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Copper(II) Triflate Catalyzed Intermolecular Aromatic Substitution of *N*,*N*-Disubstituted Anilines with Diazo Esters

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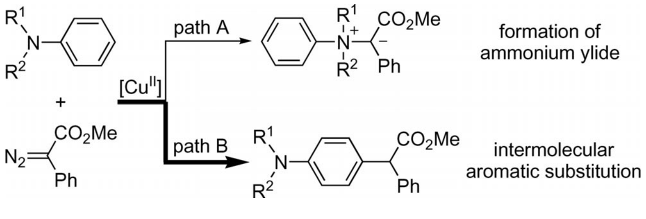
The intermolecular aromatic substitution of *N*,*N*-disubstituted anilines with diazo esters is achieved under mild conditions in the presence of a catalytic amount of copper(II) triflate (up to 89 % yield). The scope and limitations regarding substrates, diazo esters, and ligands in this reaction are described.

Introduction

Aromatic substitution of α-diazo carbonyl compounds promoted by rhodium catalysts is a powerful and efficient synthetic method for the construction of functionalized aromatic compounds, because they enable the formation of C–C bonds between aromatic and aliphatic carbon atoms under mild conditions.[1] Whereas intramolecular aromatic substitution reactions have been extensively studied, successful intermolecular examples have been quite scarce to date, except for some reactions with heteroaromatic substrates.[2,3] In 2004, Davies et al. reported that electron-deficient rhodium catalysts enhance the intermolecular aromatic substitution over C–H insertion in the study on the C–H activation of *N*,*N*-dimethylanilines.[2b] However, further studies on the intermolecular aromatic substitution have not been advanced. In the course of our studies on the formation of ammonium ylides derived from *N*,*N*-dialkylanilines and α-diazo esters in the presence of copper(II) salt (Scheme 1, path A),[4] we observed intermolecular aromatic substitution affording a *para*-substituted *N*,*N*-dialkylaniline (path B). Prompted by this result, we decided to investigate the scope and limitations of this copper(II)-catalyzed intermolecular aromatic substitution reaction.

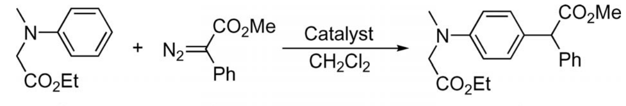


Scheme 1. Reactions of *N*,*N*-dialkylaniline with α-diazo ester in the presence of a copper(II) catalyst.

Results and Discussion

First, we examined the reaction of *N*-[(ethoxycarbonyl)-methyl]-*N*-methylaniline (**1a**) with methyl 2-diazo-2-phenylacetate (**2a**) in dichloromethane at room temperature in the presence of 10 mol-% of copper(II) acetylacetonate [Cu(acac)$_2$] (Table 1, Entry 1). Small amounts of the corresponding intermolecular aromatic substitution product **3a** were obtained in 9 % yield with recovery of the starting materials. When the reaction was carried out at reflux, the

Table 1. Screening of catalysts for the intermolecular aromatic substitution of **1a** with **2a**.



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

Entry	Catalyst (mol-%)	*T*	*t* [h]	Yield [%][a]
1	Cu(acac)$_2$ (10)	room temp.	6	9
2	Cu(acac)$_2$ (10)	reflux	3	32
3	Cu(hfacac)$_2$ (10)	room temp.	6	6
4	Cu(OAc)$_2$·H$_2$O (10)	room temp.	6	0
5	Cu(OTf)$_2$ (10)	room temp.	6	71
6	Cu(OTf)$_2$ (20)	room temp.	6	55
7	Cu(OTf)$_2$ (5)	room temp.	6	78
8	Cu(OTf)$_2$ (2)	room temp.	12	89
9	Cu(OTf)$_2$ (1)	room temp.	12	53
10	BF$_3$·OEt$_2$ (10)	room temp.	12	4
11	BF$_3$·OEt$_2$ (100)	room temp.	12	47[b]
12	BF$_3$·OEt$_2$ (100)	reflux	6	70
13	Sn(OTf)$_2$ (2)	room temp.	12	0
14	Sc(OTf)$_3$ (2)	room temp.	12	2
15	Rh$_2$(OAc)$_4$ (2)	room temp.	6	39

[a] Isolated yield. [b] Determined by ^{1}H NMR assay using acetophenone as an internal standard.

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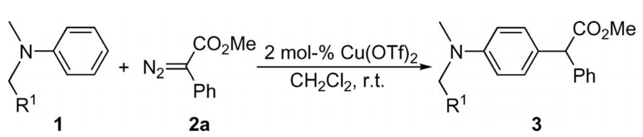
yield was slightly improved (Entry 2, 32%). To further improve the yield of **3a**, we attempted the reactions in the presence of other copper(II) salts. Copper(II) hexafluoroacetoacetate [Cu(hfacac)$_2$] (Entry 3) and copper(II) acetate [Cu(OAc)$_2$] (Entry 4) did not show any improvement. Surprisingly, copper(II) triflate [Cu(OTf)$_2$] showed a remarkable catalytic activity, and the intermolecular aromatic substitution proceeded efficiently to give **3a** in 71% yield (Entry 5). By varying the amount of catalyst from 1 to 20 mol-% (Entries 6–9), we found that the use of 2 mol-% of Cu(OTf)$_2$ afforded **3a** exclusively (Entry 8, 89%). We thought that Lewis acids might accelerate the intermolecular aromatic substitution; thus, we attempted to use other Lewis acid catalysts for this reaction (Entries 10–14). Use of 10 mol-% of boron trifluoride–diethyl ether (BF$_3$·OEt$_2$) did not show any catalytic activity (Entry 10). However, reaction in the presence of a stoichiometric amount of BF$_3$·OEt$_2$ proceeded in reasonable yields at room to reflux temperature (Entry 11, 47%; Entry 12, 70%).[5] Other Lewis acids such as tin(II) or scandium(III) triflate did not give any product (Entries 13, 14). It is worth noting that use of rhodium(II) acetate dimer [Rh$_2$(OAc)$_4$], which is usually the preferred catalyst in diazo carbonyl aromatic substitution reactions, resulted in a modest yield (Entry 15, 39%).

This method was used to carry out reactions of various types of *N*-(β-carbonylmethyl)-*N*-methylaniline derivatives **1** with **2a**, that might afford the corresponding intermolecular aromatic substitution products **3** (Table 2). As expected, reaction of benzyl ester (**1b**) and *tert*-butyl ketone (**1c**) derivatives proceeded smoothly to give **3b** and **3c**, respectively, in reasonable yields (Entry 1, 85%; Entry 2, 68%); however, phenyl ketone derivative **1d** did not give the expected product at all (Entry 3, 0%). A complex mixture of unidentified products was obtained. The acidic α-proton of **1d** might inhibit the reaction. Use of other analogs, such as the amide-type substrate **1e**, gave the adduct **3e** in lower yield (Entry 4, 42%). To determine the scope and limitations of the present method, we examined the reactions of *N*-alkyl-*N*-methylanilines under the same conditions. Interestingly, β-alkoxyethyl derivatives **1f** or **1g** were converted into **3f** or **3g**, respectively, in moderate yields (Entry 5, 59%; Entry 6, 59%). However, reactions of simpler substrates such as *N*-benzyl-*N*-methylaniline (**1h**) or *N*,*N*-dimethylaniline (**1i**) were unsatisfactory, and unreacted **2a** was recovered (Entry 7, 35%, 28% recovery of **2a**; Entry 8, 2%, 81% recovery of **2a**). An appreciable amount of any C–H insertion products was not observed.

Table 2. Intermolecular aromatic substitution of **1b**–**1i**.



Entry	R^1	Compound	*t* [h]	Yield [%][a]
1	CO$_2$Bn	**b**	12	85
2	CO*t*Bu	**c**	12	68
3	COPh	**d**	12	0
4	CONEt$_2$	**e**	12	42[b]
5	CH$_2$OBn	**f**	12	59
6	CH$_2$OMe	**g**	12	59
7	Ph	**h**	12	35
8	H	**i**	24	2

[a] Isolated yield unless otherwise noted. [b] Determined by ^{1}H NMR assay using acetophenone as an internal standard.

These results suggested that the substrates **1** function as ligands of Cu(OTf)$_2$, and the catalytic activity is determined by the structure of the complexes. Thus, we prepared ligands **4a**–**4c**, masking the *para*-position with a methyl group (Figure 1) to improve the chemical yield of **3**, and carried out reactions in the presence of 2 mol-% of Cu(OTf)$_2$–**4** complexes (Table 3). Although the yields of **3c**, **3e**, and **3g** were not improved (Entries 1–3), the reactions of **1h** were accelerated, and the yields of **3h** were improved remarkably by addition of ligands **4a** or **4b** (Entry 4, 71%; Entry 5, 73%). Ligand **4c** did not accelerate the reaction of **1h** (Entry 6, 29%). A reaction of *N*,*N*-dimethylaniline (**1i**) failed though in the presence of **4a** (Entry 7, 2%). Although the exact reason is presently unknown, it is safe to say that the initial ligand **4a** or **4b** might be exchanged by excess amounts of substrates **1c**, **1e**, **1g**, or **1i**, and their reactions

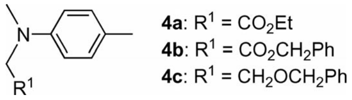
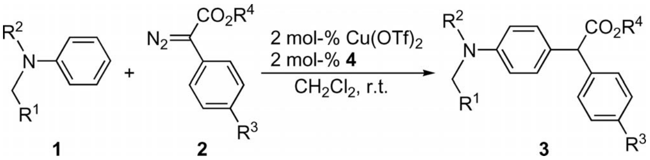


Figure 1. Structure of ligands **4a**–**4c**.

Table 3. Intermolecular aromatic substitution of **1** in the presence of ligand **4**.[a]



Entry	Aniline **1**		Diazo ester **2**		Product **3**
	R^1	R^2	R^3	R^4	Yield [%][d]
1	CO*t*Bu	Me (**1c**)	H	Me (**2a**)	60 (**3c**)
2	CONEt$_2$	Me (**1e**)	H	Me (**2a**)	25 (**3e**)
3	CH$_2$OMe	Me (**1g**)	H	Me (**2a**)	63 (**3g**)
4	Ph	Me (**1h**)	H	Me (**2a**)	71 (**3h**)
5[b]	Ph	Me (**1h**)	H	Me (**2a**)	73 (**3h**)
6[c]	Ph	Me (**1h**)	H	Me (**2a**)	29 (**3h**)[e]
7	H	Me (**1i**)	H	Me (**2a**)	2 (**3i**)
8	*p*-ClC$_6$H$_4$	Me (**1j**)	H	Me (**2a**)	64 (**3j**)
9	*p*-MeOC$_6$H$_4$	Me (**1k**)	H	Me (**2a**)	46 (**3k**)
10	Ph	Et (**1l**)	H	Me (**2a**)	62 (**3l**)
11	Ph	Bn (**1m**)	H	Me (**2a**)	72 (**3m**)
12	Ph	Me (**1h**)	Cl	Me (**2b**)	36 (**3n**)
13	Ph	Me (**1h**)	OMe	Me (**2c**)	86 (**3o**)
14	Ph	Me (**1h**)	H	Et (**2d**)	64 (**3p**)
15	Ph	Me (**1h**)	H	Bn (**2e**)	31 (**3q**)

[a] Unless otherwise noted, **4a** was used as a ligand. [b] **4b** was used as a ligand. [c] **4c** was used as a ligand. [d] Isolated yield unless otherwise noted. [e] Determined by ^{1}H NMR assay using acetophenone as an internal standard.

are not accelerated. However, substrate **1h** would not exchange with the initial ligand **4a** or **4b**, and its reaction was accelerated, because both **4a** and **4b** are able to work as chelating ligands to stabilize the complexes or intermediates.[6] Ligand **4c** might be liberated by **1h** due to its lower chelating ability. Sterically less demanding **1i** would coordinate to $Cu(OTf)_2$ strongly and deactivate the catalyst. In fact, when the reaction of **1a** with **2a** catalyzed by 2 mol-% of $Cu(OTf)_2$ (Table 1, Entry 8, 89%) was carried out in the presence of catalytic amounts of **1i** (2–10 mol-%), the yields of **3a** were decreased (2 mol-%: 63%; 5 mol-%: 31%; 10 mol-%: 8%).

The scope of substrates was further explored as shown in Entries 8–15. *N*-Alkyl-*N*-benzylanilines **1j**–**1m** reacted with **2a** in 46–72% yield (Entries 8–11). This reaction is sensitive to the structural and electronic properties of the diazo esters. Whereas a reaction of *p*-chlorophenyl diazo ester **2b** with **1h** gave a lower yield (Entry 12, 36%), a reaction of *p*-methoxyphenyl diazo ester **2c** afforded **3o** in excellent yield (Entry 13, 86%). In addition, a reaction of ethyl diazo ester **2d** with **1h** proceeded in moderate yield (Entry 14, 64%), but benzyl diazo ester **2e** did not (Entry 15, 31%).[7]

Conclusions

We have demonstrated the versatility of an intermolecular aromatic substitution reaction, which employs *N*,*N*-disubstituted anilines and diazo esters as substrates. The reaction is shown to proceed under mild conditions in the presence of catalytic amounts of copper(II) triflate–ligand complexes. The scope and limitations regarding substrates, diazo esters, and ligands has been described. Further work to develop an asymmetric reaction by using chiral ligands is in progress in our laboratory.

Experimental Section

An off-white suspension of copper(II) triflate (22 mg, 0.06 mmol) in dichloromethane (15 mL) was added to a flask containing **4a** (12 mg, 0.06 mmol) at room temperature with stirring under nitrogen. The mixture was stirred at the same temperature for over 3 h, and part of the resulting solution (1.5 mL, 0.006 mmol) was added to **1h** (89 mg, 0.45 mmol) with stirring at room temperature. Then, a solution of **2a** (53 mg, 0.30 mmol) in dichloromethane (1.5 mL) was added dropwise successively. After stirring for 12 h at the same temperature, the reaction was quenched with saturated aqueous sodium hydrogen carbonate. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate, 15:1 to 10:1) afforded **3h** (74 mg, 71% yield) as a pale yellow oil.

Supporting Information (see footnote on the first page of this article): Experimental details; spectroscopic characterization data for all compounds; copies of the ^1H and ^{13}C NMR spectra of **3a**–**q**.

Acknowledgments

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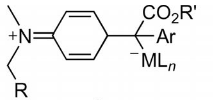
[6] Davies et al. reported that the aromatic substitution reaction, which is promoted by electron-deficient rhodium catalysts, proceeds by formation of zwitterionic intermediate **A** (ref.[2b]). Cu(OTf)$_2$ also works as an electron-deficient catalyst. However, substrates (ligands) work as electron-donors, and some of them might inhibit the formation of **A**. Although chelating ligands **4a** or **4b** coordinate to $Cu(OTf)_2$ efficiently, the ability as electron-donors might be lower than **1h**.



A

[7] We attempted reactions using diazo esters without an α-aryl substituent. However, the reactions did not succeed.

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