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

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

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

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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 (sp²) and aliphatic (sp³) 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

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 (sp²) and aliphatic (sp³) carbons.

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

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



^{*} Corresponding author. Tel.: +81 25 262 7740; fax: +81 25 262 7741. *E-mail address:* tayama@chem.sc.niigata-u.ac.jp (E. Tayama).

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Table 1

1 -

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

	CO ₂ Me	Catalyst A Catalyst B	N-	CO₂Me -√
CO ₂ Et	Ph	CH ₂ Cl ₂ rt, time	CO ₂ Et	Ph

2-

iu	20		Ju	
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	$Cu(acac)_2(1)$	$BF_3 \cdot OEt_2(1)$	6	89
5	-	$BF_3 \cdot OEt_2(1)$	6	31
6	-	$BF_3 \cdot OEt_2(1)$	24	53
7	-	_	6	0
8	Cu(acac) ₂ (0.5)	$BF_{3} \cdot OEt_{2} (0.5)$	6	92
9	$Cu(acac)_2(2)$	$BF_3 \cdot OEt_2(2)$	6	70
10	$Cu(acac)_2(1)$	$BF_3 \cdot OEt_2(2)$	6	84
11	$Cu(acac)_2(2)$	$BF_3 \cdot OEt_2(1)$	6	76
12	$Cu(OAc)_2 \cdot H_2O(1)$	$BF_3 \cdot OEt_2(1)$	6	88
13	$Cu(OAc)_2(1)$	$BF_3 \cdot OEt_2(1)$	6	86
14	$Cu(hfacac)_2 \cdot nH_2O(1)$	$BF_3 \cdot OEt_2(1)$	6	42
15	Cu(phen)Cl ₂ (1)	$BF_3 \cdot OEt_2(1)$	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.

 $Cu(acac)_2-BF_3\cdot OEt_2$.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)Cl_2], 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,Ndiethylamide 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 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

To expand the scope of $Cu(acac)_2-BF_3 \cdot OEt_2$ 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 analagous 1,3-dimethoxybenzene (**4b**) showed similar reactivity (entry 9); however, a reaction of mono-alkoxybenzene,

Table 2

Cu(II)-Lewis acid co-catalyzed intermolecular aromatic substitution of various types of ${\bf 1}$ with ${\bf 2}$



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

Entry	\mathbb{R}^1	R ²	Product	Method, yield ^a	
				A (%)	B (%)
1	CONEt ₂ (1b)	H (2a)	3b	41	42 ^b
2	COt-Bu (1c)	H (2a)	3c	54	68 ^b
3	COPh (1d)	H (2a)	3d	76	0 ^b
4	CH_2OBn (1e)	H (2a)	3e	90	59 ^b
5	$CH_2OMe(1f)$	H (2a)	3f	92	59 ^b
6	Ph (1g)	H (2a)	3ga	78	35 ^b
7	p-Cl-Ph (1h)	H (2a)	3h	79	40
8	p-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 (1 j)	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

МеО <i>—</i> ∢ 4а –4	R = => + 4c	N ₂ =	CO ₂ Me Catalyst A Catalyst B Ph CH ₂ Cl ₂ rt, 6 h 2a	→ MeO ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	CO₂Me ≺ Ph
Entry	R of 4		Catalyst A ^a (mol %)	Catalyst B (mol %)	5 ^b (%)
1	2-OMe	а	$Cu(OTf)_2(2)$	_	6
2	2-OMe	а	$Cu(acac)_2(1)$	$BF_3 \cdot OEt_2(1)$	17
3	2-OMe	а	$Cu(OAc)_2(1)$	$BF_3 \cdot OEt_2(1)$	19
4	2-OMe	а	$Cu(phen)Cl_2(1)$	$BF_3 \cdot OEt_2(1)$	53
5	2-OMe	а	[Cu(phen) ₂ Cl]Cl (1)	$BF_3 \cdot OEt_2(1)$	51
6	2-OMe	a	[Cu(phen)3]Cl2 (1)	$BF_3 \cdot OEt_2(1)$	40
7	2-OMe	a	$Cu(phen)Cl_2(1)$	$BF_3 \cdot OEt_2(5)$	66
8	2-OMe	а	[Cu(phen) ₂ Cl]Cl (1)	$BF_3 \cdot OEt_2(5)$	60
9	3-OMe	b	[Cu(phen) ₂ Cl]Cl (1)	$BF_3 \cdot OEt_2(5)$	56
10	Н	с	[Cu(phen) ₂ Cl]Cl (1)	$BF_3 \cdot OEt_2(5)$	35

^a phen = 1,10-phenanthroline.

^b Isolated yield.

specifically anisole (**4c**), resulted in a low yield (entry 10). Previously, we reported that 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.

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

Table 4

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



Entry	R ¹	х	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	Н	1	TfOH	6	3ј	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_2NH	6	3ga	27

^a Isolated yield.

^b CSA = camphorsulfonic acid.

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).

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.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.070.

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- 9. 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.
- 11. 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 more electron-deficient catalysts.