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### Triisopropyl borate mediated N-sulfinyl imine formation

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#### ABSTRACT

Triisopropyl borate effects the condensation of aldehydes with sulfinamides to give *N*-sulfinyl imines. The reaction is amenable to 1°, 2°, and 3° alkyl aldehydes, as well as aryl, heteroaryl, and  $\alpha_{,\beta}$ -unsaturated aldehydes. In addition to *tert*-butanesulfinamide, the condensation is also effective with 4-toluenesulfinamide and 2,4,6-triisopropylphenylsulfinamide. This protocol proceeds under homogeneous reaction conditions and requires no post-reaction filtration of insoluble reagents or byproducts. 2009 Elsevier Ltd. All rights reserved.

N-Sulfinyl imines are exceptionally useful intermediates in organic synthesis.<sup>1</sup> The addition of nucleophiles to N-sulfinyl imines generally occurs in a highly diastereoselective manner to give valuable chiral amine products. The condensation of sulfinamides with carbonyl compounds is among the most general and convenient methods for the synthesis of N-sulfinyl imines. N-tert-Butanesulfinyl imines, developed by Ellman and co-workers, are by far the most versatile and well-explored class of *N*-sulfinyl imines.<sup>1b,e</sup> Ellman and co-workers reported the first asymmetric synthesis of tert-butanesulfinamide 1 and its condensation with aldehydes and ketones to give N-sulfinyl imines.<sup>2</sup> Recently, we described a general method for imine formation using B(OCH<sub>2</sub>CF<sub>3</sub>)<sub>3</sub>.<sup>3</sup> This procedure was amenable to not only N-sulfinyl imines, but also N-toluenesulfonyl, N-(dimethylamino)sulfamoyl *N*-diphenylphosphinoyl and aldimines. In the course of screening various trialkyl borates, we found that triisopropyl borate, though not as powerful a condensation reagent as B(OCH<sub>2</sub>CF<sub>3</sub>)<sub>3</sub>, nonetheless gave clean conversion of 4-bromobenzaldehyde to N-tert-butanesulfinyl imine 2 at rt after 72 h (Table 1, entry 1). By increasing the temperature to 60 °C, the reaction time decreased to a more reasonable 18 h (entry 2). Triisopropyl borate has convenient physical properties: it is a non-viscous liquid that is easily transferred by either syringe or pouring, and it is non-volatile (boiling point of 140 °C at 1 atm) and odorless. It also has an excellent safety profile, with NFPA and HMIS health ratings of 0 and 1, respectively, and NFPA and HMIS reactivity hazard and physical hazard ratings of 0 and 0.4 Furthermore, B(Oi-Pr)3 is inexpensive and widely commercially available, especially

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compared with  $B(OCH_2CF_3)_3$ .<sup>5</sup> Herein, we report the scope of the use of  $B(Oi-Pr)_3$  as a reagent for *N*-sulfinyl aldimine formation.

Table 1. N-tert-Butanesulfinyl Imine Formation with B(Oi-Pr)3.



<sup>a</sup> Conversion of 4-bromobenzaldehyde to **2** as measured by HPLC analysis (220 nm).

reaction of 4-bromobenzaldehyde with tert-The butanesulfinamide 1 was performed under the optimal reaction conditions (Scheme 1). The reaction workup proved simple and convenient: after completion of the reaction as determined by HPLC analysis (consumption of 4-bromobenzaldehyde), the cooled reaction mixture was diluted with EtOAc and water, resulting in two clear phases. Importantly, B(Oi-Pr)<sub>3</sub> gave no solids or emulsions on addition of water, and thus no filtration was required. The reagent is hydrolyzed to *i*-PrOH and B(OH)<sub>3</sub>, with the former remaining in the organic phase and the latter going into the aqueous phase. After a simple extractive workup, drying and concentration of the organic phase, chromatographic purification provided the product 2 in 92% yield. Importantly, no epimerization of the sulfur stereocenter was observed, since 1 of >99.5% ee gave **2** of >99.5% ee.<sup>6</sup>

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Scheme 1. Optimized Reaction Conditions.

The scope of the reaction was subsequently explored with respect to aldehyde structure (Table 2). High yields were obtained for both electron poor (entries 1, 2 and 4) and electron rich (entries 3 and 6) aryl aldehydes. No transesterification of the methyl ester to an isopropyl ester was observed in the formation of N-sulfinyl imine 5 (entry 4). The reaction was tolerant of a substrate bearing one ortho substituent (entry 5) and even of a highly sterically demanding case with two ortho substituents (compound 7, entry 6). It is noteworthy that the previously reported synthesis of 7 employed Ti(OEt)<sub>4</sub> in THF at reflux, and gave the product in 80% yield.7 Pyridine-3-carboxaldehyde reacted smoothly to give imine 8 in 92% yield (entry 7). For this particular imine, Ellman and co-workers noted that the CuSO<sub>4</sub> procedure was ineffective, and Ti(OEt)<sub>4</sub> was required to effect its formation.<sup>2b-d</sup> The cinnamaldehyde derived  $\alpha,\beta$ -unsaturated imine 9 was formed in high yield (entry 8). Aliphatic aldehydes were also compatible with the triisopropyl borate mediated condensation. Aldehydes bearing two  $\alpha$ -hydrogens (entry 9) or one  $\alpha$ -hydrogen (entries 10 & 11), and the sterically hindered trimethylacetaldehyde (entry 12) all gave the corresponding Nsulfinyl imine products in good yields. Cha and Park reported that triisopropyl borate can induce the Meerwein-Ponndorf-Verley reduction of alkyl aldehydes, particularly secondary and tertiary aldehydes.8 We therefore used both the standard stoichiometry of 1 equiv of aldehyde as well as a separate experiment using a 3-fold excess of aldehyde relative to 1 for entries 10 and 12. For isobutyraldehyde (entry 10) and trimethylacetaldehyde (entry 12), slightly higher yields were obtained when the aldehyde was used in excess. These results suggest that the imine formation is faster than the aldehyde reduction. In the cases of hexanal (entry 9) and cyclopropanecarboxaldehyde (entry 11), good yields of Nsulfinyl imines were obtained with just one equivalent of aldehyde. This probably reflects the observation of Cha and Park that primary alkyl aldehydes were significantly less reactive towards reduction than secondary and tertiary aldehydes, and also the possibly faster condensation of 1 with the sterically less hindered aldehydes.

In addition to the *N-tert*-butanesulfinyl auxiliary developed by Ellman, the 4-tolylsulfinamide **14** introduced by Davis is another commonly used chiral auxiliary for imines.<sup>1a</sup> More recently, the bulky 2,4,6-triisopropylphenylsulfinamide **16** was developed and shown to give high diastereoselectivity for organometallic additions to the corresponding imines.<sup>1d,e</sup> We examined the utility of the triisopropyl borate mediated condensation process with these two auxiliaries (Scheme 2). Both types of sulfinamides





<sup>a</sup> Reaction conditions: 1 equiv aldehyde, 1.2 equiv 1, 3.0 equiv B(Oi-Pr)<sub>3</sub>, 60 °C, 18 h.

<sup>b</sup> Isolated yield after chromatographic purification.

<sup>c</sup> 1.0 equiv of **1**, 3.0 equiv of aldehyde.

reacted smoothly under the optimized conditions to give *N*-sulfinyl imines **15** and **17** in high yields.

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**Scheme 2.** Synthesis of 4-Tolyl and 2,4,6-Triisopropylphenyl *N*-Sulfinyl Imines.

Extending the reaction from aldehydes to ketones was also investigated (Scheme 3). The reaction of acetophenone with **1** under the standard conditions gave only a trace of ketimine **18**. Raising the temperature to 110 °C resulted in substantial conversion to the product after 24 h, but was accompanied by significant impurity formation. Ti(OEt)<sub>4</sub> and B(OCH<sub>2</sub>CF<sub>3</sub>)<sub>3</sub> thus remain the reagents of choice for *N*-sulfinyl ketimine formation.



Scheme 3. Attempted N-Sulfinyl Ketimine Formation.

In conclusion, triisopropyl borate was shown to be an efficient reagent for condensation of sulfinamides with aldehydes to make *N*-sulfinyl imines. The reaction proceeds under homogeneous conditions, and no filtration of insoluble reagents or byproducts is required in the workup. The reactions are easily worked up by simple extraction. The process was shown to be amenable to a broad spectrum of aldehydes, including sterically demanding and electron rich substrates. Importantly, triisopropyl borate is inexpensive, widely commercially available, and has favorable physical and safety properties.

#### **References and notes**

- a) Davis, F. A. J. Org. Chem. 2006, 71, 8993. b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Chem. Rev. 2010, 110, 3600. c) Morton, D.; Stockman, R. A. Tetrahedron 2006, 62, 8869. d) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. Tetrahedron Lett. 2003, 44, 4195. e) Senanayake, C. H.; Han, Z.; Krishnamurthy, D. In Organosulfur Chemistry in Asymmetric Synthesis; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008, pp 233-264.
- a) Liu, G.; Cogan, D. A.; Ellman, J. A. J. Am. Chem. Soc. 1997, 119, 9913. b) Cogan, D. A.; Ellman, J. A. J. Am. Chem. Soc. 1999, 121, 268. c) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. J. Org. Chem. 1999, 64, 1278. d) Mukade, T.; Dragoli, D. R.; Ellman, J. A. J. Comb. Chem. 2003, 5, 590.
- Reeves, J. T.; Visco, M. D.; Marsini, M. A.; Grinberg, N.; Busacca, C. A.; Mattson, A. E.; Senanayake, C. H. Org. Lett. 2015, 17, 2442.
- The Sigma-Aldrich Library of Chemical Safety Data, 2nd ed.; Lenga, R. E., Ed.; Sigma-Aldrich: Milwaukee, 1988; Vol. 2, p 3470b.

 As of March 13, 2016, B(OCH<sub>2</sub>CF<sub>3</sub>)<sub>3</sub> was available from Aldrich for \$158.50 for 10 g, whereas B(O*i*-Pr)<sub>3</sub> was available from Aldrich for \$219.00 for 750 g.

3

6. Datta, G. K.; Ellman, J. A. J. Org. Chem. 2010, 75, 6283.

- Byrne, L.; Sola, J.; Boddaert, T.; Marcelli, T.; Adams, R. W.; Morris, G. A.; Clayden, J. Angew. Chem. Int. Ed. 2014, 53, 151.
- 8. Cha, J. S.; Park, J. H. Bull. Korean Chem. Soc. 2002, 23, 1051.

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4