

# Nitro-Assisted Brønsted Acid Catalysis: Application to a Challenging Catalytic Azidation

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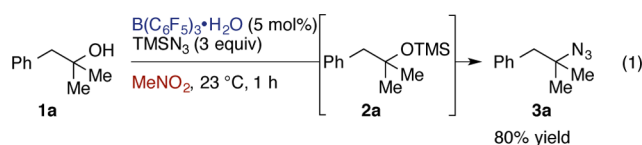
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**S** Supporting Information

**ABSTRACT:** A cocatalytic effect of nitro compounds is described for the  $B(C_6F_5)_3 \cdot H_2O$  catalyzed azidation of tertiary aliphatic alcohols, enabling catalyst turnover for the first time and with a broad range of substrates. Kinetic investigations into this surprising effect reveal that nitro compounds induce a switch from first order concentration dependence in Brønsted acid to second order concentration dependence in Brønsted acid and second order dependence in the nitro compounds. Kinetic, electronic, and spectroscopic evidence suggests that higher order hydrogen-bonded aggregates of nitro compounds and acids are the kinetically competent Brønsted acid catalysts. Specific weak H-bond accepting additives may offer a new general approach to accelerating Brønsted acid catalysis in solution.

Hydrogen bond catalysis and Brønsted acid catalysis are arguably the most common activation modes in synthetic and biological reactions.<sup>1</sup> One of the simplest ways to increase the acidity, and hence the catalytic ability, of such catalysts is to cause them to interact with other hydrogen bond donating groups,<sup>2</sup> an approach well-known to lead to dramatic rate acceleration and impressive selectivity within the molecular scaffolds of enzymes, enzyme mimics, and some organocatalysts.<sup>3,4</sup> In solution, aggregation of two or more hydrogen bond donating molecules is likewise known to cause rate acceleration, but the strict concentration dependence means that the catalyst must effectively also be the solvent.<sup>5</sup> In contrast, intermolecular interactions between hydrogen bond donating catalysts and weak hydrogen bond accepting additives can occur at low concentrations but typically attenuate the acidity of the former, leading to slower but better controlled catalysis.<sup>6</sup> Herein, we report a case where weak hydrogen bond accepting additives dramatically increase the rate of a Brønsted acid catalyzed reaction. Specifically, electron-rich nitro compounds, even when present as substoichiometric additives, act as cocatalysts in the Brønsted acid catalyzed azidation of tertiary aliphatic alcohols, enabling a rapid reaction with catalytic turnover for the first time.<sup>7–10</sup> Kinetic, electronic, and spectroscopic investigations suggest that hydrogen bonding between the nitro compound and the acid generates aggregates that are the kinetically competent Brønsted acid catalysts. Taken more broadly, weak H-bond accepting cocatalysts may constitute a new general approach to modulating Brønsted acid catalysis in solution.

We initially became intrigued by Pocker's report that the hydrochlorination of olefins proceeds more rapidly and displays unusual second order concentration dependence in HCl when the reaction is carried out in nitromethane.<sup>11,12</sup> Though it was concluded that cooperative effects between two molecules of HCl were responsible for the observed concentration dependence, no efforts were made to uncover the role of nitromethane, a well-known weak dual H-bond acceptor.<sup>13,14</sup> Speculating that the solvent might play a more active role, we elected to investigate the effect of nitro compounds in a Brønsted acid catalyzed reaction where the acid catalyst and reagents could be independently varied. We selected the azidation of tertiary aliphatic alcohols with  $TMSN_3$ , a useful but sluggish and low-yielding transformation that thus far has not been achieved with catalytic turnover.<sup>7,8</sup> We first investigated the azidation of alcohol **1a** catalyzed by  $B(C_6F_5)_3 \cdot H_2O$ , an easily weighable solid Lewis acid hydrate that is a strong Brønsted acid.<sup>15</sup> Gratifyingly, the use of nitromethane as solvent led to immediate formation of silyl ether **2a** followed by complete conversion of **2a** to azide **3a** in <1 h at room temperature in 80% isolated yield, eq 1.<sup>16</sup>

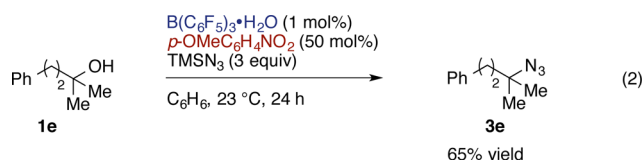


Direct submission of silyl ether **2a** to the reaction conditions also yielded **3a** with similar efficiency. Attempts in 11 other common polar and nonpolar aprotic solvents either did not result in any reaction or produced silyl ether **2a** but gave <5% azide **3a** after 1 h, though detectable amounts (<10%) of **3a** were found in  $CH_2Cl_2$  and  $(CH_2Cl)_2$ . In contrast, all five other solvents tested that contained a nitro group led to rapid progression of the reaction after 1 h, even though in some cases their dielectric constants are much lower than nitromethane (Table S1).<sup>17</sup> Azidation could even be carried out in “unreactive” solvents when nitro compounds were employed as additives. To our delight, 50 mol % *p*-nitroanisole was an effective cocatalyst for the azidation of alcohol **1e** in benzene, giving 65% isolated yield after 24 h compared to <5% in the absence of cocatalyst, eq 2.

A wide variety of tertiary aliphatic alcohols were surveyed using nitromethane as solvent or using 50 mol % *p*-nitroanisole

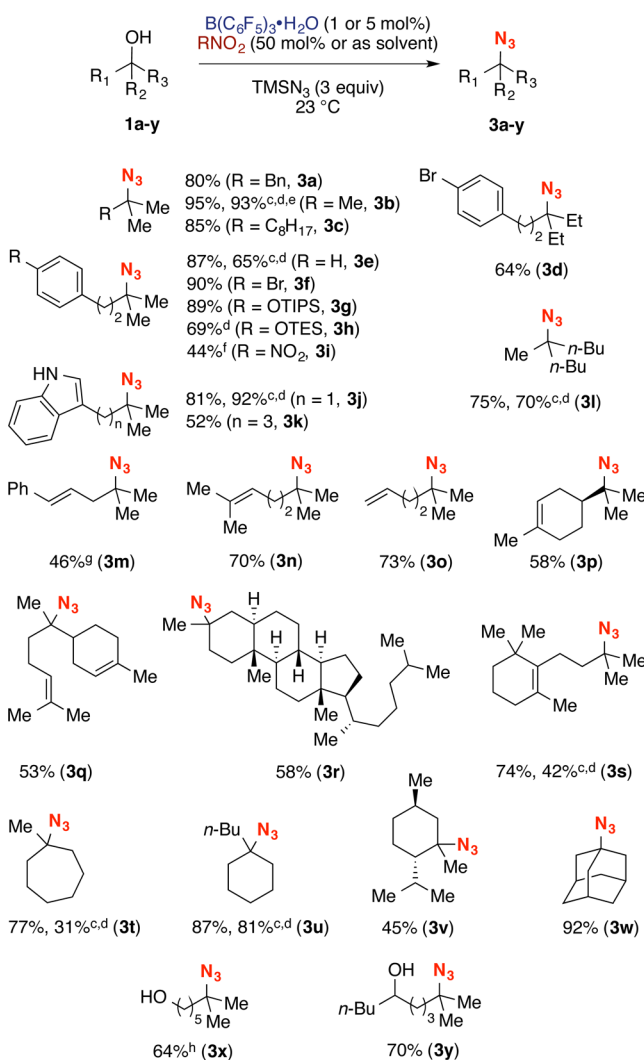
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in C<sub>6</sub>H<sub>6</sub> (Table 1). Moderate to excellent yields could be obtained in most cases. Reactions were completed in 5–60 min

**Table 1. Substoichiometric Catalytic Dehydroazidation of Tertiary Aliphatic Alcohols<sup>a,b</sup>**

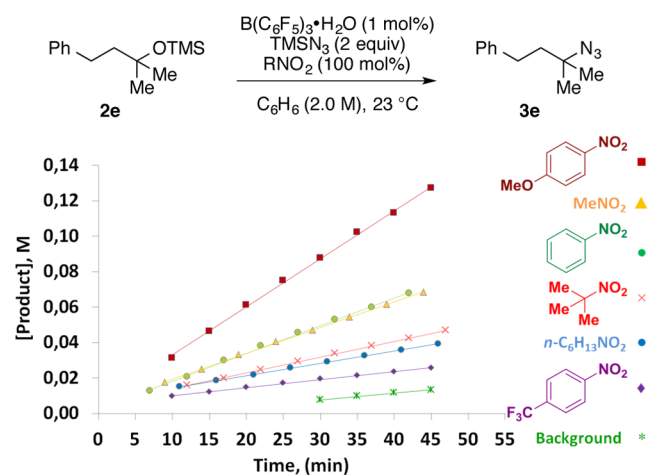


<sup>a</sup>Conditions: Alcohol (2 M in MeNO<sub>2</sub>), 5–60 min. <sup>b</sup>Isolated yields after silica gel chromatography. <sup>c</sup>50 mol % *p*-nitroanisole, C<sub>6</sub>H<sub>6</sub>, 24 h. <sup>d</sup>1 mol % B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>·H<sub>2</sub>O. <sup>e</sup>Yield estimated by <sup>1</sup>H NMR using 1.0 equiv of anisole as internal standard. <sup>f</sup>Neat, 1 h. <sup>g</sup>Reaction carried out at 0 °C. <sup>h</sup>Reaction carried out at 90 °C.

when nitromethane was the solvent. Reactions employing 50 mol % *p*-nitroanisole in C<sub>6</sub>H<sub>6</sub> completed in <24 h and were typically less efficient due to faster competing elimination in that solvent. Notably, acid-sensitive functional groups such as OTIPS (3g) and OTES (3h) ethers survive under the reaction conditions. Nitro-containing substrate 3i reacts even in the absence of nitro additive. Azidation dominates over intramolecular carbocation capture for alcohols bearing pendant indoles (3j, 3k). No bis-azidation was observed in alcohols

bearing alkenes (3m–3q, 3s). Finally, diols undergo azidation selectively at the tertiary position even when competing cyclization is possible (3x, 3y). The utility of the method is emphasized by the fact that, despite the apparent simplicity of the azides reported herein, 18 of 25 are new compounds.

Electronic effects and kinetic concentration dependencies were studied to probe the origin of the accelerating effect of the nitro compounds. A study of the initial rate of the azidation of silyl ether 2e as a function of the electronics of the nitro cocatalyst (100 mol %) in benzene shows that electron-rich nitrobenzenes have a much larger promoting effect than electron-poor analogues (Figure 1). This trend is opposite to

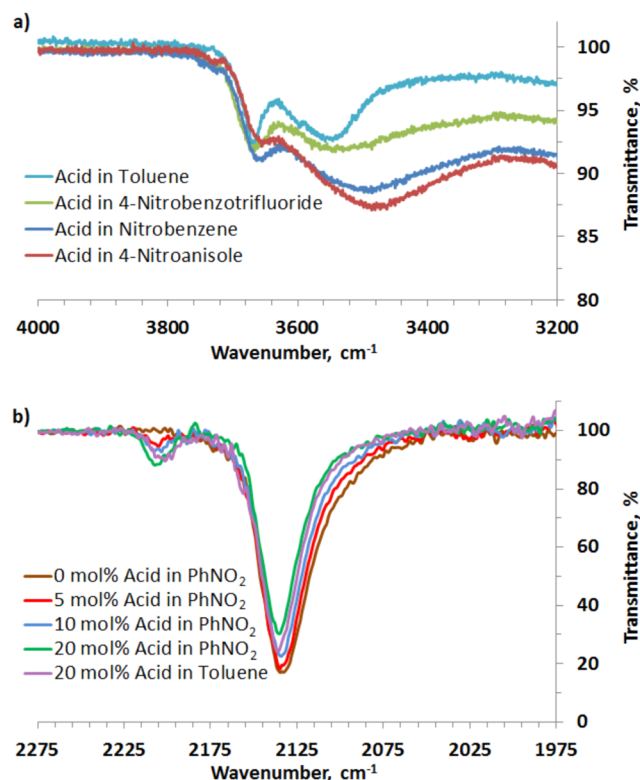


**Figure 1.** Initial rate dependence on the electronics of the nitro compound. Acid loading was reduced to slow the reaction for GC–MS analysis, resulting in a smaller rate increase relative to the background reaction.

the expected outcome if small changes in dielectric constant due to the additive were responsible for the faster rates since *p*-methoxynitrobenzene ( $\epsilon = 27.5$ ) is less polar than nitrobenzene ( $\epsilon = 36.1$ ).<sup>17</sup> The method of initial rates was used to determine the order of the individual components for the reaction of 2e in benzene. The slow background reaction that occurs in the absence of nitro additive is first order in acid ( $0.98 \pm 0.02$ ). In contrast, reactions in benzene in the presence of nitromethane reveal a second-order ( $1.96 \pm 0.04$ ) rate dependence on the concentration of nitro compound, an approximately second-order ( $1.8 \pm 0.1$ ) rate dependence on the concentration of acid, an approximately first-order ( $0.83 \pm 0.02$ ) rate dependence on the concentration of silyl ether, and a zero-order ( $-0.025 \pm 0.002$ ) rate dependence on the concentration of TMSN<sub>3</sub>, demonstrating that the nitro compound is a cocatalyst and induces a change in the concentration dependence of the Brønsted acid.

IR experiments show evidence of hydrogen bonding between the OH of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>·H<sub>2</sub>O and the nitro compounds. The magnitudes of the changes in frequency and broadness of the OH stretch increase with greater electron-rich character of the nitro compound, correlating with their cocatalytic activity. The B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>·H<sub>2</sub>O OH stretch at 3546 cm<sup>-1</sup> in toluene shifts to 3523, 3480, and 3465 cm<sup>-1</sup> in the presence of *p*-CF<sub>3</sub>-nitrobenzene, PhNO<sub>2</sub>, and *p*-nitroanisole, respectively. The observed peak broadening in the case of electron-rich nitro compounds indicates that a larger number of intermolecular interactions between B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>·H<sub>2</sub>O and the nitro compounds are accessible, an observation characteristic of aggregation

(Figure 2a). NMR experiments ( $^1\text{H}$ ,  $^{19}\text{F}$ ,  $^{29}\text{Si}$ , and  $^{11}\text{B}$ ) in  $\text{C}_6\text{D}_6$  also support the existence of hydrogen-bonding between



**Figure 2.** Stacked IR spectra showing the (a) effect of various nitro compounds on the OH stretch of  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  and (b) effect of  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  and nitrobenzene on the azide stretch of  $\text{TMSN}_3$ .

$\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  and nitro compounds. Most notably in the  $^{19}\text{F}$  NMR, the signal corresponding to the *para*-F resonance of  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  shifts significantly in the presence of nitro compounds (see SI). The influence of nitro compounds on the activation of  $\text{TMSN}_3$  by  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  can be observed by monitoring the azide stretch of the latter at  $2136\text{ cm}^{-1}$ . Mixing catalytic amounts of  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  and 1 equiv of  $\text{TMSN}_3$  in toluene results in a slight decrease of intensity of the peak at  $2136\text{ cm}^{-1}$  and the appearance of a new peak at  $2200\text{ cm}^{-1}$ . In the presence of  $\text{PhNO}_2$ , the new peak shifts slightly to  $2207\text{ cm}^{-1}$ . The peak grows with increasing concentration of  $\text{B}(\text{C}_6\text{F}_5)_3\cdot\text{H}_2\text{O}$  at the expense of the peak at  $2136\text{ cm}^{-1}$  (Figure 2b). No interactions between  $\text{PhNO}_2$  and  $\text{TMSN}_3$  were observed in the absence of acid. Mixing all three components had no effect on the N–O stretch of  $\text{PhNO}_2$ , ruling out the possibility that the nitro compound becomes silylated and functions as a silyl transfer catalyst. Taken together, the kinetic, electronic, and spectroscopic evidence suggest that mixed hydrogen-bonded aggregates of Brønsted acid and nitro compound catalyze the reaction and that the catalytically competent Brønsted acid likely contains two molecules of each component. We suspect that a similar phenomenon may be responsible for the second order concentration dependence on HCl in Pocker's olefin hydrochlorination in nitromethane<sup>11</sup> and may account for the high specificity for that solvent in other acid-catalyzed reactions.<sup>18</sup>

In conclusion, we have uncovered an unprecedented example of cocatalysis between nitro compounds and Brønsted acids, resulting in the first azidation of tertiary aliphatic alcohols with

catalytic turnover. Our results serve as a reminder that “simple” Brønsted acid catalysis can be surprisingly complex in solution, illustrating the need for mechanistic investigations. Furthermore, aggregation between weak H-bond acceptors and Brønsted acids may constitute a new modular and tunable approach to accelerating Brønsted acid catalysis in solution. Theoretical calculations are underway to gain insight into the nature of the aggregated species. Ongoing experimental efforts are aimed at applications to other reactions and the design of second-generation cocatalysts.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06055.

Table S1, additional control experiments, kinetic data, IR data, experimental procedures, and characterization data for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

- (1) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.
- (2) (a) Pihko, P. M., Ed. *Hydrogen Bonding in Organic Synthesis*; Wiley: Weinheim, 2009. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942. (c) Warshel, A.; Sharma, P. K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M. H. M. *Chem. Rev.* **2006**, *106*, 3210–3235.
- (3) For recent reviews on supramolecular catalysis with organo-catalysts and enzyme mimics, see: (a) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1660–1733. (b) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1734–1787.
- (4) For studies on anion stabilization by polyols, see: (a) Tian, Z.; Fattahi, A.; Lis, L.; Kass, S. R. J. *Am. Chem. Soc.* **2009**, *131*, 16984–16988. (b) Beletskiy, E. V.; Schmidt, J.; Wang, X.-B.; Kass, S. R. J. *Am. Chem. Soc.* **2012**, *134*, 18534–18537. (c) Shokri, A.; Wang, X.-B.; Kass, S. R. J. *Am. Chem. Soc.* **2013**, *135*, 9525–9530. (d) Shokri, A.; Wang, Y.; O'Doherty, G. A.; Wang, X.-B.; Kass, S. R. J. *Am. Chem. Soc.* **2013**, *135*, 17919–17924.
- (5) (a) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. J. *Am. Chem. Soc.* **2006**, *128*, 8421–8426. (b) Berkessel, A.; Adrio, J. A. J. *Am. Chem. Soc.* **2006**, *128*, 13412–13420. (c) Berkessel, A.; Krämer, J.; Mummy, F.; Neudörfl, J.-M.; Haag, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 739–743.
- (6) (a) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120–123. (b) Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem., Int. Ed.* **2011**, *50*,

3681–3683. (c) Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842–845.

(7) For azidation of aliphatic alcohols with  $\text{HN}_3$  and stoichiometric Brønsted, see: (a) Sasaki, T.; Eguchi, S.; Katada, T.; Hiroaki, O. *J. Org. Chem.* **1977**, *42*, 3741–3743. (b) Timberlake, J. W.; Alender, J.; Garner, A. W.; Hodges, M. L.; Ozmeral, C.; Szilagy, S.; Jacobus, J. O. *J. Org. Chem.* **1981**, *46*, 2082–2089. (c) Breton, G. W.; Daus, K. A.; Kropp, P. J. *J. Org. Chem.* **1992**, *57*, 6646–6649. (d) Bottaro, J. C.; Penwell, P. E.; Schmitt, R. J. *Synth. Commun.* **1997**, *27*, 1465–1467.

(8) For low-yielding azidation of aliphatic alcohols with  $\text{TMSN}_3$  and stoichiometric Lewis acid, see: (a) Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* **1987**, *28*, 6513–6516. (b) Zwierzak, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *75*, 51–54. For azidation with  $\text{HN}_3$  and stoichiometric Lewis acid, see: (c) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237–4244.

(9) For reviews on azides, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(10) For catalytic azidation of allylic alcohols and benzylic silyl ethers, respectively, see: (a) Rueping, M.; Vila, C.; Uria, U. *Org. Lett.* **2012**, *14*, 768–771. (b) Sawama, Y.; Nagata, S.; Yabe, Y.; Morita, K.; Monguchi, Y.; Sajiki, H. *Chem. - Eur. J.* **2012**, *18*, 16608–16611.

(11) (a) Pocker, Y. *J. Chem. Soc.* **1960**, 1292–1297. (b) Pocker, Y.; Stevens, K. D.; Champoux, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 4199. (c) Pocker, Y.; Stevens, K. D. *J. Am. Chem. Soc.* **1969**, *91*, 4205.

(12) For a report on rate acceleration of zeolite catalysis in nitromethane, see: Haw, J. F.; Nicholas, J. B.; Xu, T.; Goguen, P. W. *Nature* **1997**, *389*, 832–835.

(13) For spectroscopic observation of intermolecular hydrogen-bonding in nitro compounds, see: (a) Baitinger, W. F.; Schleyer, P.; Murty, T. S. R.; Robinson, L. *Tetrahedron* **1964**, *20*, 1635–1647. (b) Ungnade, H. E.; Roberts, E. M.; Kissinger, L. W. *J. Phys. Chem.* **1964**, *68*, 3225–3228. (c) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426. (d) Laurence, C.; Berthelot, M.; Lucon, M.; Morris, D. G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 491.

(14) For a seminal example of dual hydrogen bond catalysis of a nitroalkene, see: Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

(15)  $\text{B}(\text{C}_6\text{F}_5)_3 \cdot \text{H}_2\text{O}$  has a  $\text{pK}_a$  of 8.4 in MeCN and has been studied in detail; see: (a) Danopoulos, A. A.; Galsworthy, J. R.; Green, M. L. H.; Cafferkey, S.; Doerrer, L. H.; Hursthouse, M. B. *Chem. Commun.* **1998**, 2529–2530. (b) Bergquist, C.; Bridgewater, B. M.; Harlan, C. J.; Norton, J. R.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 10581–10590. (c) Beringhelli, T.; Maggioni, D.; D'Alfonso, G. *Organometallics* **2001**, *20*, 4927–4938. (d) Di Saverio, A.; Focante, F.; Camurati, I.; Resconi, L.; Beringhelli, T.; D'Alfonso, G.; Donghi, D.; Maggioni, D.; Mercandelli, P.; Sironi, A. *Inorg. Chem.* **2005**, *44*, 5030–5041.

(16)  $\text{TfOH}$  and  $\text{Bi}(\text{OTf})_3$  were also effective catalysts, but  $\text{B}(\text{C}_6\text{F}_5)_3 \cdot \text{H}_2\text{O}$  provided the optimal yield by minimizing competing elimination and silyl ether cleavage (Table S1). No reaction was observed in the absence of acids. Lewis acids (e.g.,  $\text{Bi}(\text{OTf})_3$ ) and protic compounds can form strong Brønsted acids *in situ*. The addition of 20 mol % proton sponge completely inhibits azidation by Lewis acids and by Brønsted acids.

(17) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd updated and enlarged ed.; Wiley-VCH: Weinheim, 2003. See also (b) Laurence, C.; Nicolet, P.; Dalati, M. T.; Abboud, J.-L.; Notario, R. *J. Phys. Chem.* **1994**, *98*, 5807–5816. (c) Borovikov, Y. Y.; Topchii, V. A. *Theor. Exp. Chem.* **1976**, *11*, 89–92.

(18) (a) Hellal, M.; Falk, F. C.; Wolf, E.; Dryzhakov, M.; Moran, J. *Org. Biomol. Chem.* **2014**, *12*, 5990–5994. (b) Wolf, E.; Richmond, E.; Moran, J. *Chem. Sci.* **2015**, *6*, 2501–2505.