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Iron(II) Triflate as a Catalyst for the Synthesis of Indoles by Intramolecular C−H Amination

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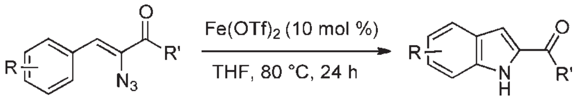
ABSTRACT



A practical iron-catalyzed intramolecular C−H amination reaction and its application in the synthesis of indole derivatives are presented. As a catalyst, commercially available iron(II) triflate is used.

Indoles are synthetically relevant compounds, and many derivatives show important biological activities.[1] Consequently, synthetic approaches toward indoles have attracted significant attention.[2] In many cases, the well-studied Fischer indole synthesis is the method of choice, but often, this approach suffers from problems such as low yield and formation of side products.[3] Alternatively, indoles have been targeted by starting from azides, where photo- or thermolytic conditions, like the Hemetsberger−Knittel reaction,[4] allow aminations of aromatic C−H bonds through nitrene insertions.[5] Safety concerns[6] stipulated the search for metal-catalyzed versions of such reactions. In this context, Driver described the ring closure of aryl azidoacrylates to give indoles and related heterocycles using rhodium(II) perfluorobutyrate as a catalyst.[7,8] Later, it was demonstrated that aryl azides could be activated by iron salts providing access to other heterocyclic systems.[9−11] Our own interest in imination reactions under iron catalysis[12,13] led us to hypothesize that, in analogy to Driver's rhodium catalysis, simple iron salts could also prove useful for direct indole syntheses. Here, we report the results of this study and reveal that iron(II) triflate[14] is a highly suitable catalyst for such intramolecular C−H amination reactions starting from azidoacrylates.[15]

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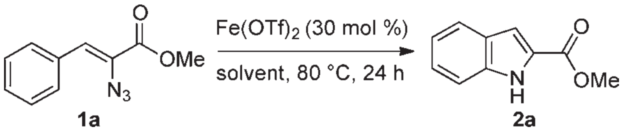
(11) 2*H*-Azirines were shown to undergo ring opening to give indoles under iron catalysis. Also here, iron nitrenes have been suggested as intermediates. Jana, S.; Clements, M. D.; Sharp, B. K; Zheng, N. *Org. Lett.* **2010**, *12*, 3736.

10.1021/ol2004066

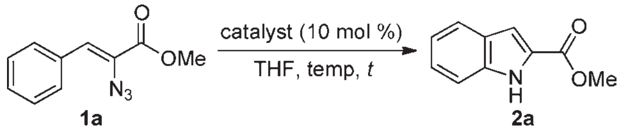
Table 1. Iron-Catalyzed C−H Amination of Azide **1a**: Influence of the Solvent



entry	solvent	yield of **2a** (%)[a]
1	DMF	--
2	acetonitrile	--
3	EtOH	--
4	water	--
5	hexane	58
6	toluene	46
7	xylene	38
8	chloroform	46
9	diethyl ether	16
10	MTBE	28
11	DME	63
12	anisole	41
13	dioxane	26
14	THF	78 (75)[b]

[a] After chromatography. [b] In parentheses, the result from an experiment performed with 10 mol % of iron triflate.

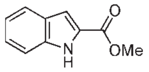
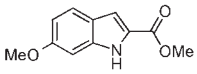
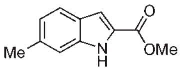
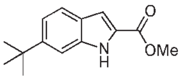
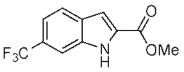
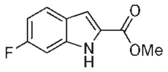
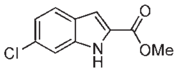
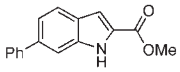
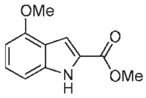
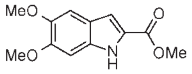
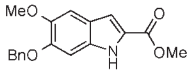
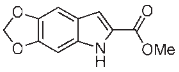
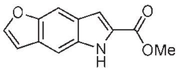
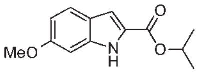
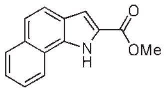
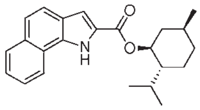
Table 2. Metal-Catalyzed Conversion Synthesis of Indole **2a**



entry	catalyst	temp (°C)	*t* (h)	yield (%)[a]
1	$Fe(OTf)_2$	80	24	75 (40)[b]
2	---	80	24	--
3	$Fe(OTf)_2$	60	24	24
4	$Fe(OTf)_2$	r.t.	24	0
5	$Fe(OTf)_2$	80	5	44
6	$Fe(OTf)_2$	80	1	13
7	TfOH	80	24	--
8	TfONa	80	24	--
9	CuOTf	80	24	--
10	$Cu(OTf)_2$	80	24	--

[a] After chromatography. [b] In parentheses, the result from an experiment performed with 1 mol % of iron triflate.

Table 3. Iron-Catalyzed Synthesis of Indole Derivatives[a]

entry	indole		yield (%)[b]
1		**2a**	75
2		**2b**	74
3		**2c**	77
4		**2d**	83
5		**2e**	60
6		**2f**	72
7		**2g**	56
8		**2h**	80
9		**2i**	70
10		**2j**	88
11		**2k**	99
12		**2l**	97
13		**2m**	99
14		**2n**	35
15		**2o**	98
16		**2p**	93

[a] Azidoacrylate **1** (1 equiv), $Fe(OTf)_2$ (0.10 equiv), THF (3 mL/mmol of **1**), 80 °C, 24 h. [b] After chromatography.

Recently, much work has been devoted to iron catalysis,[16] and commonly the applied iron salts are considered as inexpensive, nontoxic, and environmentally friendly. In sulfoxide iminations we had identified iron(II) triflate as a highly efficient and robust catalyst being superior to many other iron salts.[13e,f] Consequently, we started our current investigation using this particular iron salt as a catalyst. The test substrate was phenyl azidoacrylate **1a** that we expected to be converted into 2-carboxy-substituted indole **2a**.

As in other iron catalyses, the solvent played a major role in this reaction. Various solvents were screened, and the results are summarized in Table 1. Reactions performed (with 30 mol % of iron triflate at 80 °C) in DMF, acetonitrile, or protic polar solvents such as water and ethanol gave no product (entries 1−4). In hexane, toluene, and xylene (entries 5−7) as well as other solvents of low polarity, the yields were moderate to good (up to 58% for hexane). Ethers such as MTBE, DME, and others (entries 9−14) proved suitable too, and finally, THF was found to be the best solvent for this iron catalysis providing **2a** in 78% yield (entry 14).

Next, other reaction parameters were evaluated. The catalyst loading could be reduced from 30 to 10 mol % without significantly affecting the yield of **2a** (Table 2, entry 1). With 1 mol % for iron triflate, however, a sharp drop in yield was observed (Table 2, entry 1). As expected, no product was formed in the absence of the catalyst (Table 2, entry 2).

Both lowering the temperature (from 80 °C to ambient temperature) and shortening the reaction time decreased the yield (Table 2, entries 3−6). In order to ensure that iron was essential for the conversion of **1a**, sodium triflate and triflic acid were tested, but both proved inactive (entries 7 and 8). Based on previous observations[17] we felt obliged to test if copper showed catalytic activity. Neither copper(I) triflate nor copper(II) triflate was able to catalyze the formation of indole **2a** from azidoacrylate **1a** (Table 2, entries 9 and 10).

Finally, the reaction scope was investigated. The catalysis proceeded well with substrates having various substituents irrespective of the position at the aryl ring. Thus, azidoacrylates with methoxy, alkyl, trifluoromethyl, halo, and phenyl groups in the *para* position reacted well affording the corresponding indoles **2** in yields up to 80% (Table 3, entries 2−8). An *ortho* methoxy substituent had no significant impact, and product **2i** was obtained in 70% yield. Substrates with *meta* and *para* disubstituted aryl groups afforded only single isomers (entries 10−13 and 15), and in all cases the yields were exceptionally high (88−99%). In order to ensure that other esters could be converted, the syntheses of isopropyl and menthyl esters **2n** and **2o**, respectively, were studied. To our delight, those products also could be obtained in moderate to very high yields (35 and 93%, entries 14 and 16).

In summary, we have demonstrated that a variety of indoles can be obtained from the corresponding aryl azidoacrylate commercially available iron(II) triflate catalyst. Further studies are directed toward an expansion of the substrate scope with a particular focus on the preparation of other heterocycles.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In this study, commercially available iron(II) triflate (98% from abcr) was used.

(15) While this work was in progress, Che and co-workers described a very related iron-catalyzed amination of a C−H bond using aryl azides as a nitrogen source. There, however, a rather expensive iron porphyrin [$Fe(F_{20}TPP)Cl$ where $H_2F_{20}TPP$ stands for *meso*-tetrakis-(pentafluorophenyl)porphyrin] in toxic 1,2-dichloroethan was used as a catalyst. See: Liu, Y.; Wei, J.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 6926.

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