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The Aminomethylation of Electron-Rich Aromatics with an *N*-Silyl-*N*,*O*-Acetal Catalyzed by a Metal Triflate-TMSCl System: Facile Synthesis of Aromatic Primary Amines, 1-Aryl-trichloroethylamines

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The copper(II) triflate- and hafnium(IV) triflate-catalyzed aminomethylation of indole (**2**) with an *N*-silyl-*N*,*O*-acetal **1** containing a trichloromethyl group provides the primary amine derivative (**3a**) in modest yield. When 1 equiv of trimethylchlorosilane (TMSCl) was added to the reaction mixture, the reaction proceeded smoothly, and the yield of **3a** was dramatically improved (>90%). The use of this catalytic system permitted the introduction of an aminomethyl group onto indoles **2a**−**h** bearing a variety of functional groups, which appears to deactivate the Lewis acid, in 52−92% yields. $Hf(OTf)_4$-doped TMSCl catalyzed the successful aminomethylation of various electron-rich aromatic compounds **4a**−**j** to produce 1-aryl-trichloroethylamine derivatives **5a**−**j**.

Introductions

The Lewis acid-mediated Friedel−Crafts reaction is one of the most important reactions in organic synthesis, in that it provides a useful method for the direct introduction of a functional group onto heterocycles or aromatic compounds.[1] Among these, aminoalkylation is a quite powerful tool for the synthesis of heterocycles that contain an aminomethyl group, a structure which is broadly found in a large number of natural products and biologically active substances.[2] On the other hand, *N*,*O*-acetals, which consist of an sp^3-carbon attached to both oxygen and nitrogen atoms, are one of the more useful functional groups and have been widely applied to organic synthesis.[3] For example, the in situ generation of the corresponding imine or iminium salt via the selective cleavage of the oxygen atom of the acetal under Brønsted or Lewis acid activation, followed by a reaction with nucleophiles, leads to the formation of a new carbon−carbon bond.[4−6] Although a considerable number of the Lewis or protonic acid-mediated aminomethylations of aromatic compounds or heterocycles using an *N*,*O*-acetal have been reported,[6,7] the Lewis acid-*catalyzed* aminomethylation of aromatics with an *N*,*O*-acetal has not been extensively studied.[8] This appears to be due to the consumption of the acid by coordination to the aromatic amines as well as the extensive use of Friedel−Crafts acylation.[1] Moreover, in conventional aminomethylations,[6,7] the amines produced are mostly limited to secondary or tertiary amines or amides due to the stability of the starting compounds and the intermediate and require a further cleavage of the protecting group

(1) (a) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733−752. (c) Olah, G. A.; Krishnamurti, A. R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 3, pp 293−339. (d) Yamamoto, H., Ed. *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2.

(2) Glasby, J. S., Ed. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975.

(3) Gabbut, C. D.; Hepworth, J. D. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohnm, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 4.

(4) For selected recent papers for an *N*,*O*-acetal acting as an imine in the presence of a catalytic amount of Lewis acid with nucleophiles, see: (a) Onomura, O.; Kanda, Y.; Nakamura, Y.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2002**, *43*, 3229. (b) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827. (c) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510. (d) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477. (e) Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577. (f) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (g) Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J., III; Lectka, T. *Tetrahedron* **1999**, *55*, 8869. (h) Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 895.

(5) For selected papers for Lewis or proton acid-promoted reactions of an *N*,*O*-acetal with nucleophiles, see: (a) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165. (b) Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163. (c) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121. (d) Tsukamoto, T.; Kitazume, T. *Chem. Lett.* **1992**, 1377. (e) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795. (f) Fasseur, D.; Rigo, B.; Cauliez, P.; Debacker, M.; Couturier, D. *Tetrahedron Lett.* **1990**, *31*, 1713. (g) Fuchigami, T.; Ichikawa, S.; Konno, A. *Chem. Lett.* **1989**, 1987. (h) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056. (i) Hosomi, A.; Iijima, S.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 547. (j) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (k) Ben-Ishai, D.; Bernstein, Z. *Tetrahedron* **1977**, *33*, 3247. (l) Stewart, A. T., Jr.; Hauser, C. R. *J. Am. Chem. Soc.* **1955**, *77*, 1098.

(6) For excellent reviews for Lewis or proton acid-mediated reactions using an *N*,*O*-acetal unit and aromatics, see: (a) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (d) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (e) Zaugg, H. E. *Synthesis* **1984**, 85.

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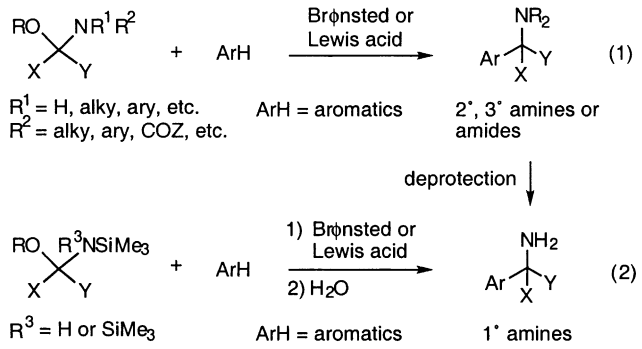
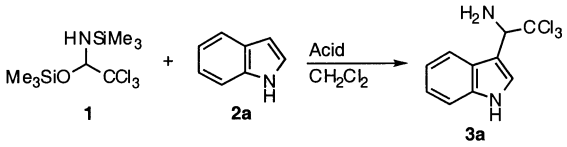
SCHEME 1



on the nitrogen atom to give the underivatized primary amines,[7d] which are more useful synthetically (eq 1 in Scheme 1).[9] Hence, the development of the Lewis acid-catalyzed aminoalkylation of *N*,*O*-acetals with aromatics that lead directly to the aromatic primary amine derivatives is quite interesting from the point of view of synthetic chemistry. We therefore attempted to utilize an *N*-silyl-*N*,*O*-acetal as an appropriate reaction substrate to achieve this synthesis,[10] because it was well known that a N−$SiMe_3$ bond can readily be converted to a N−H bond via the usual aqueous workup (eq 2 in Scheme 1).[11] During the course of our preliminary study, we have found that the Friedel−Crafts reaction of an *N*-silyl-*N*,*O*-acetal containing a trichloromethyl group with indoles having a variety of functional groups is catalyzed by $Cu(OTf)_2$ in the presence of TMSCl (1 equiv) and affords the corresponding indolyl primary amines in good to excellent yields.[12] In the previous paper, however, the aromatic compound examined was limited to an indole skeleton. Thus, we report here on a detailed reinvestigation, designed to extend the scope of the aminomethylation in the presence of a Lewis acid and TMSCl with respect to a variety of aromatic compounds.

TABLE 1. Effect of Acids on Aminomethylation[a]



run	acid (equiv)	temp (°C)	time (h)	yield (%)[b,c]
1	$BF_3{\cdot}OEt_2$ (1)	rt	72	65 (trace)
2	$TiCl_4$ (1)	0	0.3	56 (16)
3	$AlCl_3$ (1)	rt	0.2	67 (trace)
4	$SnCl_4$ (1)	rt	8	ND[d]
5	TMSOTf (1)	rt	72	62
6	TfOH (1)	rt	72	51
7	$Yb(OTf)_3$ (0.2)	rt	12	ND[d]
8	$Cu(OTf)_2$ (0.2)	rt	7	33
9	$Hf(OTf)_4$ (0.2)	rt	100	46[e]

[a] Reaction was carried out using *N*,*O*-acetal **1** (0.55 mmol), indole **2a** (0.5 mmol), Lewis acid (0.2−1.0 equiv), and TMSCl (0.55 mmol). See Experimental Section. [b] Isolated yields based on indole **2a**. [c] Isolated yields of bisindole alkane **3′a** were in parentheses. [d] ND = not determined. [e] Recovery of indole **2a** (45%).

We also report on a new catalytic system, which shows a higher activity not only for electron-rich heterocycles but also for electron-rich arenes. This method permits the facile synthesis of primary aromatic amines, 1-aryltrichloroethylamine derivatives.

Results and Discussion

Reaction of Indole with an *N*,*O*-Acetal. We first investigated the reaction of an *N*-silyl-*N*,*O*-acetal having a trichloromethyl group (**1**, 1.1 equiv),[13] a substituent that is found in a number of biologically active molecules, such as neurotoxins,[14a] fungicides,[14b] and insecticides,[14c] with indole (**2a**) in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$ to produce the corresponding primary amine, 1-(indol-3-yl)-2,2,2-trichloroethylamine (**3a**), in 65% yield, along with a trace amount of a bisindolyl adduct, 1,1-bis-indolyl-2,2,2-trichloroethane (**3′a**). Spectral data and elemental analyses were used to determine the structure of the main product **3a**. A characteristic singlet at δ 5.01 in the ^{1}H NMR spectrum (δ 65.7 in the ^{13}C NMR spectrum) was assigned to the methine proton at C-1. This observation clearly indicates the formation of a new carbon−carbon bond between acetal **1** and indole (**2a**). In addition, a broad peak at δ 2.3 in the ^{1}H NMR spectrum and a sharp peak at δ 106.7 in the ^{13}C NMR spectrum show the presence of a primary amino group and a trichloromethyl group, respectively. The present reaction was optimized in the presence of other Lewis acids, and the results are summarized in Table 1. Although typical Lewis acids provided the same product in moderate yields (runs 2, 3, and 5), stoichiometric amounts were required. Similarly, when triflic acid (TfOH) was employed as a Brønsted acid, the corresponding amine **3a** was isolated in 51% yield. In contrast, the use of $SnCl_4$ and $Yb(OTf)_3$ was not effective for the present reaction (runs 4 and 7). On the other hand,

(7) For selected papers for Lewis acid-promoted reactions of an *N*,*O*-acetal with aromatics, see: (a) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997. (b) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988. (c) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. *Tetrahedron Lett.* **1998**, *39*, 4905. (d) Clark, B. P.; Harris, J. R. *Synth. Commun.* **1997**, *27*, 4223. (e) DeNinno, M. P.; Eller, C. *Tetrahedron Lett.* **1997**, *38*, 6545. (f) Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* **1987**, *43*, 439. (g) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1982**, *23*, 785. (h) Kosugi, Y.; Hamaguchi, H.; Nagasaka, T.; Ozawa, N.; Ohki, S. *Heterocycles* **1980**, *14*, 1245. (i) Satay, I.; Peled, N.; Ben-Ishai, D. *Isr. J. Chem.* **1975**, *13*, 145.

(8) Heaney et al. have reported a Lewis acid-catalyzed intramolecular aminoalkylation using a cyclic *N*,*O*-acetal, see: El Gihani, M. T.; Heaney, H.; Shuhaibar, K. F. *Synlett* **1996**, 871.

(9) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989.

(10) Gong and Kato have quite recently reported that a similar Friedel−Crafts reaction of heteroaromatics with α-trifluoroacetaldehyde hemiaminal produced a primary amine, while most cases in this reaction needed a stoichiometric amount of Lewis acid to give satisfactory results: (a) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *108*, 83. (b) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2002**, *116*, 103.

(11) For preparation of *N*-unsubstituted amine derivatives using an N−Si bond in a Mannich-type reaction: (a) Saidi, M. R.; Mojtahedi, M. M.; Bolourtchian, M. *Tetrahedron Lett.* **1997**, *38*, 8071. (b) Barney, C. L.; Huber, E. W.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5547. (c) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157. (d) Bestmann, H. J.; Wolfel, G.; Mederer, K. *Synthesis* **1987**, 848. (e) Okano, K.; Morimoto, T.; Sekiya, M. *Chem. Pharm. Bull.* **1985**, *33*, 2228. (f) Bestmann, H. J.; Wolfel, G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 53. (g) Okano, K.; Morimoto, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* **1984**, 883. (h) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahama, S. *Synthesis* **1982**, 461.

(12) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *42*, 4821.

(13) Nishiyama, K.; Saito, M.; Oba, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 609.

(14) (a) Riederer, P.; Foley, P.; Bringmann, G.; Feineis, D.; Bruckner, R.; Gerlach, M. *Eur. J. Pharmacol.* **2002**, *442*, 1. (b) Yost, G. A.; Miller, L. L. *J. Agric. Food Chem.* **1976**, *24*, 724. (c) Chefurka, W. *Comp. Biochem. Physiol., C* **1983**, *74C*, 259.

TABLE 2. Effect of the Addition of TMSCl on Aminomethylation[a]

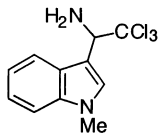
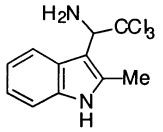
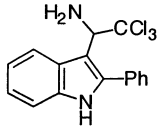
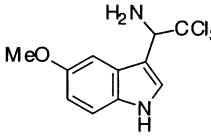
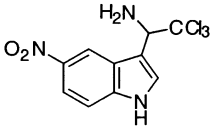
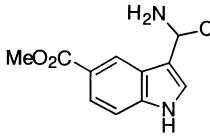
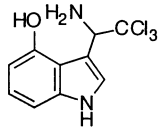
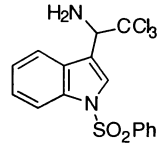
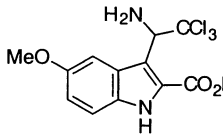
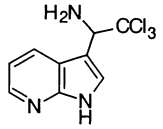
run	acid (equiv) + additive (equiv)	time (h)	yield of **3a** (%)[b]
1	$BF_3{\cdot}OEt_2$ + TMSCl (each 1)	1.5	90
2	$TiCl_4$ + TMSCl (each 1)	0.2[c]	11
3	$AlCl_3$ + TMSCl (each 1)	0.2	66
4	$ZnCl_2$ (0.2) + TMSCl (1)	8	83
5	$CuCl_2$ (0.2) + TMSCl (1)	5	70
6	**$Cu(OTf)_2$ (0.2) + TMSCl (1)**	**4**	**90**
7	$Cu(OTf)_2$ (0.05) + TMSCl (1)	20	84
8	$Cu(OTf)_2$ (0.2) + TMSCl (0.5)	53	84
9	**$Hf(OTf)_4$ (0.15) + TMSCl (1)**	**2**	**92**
10	$Hf(OTf)_4$ (0.02) + TMSCl (1)	3	82
11	$Hf(OTf)_4$ (0.15) + TMSCl (0.5)	15	52[d]
12	TMSCl (1)	10	NR[e]

[a] Reaction was carried out at room temperature. [b] Isolated yields based on indole **2a**. [c] Temperature = 0 °C. [d] Recovery of indole **2a** (47%). [e] NR = no reaction.

$Cu(OTf)_2$ and $Hf(OTf)_4$ catalyzed a Friedel−Crafts aminoalkylation, but the reaction was sluggish, and each yield decreased slightly (runs 8 and 9). Thus, we next screened the effects of some additives on the above reaction. As a consequence, surprisingly, when 1 equiv of TMSCl per acetal **1** was added to the reaction mixture involving a Lewis acid, the reaction proceeded cleanly, and the yield of **3a** was dramatically improved up to 90% without the formation of any detectable byproduct **3′a** (run 1 in Table 2).[15] Table 2 represents the detailed result of the aminoalkylation in the presence of various Lewis acids and TMSCl. $Cu(OTf)_2$ and $Hf(OTf)_4$ functioned effectively in the presence of a catalytic amount of Lewis acid for the imino Friedel−Crafts reaction, producing the corresponding primary amine in excellent yields (runs 6, 7, 9, and 10). In addition, no detectable byproducts were found in either case. It is also interesting to note that less than 1 equiv of TMSCl (0.5 equiv) required a longer reaction time or inhibited the formation of the desired amine (runs 8 and 11). The role of TMSCl will be briefly discussed below. Needless to say, in the absence of a Lewis acid, no Friedel−Crafts aminoalkylation took place.[16]

For copper(II) and hafnium(IV), it is known that $Cu(OTf)_2$ and $Hf(OTf)_4$ are stable in the presence of water and amino groups.[17] Thus, to clarify the generality of this catalytic reaction, we subsequently investigated the reaction of several indole derivatives with acetal **1** using either a copper or a hafnium catalytic system, and the results are listed in Table 3. Typically, a catalytic amount (0.1−0.2 equiv) of Lewis acid and TMSCl (1 equiv) was sufficient to complete these reactions. In general, the

TABLE 3. Lewis Acid-Catalyzed Aminomethylation of Various Indoles with an *N,O*-Acetal[a]

run	LA (eq)	time (h)	product	yield (%)[b]
1	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.15)	7 2		**3b** 74[c] 75
2	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.15)	4 4		**3c** 72 85
3	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.15)	4 24		**3d** 83 85
4	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.15)	6 3		**3e** 61 71
5	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.2)	52 24		**3f** 81 52[d]
6	$Cu(OTf)_2$ (0.2)	48		**3g** 83
7	$Cu(OTf)_2$ (0.1) $Hf(OTf)_4$ (0.2)	6 0.5		**3h** 76 77
8	$Cu(OTf)_2$ (0.2) $Hf(OTf)_4$ (0.2)	24 14		**3i** NR[e]
9	$Cu(OTf)_4$ (0.2) $Hf(OTf)_4$ (0.2)	24 24		**3j** NR[e]
10	$Hf(OTf)_4$ (0.2)	6		**3k** NR[e]

[a] TMSCl (1 equiv) was used in each reaction. [b] Isolated yields based on indole derivatives **2**. [c] The amine **3b** was isolated as a hydrochloride salt. [d] Recovery (41%) of indole derivative **2f**. [e] NR = no reaction.

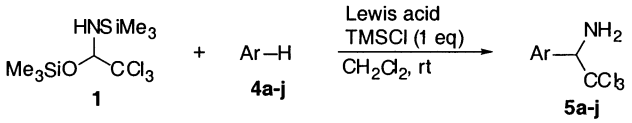
$Hf(OTf)_4$−TMSCl system was more effective in terms of conversion and reaction time (except for run 5). Treatment of N-protected or 2-substituted indoles with acetal **1** produced the expected primary amines **3b**−**d** in good yields (runs 1−3). Similarly, the reaction using an indole bearing an electron-releasing group also proceeded

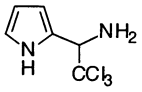
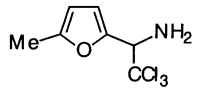
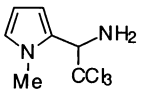
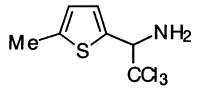
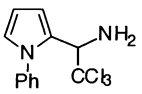
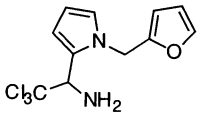
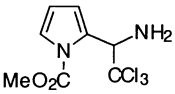
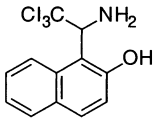
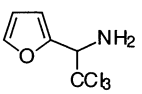
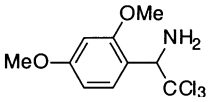
(15) For selected examples of reactions enhanced by a coexistence of Lewis acid and TMSCl, see: (a) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428. (b) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646. (c) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715. (d) Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159. (e) Mukaiyama, T.; Wariishi, K.; Saito, Y.; Hayashi, M.; Kobayashi, S. *Chem. Lett.* **1988**, 1101. (f) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(16) Heaney et al. have reported on the chlorosilane-mediated reactions of an *N,O*-acetal with aromatics, see: (a) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941. (b) Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F.; Eylet, S. C. *Tetrahedron Lett.* **1989**, *30*, 1433. (c) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1161.

(17) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739. (b) Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099.

TABLE 4. Reaction of *N,O*-Acetal 1 with Various Aromatic Compounds Leading to Aromatic Primary Amine Derivatives[a]



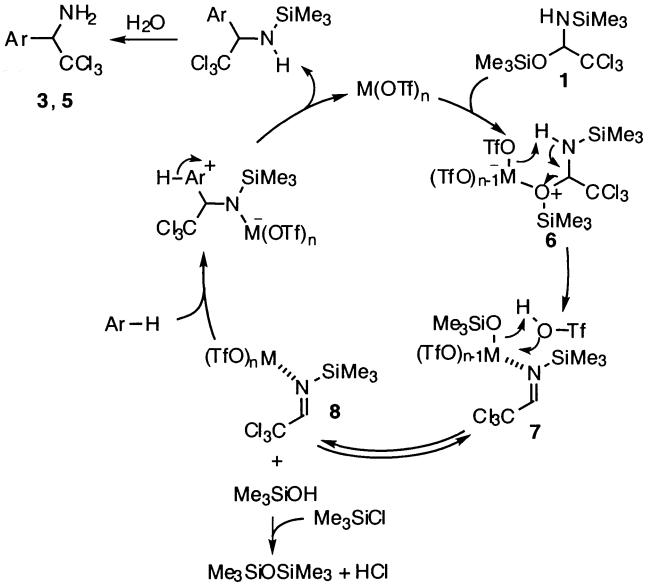
run	conditions: LA (eq)	conditions: time (h)	product	yield (%)[b]	run	conditions: LA (eq)	conditions: time (h)	product	yield (%)[b]
1	$Cu(OTf)_2$ (0.2)	48	 **5a**	trace	6	$Hf(OTf)_4$ (0.2)	6	 **5f**	89
	$Cu(OTf)_2$ (0.2)	4[c]		60					
	$Hf(OTf)_4$ (0.2)	2		93					
	BF_3•OEt_2 (1)	4		98					
2	$Hf(OTf)_4$ (0.2)	1	 **5b**	99	7[d]	$Hf(OTf)_4$ (0.2)	24	 **5g**	72
3	$Hf(OTf)_4$ (0.2)	24	 **5c**	71	8	$Hf(OTf)_4$ (0.2)	15	 **5h**	52
4	$Hf(OTf)_4$ (0.2)	10	 **5d**	61	9	$Hf(OTf)_4$ (0.2)	24	 **5i**	83
						$Cu(OTf)_2$ (0.2)	24		NR[e]
						BF_3•OEt_2 (1)	48		28
5	$Hf(OTf)_4$ (0.2)	9	 **5e**	31	10	$Hf(OTf)_4$ (0.2)	19	 **5j**	51
	BF_3•OEt_2 (1)	10		84		$Cu(OTf)_2$ (0.2)	24		NR[e]
						BF_3•OEt_2 (1)	12		25

[a] Reaction was carried out using *N,O*-acetal **1** (0.55 mmol), aromatic compounds **4a**–**j** (0.5 mmol), Lewis acid (0.2–1.0 equiv), and TMSCl (0.55 mmol). See Experimental Section. [b] Isolated yields based on aromatics **4**. [c] Temperature = 50 °C (bath temperature). [d] Three equivalents of 2-methylthiophene for *N,O*-acetal **1** was employed. [e] NR = no reaction.

smoothly to produce the corresponding amine **3e**, but in a moderate yield, probably reflecting the lower stability of product **3e** at ambient temperature (run 4). Although indoles with an electron-withdrawing group, such as nitro or ester groups, required a longer reaction time, the expected amines were obtained in high yields (runs 5, 6). As mentioned above, even in the case of an indole derivative containing an OH group, which typically deactivates a Lewis acid, the catalytic aminomethylation ran cleanly, furnishing the corresponding indole derivative **3h** (run 7). Unfortunately, in the case of indoles where the pyrrole units contained electron-withdrawing substituents, such as a benzenesulfonyl or a carbomethoxy group (**2i** or **2j**, respectively), the corresponding primary amines were not produced. Moreover, treatment of 7-azaindole (**2k**) with hafnium triflate did not afford the desired amine. It appears that the presence of electron-withdrawing groups or an electronegative atom as a nitrogen atom reduces the overall nucleophilicity of the pyrrole ring.

Reaction of Heterocycles and Electron-Rich Arenes with an *N,O*-Acetal. To demonstrate the efficiency and scope of the present method, we applied these catalytic systems to a variety of electron-rich aromatic compounds. The results are summarized in Table 4. Surprisingly, the aminomethylation of pyrrole (**4a**) with the *N,O*-acetal in the presence of a copper catalyst doped with TMSCl was unproductive at room temperature, while severe conditions (reflux) gave the corresponding product **5a** in moderate yield. In contrast, the reaction using $Hf(OTf)_4$ and BF_3·OEt_2 proceeded smoothly at room temperature to give the 2-aminomethylated product **5a** in nearly quantitative yield (run 1). Judging from these results, we found hafnium triflate to be the most effective for the present reaction. Therefore, the group 4 metal triflate was mainly employed in reactions of the other aromatic compounds. Treatment of N-protected pyrroles with acetal **1** produced the expected primary amines **5b**, **5c** in good to near quantitative yields (runs 2, 3), and when the pyrrole containing an electron-withdrawing group was used as a reaction substrate, the corresponding amine **5d** was also obtained in moderate yield (run 4). These results show that lowering the electron density on the nitrogen atom in the pyrrole unit tends to decrease the yield of the primary amine. Electron-rich heterocycles such as furan and thiophene derivatives also gave satisfactory results (runs 5–7), while the reaction of furan using hafnium triflate afforded the product in a lower yield (run 5). Interestingly, when the reaction substrate **4h**, which consists of a pyrrole and furan moiety, was employed, only the primary amine **5h**, where the aminoalkyl substituent was regioselectively introduced onto the pyrrole skeleton, was obtained in good yield (run 8). This indicates that the nucleophilic attack of an electron-rich pyrrole ring proceeds more rapidly than that of the furan ring toward *N,O*-acetal **1**.

SCHEME 2. Plausible Mechanism for M(OTf)$_n$-TMSCl Catalyzed Aminomethylation of Aromatics with *N,O*-Acetal 1



On the other hand, the aminomethylation of an acetal with electron-rich arenes such as 2-naphthol and dimethoxybenzene under the optimized conditions proceeded smoothly to give the aminomethylated products **5i**, **5j** in 83 and 51% yield, respectively, and no regioisomers were detected in either case. Unfortunately, the acetal **1** did not give primary amines when reacted with heterocycles or aromatic compounds involving benzofuran, benzothiophene, phenol, and aniline derivatives.

Mechanistic Aspects of Aminomethylation. A plausible mechanism for the metal triflate-TMSCl-catalyzed aminomethylation of aromatic compounds is shown in Scheme 2. First, the coordination of metal triflate to an oxygen atom of acetal **1** forms a cationic complex **6**, where cleavage of the C−O bond and abstraction of a proton on the nitrogen atom by a triflate ion occur simultaneously to give the *N*-silylimine **7**, M(OTf)$_{n-1}$OSiMe$_3$, and TfOH. A subsequent equilibrium would generate a silanol[18] and the imine complex **8**, composed of the imine and metal triflate. Moreover, aromatic compounds would be expected to attack the intermediate **8** to produce the corresponding amine **3** or **5**, along with the regenerated catalyst. In this system, the Lewis acid plays a dual role, first to dissociate Me_3SiO^- and subsequently to activate the intermediate imine. Although there is no clear explanation for the role of TMSCl at present, we assume that it would trap the in situ generated silanol, thus driving the equilibrium to completion,[19] considering the fact that the use of less than 1 equiv of TMSCl required a prolonged reaction time and resulted in an incomplete reaction (see runs 8 and 11 in Table 2). Moreover, the in situ formation of hexamethyldisiloxane was confirmed by GC by comparison with an authentic sample, while it is not clear which step in the plausible catalytic cycle leads to the formation of the silanol.[20] On the other hand, the role of the trichloromethyl group on complex **8** would facilitate an attack by aromatic nucleophiles, because this strong electron-withdrawing substituent increases the electrophilic nature of the imine carbon.

(18) Lectka et al. suggest that a silanol is produced by a direct elimination from an *N,O*-acetal in a Mannich-type reaction: see refs 4f,g.

(19) When the amount of TMSCl for the acetal was increased to 5 equiv, the yield of product **3a** and the reaction time were not improved.

Conclusion

Cu(OTf)$_2$ and Hf(OTf)$_4$, in the presence of TMSCl, successfully catalyze the reaction of the *N*-silyl-*N,O*-acetal containing a trichloromethyl group with various indole derivatives leading to indolyl primary amines. It is noteworthy that the catalytic system using Hf(OTf)$_4$-doped TMSCl shows a higher activity and can be applied not only to electron-rich heterocycles other than indoles, but also to electron-rich arenes to afford various 1-aryltrichloroethylamine derivatives in good to excellent yields. Although the role of TMSCl is not clear at this stage, TMSCl is an essential activator for a smooth and complete conversion in the present reaction. In addition, this method could be used for the synthesis of arylated glycine derivatives because the trichloromethyl group is easily hydrolyzed by an alkaline solution to produce the carboxylic acid. Studies of this aspect are currently in progress.

Experimental Section

General Methods. Melting points are uncorrected. Column chromatography was performed using Silica gel 60 (Merck). Dichloromethane was distilled from P_2O_5 and dried over MS4A. Solutions of commercially available $SnCl_4$, $TiCl_4$, $ZnCl_2$ in CH_2Cl_2 (1 M) were used without further purification. Cu(OTf)$_2$ was used after heating in vacuo. BF_3·OEt_2 was distilled before use. Hf(OTf)$_4$[21] and TMSOTf[22] were prepared according to reported procedures. According to the literature,[13] the *N*-silyl-*N,O*-acetal **1** was prepared from hexamethyldisilazane and chloral in the presence of $ZnCl_2$. All reactions were carried out under an argon atmosphere, unless otherwise noted. Organic materials were dried and distilled prior to use.

Typical Procedure for the Lewis Acid-Mediated Primary Aminomethylation of Aromatics with an *N,O*-Acetal. The *N,O*-acetal **1** (169.4 mg, 0.55 mmol), aromatics **2a**−**h** or **4a**−**j** (0.5 mmol), and freshly distilled trimethylchlorosilane (0.55 mmol) were successively mixed together in CH_2Cl_2 (5 mL) at room temperature with stirring. After 3 min, the Lewis acid (0.02−1.0 equiv) was added, and the thick suspension was stirred until the reaction reached completion, as shown by TLC (hexane/AcOEt = 2:1) or GC. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The combined organic layer was dried over sodium carbonate and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford the corresponding amine and, if necessary, further purified by a Recycling Preparative HPLC equipped with a GPC column (chloroform as the eluent).

1-(Indol-3-yl)-2,2,2-trichloroethylamine (3a). Mp 143−144 °C (colorless needles from AcOEt-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (br s, 2H), 5.01 (s, 1H), 7.12 (t, 1H, J = 8.5 Hz), 7.16 (t, 1H, J = 8.5 Hz), 7.29 (s, 1H), 7.32 (d, 1H, J = 8.5 Hz), 7.75 (d, 1H, J = 8.5 Hz), 9.04 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.7, 106.7, 111.4, 112.4, 119.5, 119.9, 122.1, 123.9, 126.9, 135.5. MS (EI): *m/z* 264, 262 (M^+, 5%),

(20) The formation of a siloxane by condensation of a silanol and an alcohol in the presence of acid catalysts has been reported, see: Grubb, T. T. *J. Am. Chem. Soc.* **1954**, *76*, 3408.

(21) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.

(22) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 745.

145 ($M^+ - CCl_3$, 100%). Anal. Calcd for $C_{10}H_9Cl_3N_2$: C, 45.57; H, 3.44; N, 10.63. Found: C, 45.59; H, 3.54; N, 10.73.

1,1-Bis-indolyl-2,2,2-trichloroethane (3′a). Mp (decomp.) 152.7 °C (colorless needles from CH_2Cl_2−hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (s, 1H), 7.11 (t, 2H, J = 7.5 Hz), 7.16 (t, 2H, J = 7.5 Hz), 7.30 (d, 2H, J = 7.5 Hz), 7.44 (s, 2H), 7.66 (d, 2H, J = 7.5 Hz), 8.05 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.9, 103.9, 111.2, 114.5, 119.0, 119.9, 122.2, 123.9, 127.7, 135.3. MS (FAB): m/z 363 ($M^+ + H$, 10%), 172 ($M^+ - CCl_3$, 100%). Anal. Calcd for $C_{18}H_{13}Cl_3N_2$: C, 59.45; H, 3.60; N, 7.70. Found: C, 59.27; H, 3.92; N, 7.91.

1-(Pyrrol-2-yl)-2,2,2-trichloroethylamine (5a). Mp 86.9−88.0 °C (colorless crystals from CH_2Cl_2−hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (br s, 2H), 4.67 (s, 1H), 6.21 (t, 1H, J = 6 Hz), 6.37 (dd, 1H, J = 6, 1.4 Hz), 6.75 (dd, 1H, J = 6, 1.4 Hz), 8.87 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.4, 104.8, 108.4, 109.3, 118.1, 126.3. MS (EI): m/z 214 (M^+, 10%), 95 ($M^+ - CCl_3$, 100%). Anal. Calcd for $C_6H_7Cl_3N_2$: C, 33.76; H, 3.30; N, 13.12. Found: C, 33.90; H, 3.17; N, 13.11.

Acknowledgment. This work was partially supported by a grant from the Japan Private School Promotion Foundation and a grant for High Technology Research Centers of Private Universities. The authors thank Central Glass Co., Ltd., and Dow Corning Toray Silicone Co., Ltd., for the gift of trifluoromethanesulfonic acid (TfOH) and hexamethyldisilazane (HMDS), and they also acknowledge the staff in High Technology Research Centers of Tokyo University of Science for the performance of elemental analyses.

Supporting Information Available: Detailed spectral data for **3b**−**h** and **5b**−**j**, and ^{1}H and ^{13}C NMR spectra for **3b**, **3h**, **5b**, **5e**, **5f**, **5h**, and **5j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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