



Copper(II)–acid co-catalyzed intermolecular substitution of electron-rich aromatics with diazoesters

Eiji Tayama*, Moe Ishikawa, Hajime Iwamoto, and Eietsu Hasegawa

Department of Chemistry, Faculty of Science, Niigata University, Niigata 950-2181, Japan

ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Aromatic substitution
Co-catalysis
Synthetic method
Arene
Diazo compound

ABSTRACT

The intermolecular aromatic substitution of *N,N*-dialkylanilines and alkoxybenzenes with diazoesters is shown to proceed in the presence of catalytic amounts of both copper(II) salt and acid (Lewis or Brønsted). This method is a mild and rare metal-free C–C bond formation reaction between aromatic (sp^2) and aliphatic (sp^3) carbons.

2009 Elsevier Ltd. All rights reserved.

Transition metal-catalyzed aromatic substitution using α -diazocarbonyl compounds (formally, an aromatic C–H insertion) is a powerful and efficient synthetic method that enables the formation of C–C bonds between aromatic (sp^2) and aliphatic (sp^3) carbons under mild conditions.¹ These are several well-studied examples of successful intramolecular benzofused-ring formations catalyzed by rhodium complexes; however, examples of the intermolecular version are rare,² except for some reactions with heteroaromatic compounds.³ Furthermore, whereas rhodium complexes are among the most efficient catalysts for the reactions, these complexes are too expensive to use for large-scale synthesis. As such, it is important to develop catalysts composed of earth-abundant metals such as copper.⁴ Recently, we reported that the intermolecular aromatic substitution of *N,N*-disubstituted aniline **1** with diazoester **2** proceeded in the presence of copper(II) triflate, [Cu(OTf)₂] (Scheme 1).^{5,6} In the course of our research, we found that co-catalysts derived from a non-Lewis acidic copper(II) salt and a common acid catalyst also accelerated the aforementioned intermolecular aromatic substitution.^{7,8} Herein, we report the development of the Cu(II)–acid co-catalyzed version of the aromatic substitution reaction using diazoesters. This method is a mild and rare metal-free C–C bond formation reaction between aromatic (sp^2) and aliphatic (sp^3) carbons.

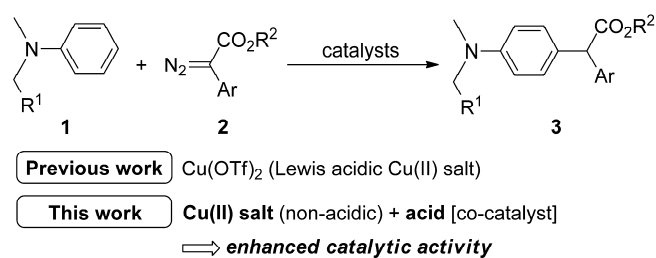
In our previous paper, we reported the intermolecular aromatic substitution of *N,N*-dialkylaniline **1a** with diazoester **2a** catalyzed by Cu(OTf)₂ (Table 1, entries 1, 2). The reaction proceeded smoothly in the presence of 2 mol% Cu(OTf)₂ generating the desired *para*-substituted adduct **3a** in good yield. In contrast, the use of a non-Lewis acidic copper(II) salt such as copper(II)

acetylacetonate [Cu(acac)₂] resulted in a lower yield (entry 3). These results suggest that a combination of a copper(II) salt (Catalyst A) and a common Lewis acid (Catalyst B) might also catalyze the intermolecular aromatic substitution. Thus, we attempted the reaction in the presence of a co-catalyst derived from 1 mol% Cu(acac)₂ and 1 mol% boron trifluoride diethyl etherate, (BF₃•OEt₂) (entry 4). As expected, the reaction afforded the desired product with a yield similar to the original reaction with 2 mol% Cu(OTf)₂. To clarify the effects of the Cu(acac)₂–BF₃•OEt₂ co-catalyst, we examined the reactions without Cu(acac)₂ and/or BF₃•OEt₂ (entries 5–7). These reactions were unsuccessful. After further screening with a number of different copper(II) salts, Lewis acids, and their catalytic amounts (entries 8–18), we found that the best yields were obtained from reactions with 1 to 2 mol% (total amount) co-catalyst derived from Cu(acac)₂–BF₃•OEt₂.⁹ The use of other common copper(II) salts, such as copper(II) acetate, hexafluoroacetylacetonate [Cu(hfacac)₂], dichloro(1,10-phenanthroline)copper(II) [Cu(phen)Cl₂], or Lewis acids showed no further improvement on the yield.

With the method in hand, we investigated the reactions of various types of *N,N*-dialkylanilines **1** with **2** in the presence of Cu(acac)₂–BF₃•OEt₂ co-catalyst (Method A) and compared the catalytic activity with Cu(OTf)₂ (Method B) (Table 2). The reaction of *N,N*-diethylamide **1b** and *tert*-butylketone derivatives **1c** under co-catalyzed conditions afforded **3b** and **3c**, respectively, in yields similar to those reactions using only Cu(OTf)₂ (entries 1, 2). Interestingly, the reaction of phenylketone derivative **1d** proceeded without unfavorable side reactions under co-catalyzed conditions (entry 3); the yield of the

* Corresponding author. Tel.: +81-25-262-7740; fax: +81-25-262-7741; e-mail: tayama@chem.sc.niigata-u.ac.jp

desired product **3d** was improved to 76% (Method A) from 0% (Method B). Favorable effects of the Cu(acac)₂-BF₃·OEt₂ co-catalyst were also observed in the reactions of substrates **1e–1i** with **2a–2c**¹⁰ (entries 4–10); however, the reactions of *N,N*-dimethylaniline (**1j**) failed (entry 11), even with stoichiometric amounts of BF₃·OEt₂ (entry 12). Any C–H insertion products into the *N*-methyl group^{2b} as in **1** were not obtained.¹¹



Scheme 1 The catalytic effect in the intermolecular aromatic substitution of *N,N*-disubstituted aniline **1** with diazoester **2**

Table 1 Screening of Cu(II) and Lewis acid catalysts for the intermolecular aromatic substitution of **1a** with **2a**

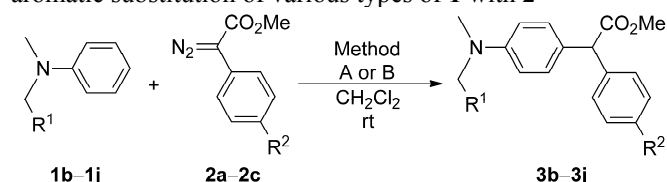
Entry	Catalyst A (mol%)	Catalyst B (mol%)	Time (h)	3a (%) ^a
1	Cu(OTf) ₂ (2)	–	12	89 ^b
2	Cu(OTf) ₂ (1)	–	12	53 ^b
3	Cu(acac) ₂ (1)	–	12	31
4	Cu(acac) ₂ (1)	BF ₃ ·OEt ₂ (1)	6	89
5	–	BF ₃ ·OEt ₂ (1)	6	31
6	–	BF ₃ ·OEt ₂ (1)	24	53
7	–	–	6	0
8	Cu(acac) ₂ (0.5)	BF ₃ ·OEt ₂ (0.5)	6	92
9	Cu(acac) ₂ (2)	BF ₃ ·OEt ₂ (2)	6	70
10	Cu(acac) ₂ (1)	BF ₃ ·OEt ₂ (2)	6	84
11	Cu(acac) ₂ (2)	BF ₃ ·OEt ₂ (1)	6	76
12	Cu(OAc) ₂ ·H ₂ O (1)	BF ₃ ·OEt ₂ (1)	6	88
13	Cu(OAc) ₂ (1)	BF ₃ ·OEt ₂ (1)	6	86
14	Cu(hfacac) ₂ ·nH ₂ O (1)	BF ₃ ·OEt ₂ (1)	6	42
15	Cu(phen)Cl ₂ (1)	BF ₃ ·OEt ₂ (1)	6	38
16	Cu(acac) ₂ (1)	Sc(OTf) ₃ (1)	6	65
17	Cu(acac) ₂ (1)	Zn(OTf) ₂ (1)	6	29
18	Cu(acac) ₂ (1)	Sn(OTf) ₂ (1)	6	67

^a Isolated yield. ^b Reported data in ref. 5.

To expand the scope of Cu(acac)₂-BF₃·OEt₂ co-catalyzed intermolecular aromatic substitution, we examined reactions of alkoxybenzenes **4**, which, due to their alkoxy substituents, are poorer electron donors and thus potentially less reactive (Table 3). First, we selected 1,2-dimethoxybenzene (**4a**) as a substrate and carried out the reactions in the presence of either Cu(II)-BF₃·OEt₂ co-catalyst or Cu(OTf)₂ alone. Unfortunately, these reactions were unsuccessful (entries 1–3). We tested a variety of Cu(II) salts for this reaction and found that 1,10-phenanthroline Cu(II) complexes, [Cu(phen)_mCl_n], gave the desired adduct **5a** in low yields (entries 4–6). Increasing the amount of catalyst to 5 mol% BF₃·OEt₂ with 1 mol% Cu(phen)_mCl_n produced **5a** in

acceptable yields (entries 7, 8). The analogous 1,3-dimethoxybenzene (**4b**) showed similar reactivity (entry 9); however, a reaction of mono-alkoxybenzene, specifically anisole (**4c**), resulted in a low yield (entry 10). Previously, we reported that the substrates such as **1** function as ligands of Cu(II) salts, and the catalytic activity is determined by the structure of the complexes.⁵ 1,2-Dimethoxybenzene **4a** also function as ligands; however, the catalytic activity is lowered (entry 1–3). 1,10-Phenanthroline, as in Cu(phen)_mCl_n may not exchange with **4a** because of its higher chelating ability and the catalytic activity may be maintained.

Table 2 Cu(II)-Lewis acid co-catalyzed intermolecular aromatic substitution of various types of **1** with **2**



Method A: 1 mol% Cu(acac)₂, 1 mol% BF₃·OEt₂, 6 h
 Method B: 2 mol% Cu(OTf)₂, 12–24 h

Entry	R ¹	R ²	Product	Method, Yield ^a	
				A (%)	B (%)
1	CONEt ₂ (1b)	H (2a)	3b	41	42 ^b
2	CO t -Bu (1c)	H (2a)	3c	54	68 ^b
3	COPh (1d)	H (2a)	3d	76	0 ^b
4	CH ₂ OBn (1e)	H (2a)	3e	90	59 ^b
5	CH ₂ OMe (1f)	H (2a)	3f	92	59 ^b
6	Ph (1g)	H (2a)	3ga	78	35 ^b
7	<i>p</i> -Cl-Ph (1h)	H (2a)	3h	79	40
8	<i>p</i> -MeO-Ph (1i)	H (2a)	3i	89	28
9	Ph (1g)	Cl (2b)	3gb	90	36
10	Ph (1g)	OMe (2c)	3gc	78	86
11	H (1j)	H (2a)	3j	4	2
12	H (1j)	H (2a)	3j	25 ^c	–

^a Isolated yield. ^b Reported data in ref. 5. ^c 100 mol% BF₃·OEt₂ was used.

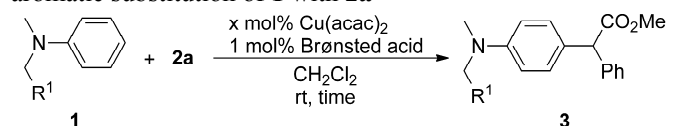
Table 3 The intermolecular aromatic substitution of alkoxybenzenes **4** with **2a**

Entry	R of 4		Catalyst A (mol%) ^a	Catalyst B (mol%)	5 (%) ^b
1	2-Ome	a	Cu(OTf) ₂ (2)	–	6
2	2-Ome	a	Cu(acac) ₂ (1)	BF ₃ ·OEt ₂ (1)	17
3	2-Ome	a	Cu(OAc) ₂ (1)	BF ₃ ·OEt ₂ (1)	19
4	2-Ome	a	Cu(phen)Cl ₂ (1)	BF ₃ ·OEt ₂ (1)	53
5	2-Ome	a	[Cu(phen) ₂ Cl]Cl (1)	BF ₃ ·OEt ₂ (1)	51
6	2-Ome	a	[Cu(phen) ₃]Cl ₂ (1)	BF ₃ ·OEt ₂ (1)	40
7	2-Ome	a	Cu(phen)Cl ₂ (1)	BF ₃ ·OEt ₂ (5)	66
8	2-Ome	a	[Cu(phen) ₂ Cl]Cl (1)	BF ₃ ·OEt ₂ (5)	60
9	3-Ome	b	[Cu(phen) ₂ Cl]Cl (1)	BF ₃ ·OEt ₂ (5)	56
10	H	c	[Cu(phen) ₂ Cl]Cl (1)	BF ₃ ·OEt ₂ (5)	35

^a phen = 1,10-phenanthroline. ^b Isolated yield.

We expected that the reaction might be accelerated with a Brønsted acid instead of a Lewis acid catalyst. Thus, we attempted the Cu(II)–acid co-catalyzed intermolecular aromatic substitution of **1a** with **2a** in the presence of 1 mol% common sulfonic acid as an acid component (Table 4, entries 1–4). The use of a strongly acidic Brønsted acid such as triflic acid afforded the adduct **3a** in excellent yield (entry 4). Interestingly, the reaction of **1a** proceeded smoothly without Cu(II) salts (entry 5). When reactions of the less-reactive substrate **1** were examined, the addition of Cu(acac)₂ was necessary to obtain adduct **3** in acceptable yields (entries 6–11). Again, the reaction of *N,N*-dimethylaniline (**1j**) did not proceed under these conditions (entry 12). The analogue of triflic acid, bistriflimide (Tf₂NH), also worked as a Brønsted acid catalyst; however, the catalytic activity was lowered (entries 13–17).

Table 4 Cu(II)–Brønsted acid co-catalyzed intermolecular aromatic substitution of **1** with **2a**



Entry	R ¹	x	Brønsted acid	Time (h)	Product	3 ^a (%)
1	CO ₂ Et	1	TsOH•H ₂ O	24	3a	30
2	CO ₂ Et	1	DL-CSA ^b	24	3a	37
3	CO ₂ Et	1	PPTS	24	3a	6
4	CO ₂ Et	1	TfOH	6	3a	86
5	CO ₂ Et	0	TfOH	6	3a	91
6	CONEt ₂	1	TfOH	6	3b	69
7	CONEt ₂	0	TfOH	6	3b	0
8	CH ₂ OMe	1	TfOH	6	3f	78
9	CH ₂ OMe	0	TfOH	6	3f	6
10	Ph	1	TfOH	6	3ga	85
11	Ph	0	TfOH	6	3ga	61
12	H	1	TfOH	6	3j	5
13	CO ₂ Et	1	Tf ₂ NH	6	3a	77
14	CO ₂ Et	0	Tf ₂ NH	6	3a	51
15	CONEt ₂	1	Tf ₂ NH	6	3b	11
16	CH ₂ OMe	1	Tf ₂ NH	6	3f	28
17	Ph	1	Tf ₂ NH	6	3ga	27

^a Isolated yield. ^b CSA = camphorsulfonic acid.

In conclusion, we have demonstrated the Cu(II)–acid co-catalyzed intermolecular aromatic substitution of *N,N*-dialkylanilines or alkoxybenzenes with diazoesters. This method is a mild and rare metal-free C–C bond formation reaction between aromatic (sp²) and aliphatic (sp³) carbons.

Acknowledgments

This work was supported by Grant for Basic Science Research Projects from The Sumitomo Foundation (110187).

References and notes

- For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T.; *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley: New York, 1998; (b) Davies, H. M. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming I., Eds.; Pergamon: Oxford, 1991, Vol. 4, Chapter 4.8.

- (a) Park, C. P.; Nagle, A.; Yoon, C. H.; Chen, C.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 6231–6236; (b) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769–1772; (c) Davies, H. M. L.; Smith, H. D.; Hu, B.; Klenzak, S. M.; Hegner, F. J. *J. Org. Chem.* **1992**, *57*, 6900–6903; (d) Toda, M.; Hattori, M.; Okada, K.; Oda, M. *Chem. Lett.* **1987**, *16*, 1263–1266; (e) Ledon, H.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1973**, 2065–2071.
- Examples of intermolecular aromatic substitution using heteroaromatic compounds, see: (a) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604–607; (b) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109–1119 and references therein.
- An example of rhodium and copper catalyzed intramolecular aromatic substitution and their mechanistic studies, see: Kim, J.; Ohk, Y.; Park, S. H.; Jung, Y.; Chang, S. *Chem. Asian J.* **2011**, *6*, 2040–2047.
- Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, 6719–6721.
- Previous examples of acid-promoted intramolecular aromatic substitution, see: (a) Wang, H.-L.; Li, Z.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2011**, *47*, 11336–11338; (b) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017–1022; (c) Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1277–1286; (d) Newman, M. S.; Eglinton, G.; Grotta, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 349–352.
- For a review of Brønsted acid catalyzed reaction using diazo compounds, see: Johnston, J. N.; Muchalski, H.; Troyer, T. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2290–2298.
- Examples of transition metal–acid co-catalyzed reaction using diazo compounds, see: (a) Xu, X.; Zhou, J.; Yang, L.; Hu, W. *Chem. Commun.* **2008**, 6564–6566; (b) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783.
- Although the reactions of entry 4 (total 2 mol%) and entry 8 (total 1 mol%) in Table 1 were quenched for 1 h, a remarkable difference between the yields was not observed (entry 4: 38%, entry 8: 30%).
- We attempted reactions using diazoesters without an α -aryl substituent such as cyclohexyl 2-diazoacetate or cyclohexyl 2-diazo-3-oxobutanoate; however, the corresponding products were not obtained.
- Davies et al. reported that the electrophilic aromatic substitution reaction proceeds in the presence of electron-deficient rhodium catalysts (ref. 2b). Acid catalysts may interact with the ligands around Cu(II), leading to a more electron-deficient catalysts.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.