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Iron-catalyzed Oxidative Coupling of Alkylamines with Arenes, Nitroalkanes, and 1,3-Dicarbonyl Compounds

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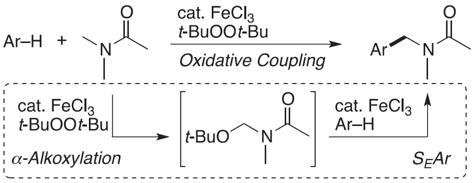
$FeCl_3$ in combination with *t*-BuOO*t*-Bu as an oxidant was found to catalyze oxidative coupling of alkylamines with arenes, nitroalkanes, and 1,3-dicarbonyl compounds to give arylmethylamines, β-nitroalkylamines, and 2-(aminomethyl)-1,3-dicarbonyl compounds, respectively.

A sequence consisting of oxidation of a C–H bond adjacent to a nitrogen atom and substitution reaction of the resulting oxidation product with a carbon nucleophile is useful for introduction of carbon substituents into nitrogen-containing compounds. From operational simplicity, methods of conducting the sequence in one batch have recently attracted attention. In this context, we have reported that a combination of $FeCl_3$ and *t*-BuOO*t*-Bu as a catalyst and an oxidant, respectively, is effective for oxidative coupling of alkylamides with arenes, where $FeCl_3$ works efficiently in both the oxidation and electrophilic aromatic substitution (S_EAr) steps (Scheme 1).[1] In contrast to the fact that only a few examples are available for alkylamides,[2,3] more readily oxidizable alkylamines have been used for oxidative couplings with heteroarenes,[4] nitroalkanes,[5] and 1,3-dicarbonyl compounds.[6,7] However, a single oxidation system applicable to a wide range of nucleophiles has not been reported. Here we report that the $FeCl_3$–*t*-BuOO*t*-Bu system is effective for oxidative coupling of alkylamines with arenes, nitroalkanes, and 1,3-dicarbonyl compounds.

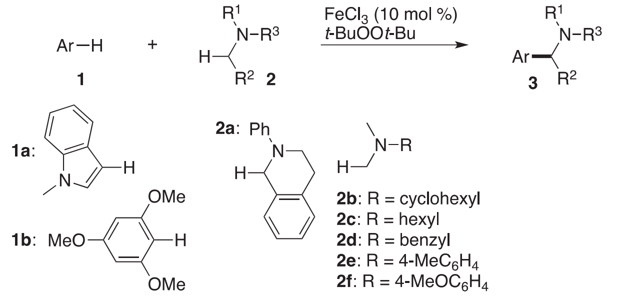
The reaction of *N*-methylindole (**1a**: 1 equiv) with 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**2a**: 4 equiv) using $FeCl_3$ (10 mol %) and *t*-BuOO*t*-Bu (2 equiv) in 1,2-dichloroethane (DCE) at 80 °C for 9 h gave 1-(1-methyl-3-indolyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**) in 95% yield (Entry 1 of Table 1).[8] Saturated alkylamines also underwent the oxidative coupling with **1a**, though a higher temperature (110 °C) was required (Entries 2 and 3). To the best of our knowledge, there have been no reports that amines having no unsaturated bonds are used for oxidative coupling with arenes. The coupling proceeded also with *N*,*N*-dimethylbenzylamine (**2d**) (Entry 4). Amines having methyl groups on the nitrogen atom were arylated selectively on the methyl group. The present iron-catalyzed reaction is applicable to a benzene derivative (Entries 5 and 6), contrasting with the previous methods.[4,9] The yields were higher by use of $FeCl_2$ instead of $FeCl_3$ in these cases.

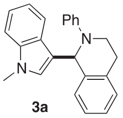
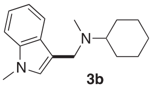
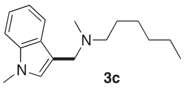
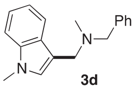
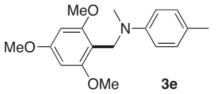
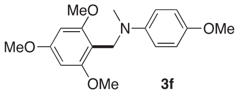
Addition of *N*-methylindole (**1a**) to a reaction mixture of tetrahydroisoquinoline **2a**, $FeCl_3$, and *t*-BuOO*t*-Bu after full consumption of *t*-BuOO*t*-Bu gave 71% of coupling product **3a** (Scheme 2).[15] Although we were not able to identify any intermediates derived from oxidation of **2a**, the result shows that the present oxidative coupling consists of oxidation of alkylamines and S_EAr with the oxidized intermediate as is the case with alkylamides shown in Scheme 1. A higher yield observed



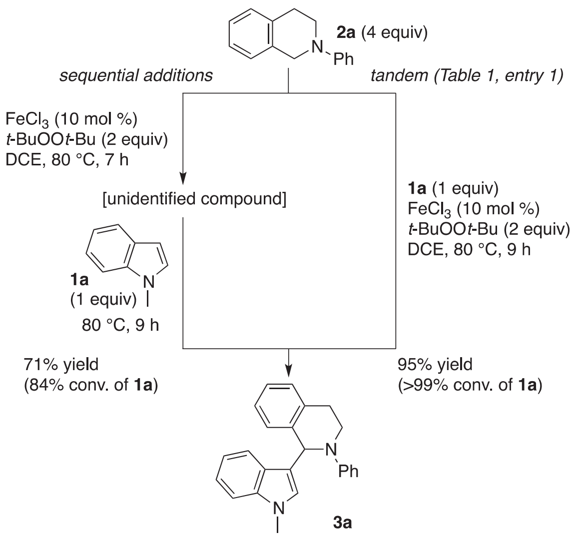
Scheme 1.

Table 1. Oxidative coupling of alkylamines with arenes[a]

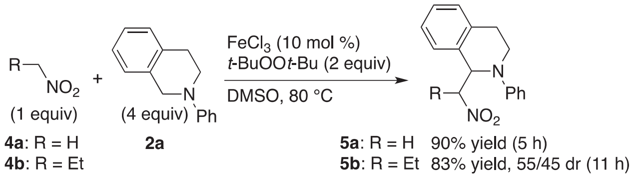


Entry	1	2	Cond.[a]	Time/h	Yield/%	Product
1	**1a**	**2a**	A	9	95	 **3a**
2	**1a**	**2b**	B	2	70	 **3b**
3	**1a**	**2c**	B	8	52	 **3c**
4	**1a**	**2d**	C	2	63	 **3d**
5	**1b**	**2e**	D	48	74	 **3e**
6	**1b**	**2f**	D	30	78	 **3f**

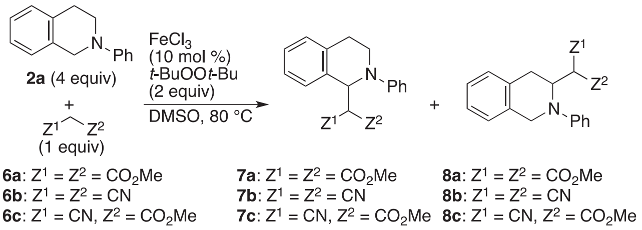
[a] The reaction was carried out in a solvent (1.0 mL) under a nitrogen atmosphere using an arene **1** (0.25 mmol), an amine **2**, and *t*-BuOO*t*-Bu in the presence of $FeCl_3$ (0.025 mmol). Conditions (solvent, temperature, **1**/**2**/*t*-BuOO*t*-Bu) are as follows. A: 1,2-dichloroethane, 80 °C, 1/4/2. B: 1,2-dichloro-2-methylpropane, 110 °C, 1/6/3. C: DMSO, 80 °C, 1/5/2. D: DMSO, 80 °C, 1/6/3; use of $FeCl_2$ instead of $FeCl_3$.[15]



Scheme 2.



Scheme 3.

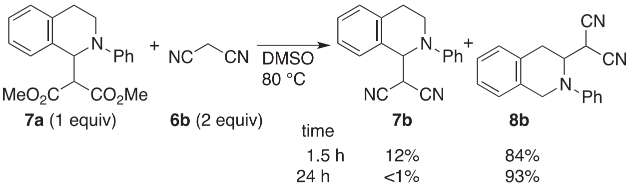


6	time	yield	7:8	products	
6a	3 h	84%	>99:1	**7a**	
6b	24 h	87%	1:>99	**8b**	
6b	1 h	68%	51:49	**7b** + **8b**	**6b** was not fully consumed.
6c	7 h	65%	1:>99	**8c**	diastereomer ratio = 81:19

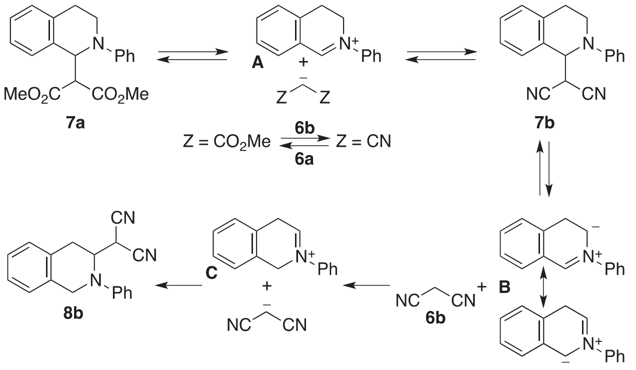
Scheme 4.

in the tandem reaction offers an advantage over the sequential additions in utilization of unstable intermediates.

The combination of FeCl$_3$ with *t*-BuOO*t*-Bu was effective for the coupling of tetrahydroisoquinoline **2a** with nitroalkanes **4** (Scheme 3).[15] The reaction of **2a** with dimethyl malonate (**6a**) gave 1-alkylated isoquinoline **7a** (Scheme 4).[15] To our surprise, the regiochemistry was completely changed by use of malononitrile (**6b**) as a nucleophile to give 3-alkylated product **8b** as the exclusive isomer. A reaction mixture of **2a** and **6b** quenched at 1 h, before full consumption of **6b**, contained 1-alkylated product **7b** in addition to **8b**,[10] showing that the malononitrile moiety shifts from 1-position to 3 under the reaction conditions. The same 3-selectivity was observed with methyl 2-cyanoacetate (**6c**) to give **8c**.



Scheme 5.



Scheme 6.

As shown in Scheme 5, the reaction of **7a** (1 equiv) with **6b** (2 equiv) at 80 °C for 1.5 h gave a mixture of isoquinolines having CH(CN)$_2$ at 1-position (**7b**: 12%) and 3-position (**8b**: 84%), whereas only **8b** was observed after 24 h.[11,12,15] Iminium salt **A** in Scheme 6 should be an intermediate in the transformation of **7a** to **7b**. Although it is unclear why the 1,3-shift is operative with dicyanomethyl but not with bis(methoxycarbonyl)methyl, we assume participation of azomethine ylide **B** as an intermediate.[13] Deprotonation from **6b** by **B** and the following nucleophilic addition to **C** gives **8b**.[14]

In conclusion, we have disclosed that FeCl$_3$ in combination with a stoichiometric amount of *t*-BuOO*t*-Bu catalyzes oxidative coupling of amines with various nucleophiles to give aminomethylarenes, β-aminonitroalkanes, and 2-(aminomethyl)-1,3-dicarbonyl compounds.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

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10 Although **7b** appears in both refs. 6a and 5d, the reported NMR data are different. The data of **7b** in ref. 5d correspond to those of **8b** in our hands. We concluded that the characterization in ref. 5d is incorrect, and that the platinum-catalyzed reaction of **2a** with **6b** also gives **8b**, which has never appeared in the literature.

11 The same transformation took place also in the presence of FeCl$_3$ (10 mol %), where no acceleration effect of FeCl$_3$ was observed.

12 Isoquinoline **8a** having CH(CO$_2$Me)$_2$ at 3-position was not observed in any case. Upon treatment with **6a** instead of **6b** in the same way as shown in Scheme 5, no isomerization of **7a** took place.

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14 If **B** is generated by deprotonation from **A** by $^{-}$CH(CN)$_2$, more basic $^{-}$CH(CO$_2$Me)$_2$ has to be more efficient. As this is not the case, formation of **B** from **7b** possibly includes some concerted mechanism, where the nitrogen atom of nitriles takes a position suitable for abstraction of a proton from 3-position. The pK_a values of CH$_2$(CO$_2$Me)$_2$ (**6a**) and CH$_2$(CN)$_2$ (**6b**) in DMSO are reported to be 16.4 (ref. a) and 11.1 (ref. b), respectively. a) W. N. Olmstead, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3299. b) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier, *J. Am. Chem. Soc.* **1975**, *97*, 7006.

15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.