Copper-Catalyzed Direct N-Arylation of Naphthalimides Using Diaryliodonium Salts

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Abstract: An effective copper-catalyzed N-arylation of naphthalimides with diaryliodonium salts in toluene at 100 °C has been developed. This cross-coupling reaction gives the desired N-arylated 1,8-naphthalimides in moderate to good yields. The synthetic potential of this coupling is applied in functional materials based on N-arylated 1,8-naphthalimides, such as molecular probes.

Key words: arylation, copper catalysis, diaryliodonium salts, naphthalimides, C–N cross coupling

Reactions involving C–N cross-coupling have captured considerable attention from organic chemists over several decades because numerous pharmaceuticals, agrochemicals, polymers, and biologically relevant molecules contain the aryl nitrogen functionality.[1] Transition-metal-catalyzed C–N bond formation has revolutionized organic synthesis during the past decades. Since the founding work of Ullmann and Goldberg[2] and the pioneering work of Buchwald and Hartwig[3] were reported, there have been a number of recent advances in the field of transition-metal-promoted C–N cross-coupling reactions.[4]

Hypervalent iodine reagents have been extensively used in organic synthesis.[5] As one of the most versatile hypervalent iodine compounds, diaryliodonium(III) salts have been used as electrophilic arylating agents in various reactions, such as nucleophilic substitution reactions with nitrogen nucleophiles,[6] carbon nucleophiles,[7] and others, [5b] as well as Cu- and Pd-catalyzed coupling reactions,[5c,8] and trapping reactions (in which they are used as benzyne precursors).[9] Recently, Cu-promoted heteroatom coupling reactions between various amines, amides[6a] and azoles[6b] with diaryliodonium salts have been reported. However, the use of imides as coupling partners in this process is rare.

In recent years, 1,8-naphthalimide derivatives have been the subject of numerous synthetic efforts, and they have been applied in dyeing synthetic polymers and textile materials,[10] in solar energy collectors,[11] as fluorescent tags for use in molecular biology,[12] for potential photosensitizing biological activity,[13] and in liquid-crystalline displays.[14] Dehydrative condensation of 1,8-naphthalic anhydride with amines, the cyclization of N-substituted amic acid in the presence of acidic reagents, direct N-alkylation under Mitsunobu conditions, and the condensation of iminophosphoranes with phthaloyl dichloride followed by alkaline hydrolysis are available methods for the synthesis of naphthalimides.[15] Generally, N-arylated 1,8-naphthalimide derivatives can be synthesized by condensation of 1,8-naphthalic anhydride with aromatic amines,[15a,16] cross-coupling between 1,8-naphthalimides and arylboronic esters,[17] aminocarbonylation of 1,8-diiodonaphthalene,[18] and direct N-arylation of 1,8-naphthalimides with arenes.[19] Recently, we have been interested in the use of diaryliodonium salts in organic synthesis.[20] Herein, we report a new approach to the synthesis of N-arylated 1,8-naphthalimide derivatives through copper-catalyzed direct N-arylation of naphthalimides with diaryliodonium salts, which are efficient, mild, nontoxic and selective arylating reagents.

To test our N-arylation of naphthalimides, we treated 1,8-naphthalimide (**1a**) with 1.2 equivalents diphenyliodonium tetrafluoroborate (**2a**) and *t*-BuOK as base, in toluene at 80 °C for 12 hours, which were the standard conditions adopted in our previous study.[20a] We were pleased to find that N-arylation proceeded to give **3a** in 9% yield (Table 1, entry 1). Fortunately, in the presence of 10 mol% CuI, the desired arylated product **3a** was observed in 65% yield after 30 minutes (Table 1, entry 2). Investigation of reaction temperature revealed that 100 °C was the most efficient temperature to generate **3a** (80% yield; Table 1, entries 2–4). Prolonging the reaction time, did not lead to a better result (Table 1, entry 5). Decreasing the catalyst loading to 5 mol% had a negative impact on yield (Table 1, entry 6). Modifying the nature of the copper source established CuI as the most efficient catalyst (Table 1, entries 3, 7, and 8). A range of bases including *t*-BuOK, KOH, K_2CO_3, Et_3N were screened (Table 1, entries 3 and 9–11), and *t*-BuOK was found to be the most suitable. The influence of solvents was examined and toluene proved to

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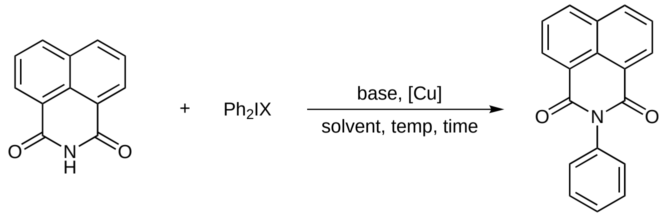
Table 1 Optimization of Cu-Catalyzed N-Arylation of Naphthalimide (**1a**)[a]



1a **2** **3a**

Entry	X	Base	[Cu] (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	BF_4	*t*-BuOK	–	toluene	80	12	9
2	BF_4	*t*-BuOK	CuI (10)	toluene	80	0.5	65
3	BF_4	*t*-BuOK	CuI (10)	toluene	100	0.5	80
4	BF_4	*t*-BuOK	CuI (10)	toluene	120	0.5	76
5	BF_4	*t*-BuOK	CuI (10)	toluene	100	2	78
6	BF_4	*t*-BuOK	CuI (5)	toluene	100	0.5	40
7	BF_4	*t*-BuOK	CuBr (10)	toluene	100	0.5	55
8	BF_4	*t*-BuOK	$Cu(OTf)_2$ (10)	toluene	100	0.5	35
9	BF_4	KOH	CuI (10)	toluene	100	0.5	23
10	BF_4	K_2CO_3	CuI (10)	toluene	100	0.5	43
11	BF_4	Et_3N	CuI (10)	toluene	100	0.5	60
12	BF_4	*t*-BuOK	CuI (10)	1,4-dioxane	100	0.5	57
13	BF_4	*t*-BuOK	CuI (10)	DMF	100	0.5	10
14	Br	*t*-BuOK	CuI (10)	toluene	100	0.5	26
15	OTs	*t*-BuOK	CuI (10)	toluene	100	0.5	33
16	OTf	*t*-BuOK	CuI (10)	toluene	100	0.5	50

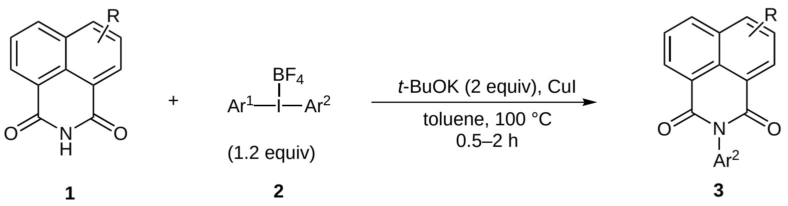
[a] Reaction conditions: 1,8-naphthalimide (0.4 mmol, 1 equiv), diphenyliodonium salt (0.48 mmol, 1.2 equiv), copper catalyst, base (0.8 mmol, 2 equiv), solvent (3 mL).

[b] Yield of isolated product.

be the most suitable; more polar solvents led to lower yields (Table 1, entries 3, 12, and 13). Furthermore, diaryliodonium salts **2**, bearing different counteranions (Table 1, entries 3, 14–16) were studied. Among all the tested reagents, tetrafluoroborate diaryliodonium furnished the desired product **3a** in good yield (80%; Table 1, entry 3), whereas bromide, *p*-toluenesulfonate, and triflate diaryliodonium salts gave only moderate yields (Table 1, entries 14–16).

With the optimized conditions in hand, the scope of the N-arylation of naphthalimides was explored by using a variety of symmetrical and unsymmetrical diaryliodonium salts. First, various substituted diaryliodonium salts were prepared and used for the direct coupling toward 1,8-naphthalimide. As shown in Table 2, diaryliodonium salts with halogen substituents gave the corresponding products in moderate yields (Table 2, entries 2–4), whereas the carboxyl-substituted diaryliodonium salts afforded no desired product (Table 2, entry 5). The presence of an *ortho*-methyl group with steric hindrance gave a dramatically decreased yield (Table 2, entry 6), however, no reaction was observed when the diaryliodonium salt was *para*-methyl-substituted. It is worth mentioning that the unsymmetrical salt **2g** selectively transferred the phenyl group to the 1,8-naphthalimide in moderate yield (55%; Table 2, entry 7). However, no desired products were obtained when (4-methylphenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate or (4-ethoxycarbonyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate were employed. Further exploration of the scope of the reaction was conducted with various substituted naphthalimides. With **2a**, substituted naphthalimides with 3-nitro, 4-bromo and 4-phenylethynyl were found to be compatible with the reaction conditions, undergoing N-arylation to give the corresponding products in 42, 57 and 53% yields, respectively (Table 2, entries 8–10). Use of 1,8-naph-

Table 2 Scope of the N-Arylation of Naphthalimides[a]



Entry	**1**	R	**2**	Ar^1	Ar^2	*t* (h)	**3**	Yield (%)[b]
1	**1a**	H	**2a**	Ph	Ph	0.5	**3a**	80
2	**1a**	H	**2b**	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$	2	**3b**	75
3	**1a**	H	**2c**	4-BrC$_6$H$_4$	4-BrC$_6$H$_4$	2	**3c**	45
4	**1a**	H	**2d**	4-FC$_6$H$_4$	4-FC$_6$H$_4$	0.5	**3d**	64
5	**1a**	H	**2e**	3-HO$_2$CC$_6$H$_4$	3-HO$_2$CC$_6$H$_4$	2	n.d.	n.d.
6	**1a**	H	**2f**	2-MeC$_6$H$_4$	2-MeC$_6$H$_4$	2	**3e**	36
7	**1a**	H	**2g**	Mesityl	Ph	2	**3a**	55
8	**1b**	3-NO$_2$	**2a**	Ph	Ph	2	**3f**	42
9	**1c**	4-Br	**2a**	Ph	Ph	2	**3g**	57
10	**1d**	4-phenylethynyl	**2a**	Ph	Ph	2	**3h**	53
11	**1e**	4-morpholinyl	**2a**	Ph	Ph	0.5	**3i**	82
12	**1e**	4-morpholinyl	**2b**	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$	2	**3j**	44
13	**1e**	4-morpholinyl	**2f**	2-MeC$_6$H$_4$	2-MeC$_6$H$_4$	2	**3k**	52

[a] Reaction conditions: naphthalimide (0.4 mmol, 1 equiv), iodonium salt (0.48 mmol, 1.2 equiv), CuI (10 mol%), *t*-BuOK (0.8 mmol, 2 equiv), toluene (3 mL), 100 °C, 0.5–2 h.

[b] Yield of isolated product.

thalimide substituted with the strong electron-donating morpholinyl group **1e** gave a good yield of the desired product (82%; Table 2, entry 11). In addition, use of **1e** as substrate gave moderate yields with 4-Cl- and 2-Me-substituted diaryliodonium salts (Table 2, entries 12 and 13).

In summary, we have developed a new protocol for the N-arylation of naphthalimides using diaryliodonium salts as the electrophilic coupling partners.[21] The overall process avoids extended periods of time and is easy to handle without the need for an inert atmosphere. This methodology provides an efficient way to prepare N-arylated 1,8-naphthalimides, which can be applied in functional materials.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **N-Arylation of Naphthalimides with Diaryliodonium Salts; General Procedure:** A mixture of 1,8-naphthalimide (0.4 mmol), diaryliodonium salt (0.48 mmol), *t*-BuOK (2 equiv), CuI (10 mmol%) and toluene (3 mL) was taken in a 10 mL reaction tube and heated at 100 °C for 0.5–2 h under vigorous stirring. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure, and the crude compound was purified by chromatography on a silica gel column (EtOAc–petroleum ether) to afford the desired product.