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Lewis Acid-Promoted Imine Synthesis by the Insertion of Isocyanides into C–H Bonds of Electron-Rich Aromatic Compounds

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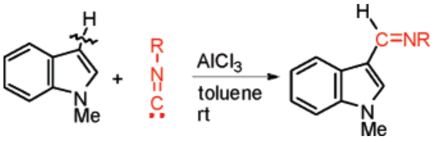
ABSTRACT



The Lewis acid-promoted insertion of isocyanides into aromatic C–H bonds is reported. An imine functionality containing an array of N-substituents can be introduced directly into electron-rich aromatics in good yields.

Due to the presence of a formally divalent carbon atom, isocyanides occupy a unique position in the field of organic chemistry, and have enjoyed widespread use in organic synthesis,[1] especially in multicomponent transformations.[2] The chemistry of isocyanides is dominated by the nucleophilicity of the isocyano carbon atom as a result of the interaction of the vacant p_π orbital with the lone pair of electrons on the nitrogen atom (Figure 1, a). It should also be noted that isocyanides could serve as an electrophile as well, in which the π^* orbital of the isocyano group accepts an electron from the nucleophile (Figure 1, b). However, this type of reactivity of isocyanides has only been observed in case of strong nucleophiles, such as organolithium,[3a] -magnesium,[3a] and -zinc[3b] reagents.[4] Obviously, broadening the range of nucleophiles used in this α-addition reaction should further increase the synthetic utility of isocyanides. A simple strategy toward achieving this goal would be to enhance the electrophilicity of isocyanides by Lewis acid complexation (Figure 1, c). Although several Lewis acid–isocyanide complexes have been reported to date,[5] such species, to our surprise, have rarely been exploited in organic

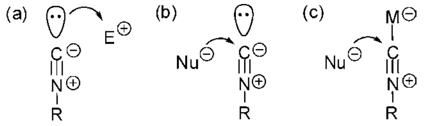


Figure 1. Ambiphilic reactivity of isocyanide serving (a) as nucleophile, (b) as electrophile, and (c) as electrophile in which isocyanide is activated by Lewis acid (M).

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(1) Suginome, M.; Ito, Y. In *Science of Synthesis*; Murahashi, S.-I. Ed.; Thieme, Stuttgart, 2004, Vol. 19; pp. 445–530.

(2) For recent reviews, see: Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu. S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(3) (a) Niznic, G. E.; Morrison, W. H.; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600. (b) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1988**, *53*, 4158.

(4) Reversible addition of weak nucleophiles to isocyanides has been proposed in the intramolecular cyclization of 2-alkynylisocyanobenzenes: Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977.

(5) B: Jacobsen, H.; Berke, H.; Doring, S.; Kehr, G.; Erker, G.; Frohlich, R.; Mayer, O. *Organometallics* **1999**, *18*, 1724. Al: Fisher, J. D.; Wei, M.-Y.; Willett, R.; Shapiro, P. J. *Organometallics* **1994**, *13*, 3324. Zr: Brackemeyer, T.; Erker, G.; Frohlich, R. *Organometallics* **1997**, *16*, 531. Ti: Carofiglio, T.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Inorg. Chem.* **1989**, *28*, 4417.

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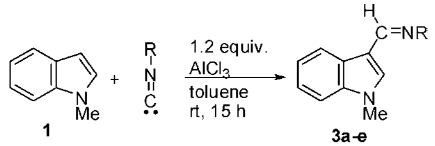
synthesis,[6] except for the polymerization of isocyanides.[7] Herein, we report that Lewis acids promote the addition of weak nucleophiles, specifically, electron-rich aromatic compounds, onto isocyanides.

During investigations into the reactivity of isocyanides in the presence of Lewis acids, we found that 1-methylindole (**1**) can be added to 2,6-xylyl isocyanide (**2a**) effectively, furnishing the 3-iminoindole **3a** (Scheme 1).[8] Lewis acids containing group 13 elements proved to be excellent promoters for this α-addition with indoles: $BF_3{\cdot}OEt_2$ (68%), $AlCl_3$ (88%), $GaCl_3$ (86%), and $In(OTf)_3$ (90%).[9,10] The transformation shown in eq 1 represents the insertion of isocyanides into an aromatic C−H bond. Although such a process has been reported to proceed in the presence of a rhodium complex under photochemical conditions[11] or when applied to an intramolecular reaction of one specific substrate,[12] *thermal intermolecular variants are unprecedented.* Under the influence of inexpensive $AlCl_3$, the α-addition with indole **1** appears to be quite general in the context of isocyanide architecture. The presence of two ortho substituents in aromatic isocyanides, as in **2a**, is not essential for the present insertion reaction (Scheme 1). Electron-rich (**2c**) and -deficient (**2d**) phenyl isocyanides, as well as alkyl isocyanides (**2e**), all furnished the corresponding 3-imino indoles in good yields. It is noteworthy that the byproducts arising from the addition of indole **1** to the imine **3** were not observed in any case, although such aza-Friedel−Crafts reactions of indoles are well-known processes.[13]

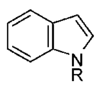
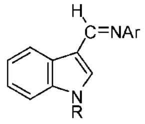
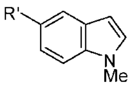
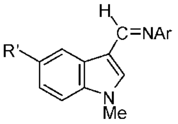
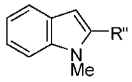
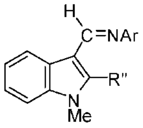
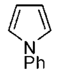
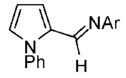
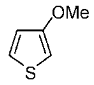
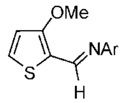
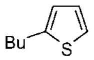
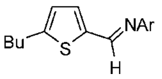
Scheme 1



R = 2,6-$Me_2C_6H_3$ (**2a**)	88%
3,5-$Me_2C_6H_3$ (**2b**)	68%
4-$MeOC_6H_4$ (**2c**)	79%
4-ClC_6H_4 (**2d**)	64%
benzyl (**2e**)	82%

The scope of the reaction with respect to indoles was next investigated by employing isocyanide **2a** (Table 1). Other than a methyl group, benzyl and aryl groups are suitable as N-substituents of indoles (entries 2 and 3), while electron-withdrawing groups, such as benzoyl and *p*-toluenesulfonyl, are not. These results indicate the importance of the π-nucleophilicity of indoles in the present isocyanide insertion to proceed. Notably, the free indole exhibited a comparable reactivity, resulting in the formation of 3-imino indole without competing with the N−H insertion (entry 4).[14] The introduction of both electron-donating and -withdrawing substituents, including alkyl and aryl groups, ethers, bromides, and esters, was well tolerated (entries 5−9), whereas no insertion products were obtained when highly electron-deficient 5-cyano- and 5-nitroindoles were used. In addition, by applying this methodology to 2-substituted indoles, imino groups can be installed effectively at the sterically congested positions (entries 10 and 11). It is important to note that the reaction can successfully be extended to other electron-rich aromatics, including pyrroles and thiophenes, which furnish

Table 1. $AlCl_3$-Promoted Insertion Reaction of Isocyanide **2a** into C−H Bonds of Aromatic Compounds[a]

entry	aromatics	product[b]		yield (%)[c]
1			R = Me	88
2			R = CH_2Ph	81
3			R = 4-MeC_6H_4	93
4			R = H	78
5			R' = Me	76
6			R' = Ph	73
7			R' = OMe	80
8			R' = Br	89
9			R' = CO_2Me	83
10[d]			R'' = Me	85
11			R'' = Ph	92
12				84[e]
13				78
14[d]				82

[a] Reaction conditions: indole (1.0 mmol), 2,6-dimethylphenyl isocyanide (1.1 mmol), $AlCl_3$ (1.2 mmol) in toluene (2 mL) at rt, 15 h. [b] Ar = 2,6-dimethylphenyl. [c] NMR yields. [d] Run at 60 °C. [e] The 3-substituted isomer was also observed as a minor product (6%).

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(6) For recent examples of Lewis acid-promoted reactions of isocyanides, see; Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991. Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697. Winkler, J. D.; Asselin, S. M. *Org. Lett.* **2006**, *8*, 3975. Korotkov, V. S.; Larionov, O. V.; de Meijere, A. *Synthesis* **2006**, 3542.

(7) Millich, F. *Chem. Rev.* **1972**, *72*, 101.

(8) The process is closely related to Vilsmeir-Haack reaction, in which chloroiminium salts work as an electrophile. Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1.

(9) Throughout the paper, yields refer to those determined by NMR measurement of the crude reaction mixture after an aqueous workup. The imines can be isolated by chromatography (Al_2O_3), but with reduced yields. For example, the isolated yield of entry 12 in Table 1 was 65%.

(10) Yields with other acids; $TiCl_4$ (24%), HCl (26%), TfOH (51%), and TFA (0%).

(11) Tanaka, M.; Sakakura, T.; Tokunaga, Y.; Sodeyama, T. *Chem. Lett.* **1987**, 2373. Jones, W. D.; Foster, G. P.; Putinas, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5047. Jones, W. D.; Hessell, E. T. *Organometallics* **1990**, *9*, 718.

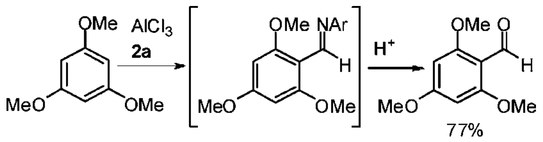
(12) Kobayashi, K.; Matoba, T.; Irisawa, S.; Matsumoto, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1998**, 551.

(13) Xie, W.; Bloomfield, K. M.; Jin, Y.; Dolney, N. Y.; Wang, P. G.*Synlett* **1999**, 498.

(14) Transition metal-mediated insertion of isocyanides into the N−H bond in indoles: Jones, W. D.; Kosar, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 5640.

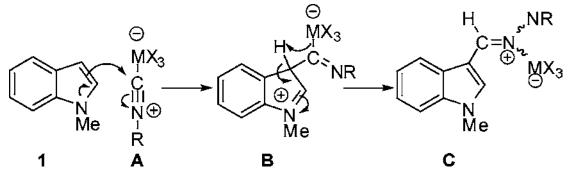
the corresponding C−H insertion products in a regioselective manner (entries 12−14). Moreover, an electron-rich benzene ring can serve as a good nucleophile for the α-addition with isocyanides (Scheme 2).

Scheme 2



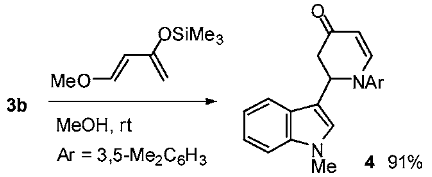
To gain insights into the reaction mechanism, NMR experiments were carried out with $GaCl_3$,[15] which is more soluble in nonpolar solvents. Upon treatment of 2,6-xylyl isocyanide (**2a**) with 1 equiv of $GaCl_3$ in C_6D_6, the resonance corresponding to the methyl group in **2a** immediately shifted upfield from 2.06 to 1.62 ppm, indicating the formation of isocyanide−Lewis acid adduct, as in **A** (Scheme 3).[5] When a solution of the isocyanide−$GaCl_3$ adduct was treated with indole **1**, the formation of the insertion product **3a** was observed after an aqueous workup. In addition, labeling studies revealed that the hydrogen atom originally located at the 3-position of indole is transferred to the imino hydrogen of the product.[15] On the basis of the above results, we propose a mechanism that involves (i) the nucleophilic attack of indoles to the isocyanide−Lewis acid adduct **A** to generate intermediate **B** and (ii) aromatization via deprotonation and protonolysis of the carbon−metal bond, leading to the inserted product (Scheme 3).[16,17] A preliminary initial rate measurement exhibited no significant kinetic isotope effect,[15] indicating that the formation of the intermediate **B** is rate-limiting.

Scheme 3



The imines synthesized through the isocyanide insertion reaction are amenable to further synthetic elaboration. For example, the [4+2] cycloaddition[19] with Danishefsky's diene provides dihydropyridone **4**, which is a versatile intermediate for the synthesis of indole alkaloids and analogues thereof (Scheme 4).[20]

Scheme 4



In summary, we report on the first α-addition of isocyanides with aromatic compounds, promoted by inexpensive Lewis acids, such as $AlCl_3$. The method can provide a direct and practical access to a wide array of imines via aromatic C−H bond functionalization. Ongoing work seeks to explore the new isocyanide insertion process into other chemical bonds.

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Supporting Information Available: Detailed experimental procedures and the characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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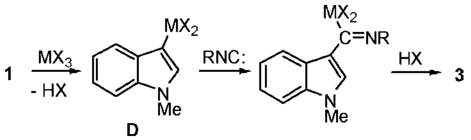
[15] See the Supporting Information for details.

[16] A crossover experiment indicates that the major part of the proton migration occurs intramolecularly, although an intermolecular process can be operating as a minor path. See Supporting Information for details.

[17] An alternative mechanistic possibility would be the intermediacy of a 3-indolylmetal species, such as **D** (see below).[18] We observed the interaction between indole **1** and $GaCl_3$ by ^1H NMR. However, no such interaction was observed when a 1:1 mixture of **1** and **2a** was treated with $GaCl_3$, and only the resonance of **2a** was shifted. Thus, we currently believe that the dominant species in our reaction is the isocyanide−Lewis acid adduct, as in **A**, and the insertion proceeds through **A**.



[18] Ottoni, O.; de V. F. Neder, A.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005.

[19] Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309.

[20] Tasber, E. S.; Garbaccio, R. M. *Tetrahedron Lett.* **2003**, *44*, 9185. Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863.