LETTER

Copper(I)-Catalyzed C–C and C–O Coupling Reactions Using Hydrazone Ligands

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Abstract: Copper-catalyzed C–C coupling reaction of aryl iodides with diethylmalonate in toluene at 90 °C gave arylated malonates using 5 mol% of CuI with hydrazone **1a** as a ligand in good yields under an aerobic atmosphere. We also found CuI/hydrazone **1b** in toluene to be an efficient catalytic system for C–O coupling reactions of aryl bromides with phenols to give aryl ethers in good yields at 110 °C under an aerobic atmosphere.

Key words: copper catalyst, hydrazone, C–C coupling, C–O coupling, malonate, aryl ether

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–C,³ and C–O^{2b,c,4} bond formation reactions could be carried out at relatively low temperatures. We recently reported on CuI-catalyzed C–N bond formation reactions such as Goldberg-type N-arylation of amides and Ullmann-type N-arylation of azoles, using phosphine-free hydrazone ligands.⁵ We now report the use of air-stable, phosphine-free hydrazone ligands **1a–d**⁶ for copper-catalyzed C–C and C–O bond formation reactions (Figure 1).





Initially, we examined the copper-catalyzed C–C bond formation reaction – the Hurtley reaction⁷ – using hydrazone ligand. We optimized the conditions for C-arylation of diethyl malonate with iodobenzene using 5 mol% of CuI as a catalyst for 24 hours at 90 °C under an aerobic atmosphere (Table 1). In the presence of Cs_2CO_3 as base in cyclopentyl methyl ether (CPME) as solvent, hydrazone

SYNLETT 2009, No. 15, pp 2457–2460 Advanced online publication: 17.08.2009 DOI: 10.1055/s-0029-1217822; Art ID: U05809ST © Georg Thieme Verlag Stuttgart · New York **Table 1** Optimization of the Reaction Conditions for Copper-Catalyzed C-Arylation of Diethyl Malonate with Iodobenzene^a

PhI +	Eto		u catalyst, liga base, solven 90 °C, 24 h, a	and t air EtC	O O Ph 2a
Entry	Ligand	Cu catalyst	Base	Solvent ^b	Yield (%) ^c
1	1a	CuI	Cs ₂ CO ₃	CPME	55
2	1b	CuI	Cs ₂ CO ₃	CPME	39
3	1c	CuI	Cs ₂ CO ₃	CPME	45
4	1d	CuI	Cs ₂ CO ₃	CPME	35
5	-	CuI	Cs ₂ CO ₃	CPME	32
6	1a	CuBr	Cs ₂ CO ₃	CPME	46
7	1a	CuCl	Cs ₂ CO ₃	CPME	29
8	1a	Cu ₂ O	Cs ₂ CO ₃	CPME	44
9	1a	CuI	K ₃ PO ₄	CPME	32
10	1a	CuI	t-BuOK	CPME	7
11	1a	CuI	Cs ₂ CO ₃	DMF	30
12	1a	CuI	Cs ₂ CO ₃	DMSO	39
13	1a	CuI	Cs ₂ CO ₃	toluene	67
14	1a	CuI	Cs ₂ CO ₃ ^d	toluene	73

^a Reaction conditions: Iodobenzene (2 mmol), diethyl malonate (4 mmol), base (3 mmol), solvent (2 mL), Cu source (0.10 mmol), ligand (0.20 mmol).

^b CPME: cyclopentyl methyl ether.

 $^{\rm c}$ GC yield; 2-methoxynaphthalene was used as an internal standard. $^{\rm d}$ Cs_2CO_3 (4 mmol) was added.

1a was found to be the most appropriate ligand (entry 1 vs. entries 2–4). In the absence of ligand **1a**, the yield was decreased (entry 1 vs. entry 5). We then investigated the effect of copper catalysts (entries 1, and 6–8). In the case of using CuBr, CuCl, and Cu₂O, the yields were decreased; CuI proved to be the best copper source for the C-arylation (entry 1). The effect of various bases was investigated (entries 1, and 9–10) and Cs₂CO₃ proved to be the most successful. The effect of various solvents was also inves-

tigated (entries 1, and 11–13) and toluene was found to be the most suitable (entry 13). After increasing the added amount of Cs_2CO_3 , we obtained diethyl phenylmalonate **2a** with good yield (entry 14).

With the best reaction conditions established (Table 2, entry 1),⁸ we screened a range of different aryl iodides in order to explore the scope of the C-arylation of diethyl malonate (Table 2).⁹ Using 4-substituted aryl iodides led to good yields of the desired products (entries 2–5). Moreover, the reaction of 3-substituted and 2-substituted aryl iodides also led to good yields (entries 6–10). In the reactions of 1-iodonaphthalene, the corresponding product **2k** was obtained in 58% (entry 11).

 Table 2
 Copper-Catalyzed C-Arylation of Diethyl Malonate with Aryl Iodides^a

Arl + Et	2 equiv	Cul (5 mol%) ligand 1a (10 mol%) Cs ₂ CO ₃ (2 equiv) PhMe (1.0 M) 90 °C, 24 h, air	Eto Ar OEt
Entry	Ar	Product	Yield (%) ^b
1	Ph	2a	69
2	$4-MeC_6H_4$	2b	68
3	4-MeOC ₆ H ₄	2c	59
4	$4-CF_3C_6H_4$	2d	50
5°	$4-AcC_6H_4$	2e	62
6	$3-MeC_6H_4$	2 f	53
7	$3-F_3CC_6H_4$	2g	67
8	$3,5-Me_2C_6H_3$	2h	64
9	$2-MeC_6H_4$	2i	52
10	2-MeOC ₆ H ₄	2j	50
11	1-Naph	2k	58

^a Reaction conditions: Aryl iodide (2 mmol), diethyl malonate (4 mmol), Cs_2CO_3 (4 mmol), toluene (2 mL), CuI (0.10 mmol), ligand **1a** (0.20 mmol).

^b Isolated yield.

^c This reaction was carried out at 80 °C.

We next investigated the copper-catalyzed C–O bond formation reaction using hydrazones **1a–d** as ligands. Although Liu recently reported C–O bond formation with hydrazone-type ligands such as glyoxal bis(phenylhydrazone), 10 mol% of CuI was used as a catalyst under N₂ atmosphere.¹⁰ We wanted to find the optimal reaction conditions using 5 mol% of CuI as a catalyst under an aerobic atmosphere. Bromobenzene and *p*-cresol were chosen as model substrates, and the reactions were carried out for five hours at 110 °C (Table 3). When the reaction was carried out using hydrazone ligand **1b**, the product **3a** was obtained in higher yield than in the the case of **1a**, **1c** or 1d (entry 2 vs. entries 1, 3, and 4). In the absence of ligand, the yield was decreased (entry 5). We investigated the effect of copper catalysts, bases, and solvents in this reaction (entries 2, and 6–14). In the presence of CuI as catalyst and K_3PO_4 as a base in toluene, product **3a** was obtained in good yield (entry 2).

 Table 3
 Optimization of Reaction Conditions for the Copper-Catalyzed O-Arylation of *p*-Cresol with Bromobenzene^a

PhBr +	но-	Me $\frac{Cu}{t}$	catalyst, liga base, solven 0 °C, 5 h, ai	nd, t r PhC	Me
					3a
Entry	Ligand	Cu catalyst	Base	Solvent	Yield (%) ^b
1	1 a	CuI	K_3PO_4	toluene	78
2	1b	CuI	K_3PO_4	toluene	83
3	1c	CuI	K_3PO_4	toluene	71
4	1d	CuI	K_3PO_4	toluene	74
5	-	CuI	K_3PO_4	toluene	67
6	1b	CuBr	K_3PO_4	toluene	80
7	1b	CuOAc	K_3PO_4	toluene	69
8	1b	Cu ₂ O	K_3PO_4	toluene	58
9	1b	CuI	Cs ₂ CO ₃	toluene	trace
10	1b	CuI	K_2CO_3	toluene	59
11	1b	CuI	t-BuOK	toluene	no reaction
12	1b	CuI	K_3PO_4	DMF	10
13	1b	CuI	K_3PO_4	NMP	18
14	1b	CuI	K_3PO_4	DMSO	20

^a Reaction conditions: Bromobenzene (0.5 mmol), *p*-cresol (1.0 mmol), base (1 mmol), solvent (1 mL), Cu source (0.025 mmol), ligand (0.0.25 mmol).

^b Isolated yield.

In an attempt to probe the generality of the method, the reaction of phenols with a variety of aryl bromides was conducted (Table 4).¹¹ The reaction of bromobenzene and *para*-substituted aryl bromides with *p*-cresol gave the corresponding products in good yields (entry 1–6). The reaction of 1-bromonaphthalene, with *meta*- and *ortho*-substituted aryl bromides such as 3-bromotoluene and 2-bromotoluene gave moderate to good yields of the corresponding products (entries 7–9). Furthermore, the reaction of 4-bromotoluene with 4-chlorophenol and *m*-cresol also gave the corresponding products with good to high yields (entries 10 and 11).

In conclusion, we have found that hydrazone **1a** is useful as an air-stable, phosphine-free ligand for the coppercatalyzed C–C coupling reaction of aryl iodides with diethyl malonate. Hydrazone **1b** was an efficient ligand for C–O coupling reactions of aryl bromides with phenols.

A 10	A 2014	Cul (5 mol%) ligand 1b (5 mol%) K ₃ PO ₄ (2 equiv) PhMe (0.5 M)	- A-1 O	A-2
Ar'Br	+ Ar ² OH	110 °C, 5 h, air	→ Ar'—O	—Ar≏
	2 equiv		3	
Entry	Ar^1	Ar ²	Product	Yield (%) ^b
1	Ph	$4-MeC_6H_4$	3 a	83
2	$4-MeC_6H_4$	$4-MeC_6H_4$	3b	69
3	4-t-BuC ₆ H ₄	$4-MeC_6H_4$	3c	71
4	$4-NCC_6H_4$	$4-MeC_6H_4$	3d	94
5	$4-O_2NC_6H_4$	$4-MeC_6H_4$	3e	86
6 ^c	4-MeOC ₆ H ₄	$4-MeC_6H_4$	3f	81
7°	1-Naph	$4-MeC_6H_4$	3g	74
8	$3-MeC_6H_4$	$4-MeC_6H_4$	3h	78
9°	$2-MeC_6H_4$	$4-MeC_6H_4$	3i	75
10	$4-MeC_6H_4$	$4-ClC_6H_4$	3j	78
11°	4-MeC ₆ H ₄	$3-\text{MeC}_6\text{H}_4$	3h	90

^a Reaction conditions: Aryl bromide (0.5 mmol), phenol (1.0 mmol), K_3PO_4 (1 mmol), toluene (1 mL), CuI (0.025 mmol), ligand **1b** (0.025 mmol).

^b Isolated yields.

^c This reaction was carried out for 18 h.

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- (8) We tried the reaction at 110 °C in toluene for 24 h, however, the yield of 2a decreased to 28% and ethyl phenylacetate was also obtained (8% NMR yield).
- (9) General procedure for copper-catalyzed C-arylation of diethyl malonate with aryl iodides (Table 2): Under an atmosphere of air, aryl iodide (2.0 mmol) was added to a mixture of diethyl malonate (4.0 mmol), Cs₂CO₃ (4.0 mmol), ligand 1a (0.20 mmol), and CuI (0.10 mmol) in toluene (2 mL) at r.t. The mixture was stirred at 90 °C for 24 h, then diluted with EtOAc and H₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane–EtOAc) to provide the desired product. All prepared compounds 2, except 2f, were previously known and identified by ¹H NMR, ¹³C NMR and MS.

Compound **2f** (Table 2, entry 6): Yield: 53%; brown liquid; ¹H NMR (CDCl₃): δ = 1.26 (t, *J* = 7.1 Hz, 6 H), 2.35 (s, 3 H), 4.16–4.27 (m, 4 H), 4.57 (s, 1 H), 7.13–7.28 (m, 4 H); ¹³C NMR (CDCl₃): δ = 14.0, 21.4, 57.9, 61.7, 126.3, 128.4, 128.9, 129.9, 132.6, 138.2, 168.2; EI-MS: *m/z* (%) = 250 (25) [M⁺]; HRMS (FAB-MS): *m/z* calcd for C₁₄H₁₉O₄: 251.1283; found: 251.1284.

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- (11) General procedure for copper-catalyzed O-arylation of phenols with aryl bromides (Table 4): Under an atmosphere of air, aryl bromide (0.5 mmol) was added to a mixture of phenol (1.0 mmol), K₃PO₄ (1.0 mmol), ligand 1b (0.025 mmol), and CuI (0.025 mmol) in toluene (1 mL) at r.t. The mixture was stirred at 110 °C for either 5 h or 18 h, then the mixture was diluted with EtOAc and H₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane–EtOAc) to provide the desired product. All prepared compounds 3, except 3g and 3h, were known and identified by ¹H NMR, ¹³C NMR and MS.

Compound **3g** (Table 4, entry 7): Yield: 74%; colorless oil; ¹H NMR (CDCl₃): δ = 2.34 (s, 3 H), 6.88 (d, *J* = 7.6 Hz, 2 H), 6.94–6.97 (m, 2 H), 7.15 (d, J = 8.6 Hz, 2 H), 7.35 (t, J = 8.0 Hz, 1 H), 7.45–7.54 (m, 2 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.84–7.87 (m, 1 H), 8.22–8.25 (m, 1 H); ¹³C NMR (CDCl₃): $\delta = 20.7$, 112.6, 118.8, 122.1, 122.9, 125.8, 125.8, 126.5, 126.7, 127.7, 130.3, 132.8, 134.9, 153.6, 155.3; EI-MS: m/z (%) = 234 (100) [M⁺]; HRMS (FAB-MS): m/z calcd for C₁₇H₁₄O: 234.1045; found: 234.1027.

Compound **3h** (Table 4, entry 8): Yield: 78%; colorless oil; ¹H NMR (CDCl₃): δ = 2.31 (s, 3 H), 2.33 (s, 3 H), 6.77–6.80 (m, 2 H), 6.87–6.93 (m, 3 H), 7.12–7.21 (m, 3 H); ¹³C NMR (CDCl₃): δ = 20.7, 21.4, 115.3, 119.0, 119.1, 123.6, 129.3, 130.2, 132.7, 140.0, 154.8, 157.7; EI-MS: *m/z* (%) = 198 (100) [M⁺]; HRMS (FAB-MS): *m/z* calcd for C₁₄H₁₄O: 198.1045; found: 198.1046. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.