields are usually obtained for highly activated aryl halides).[11] An improved process was subsequently reported in 1993 employing a catalytic amount of CuI and K_2CO_3 in DMSO at 120 °C for the α-arylation of activated methylene compounds.[12] Under these reaction conditions, the products were readily decomposed, and thus good yields were only obtained in particular cases. A milder protocol in accessing a variety of arylated malonates from aryl iodides was reported by Buchwald and Hennessy in 2002.[9a] In the presence of 5 mol % of CuI and 10 mol % of 2-phenylphenol monodentate ligand at 70 °C, a number of corresponding arylated malonates were afforded in good yield. This investigation indicated the importance of the supporting ligand in achieving milder reaction conditions. In 2005, Ma and co-workers reported a catalytic system with 20 mol % of CuI and 40 mol % of L-proline ligand, which could be efficiently applied in the coupling of aryl halides with diethyl malonate in DMSO solvent.[9e] Although improvements have been made, a general Ullmann protocol for C−C bond construction, which can be carried out at ambient temperature with relatively nontoxic solvent and low catalyst loading, remains challenging. We were intrigued by the notable success in the recent Cu-catalyzed C−N coupling reaction that can be efficiently performed at room temperature.[13] Herein, we report our explicit use of supporting ligand in achieveing an unexplored room-temperature Ullmann-type C−C bond formation.

We initially tested the feasibility of using monodentate oxygen donor ligands for the arylation of diethyl malonate (Table 1). However, significant catalyst deactivation was observed through competitive O-arylation of the ligand (**L1**−**L3**).[14] In general, the more the phenolic ligand is sterically hindered, the less the tendency to be subjected to O-arylation. A 4-fold excess of **L** to CuI was necessary to compensate for this undesirable ligand arylation (Table 1, entries 4 vs 5). Although hindered phenolic ligands showed better catalytic activity, the extremely congested phenol **L6** was not effective (Table 1, entry 6).

Table 1. An Investigation on the Ligand Effect in Cu-Catalyzed Arylation of Malonate[a]



entry	Cu:**L**	ligand **L**	temp/°C	yield/%[b]
1	1:2	**L1**	70 °C	2
2	1:2	**L2**	70 °C	4
3	1:2	**L3**	70 °C	9
4	1:2	**L4**	70 °C	83
5	1:4	**L4**	70 °C	90
6	1:2	**L5**	70 °C	15
7	1:2	**L6**	70 °C	<1
8	1:2	**L7**	70 °C	79
9	1:2	**L8**	70 °C	60
10	1:2	**L9**	70 °C	66
11	1:2	**L10**	70 °C	99
12	1:4	**L4**	room temp.	48
13	1:2	**L10**	room temp.	99



[a] Reaction conditions: ArI (1.0 mmol), malonate (2.0 mmol), CuI (0.05 mmol), **L** (0.1−0.2 mmol), Cs_2CO_3 (3.0 mmol), and dioxane (1.0 mL) at rt to 70 °C under N_2 atm for 20 h. [b] Calibrated GC yields in average of two independent runs (dodecane as internal standard).

Since the monodentate ligands were not satisfactory, we turned to investigating the applicability of the bidentate ligands (**L7**−**L10**). To our delight, benzoic acid **L7** provided good catalytic activity in this transformation. On the basis of this ligand prototype, we examined the bidentate O,S and O,N ligands (Table 1, entries 8−10). Commercially available 2-picolinic acid **L10** showed significant rate acceleration in the arylation of malonate (Table 1, entry 11). The efficiency of the ligand **L10** can be further demonstrated by its catalytic activity at room-temperature conditions (Table 1, entry 13).

(6) For recent selected references, see: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (d) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (e) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (f) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (g) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (h) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (i) Ma, D.; Cai, Q. *Synlett* **2004**, 128. (j) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (k) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888. (l) Deng, W.; Wang, Y.; Zou, W.; Liu, L.; Guo, Q. *Tetrahedron Lett.* **2004**, *45*, 2311. (m) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (n) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643. (o) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973.

(7) For recent selected references, see: (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. (g) Nonappa, P. D.; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, ASAP.

(8) For recent selected references, see: (a) Kwong, F. Y.; 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.

(9) (a) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269. (b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (c) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934. (d) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441. (e) Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693.

(10) (a) Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870. For canonical procedures, see: (b) Bruggink, A.; Ray, S. J.; McKillop, A. *Org. Synth.* **1978**, *58*, 52.

(11) (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.

(12) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606.

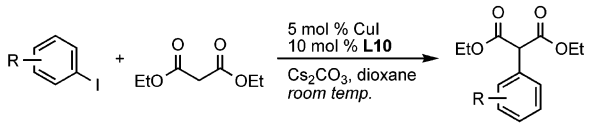
(13) For the first general Ullmann-type C−N coupling at room temperature see: Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

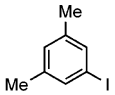
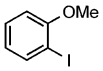
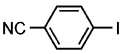
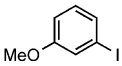
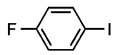
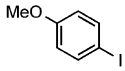
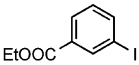
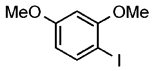
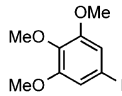
(14) The observations of ligand O-arylation were judged by GC-MS analysis.

Soluble organic bases such as triethylamine and DBU (diazabicyclo[5.4.0]undec-7-ene) completely inhibit the reaction, likely by saturating the coordination sphere of copper. Upon screening commonly used inorganic bases, it was found that the use of Cs_2CO_3 is crucial to the success of the reaction. K_3PO_4 was considerably less effective, while K_2CO_3 and Na_2CO_3 did not afford any reaction at all.[15] Sovlent effects were preliminary surveyed. THF and dioxane solvents were comparably efficient. However, toluene, *tert*-amyl alcohol, and DMF were found to be inferior.

To test the effectivness of the CuI/picolinic acid catalytic system, a diverse array of aryl iodides were examined in the arylation reaction (Table 2). In general, the reaction proceeds smoothly to afford the desired product at room temperature. These results highlighted the excellent catalytic activity of the CuI/picolinic acid system. Particularly noteworthy is that the catalyst loading can be down to 1 mol % of CuI at 70 °C, without sacrifice of the product yield (Table 2, entry 3). Functional groups such as methoxy, nitrile, fluoro, and ester were found to be compatible in these mild reaction conditions (Table 2, entries 11−13). In addition to aryl iodides, the CuI/**L10** catalyst was applied to some heterocyclic iodides. Good to excellent yields were obtained when the reactions were performed at room temperature (Table 2, entries 15−17). All previous unknown compounds gave satifactory ^{1}H NMR, ^{13}C NMR, MS, and HRMS data. Moreover, the arylated malonate (from entry 7) was unambigously characterized by X-ray crystallography (Figure 1 and the Supporting Information).

Table 2. Copper-Catalyzed α-Arylation of Malonate[a]



entry	ArI	time	% yield[b]	entry	ArI	time	% yield[b]
1		20 h	92	10		28 h	88
2[c]		2 h	93				
3[c,d]		20 h	90				
4		20 h	92	11		20 h	82
5		20 h	79	12		20 h	73
6		20 h	80	13		20 h	96
7[c]		25 h	88	14[e]		20 h	95
8		28 h	81	15		20 h	90
				16		20 h	77
9[c,e]		20 h	84	17		20 h	68

[a] Reaction conditions: ArI (1.0 mmol), malonate (2.0 mmol), CuI (0.05 mmol), **L10** (0.1 mmol), Cs_2CO_3 (3.0 mmol), and dioxane (1.0 mL) at rt under N_2 atm for the indicated time. [b] Isolated yields. [c] At 70 °C. [d] 1 mol % of CuI was used. [e] 10 mol % of CuI was used.

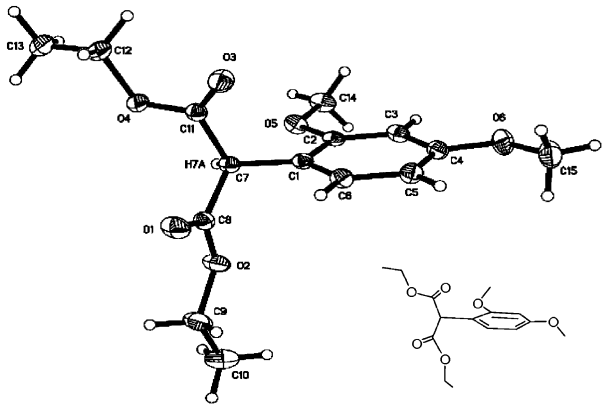
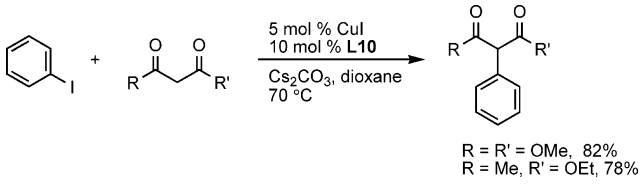


Figure 1. ORTEP diagram of the single-crystal X-ray structure of diethyl 2-(2,4-dimethoxyphenyl)malonate.

The scope of CuI/picolinic acid system was extended to the arylation of other 1,3-dicarbonyl compounds. Dimethyl malonate and β-ketoester were found to be effective in this α-arylation process (Scheme 1).

Scheme 1. Copper-Catalyzed α-Arylation of Malonate and Ketoester[a]



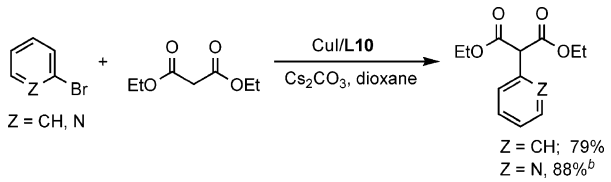
[a] Reaction conditions: PhI (1.0 mmol), malonate or ketoester (2.0 mmol), CuI (0.05 mmol), **L10** (0.1 mmol), Cs_2CO_3 (3.0 mmol), and dioxane (1.0 mL) at 70 °C under N_2 atm for 25 h.

In addition to aryl iodides, aryl bromides could undergo α-arylation at elevated temperature. Bromobenzene and 2-bromopyridine furnished the corresponding arylated malonates in good yields (Scheme 2). However, aryl chlorides did not show any significant conversion in this catalytic system.

In summary, a general protocol for room-temperature coupling of aryl iodides with malonates has been described. The catalyst is easily formed in situ by combining air-stable CuI with commercially available 2-picolinic acid **L10**. The

(15) Same reaction conditions as in Table 1. Cs_2CO_3, K_3PO_4, K_2CO_3, and Na_2CO_3 provide 99%, 62%, <1%, and <1%, respectively.

Scheme 2. Copper-Catalyzed α-Arylation of Malonate with Aryl Bromides[a]



[a] Reaction conditions: ArBr (1.0 mmol), malonate (2.0 mmol), CuI (0.1 mmol), **L10** (0.2 mmol), Cs_2CO_3 (3.0 mmol), and dioxane (1.0 mL) in N_2 atm under reflux conditions for 32 h. [b] 5 mol % of CuI.

delocalized pyridyl carboxylate is relatively robust and less prone to ligand deactivation (ligand O-arylation). This simple and remarkably active catalytic system represents the first room-temperature Ullmann-type C−C bond formation, which potentially offers an efficient protocol in accessing a variety of α-arylated dicarbonyl compounds.

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Supporting Information Available: Detail experimental procedures, compound characterization data, copies of ^1H NMR, ^{13}C NMR, and MS spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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