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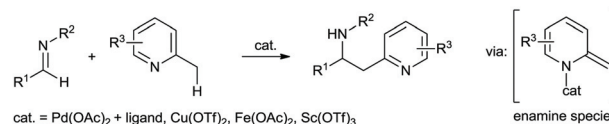
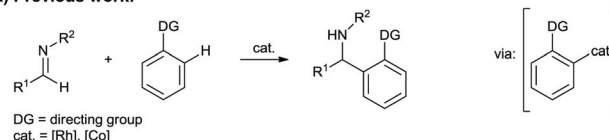
3-Component synthesis of α -substituted sulfonamides *via* Brønsted acid-catalyzed $C(sp^3)$ -H bond functionalization of 2-alkylazaarenes†

T. Beisel, J. Kirchner, T. Kaehler,‡ J. Knauer,‡ Y. Soltani‡ and G. Manolikakes*

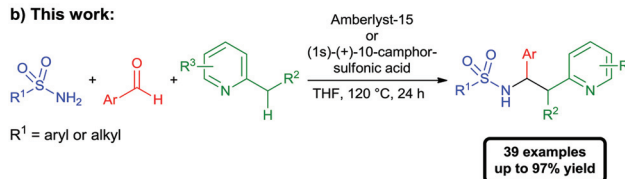
A Brønsted acid-catalyzed addition of 2-alkylazaarenes to *in situ* generated *N*-sulfonylimines through selective $C(sp^3)$ -H bond functionalization has been developed. This protocol provides an atom- and step-economic approach to α -substituted sulfonamides.

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-economic² 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 bonds⁶ 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 synthesis⁹ and would lead to a more atom- as well as step-economic¹⁰ 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.

a) Previous work:



b) This work:



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 acids¹¹ 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 catalyst¹² (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

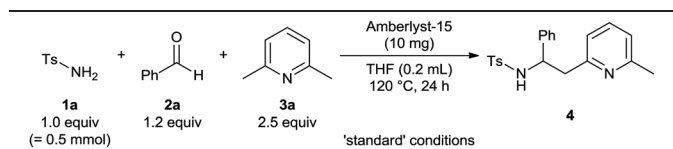
Department of Organic Chemistry and Chemical Biology, Goethe-University Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt am Main, Germany.

E-mail: g.manolikakes@chemie.uni-frankfurt.de

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‡ These authors contributed equally.



Table 1 3-Component synthesis of α -substituted sulfonamides via Brønsted acid-catalyzed C(sp³)-H bond functionalization of 2-alkylazaarenes: influence of reaction parameters

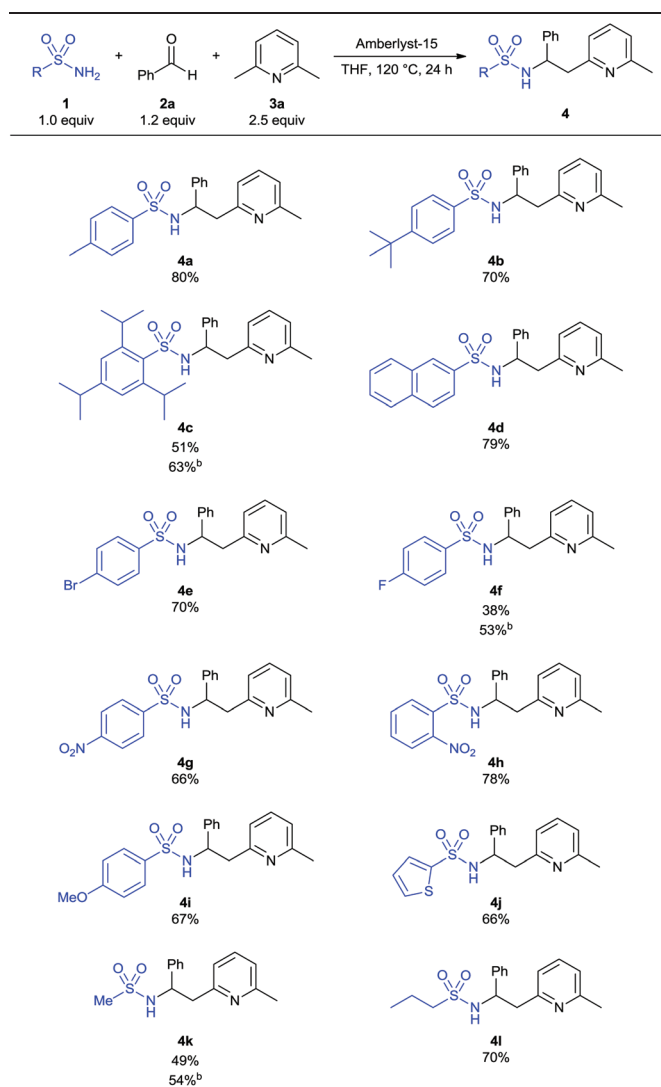
Entry	Variation from the 'standard' conditions	Yield ^a (%)
1	None	80
2	(1 <i>S</i>)-(+)-10-Camphorsulfonic acid (5 mol%), instead of Amberlyst-15	75 ^b
3	2,6-Dinitrobenzenesulfonic acid (5 mol%), instead of Amberlyst-15	69
4	Mg(OTf) ₂ (5 mol%), instead of Amberlyst-15	68
5	Zn(OTf) ₂ (5 mol%), instead 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 (1*S*)-(+)-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

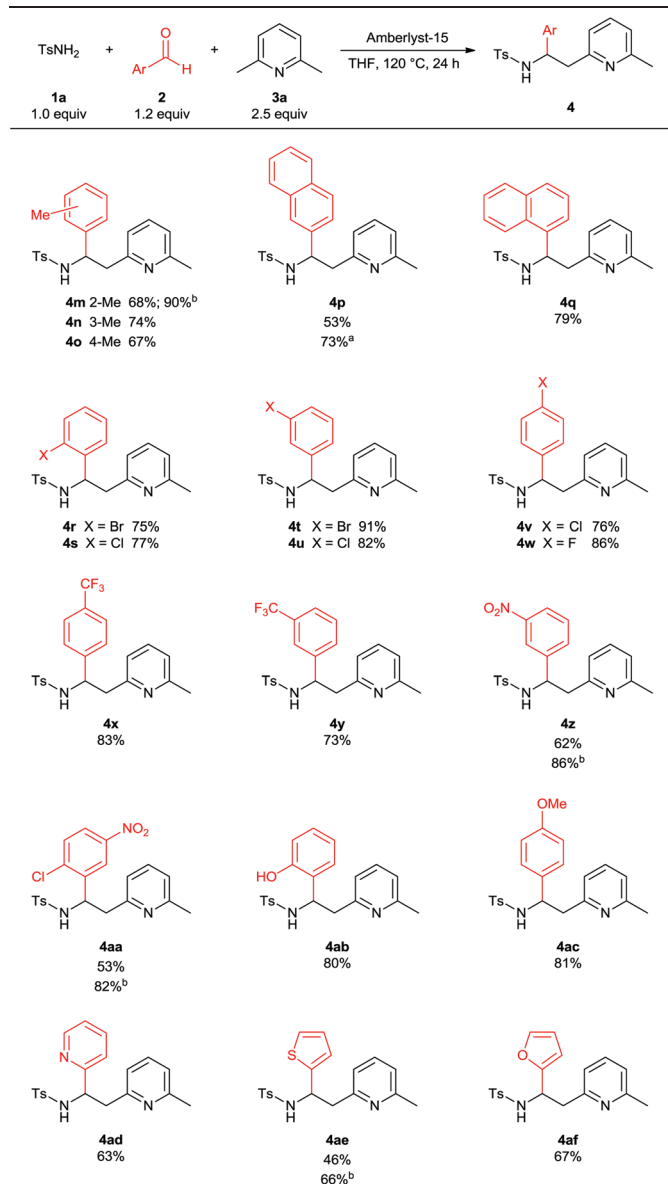
Table 2 Variation of sulfonamides^a

^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 (1*S*)-(+)-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% (1*S*)-(+)-10-camphorsulfonic acid as catalyst provided approximately 20% higher yields (**4m**, **4p**, **4z**, **4aa** and **4ac**). Reactions with other aldehyde components, such as alkyl aldehydes or glyoxalates were unsuccessful.

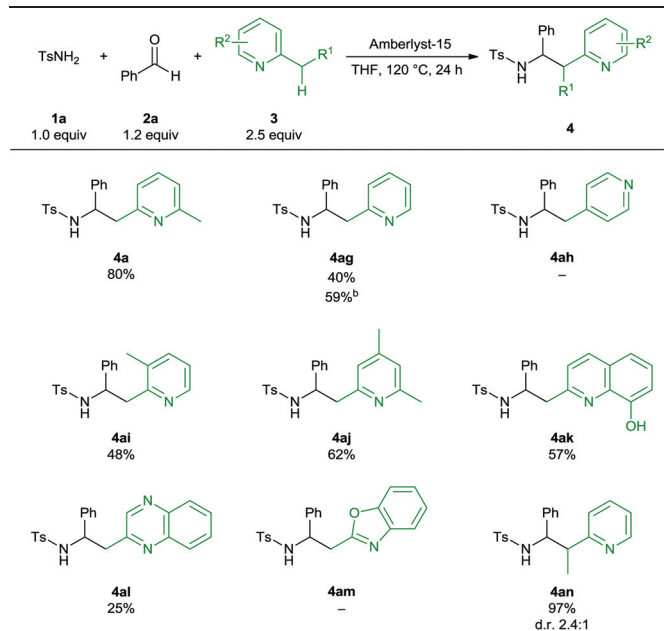
Subsequently, we examined reactions with various 2-alkylazaarenes (Table 4). Unfortunately, the substrate scope in terms of the 2-alkylazaarenes component is not as broad as that for the other two reactants. Compared to 2,6-lutidine (**4a**),



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 (1*S*)-(+)-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 (1*S*)-(+)-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 (1*S*)-(+)-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-alkylazaarenes, aryl aldehydes and sulfonamides. This method is based on the combination of an *in situ* imine generation and an acid-catalyzed selective C(sp³)-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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