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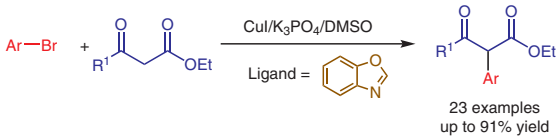
Copper(I) Iodide-Catalyzed (Het)arylation of Diethyl Malonate with (Het)aryl Bromides by Using 1,3-Benzoxazole as a Ligand

Yu Zeng[a]
Hao-liang Zheng[b]
Zhao Yang[c]
Cheng-Kou Liu[a]
Zheng Fang[*a]
Kai Guo[*a,d]

[a] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, 30 Puzhu South Road, Nanjing, 211816, P. R. of China
fzcpu@163.com
guok@njtech.edu.cn
[b] School of Chemistry and Molecular Biosciences, Faculty of Chemistry, The University of Queensland, Brisbane, Queensland, Australia
[c] College of Engineering, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing, 210003, P. R. of China
[d] State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, 30 Puzhu South Road, Nanjing, 211816, P. R. of China



- broad substrate scope (heterocyclic and benzene ring bromides)
- good functional group tolerance (OMe, Me, Ac, CN, NO_2, F, Cl)
- less time consumed to reach the full conversion (3–9 h)

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Abstract An efficient Ullmann-type coupling of aryl bromides with diethyl malonate in the presence of copper(I) iodide and 1,3-benzoxazole is presented. This method has a broad substrate scope (heterocyclic and phenyl bromides) and good functional-group tolerance (OMe, Me, Ac, CN, NO_2, F, and Cl). Moreover, less time is needed to reach full conversion (3–9 hours).

Key words Ullmann coupling, benzoxazole, copper catalysis, aryl bromides, hetarylation, arylation

α-Aryl carboxylic acids are key structural elements of many natural products[1] and pharmaceuticals,[2] especial nonsteroidal anti-inflammatory drugs (Figure 1).

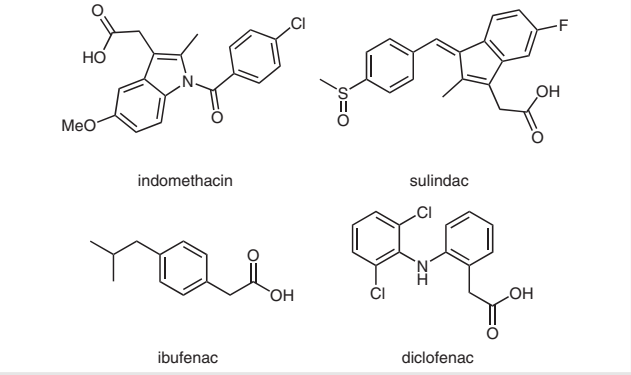
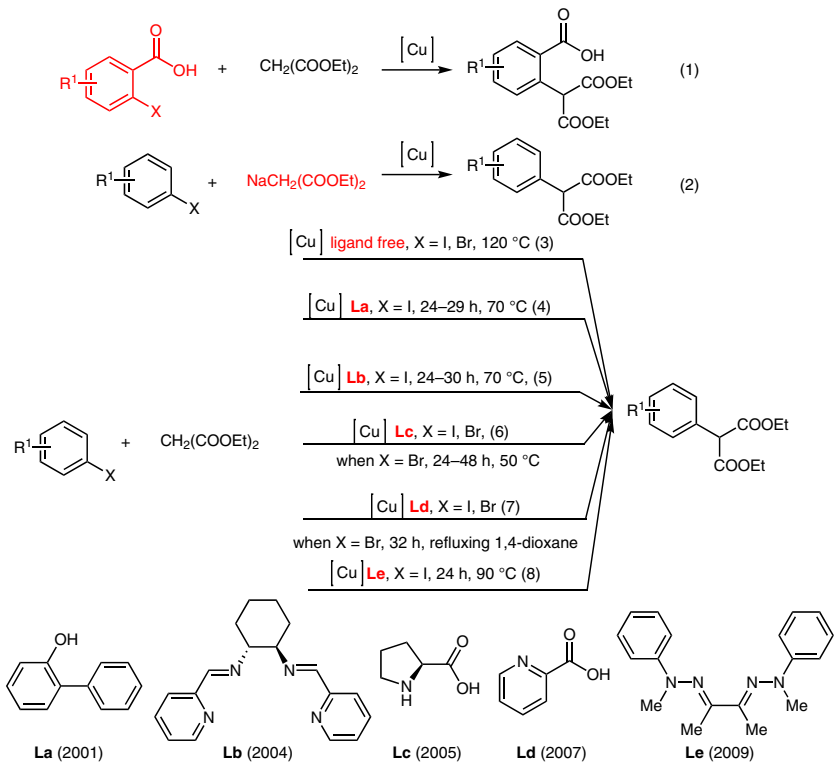


Figure 1 Marketed drugs with α-aryl carboxylic acid structures

α-Aryl carboxylic acids are usually synthesized by hydrolysis and decarboxylation of arylmalonates, which is an effective method. Moreover, arylmalonates can also serve as useful precursors for the construction of various heterocycles,[3] such as indoles,[4] isoquinolines,[5] quinoxalinones,[6] or chromenes.[7] The Ullmann-type coupling of malonates with aryl halides has generally been used to synthesize α-aryl carbonyl compounds. Initially, this reaction was restricted by the harsh conditions necessary (high temperatures, long reaction times),[8] the need for equivalent or even excess amounts of copper salts, and low yields. Later, a breakthrough was achieved by the development of palladium-catalyzed coupling reactions.[9] However, the use of the noble medal palladium is uneconomical. In addition, the need for strong alkalis such as *t*-BuOK impairs the scope and functional-group tolerance of the reaction. In recent decades, many efforts have been devoted to the development of copper-catalyzed Ullmann-type coupling reactions. The Hurtley reaction permits the arylation of malonates (Scheme 1, eq. 1), but only 2-bromobenzoic acid and closely related bromides can be transformed into the desired products. Numerous efforts have been devoted to expanding the substrate scope of the Hurtley reaction. Later, it was found that many aryl halides besides 2-bromobenzoic acid could be successfully coupled with enolate anions (Scheme 1, eq. 2), but this method is limited by the multistep process and the use of a stoichiometric amount of the copper salt. At the end of 20th century, Okuro and co-workers reported the first coupling reaction of aryl iodides with activated methylene compounds in the presence of a catalytic amount of copper(I) iodide (Scheme 1, eq. 3).[10] This

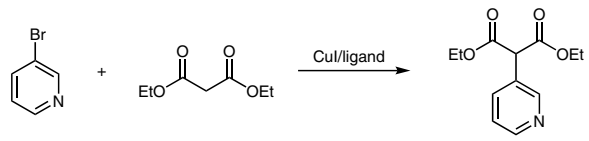


Scheme 1 Previous methods

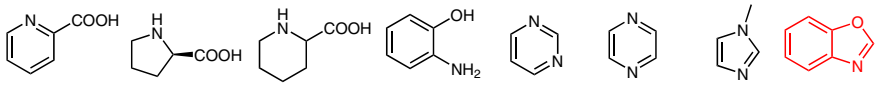
reaction was carried out at 120 °C and gave low to moderate yields, as the coupling products tended to decompose under these conditions. Moreover, only 16% yield of the desired product was obtained when bromobenzene was used. It is noteworthy that no ligand was added in this reaction, which might explain why a high temperature was necessary. In recent years, it has been shown that the use of a ligand is crucial to the success of the reaction.[11] Many catalytic reactions that occur under mild conditions in the presence of certain ligands, such as N,N-[12] or N,O-bidentate[13] compounds, have been reported (Scheme 1, eqs. 4–8). Recently, several copper-nanoparticle-catalyzed coupling reactions of aryl halides with diethyl malonate to effect the arylation of malonates under ligand-free conditions have been established.[14] Although considerable progress has been achieved by these methods, several drawbacks remain. First, the reactivity is still a slightly unsatisfactory, and many methods are limited to aryl iodides (Scheme 1, eqs. 4, 5, and 8) as, although aryl bromides are compatible with some reactions, longer times (20–36 h) and higher temperatures are necessary (Scheme 1, eqs. 6 and 7). Secondly, as far as we know, there have been only a few reports on the coupling of malonates with heterocyclic halides. Because, many heterocyclic compounds have physiological activities, particular attention has been paid to the design and synthesis of heterocyclic compounds with potential physiological activities. Furthermore, the development of more effective approaches with broad substrate scopes compatible with various heterocyclic halides is still an attractive goal. Here, we describe the use of 1,3-benzoxazole as ligand to achieve an effective Ullmann-type C–C bond formation.

We examined the coupling reaction of 3-bromopyridine with diethyl malonate to optimize the reaction conditions, as summarized in Table 1. Initially, various N,N- and N,O-bidentate ligands were tested (Table 1, entries 1–8). 1,3-Benzoxazole was the most effective ligand, giving an 86% yield of the desired product in DMSO (Table 1, entry 8). Only a trace of the desired product was detected in the absence of a ligand (Table 1, entry 9). Subsequently, the effect of the base was investigated (Table 1, entries 8 and 10–15). Soluble organic bases failed to give the desired product (Table 1, entries 13–15), whereas inorganic bases tended to exhibit superior reactivities (Table 1, entries 8 and 10–15). However, the reaction gave a significantly lower yield (15%) in the presence of Cs_2CO_3 (Table 1, entry 10), and only traces of the desired product were obtained when the reaction was performed in the presence of K_2CO_3 or NaOAc (Table 1, entries 11 and 12). K_3PO_4 turned out to be the best base, giving an 86% isolated yield (Table 1, entry 8). Next, we examined various solvents (Table 1, entries 8 and 16–19). Surprisingly, other solvents gave poorer yields than DMSO.

Table 1 Optimization of the Conditions for the Coupling of Diethyl Malonate with 3-Bromopyridine[a]



Entry	Catalyst	Ligand	Catalyst/Ligand (equiv)	Base	Solvent	Temp (°C)	Yield[b] (%)
1	CuI	**L1**	1:2	K_3PO_4	DMSO	50	22
2	CuI	**L2**	1:2	K_3PO_4	DMSO	50	16
3	CuI	**L3**	1:2	K_3PO_4	DMSO	50	30
4	CuI	**L4**	1:2	K_3PO_4	DMSO	50	43
5	CuI	**L5**	1:2	K_3PO_4	DMSO	50	11
6	CuI	**L6**	1:2	K_3PO_4	DMSO	50	14
7	CuI	**L7**	1:2	K_3PO_4	DMSO	50	24
8	CuI	**L8**	1:2	K_3PO_4	DMSO	50	86
9	CuI	–	–	K_3PO_4	DMSO	50	trace
10	CuI	**L8**	1:2	Cs_2CO_3	DMSO	50	15
11	CuI	**L8**	1:2	K_2CO_3	DMSO	50	trace
12	CuI	**L8**	1:2	NaOAc	DMSO	50	trace
13	CuI	**L8**	1:2	Et_3N	DMSO	50	NO
14	CuI	**L8**	1:2	DIPEA	DMSO	50	NO
15	CuI	**L8**	1:2	py	DMSO	50	NO
16	CuI	**L8**	1:2	K_3PO_4	DMF	50	32
17	CuI	**L8**	1:2	K_3PO_4	1,4-dioxane	50	NO
18	CuI	**L8**	1:2	K_3PO_4	toluene	50	NO
19	CuI	**L8**	1:2	K_3PO_4	THF	50	trace
20	CuI	**L8**	1:2	K_3PO_4	DMSO	80	74
21	CuI	**L8**	1:2	K_3PO_4	DMSO	70	79
22	CuI	**L8**	1:2	K_3PO_4	DMSO	60	87
23	CuI	**L8**	1:2	K_3PO_4	DMSO	40	71
24	CuI	**L8**	1:2	K_3PO_4	DMSO	30	17
25	CuBr	**L8**	1:2	K_3PO_4	DMSO	50	24
26	$CuBr_2$	**L8**	1:2	K_3PO_4	DMSO	50	12
27	$Cu(OAc)_2$	**L8**	1:2	K_3PO_4	DMSO	50	19
28	CuO	**L8**	1:2	K_3PO_4	DMSO	50	8
29[c]	CuI	**L8**	1:2	K_3PO_4	DMSO	50	85
30[d]	CuI	**L8**	1:2	K_3PO_4	DMSO	50	76
31[c]	CuI	**L8**	1:1.5	K_3PO_4	DMSO	50	88
32[c]	CuI	**L8**	1:1.2	K_3PO_4	DMSO	50	79

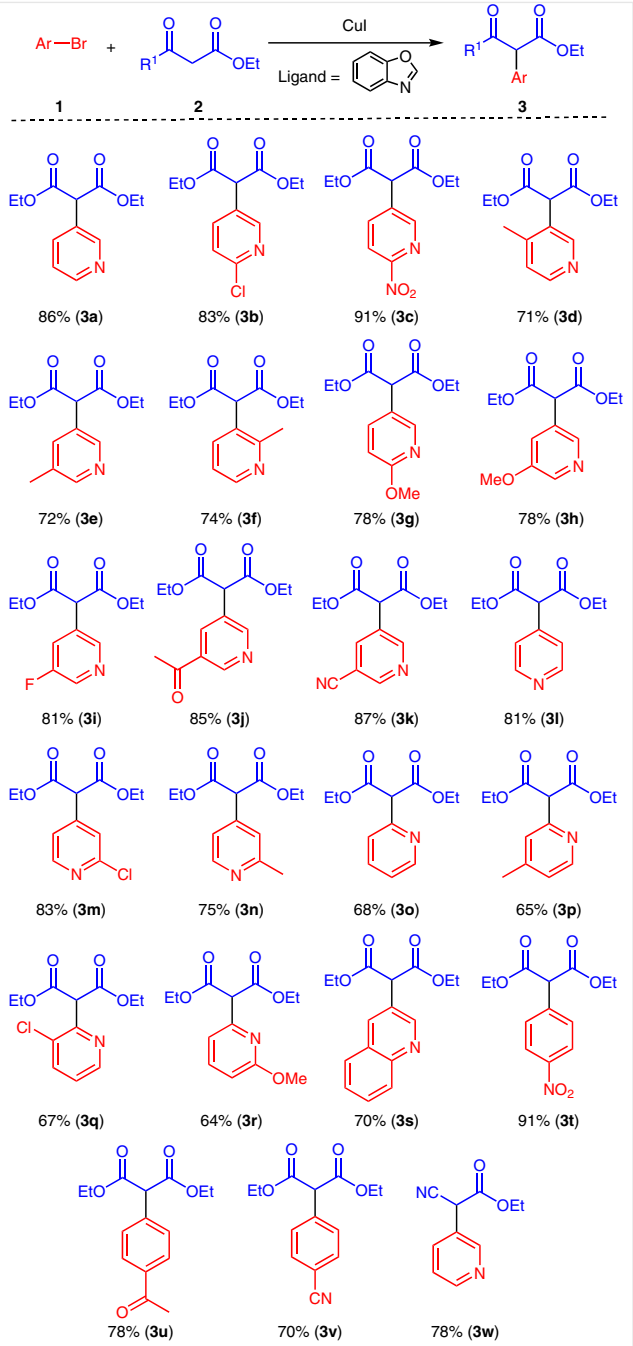


L1 **L2** **L3** **L4** **L5** **L6** **L7** **L8**

[a] Reaction conditions: 3-bromopyridine (1 mmol), diethyl malonate (1.5 mmol), CuI (0.1 mmol), ligand (0.2 mmol), base (3 mmol), solvent (2 mL), under argon, 6 h.
[b] Isolated yield.
[c] CuI (0.08 mmol) was used.
[d] CuI (0.05 mmol) was used.

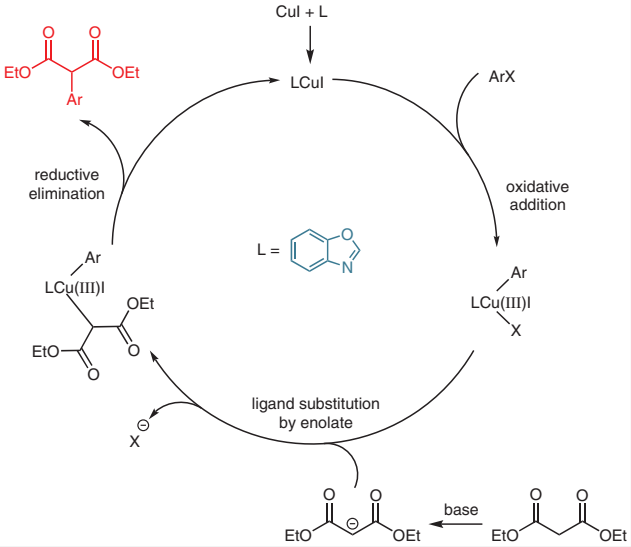
When the temperature was increased to 60 °C, a comparable yield was obtained (Table 1, entry 22), but a further increase in the temperature resulted in a decrease in the yield (Table 1, entries 20 and 21), possibly because of decomposition of the product. Lower temperatures gave lower yields than that obtained at 50 °C (Table 1, entries 8, 23, and 24). Next, the catalytic activity of various copper salts was explored (Table 1, entries 8, 25–28). Markedly lower yields were obtained when CuI was replaced by other copper compounds such as CuBr, $CuBr_2$, $Cu(OAc)_2$, or CuO. Screening of the catalyst load showed that 8 mol% catalyst was necessary (Table 1, entries 8, 29, and 30). Moreover, the ratio of the concentration of the catalyst to that of the ligand was examined (Table 1, entries 8, 31, 32), and a ratio of 1 to 1.5 was found to be the best choice. Therefore, the screening of the reaction parameters showed that the optimal reaction conditions are as follows: ArBr (1.0 mmol), diethyl malonate (1.5 mmol), CuI (0.08 mmol), 1,3-benzoxazole (0.12 mmol), K_3PO_4 (3 mmol), and DMSO (2 mL) at 50 °C under argon for six hours.

By using these optimized conditions, we examined the scope and functional-group tolerance of the reaction. To our delight, moderate to good yields (64–91%) were obtained when electron-deficient or electron-rich hetaryl bromides were used (Scheme 2; **3a–s**). However, the electron-rich hetaryl bromides showed inferior reactivities to the electron-deficient ones. Despite lower reactivities of the electron-rich hetaryl bromides, good yields of products **3g**, **3h**, and **3r** were nevertheless obtained by prolonging the reaction time. Moreover, substituents at various positions on the pyridine ring did not affect the reaction efficiency (**3d–f**). Generally, the reaction efficiency was affected by steric hindrance but, fortunately, sterically hindered pyridine ring bromides still gave good yields (**3d**, **3f**, and **3q**). Notably, 2-bromopyridine showed a lower activity than 4-bromopyridine or 3-bromopyridine (**3a**, **3l**, and **3o**), and a longer time was necessary to reach the full conversion with the 2-bromo isomers (**3o–r**). A number of functional groups, including F, Cl, MeCO, NO_2, CN, Me, and OMe, were tolerated under our reaction conditions (**3a–v**). Good to excellent yields were also obtained when 3-bromoquinoline or some bromobenzene derivatives were used (**3s–v**). However, bromobenzene and electron-rich bromobenzenes failed to give the corresponding products, and almost no product was detected when electron-rich or electron-deficient aryl chloride was used. When diethyl malonate was replaced by ethyl cyanoacetate, a good yield of the corresponding product **3w** was obtained.



Scheme 2 Copper-catalyzed (het)arylations of diethyl malonate and ethyl cyanoacetate. *Reagents and conditions*: ArBr (1.0 mmol), diethyl malonate (1.5 mmol), CuI (0.1 mmol), 1,3-benzoxazole (0.2 mmol), K_3PO_4 (3 mmol), DMSO (2 mL) at 50 °C under Ar. Yields of the isolated products are reported.

A proposed mechanism, shown in Scheme 3 [9a,12a,14b] involves oxidative addition, ligand substitution by the enolate, and reductive elimination. The ligand assists by preventing aggregation of the metal and by increasing its solubility or stability.



Scheme 3 Proposed mechanism

In summary, a practical and effective CuI/1,3-benzoxazole-promoted Ullmann-type coupling method has been developed.[15] This method features a higher efficiency (shorter time to reach full conversion), a broad substrate scope (phenyl and heterocyclic bromides), good functional-group tolerance, and offers a potential protocol for the synthesis of heterocyclic drugs.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591210.

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(15) **Diethyl (Het)arylmalonates 3a–v; General Procedure**

DMSO (2 mL), the appropriate (het)aryl bromide **1** (1.0 mmol), diethyl malonate (**2**; 1.5 mmol), CuI (0.1 mmol), 1,3-benzoxazole (0.2 mmol), and K_3PO_4 (3 mmol) were successively added to a sealed tube under argon. The mixture was stirred at 50 °C for 3–9 h until the reaction was complete (TLC) and then poured into sat. aq NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the organic phases were combined and washed with sat. aq NH_4Cl (2 × 20 mL) and H_2O (2 × 20 mL). The separated organic layer was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, hexane/EtOAc).

Diethyl Pyridin-3-ylmalonate (3a)

Purified by column chromatography [silica gel, hexane/EtOAc (6:1)] to give a yellowish oil; yield: 204 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55–8.51 (m, 2 H), 7.80 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.27 (dd, *J* = 7.9, 4.8 Hz, 1 H), 4.59 (s, 1 H), 4.24–4.11 (m, 4 H), 1.21 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.43, 150.28, 149.53, 136.93, 128.97, 123.52, 62.19, 55.43, 13.97. HRMS (TOF): *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}NO_4$: 238.1074; found: 238.1084.