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3-Component synthesis of α-substituted sulfonamides *via* Brønsted acid-catalyzed C(sp^3)–H bond functionalization of 2-alkylazaarenes†

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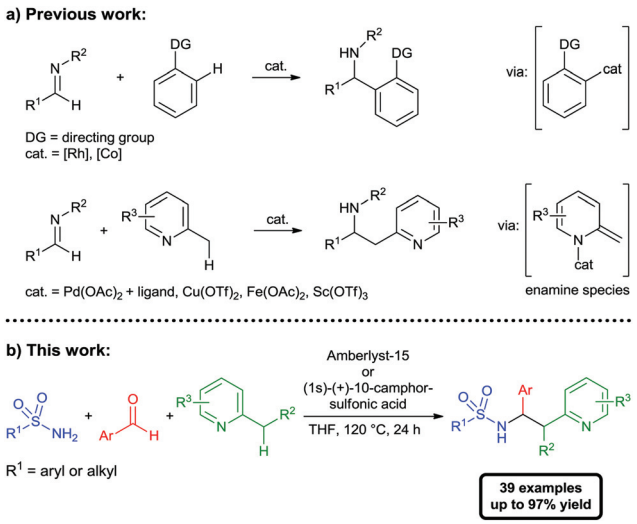
A Brønsted acid-catalyzed addition of 2-alkylazaarenes to *in situ* generated *N*-sulfonylimines through selective C(sp^3)–H bond functionalization has been developed. This protocol provides an atom- and step-economic approach to α-substituted sulfonamides.

The selective functionalization of C–H bonds plays a key role in the development of more efficient and sustainable bond forming reactions.[1] In the past two decades metal-catalyzed activations of C–H bonds have emerged as a valuable and efficient tool for the atom-economic[2] construction of carbon–carbon and carbon–heteroatom bonds.[3] In this context, the metal-catalyzed addition of C–H bonds to imines provides a powerful method for the synthesis of α-branched amines, a prevalent structural motif in drugs and natural products. So far transition-metal catalyzed addition reactions of aromatic and vinylic C(sp^2)–H bonds to imines[4,5] as well as transition metal- and Lewis acid-catalyzed benzylic additions of azaarenes *via* activation of C(sp^3)–H bonds[6] have been reported (Scheme 1). Although concise and atom-economic, the overall synthetic utility of these methods is hampered by the additional step required for the preparation of the imine. Based on our continued interest in acyl- and sulfonylimine-based multicomponent reactions,[7] we considered a possible *in situ* generation of the reactive imine in such C–H functionalization reactions.[8] This approach would combine all the advantages of C–H functionalization reactions and multicomponent synthesis[9] and would lead to a more atom- as well as step-economic[10] synthesis of α-branched sulfonamides. Herein we report, to our knowledge, the first example of an addition of a C(sp^3)–H bond to an *in situ* generated *N*-sulfonylimine *via* Brønsted acid catalyzed C–H functionalization.



Scheme 1 Direct C–H bond functionalization: general view of previous work and this report.

As starting point to investigate a possible combination of C–H functionalization and *in situ* imine formation we chose reactions with 2-alkylazaarenes. We envisioned, that the reported Lewis or Brønsted acids[11] used for functionalization of the benzylic C(sp^3)–H bond could simultaneously catalyze the generation of an reactive imine species *via* condensation of an amide and an aldehyde. To identify an appropriate catalyst and to optimize the reaction conditions, we chose the reaction between *p*-toluenesulfonamide (**1a**), benzaldehyde (**2a**) and 2,6-dimethylpyridine (**3a**) (Table 1).

To our delight, several Brønsted as well as Lewis acids could catalyze this reaction and provided the desired product **4a** in 69–80% yield (entries 1–6). Best results were obtained with Amberlyst-15, a commercial available heterogeneous sulfonic acid catalyst[12] (entry 1). Although (1s)-(+)-10-camphor-sulfonic acid (entry 2) as well as several metal triflates, for example Zn(OTf)$_2$ or Yb(OTf)$_3$ (entries 5 and 6), displayed almost identical catalytic activities, we chose Amberlyst-15 due

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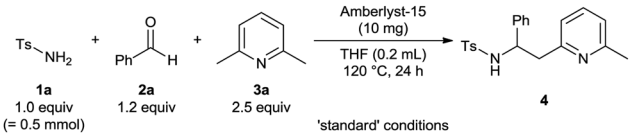
Table 1 3-Component synthesis of α-substituted sulfonamides *via* Brønsted acid-catalyzed C(sp^3)–H bond functionalization of 2-alkylazaarenes: influence of reaction parameters



Entry	Variation from the 'standard' conditions	Yield[a] (%)
1	None	**80**
2	(1s)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15	75[b]
3	2,6-Dinitrobenzenesulfonic acid (5 mol%), instead of Amberlyst-15	69
4	$Mg(OTf)_2$ (5 mol%), instead of Amberlyst-15	68
5	$Zn(OTf)_2$ (5 mol%), instead of Amberlyst-15	75
6	$Yb(OTf)_3$ (5 mol%), instead of Amberlyst-15	78
7	No catalyst	20–30
8	0.3 mL THF, instead of 0.2 mL	66
9	0.5 mL THF, instead of 0.2 mL	65
10	100 °C, instead of 120 °C	42–77
11	1.5 equiv. 2,6-lutidine, instead of 2.5 equiv.	39
12	3.5 equiv. 2,6-lutidine, instead of 2.5 equiv.	79

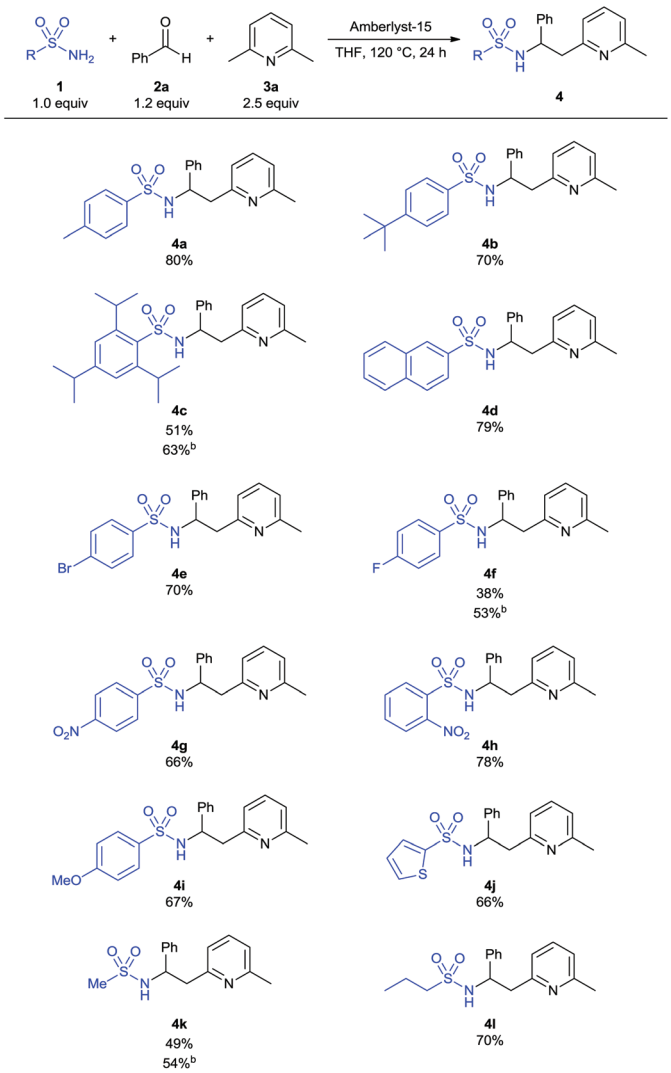
[a] Yields of isolated products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. [b] No asymmetric induction was observed.

to its additional advantages such as low cost, simple catalyst separation by filtration and potential catalyst recycling. Without catalyst product **4a** was obtained in 20–30% yield (entry 7). Generation of the enamine species by C–H cleavage of the benzylic C–H bond of 2-substituted alkylazaarenes at high temperatures is known from literature.[6e] Hence, it is expected that the Brønsted acid is mainly required for the *in situ* generation of the sulfonylimine. Initial studies revealed that THF constituted the best solvent for this transformation. Performing the reaction at high temperatures (100–120 °C), using high concentrations (2.5 M) and at least 2.5 equivalents of the 2-alkylazaarene proved to be crucial for obtaining high yields (compare entries 1 and 8–12). A reaction temperature of 120 °C provided the highest and most reproducible yields.

With the optimized conditions at hand, we investigated the scope and limitations of our method. The 3-component reaction with various electron-rich and -poor as well as halogenated aryl sulfonamides or the heterocyclic thiophene-2-sulfonamide proceeded smoothly and afforded the corresponding products **4a–4j** in good yields (Table 2). Moreover, alkyl sulfonamides can be used as amide component, furnishing the desired α-branched sulfonamides in 54 and 70% yields (**4k** and **4l**). In some cases (**4c**, **4f**, **4k**) better yields were obtained with (1s)-(+)-10-camphorsulfonic acid as catalyst. This might be due to the fact, that the reaction temperature of 120 °C corresponds to the maximum operating temperature for Amberlyst-15 and catalyst decomposition might occur.[12,13]

Next we investigated the scope of the reaction in terms of the aldehyde component. As shown in Table 3, a broad range of aryl aldehydes are suitable substrates for the 3-component

Table 2 Variation of sulfonamides[a]

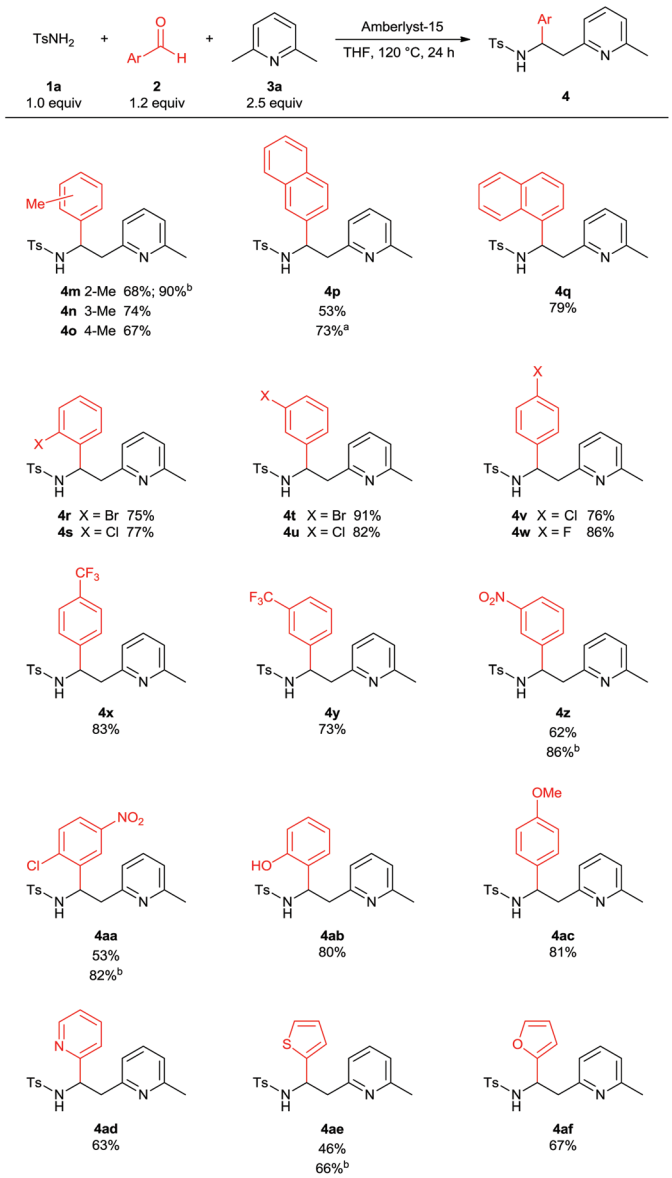


[a] The reported yields are those of the isolated products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. Reaction times were not optimized. [b] (1s)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15.

synthesis. Substituents at various positions on the aryl ring were tolerated. Reactions of electron-donating or -withdrawing as well as halogen substituted aryl aldehydes gave the corresponding products **4m–4ac** in good to high yields. Heterocyclic aldehydes displayed a similar reactivity and the α-substituted sulfonamides **4ad–4af** were isolated in 46–67% yields. As shown before, in some cases the use of 5 mol% (1s)-(+)-10-camphorsulfonic acid as catalyst provided approximately 20% higher yields (**4m**, **4p**, **4z**, **4aa** and **4ae**). Reactions with other aldehyde components, such as alkyl aldehydes or glyoxalates were unsuccessful.

Subsequently, we examined reactions with various 2-alkylazaarenes (Table 4). Unfortunately, the substrate scope in terms of the 2-alkylazaarenes component is not as broad as that for the other two reactants. Compared to 2,6-lutidine (**4a**),

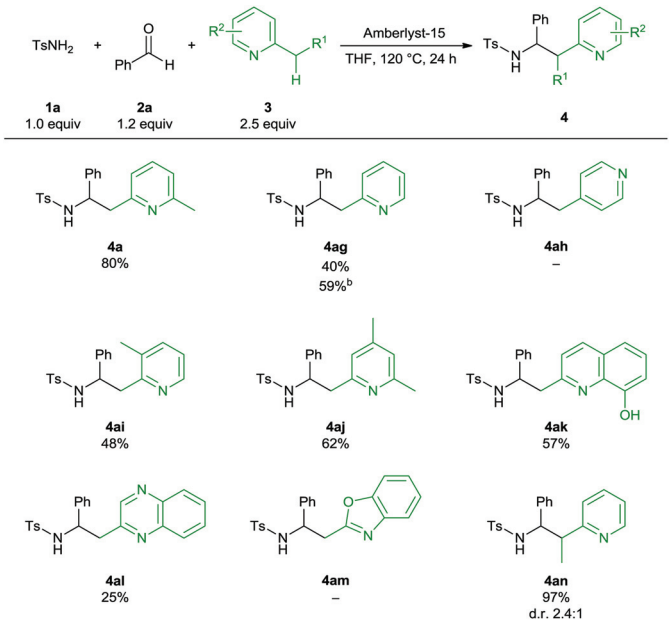
Table 3 Variation of aryl aldehydes[a]



[a] The reported yields are those of the isolated products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. Reaction times were not optimized. [b] (1s)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15.

reactions of other substituted pyridine or quinoline derivatives, such as 2,3-lutidine or 8-hydroxyquinoline, gave the desired α-branched sulfonamides in only moderate yields (**4ag**, **4ai–4al**). Only in the case of 2-picoline a substantial increase in yield could be achieved with (1s)-(+)-10-camphorsulfonic acid as catalyst. Interestingly, 4-methylpyridine did not react at all under our reaction conditions. Contrary to literature reports on Lewis acid catalyzed reactions[6b,c] we did not observe γ-functionalization. 5-Membered 2-alkyl-substituted nitrogen heterocycles, such as 2-methylbenzo[d]oxazole, or various diazines did not react under the standard reaction conditions.

Table 4 Variation of 2-alkylazaarenes[a]



[a] The reported yields are those of the isolated products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. Reaction times were not optimized. [b] (1s)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15.

Only in the case of quinoxaline the desired product was isolated in low yield (**4al**). 2-Ethylpyridine proved to be an excellent substrate for this 3-component synthesis, furnishing the α-substituted amine **4an** in 97% yield as a 2.4 : 1 mixture of diastereomers.

Conclusions

In summary, we have developed a Brønsted acid-catalyzed 3-component synthesis of α-substituted sulfonamides from 2-aklyazaarenes, aryl aldehydes and sulfonamides. This method is based on the combination of an *in situ* imine generation and an acid-catalyzed selective C(sp^3)–H bond activation. The reaction has a broad scope and is simple to perform. With water as only byproduct this protocol provides an atom- and step-economic, sustainable approach to various heterocyclic α-substituted sulfonamides. In addition, this method represents an example for the successful merger of two synthetically very useful transformations, the selective functionalization of C–H bonds and multicomponent reactions. Further extensions of this concept to various metal-catalyzed C–H activation reactions are currently investigated in our laboratory.

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Notes and references

1 (*a*) J. Yamaguchi, K. Itami and A. D. Yamaguchi, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*b*) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (*c*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*d*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*e*) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. – Eur. J.*, 2010, **16**, 2654; (*f*) R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 575; (*g*) R. G. Bergman, *Nature*, 2007, **446**, 391; (*h*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*i*) G. Dyker, *Handbook of C-H Transformations*, Wiley-VCH, Weinheim, 2005; (*j*) K. I. Goldberga and A. S. Goldman, *Activation and Functionalization of C-H Bonds* (ACS Symposium), Oxford University Press, Oxford, 2004; (*k*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077; (*l*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507; (*m*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633; (*n*) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698.

2 (*a*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695; (*b*) B. M. Trost, *Science*, 1991, **254**, 1471.

3 (*a*) L. Yang and H. Huang, *Chem. Rev.*, 2015, **115**, 3468; (*b*) K. Gao and N. Yoshikai, *Acc. Chem. Res.*, 2014, **47**, 1208; (*c*) G. Yan, X. Wu and M. Yang, *Org. Biomol. Chem.*, 2013, **11**, 5558; (*d*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*e*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*f*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*g*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*h*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*i*) P. Thansandote and M. Lautens, *Chem. – Eur. J.*, 2009, **15**, 5874; (*j*) D. Alberico, M. S. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*k*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*l*) Y. Guari, S. Sabo-Etienne and B. Chaudret, *Eur. J. Inorg. Chem.*, 1999, 1047.

4 For the rhodium-catalyzed intermolecular addition of aromatic and vinylic C(sp^2)–H bonds to imines, see: (*a*) A. Wangweerawong, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2014, **136**, 8520; (*b*) K. Parthasarathy, A. R. Azcargorta, Y. Cheng and C. Bolm, *Org. Lett.*, 2014, **16**, 2538; (*c*) B. Zhou, Y. Yang, S. Lin and Y. Li, *Adv. Synth. Catal.*, 2013, **355**, 360; (*d*) M. E. Tauchert, C. D. Incarvito, A. L. Rheingold, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2012, **134**, 1482; (*e*) Y. Li, X.-S. Zhang, H. Li, W.-H. Wang, K. Chen, B.-J. Li and Z.-J. Shi, *Chem. Sci.*, 2012, **3**, 1634; (*f*) Y. Li, X.-S. Zhang, Q.-L. Zhu and Z.-J. Shi, *Org. Lett.*, 2012, **14**, 4498; (*g*) K. D. Hesp, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2012, **14**, 2304; (*h*) Y. Li, B.-J. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 2115; (*i*) A. S. Tsai, M. E. Tauchert, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 1248.

5 For cobalt-catalyzed intermolecular addition of aromatic and vinylic C(sp^2)–H bonds to imines, see: (*a*) T. Yoshino, H. Ikemoto, S. Matsunaga and M. Kanai, *Chem. – Eur. J.*, 2013, **19**, 9142; (*b*) T. Yoshino, H. Ikemoto, S. Matsunaga and M. Kanai, *Angew. Chem., Int. Ed.*, 2013, **52**, 2207; (*c*) K. Gao and N. Yoshikai, *Chem. Commun.*, 2012, **48**, 4305.

6 (*a*) L. S. Rocha and I. P. Beletskaya, *Russ. Chem. Bull., Int. Ed.*, 2014, **63**, 2686; (*b*) D. Best, S. Kujawa and H. Wai Lam, *J. Am. Chem. Soc.*, 2012, **134**, 18193; (*c*) H. Komai, T. Yoshino, S. Matsunaga and M. Kanai, *Synthesis*, 2012, 2185; (*d*) M. Rueping and N. Tolstoluzhsky, *Org. Lett.*, 2011, **13**, 1095; (*e*) Y. Yan, K. Xu, Y. Fang and Z. Wang, *J. Org. Chem.*, 2011, **76**, 6849; (*f*) B. Qian, P. Xie, Y. Xie and H. Huang, *Org. Lett.*, 2011, **13**, 2580; (*g*) B. Qian, S. Guo, C. Xia and H. Huang, *Adv. Synth. Catal.*, 2010, **352**, 3195; (*h*) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2010, **132**, 3650.

7 (*a*) T. Beisel and G. Manolikakes, *Synthesis*, 2015, A–H; (*b*) T. Beisel and G. Manolikakes, *Org. Lett.*, 2015, **17**, 3162; (*c*) T. Beisel and G. Manolikakes, *Org. Lett.*, 2013, **15**, 6046; (*d*) J. Halli and G. Manolikakes, *Eur. J. Org. Chem.*, 2013, 7471; (*e*) A. E. Schneider and G. Manolikakes, *Synlett*, 2013, 2057; (*f*) A. E. Schneider, T. Beisel, A. Shemet and G. Manolikakes, *Org. Biomol. Chem.*, 2014, **12**, 2356.

8 A different approach for the oxidative in situ imine formation from the corresponding amino acid has been reported by Huang, see: Z.-Q. Zhu, P. Bai and Z.-Z. Huang, *Org. Lett.*, 2014, **16**, 4881.

9 (*a*) J. Zhu and H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005; (*b*) H. Bienaymé, C. Hulme, G. Oddon and P. Schmidt, *Chem. – Eur. J.*, 2000, **6**, 3321; (*c*) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123.

10 P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40.

11 The use of Brønsted acid catalysts for the benzylic addition of 2-azaarenes has been reported for reactions with carbonyl and nitroso compounds but not with imines, see: (*a*) X. Gao, F. Zhang, G. Deng and L. Yang, *Org. Lett.*, 2014, **16**, 3664; (*b*) A. I. Lansakara, D. P. Farrell and F. C. Pigge, *Org. Biomol. Chem.*, 2014, **12**, 1090; (*c*) J.-J. Jin, D.-C. Wang, H.-Y. Niu, S. Wu, G.-R. Qu, Z.-B. Zhang and H.-M. Guo, *Tetrahedron*, 2013, **69**, 6579; (*d*) R. Niu, J. Xiao, T. Liang and X. Li, *Org. Lett.*, 2012, **14**, 676; (*e*) F.-F. Wang, C.-P. Luo, Y. Wang, G. Deng and L. Yang, *Org. Biomol. Chem.*, 2012, **10**, 8605.

12 R. Pal, T. Sarkar and S. Khasnobis, *ARKIVOC*, 2012, **I**, 570.

13 Due to this fact all attempts to recycle the Amberlyst-15 catalyst were unsuccessful. A sharp decrease in yield was observed even in the 2nd cycle.

