

## Scandium as a pre-catalyst for the deoxygenative allylation of benzylic alcohols

 Ivan Šolić,<sup>a</sup> Pattarakiat Seankongsuk,<sup>b</sup> Joanna Kejun Loh,<sup>a</sup> Tirayut Vilaivan,<sup>b</sup> Roderick W. Bates\*<sup>a</sup>

 Received 00th January 20xx,  
Accepted 00th January 20xx

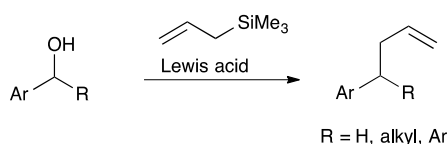
DOI: 10.1039/x0xx00000x

www.rsc.org/ea

Scandium triflate is an effective pre-catalyst for the deoxygenative allylation of benzylic alcohols with a narrow substrate window. The reaction is shown to proceed through a “hidden Brønsted acid” mechanism. The reaction is efficient provided that the aryl group is neither too electron rich nor too electron poor. It is shown that this allows useful selectivity. The reaction also works for benzyhydril alcohols with broader scope. The reaction may also be catalysed by Nafion.

### Introduction

Numerous methods have been reported for the deoxygenative allylation of benzyl alcohols, benzyhydril alcohols and related compounds. All of these employ Lewis acids,<sup>1</sup> including Brønsted acids,<sup>2</sup> to mediate the reaction (Scheme 1). Not all of these reactions are catalytic as some Lewis acids employed are deactivated by the reaction conditions. Arising from our new-found interest in the use of lanthanide ions as Lewis acid catalysts,<sup>3</sup> we were surprised to find no reports of their effective use in this reaction. To the best of our knowledge, there are just a few reports of their unsatisfactory or limited application.<sup>1c,1g,1r, 1t, 2e</sup>

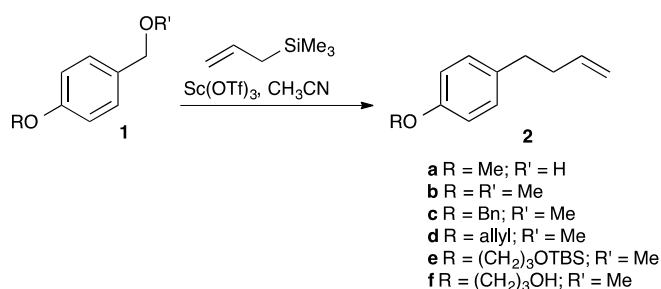


Scheme 1. Deoxygenative allylation

### Results and Discussion

Anticipating a carbocation intermediate, we selected *p*-methoxybenzyl alcohol **1a** for exploratory studies (Scheme 2). While treatment with allyltrimethylsilane and a sub-stoichiometric amount of scandium triflate<sup>4</sup> in

dichloromethane gave only modest results, a rapid reaction ensued when we employed acetonitrile<sup>5</sup> as the solvent at 40°C, giving alkene **2a** in good yield (Table 1, entry 1).



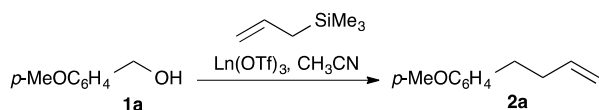
Scheme 2. Deoxygenative allylation of benzylic alcohols

As we wished for a robust synthetic method, we employed “bench” acetonitrile, with no attempt at drying of the solvent or the glassware. Karl Fischer titration showed that this solvent contained approximately 130 ppm of water. Lanthanide triflates have been claimed to be water tolerant Lewis acids.<sup>6</sup> We tested this by running the same reaction in acetonitrile to which a small amounts of water, from 2.5 to 10% by volume, had been added (entries 2-5). At most, only traces of the product could be observed. To our further surprise, the reaction using the 10% v/v mixture (entry 4) failed to proceed even at 90°C. Interestingly, when dried acetonitrile (approx. 45 ppm water) was employed (entry 5), the reaction was much less efficient, giving only 24 % yield in the same time as the original experiment. Three true lanthanide triflate salts were also tested, but gave much lower yields than scandium, even with extended reaction times (entries 6-8).

<sup>a</sup> Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

<sup>b</sup> Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Phayathai Road, Patumwan, Bangkok 10330, Thailand.

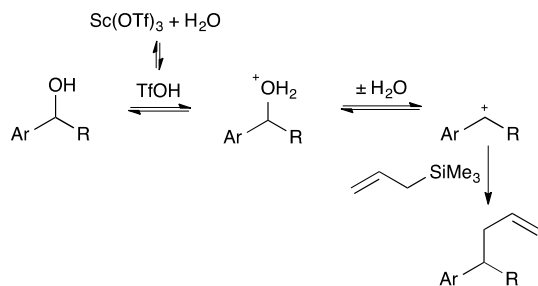
Electronic Supplementary Information (ESI) available: General procedures ; experimental details and NMR spectra for compounds **1c**, **1e**, **1l**, **8a-j**, **2a**, **c**, **d**, **f**, **h**, **j**, **l'**, **m**, **4-7**, **9a**, **b**, **c**, **d**, **e**, **f**, **h**, **l**, **j**.

Table 1. Deoxygenative allylation of *p*-methoxybenzyl alcohol: water content and pre-catalyst

entry	pre-catalyst	solvent	time	yield (%)
1	Sc(OTf) <sub>3</sub>	bench CH <sub>3</sub> CN <sup>b</sup>	1 h	71
2	Sc(OTf) <sub>3</sub>	2.5% H <sub>2</sub> O in CH <sub>3</sub> CN	1 h	trace <sup>d</sup>
3	Sc(OTf) <sub>3</sub>	5% H <sub>2</sub> O in CH <sub>3</sub> CN	2 h	-
4	Sc(OTf) <sub>3</sub>	10% H <sub>2</sub> O in CH <sub>3</sub> CN	2 h	-
5	Sc(OTf) <sub>3</sub>	dried CH <sub>3</sub> CN <sup>c</sup>	1 h	24
6	La(OTf) <sub>3</sub>	bench CH <sub>3</sub> CN	1 h	23
7	Gd(OTf) <sub>3</sub>	bench CH <sub>3</sub> CN	20 h	15
8	Lu(OTf) <sub>3</sub>	bench CH <sub>3</sub> CN	20 h	8 <sup>d</sup>

a: Solutions were 0.5M in substrate, using 4 equivalents of the allyl silane; reactions were stirred at 40°C for the indicated time. b: Water content: 130 ppm. c: Water content: 45 ppm. d: Accompanied by some decomposition

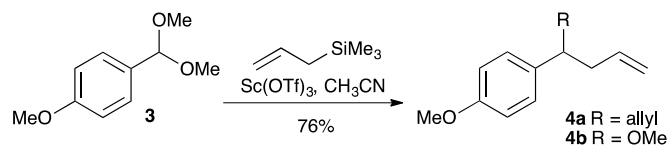
Spencer<sup>7</sup> has demonstrated that the real catalyst when many metal salts are employed as Lewis acids is actually *in situ* generated H<sup>+</sup> i.e. a “hidden Brønsted acid”.<sup>8</sup> Following the work of Spencer, we tested for this by addition of di-*t*-butyl-4-methylpyridine which, for steric reasons, is capable of sequestering a proton, but not a Lewis acid.<sup>9</sup> In the presence of this additive, two equivalents relative to scandium, the reaction did not proceed at 40°C. Even at 90°C only a 60% conversion was observed after 22 hours. This experiment indicates that the reaction is actually catalysed by a Brønsted acid (Scheme 3), likely to have formed by hydrolysis of the scandium salt<sup>8b</sup> and that, in the absence of a proton source, substantially more forcing conditions are required. Scandium triflate is, therefore, a pre-catalyst unless those more forcing conditions are applied. Catalysis of this reaction by Brønsted acids is well documented.<sup>2</sup> Indeed, the reaction was also catalysed by triflic acid giving 75% conversion in 2 hours. Given that triflic acid was a less effective catalyst than scandium triflate it seems that, although a hidden Brønsted acid mechanism operates, there is a modest synergistic effect due to the scandium. The addition of water, of course, inhibits the reaction by diluting the acid, while concentrations of water that are too low prevent the formation of a sufficient Brønsted acid concentration.



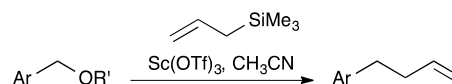
Scheme 3. The “hidden Brønsted acid mechanism”

Consistent with the need to form a strong Brønsted acid by hydrolysis to catalyse the reaction, no reaction was observed when scandium acetate was employed.

As would be expected from the mechanism, the corresponding methyl ether **1b** performed equally well (Table 2, entry 2). In contrast, various other benzyl alcohols performed very poorly. No product could be obtained when benzyl alcohol **1g** (entry 6), *m*-methoxybenzyl alcohol **1i** (entry 8) and *p*-chlorobenzyl alcohol **1k** (entry 10) were employed; low yields were obtained with *o*-methoxybenzyl alcohol **1h** (entry 7) and piperonyl alcohol **1j** (entry 9). Both of these examples would be expected to be less electron rich or less effective at stabilising a benzylic cation. The lower reactivity is, therefore, to be expected. Such selectivity is, of course, valuable: when *p*-benzyloxybenzyl methyl ether **1c** was employed as the substrate (entry 3), selective allylation at only the more electron rich benzylic position was observed. *p*-Allyloxybenzyl methyl ether **1d** also underwent efficient deoxygenative allylation. A substrate **1e** with a TBS group, however, did not survive the reaction conditions, predominantly yielding the corresponding allylated compound **1f** with a free alcohol group.<sup>10</sup> In addition, the dimethoxy acetal of *p*-methoxybenzaldehyde **3** underwent diallylation, giving diene **4a**, contaminated by some of the mono-allylated product **4b** in a 3.2:1 ratio.



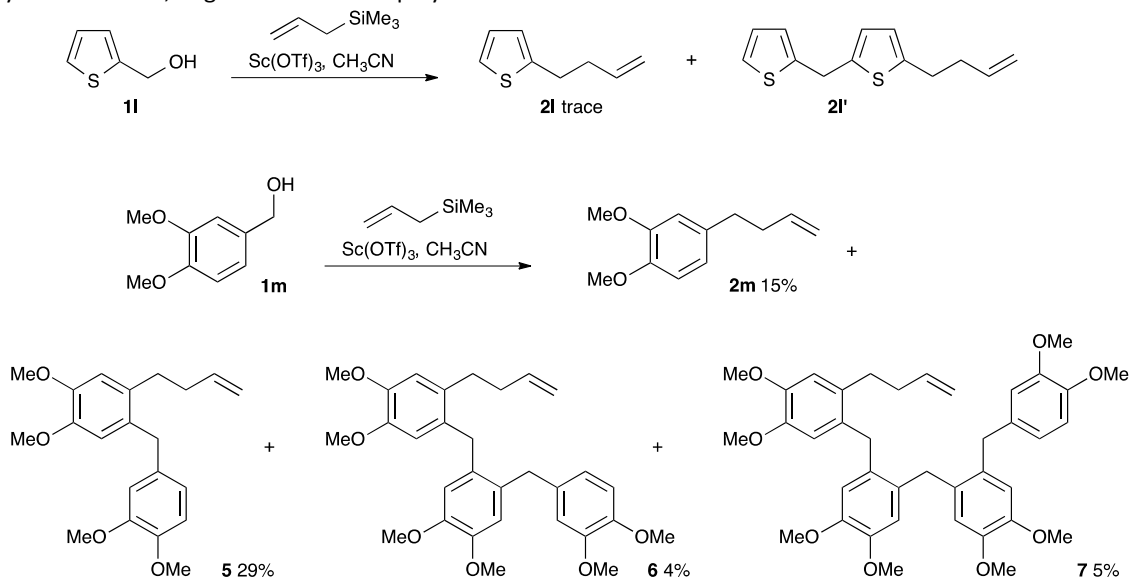
Scheme 4. Use of an acetal as the substrate.

Table 2. Deoxygenative allylation of benzylic alcohols and ethers using Sc(OTf)<sub>3</sub><sup>a</sup>

entry	substrate	Ar	R'	product, yield (%)
1	<b>1a</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	<b>2a</b> 71
2	<b>1b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>2a</b> 77
3	<b>1c</b>	<i>p</i> -BnOC <sub>6</sub> H <sub>4</sub>	Me	<b>2c</b> 97
4	<b>1d</b>	<i>p</i> -allylO C <sub>6</sub> H <sub>4</sub>	Me	<b>2d</b> 94
5	<b>1e</b>	<i>p</i> -TBSO(CH <sub>2</sub> ) <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	Me	<b>2e</b> 6 <b>2f</b> 51 <sup>b</sup>
6	<b>1g</b>	Ph	H	0
7	<b>1h</b>	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	<b>2h</b> 24
8	<b>1i</b>	<i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	0
9	<b>1j</b>	<i>o,m</i> -OCH <sub>2</sub> OC <sub>6</sub> H <sub>3</sub>	H	<b>2j</b> 10
10	<b>1k</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	<b>2k</b> 0
11	<b>1l</b>	2-thiophenyl	H	<b>2l</b> trace <sup>c</sup>
12	<b>1m</b>	<i>m,p</i> -(MeO) <sub>2</sub>	H	<b>2m</b> 15 <sup>c</sup>

a: Solutions were 0.5M in substrate, using 4 equivalents of the allyl silane; reactions were stirred at 40°C for the indicated time. b: Desilylated product. c: Oligomerisation was also observed: see Scheme 5.

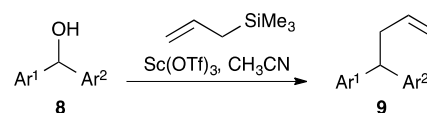
Thiophenylmethanol **1l** (entry 11) gave a trace of the volatile allylation product **2l**, accompanied by oligomerisation products, amongst which the pseudodimer **2l'** could be isolated (scheme 5). We were interested to find what would happen with an aryl group bearing more electron donating groups. Veratryl alcohol **1m** reacted rapidly under these conditions, but gave a mixture of products. The expected allylation product **2m** was obtained in 15% yield (entry 12), but the pseudo-dimer **5**, isolated in 29% yield, proved to be the major product. We were also able to isolate the pseudo-trimer **6** and pseudo-tetramer **7** in 4 and 5% yields respectively. Dimerisation, oligomerisation and polymerisation



Scheme 5. Oligomerisation reactions.

The deoxygenative allylation has been widely used with benzhydryl alcohols.<sup>12</sup> Indeed, under our conditions, a range of benzhydryl alcohols **8** underwent deoxygenative allylation, giving the products **9** in good yields (Table 3). Notably, a ferrocenyl group could be one of the aromatic groups (entry 5). One exception was phenyl 2-furyl carbinol **8g** (entry 7). We suspect this is due to the well-known acid sensitivity of furans. Thiophenes are regarded as more stable and phenyl 2-thiophenyl carbinol **8f** did give a better yield (entry 6). Phenyl cyclopropyl carbinol **8h** gave a modest yield of the allylated product **9h** (entry 8). A small amount of 4-phenylbut-3-en-1-ol (4%) was also isolated. This appears to be a Julia product<sup>13</sup> arising from cyclopropane ring opening during return of water to the carbocation intermediate.

Table 3. Deoxygenative allylation of benzhydryl alcohols using Sc(OTf)<sub>3</sub><sup>a</sup>

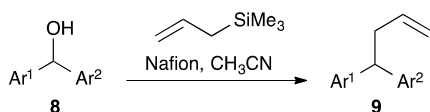


entry	substrate	Ar <sup>1</sup>	Ar <sup>2</sup>	product, yield (%)
1	<b>8a</b>	Ph	Ph	<b>9a</b> 96
2	<b>8b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>9b</b> 94
3	<b>8c</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	<b>9c</b> 95
4	<b>8d</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>9d</b> 84
5	<b>8e</b>	Ph	ferrocenyl	<b>9e</b> 93
6	<b>8f</b>	Ph	2-thiophenyl	<b>9f</b> 52
7	<b>8g</b>	Ph	2-furyl	0 (dec.)
8	<b>8h</b>	Ph	cyclopropyl	<b>9h</b> 48 <sup>b</sup>
9	<b>8i</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>m</i> -Br	<b>9i</b> 94
10	<b>8j<sup>c</sup></b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>m</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	<b>9j</b> 96

a: Solutions were 0.5M in substrate, using 4 equivalents of the allyl silane; reactions were stirred at 40°C for the indicated time. b: A small amount of ring opened product was also isolated. c: The corresponding methyl ether was used as the substrate, rather than the alcohol.

Returning to the concept of Brønsted acid catalysis, we wondered whether we could employ a solid supported catalyst. This modification would simplify the work-up procedure and be of future use in flow chemistry. Given that we were using the triflate of scandium, we employed Nafion, a perfluorinated sulfonic acid resin (Table 4).<sup>14</sup> Pleasingly, under these conditions, benzhydryl alcohol **8a** was converted to its allylated derivative **9a** in 42% yield (entry 1). A number of other benzhydryl alcohols could also be allylated (entries 3–5). In contrast, no reaction was observed when nafion-supported scandium(III)<sup>15</sup> was used (entry 2), indicating that this polymer does not undergo significant hydrolysis under these conditions.

Table 4. Deoxygenative allylation of benzhydryl alcohols using Nafion



entry	substrate <sup>a</sup>	Ar <sup>1</sup>	Ar <sup>2</sup>	product, yield (%)
1	<b>8a</b>	Ph	Ph	<b>9a</b> 42
2	<b>8a</b>	Ph	Ph	0 <sup>b</sup>
3	<b>8b</b>	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>9b</b> 74
4	<b>8c</b>	Ph	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>9c</b> 57
5	<b>8f</b>	Ph	2-thiophenyl	<b>9f</b> 51

a: 0.5 M in substrate using 125 mg of Nafion per mmole. b: Nafion supported Sc<sup>3+</sup> was used.

## Conclusions

Scandium triflate is an effective catalyst for the deoxygenative allylation of benzhydryl alcohols, and displays significant and potentially useful selectivity in the same reaction with benzyl alcohols. The reaction proceeds through a hidden Brønsted acid mechanism. Scandium triflate is, therefore, better considered as a pre-catalyst! Claims in the literature that this allylation (and other) reactions are Lewis acid catalysed should be viewed with caution if no appropriate test has been carried out.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the Agency for Science Technology and Research (A-Star) for financial support of this work (PSF grant number 1321202095) and the Graduate School, Chulalongkorn University (Overseas Research Experience Scholarship for Graduate Student, to PS).

## Notes and references

- Lewis acids: BF<sub>3</sub>: (a) J. A. Cella, *J. Org. Chem.* **1982**, *47*, 2125; B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>: (b) M. Rubin, V. Gevorgyan, *Org. Lett.* **2001**, *3*, 2705; indium halides: (c) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chemie, Int. Ed.* **2004**, *43*, 1414; (d) S. H. Kim, C. Shin, A. N. Pae, H. Y. Koh, M. H. Chang, B. Y. Chung, Y. S. Cho, *Synthesis* **2004**, 1581; (e) T. Saito, M. Yasuda, A. Baba, *Synlett* **2005**, 1737; (f) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516; BiCl<sub>3</sub>: (g) S. K. De, R. A. Gibbs, *Tetrahedron Lett.* **2005**, *46*, 8345; *n*-BuLi + BCl<sub>3</sub>: (h) G. W. Kabalka, M.-L. Yao, S. Borella, *J. Am. Chem. Soc.* **2006**, *128*, 11320; (i) G. W. Kabalka, S. Borella, M.-L. Yao, *Synthesis* **2008**, 325; ZrCl<sub>4</sub>: (j) G. V. M. Sharma, K. L. Reddy, P. S. Lakshmi, K. Ravi, C. Ajit, *J. Org. Chem.* **2006**, *71*, 3967; I<sub>2</sub>: (k) J. S. Yadav, B. V. Subba Reddy, A. Srinivas Reddy, B. Eeshwaraiah, *Chem. Lett.* **2007**, *36*, 1500; Me<sub>3</sub>SiBr-I<sub>2</sub>: (l) M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2015**, *17*, 3000; FeCl<sub>3</sub>: (m) J. Han, Z. Cui, J. Wang, Z. Liu, *Syn. Commun.* **2010**, *40*, 2042; (n) X. Fan, X.-M. Cui, Y.-H. Guan, L.-A. Fu, H. Lv, K. Guo, H.-B. Zhu, *Eur. J. Org. Chem.* **2014**, 498; (o) Y. Sawama, R. Goto, S. Nagata, Y. Shishido, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2014**, *20*, 2631; Fe(OTf)<sub>3</sub>: (p) L. Y. Chan, S. Kim, W. T. Chung, C. Long, S. Kim, *Synlett* **2011**, 415; Rh(I) complex: (q) G. Onodera, E. Yamamoto, S. Tonegawa, M. Iezumi, R. Takeuchi, *Adv. Syn. Cat.* **2011**, *353*, 2013; Bi(OTf)<sub>3</sub>: (r) K. Nurayana, K. K. Laali, *Org. Biomol. Chem.* **2012**, *10*, 7347; TiCl<sub>4</sub>: (s) A. Hassner, C. R. Bandi, *Synlett* **2013**, *24*, 1275. The rhodium catalysed reaction of benzylic acetates has been reported: (t) a single example using La(OTf)<sub>3</sub> in nitromethane at 100 °C, can be found in M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima, K. Ishii, *J. Org. Chem.* **2003**, *68*, 9340.
- Brønsted acids: (a) G. Kaur, M. Kaushik, S. Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521; (b) H. A. I. Yoshihara, G. Chiellini, T. J. Michison, T. S. Scanlan, *Bioorg. Med. Chem.* **1998**, *6*, 1179; (c) K. Motokura, N. Nakagiri, E. Tomoo, K. Ebitani, K. Kaneda, *J. Org. Chem.* **2007**, *72*, 6006; (d) A. Devineau, G. Pousse, C. Tallier, J. Blanchet, J. Rouden, V. Dalla, *Adv. Syn. Cat.* **2010**, *352*, 2881; (e) S. T. Kadam, H. Lee, S. S. Kim, *App. Organomet. Chem.* **2010**, *24*, 67; (f) J. Wang, Y. Masui, M. Onaka, *Tetrahedron Lett.* **2010**, *51*, 3300; (g) M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, C. Piccinini, *Synthesis*, **2010**, 315; (h) K. Murugan, C. Chen, *Tetrahedron Lett.* **2011**, *52*, 5827; (i) I. Orizu, Y. Bolshan, *Tetrahedron Lett.* **2016**, *57*, 5798.
- I. Šolić, D. Reich, J. Lim R. W. Bates, *Asian J. Org. Chem.* **2017**, *6*, 658.
- S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15. Scandium may be considered as a pseudo-lanthanide.
- Despite the use of this solvent, we observed no products from the Ritter reaction.
- S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.*, **2002**, *102*, 2227.
- T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484.
- For some recent studies of “hidden Brønsted acids”, see (a) Liu, Z.; Ganguly, R.; Vidović, D. *Dalton Trans.* **2017**, *46*, 753; (b) Kaźmierczak, J.; Kuciński, K.; Hreczycho, G. *Inorg. Chem.* **2017**, *56*, 9337; (c) Kim, N.; Brooner, R. E. M.; Widenhoefer, R. A. *Organometallics* **2017**, *36*, 673; (d) Jin, H. J.; Kim, J. H.; Kang, E. J. *Synthesis* **2017**, *49*, 3137; (e) von der Heiden, D.; Bozkus, S.; Klusmann, M.; Breugst, M. *J. Org. Chem.* **2017**, *82*, 4037; (f) T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.*, **2011**, *76*, 9353; (g) Taylor, J. G.; Adrio, L. A.; Hii, K. K. *Dalton Trans.* **2010**, *39*, 1171; (h) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562.
- B. Kanner, H. C. Brown, *J. Am. Chem. Soc.* **1953**, *75*, 3865.

- 10 T. Oriyama, Y. Kobayashi, K. Noda, *Synlett* **1998**, 1047.
- 11 More nucleophilic by four orders of magnitude: G. Hagen, H. Mayr, *J. Am. Chem. Soc.* **1991**, *113*, 4954.
- 12 For the most recent contribution see ref. 2i.
- 13 M. Julia, S. Julia, R. Guegan, *Bull. Soc. Chim. Fr.* **1960**, 1072.
- 14 G. Gelbard, *Ind. Eng. Chem. Res.* **2005**, *44*, 8468. Low yields have been reported for the use of Nafion (ref. 2e).
- 15 L. Yu, D. Chen, J. Li, G. Wang, *J. Org. Chem.* **1997**, *62*, 3575.