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# 3-Component synthesis of $\alpha$ -substituted sulfonamides *via* Brønsted acid-catalyzed C(sp<sup>3</sup>)– H bond functionalization of 2-alkylazaarenes†

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a) Previous work:

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  $\alpha$ -substituted sulfonamides.

The selective functionalization of C-H bonds plays a key role in the development of more efficient and sustainable bond forming reactions.<sup>1</sup> In the past two decades metal-catalyzed activations of C-H bonds have emerged as a valuable and efficient tool for the atom-economic<sup>2</sup> construction of carboncarbon 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  $\alpha$ -branched amines, a prevalent structural motif in drugs and natural products. So far transition-metal catalyzed addition reactions of aromatic and vinylic C(sp<sup>2</sup>)-H bonds to imines<sup>4,5</sup> as well as transition metal- and Lewis acid-catalyzed benzylic additions of azaarenes via activation of C(sp<sup>3</sup>)-H bonds<sup>6</sup> 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 sulfonyliminebased multicomponent reactions,<sup>7</sup> 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 synthesis9 and would lead to a more atom- as well as stepeconomic<sup>10</sup> synthesis of  $\alpha$ -branched sulfonamides. Herein we report, to our knowledge, the first example of an addition of a C(sp<sup>3</sup>)-H bond to an *in situ* generated N-sulfonylimine via Brønsted acid catalyzed C-H functionalization.

# $\begin{array}{c} \begin{array}{c} & & \\ R^{1} \\ R^{1} \\ H \end{array} \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{2} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{3} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \end{array} \overset{R}{} + & \\ \begin{array}{c} & \\ R^{1} \\ \end{array} \overset{R}{} \overset{R}{}$

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<sup>11</sup> 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<sup>12</sup> (entry 1). Although (1s)-(+)-10-camphorsulfonic acid (entry 2) as well as several metal triflates, for example  $Zn(OTf)_2$  or Yb(OTf)<sub>3</sub> (entries 5 and 6), displayed almost identical catalytic activities, we chose Amberlyst-15 due



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**Table 1** 3-Component synthesis of  $\alpha$ -substituted sulfonamides *via* Brønsted acid-catalyzed C(sp<sup>3</sup>)–H bond functionalization of 2-alkylazaarenes: influence of reaction parameters



Entry	Variation from the 'standard' conditions	Yield <sup>a</sup> (%)
1	None	80
2	(1s)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15	75 <sup>b</sup>
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) <sub>2</sub> (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

<sup>*a*</sup> Yields of isolated products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. <sup>*b*</sup> 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.<sup>6e</sup> 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  $\alpha$ -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.<sup>12,13</sup>

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





<sup>*a*</sup> 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. <sup>*b*</sup> (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  $\alpha$ -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<sup>a</sup>



<sup>*a*</sup> 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. <sup>*b*</sup> (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  $\alpha$ -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<sup>6b,c</sup> we did not observe  $\gamma$ -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.





<sup>*a*</sup> 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. <sup>*b*</sup> (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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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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### Communication

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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<sup>2</sup>)-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.

- <sup>5</sup> For cobalt-catalyzed intermolecular addition of aromatic and vinylic C(sp<sup>2</sup>)-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.