Organic LETTERS

Letter

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A General Method for Imine Formation Using $B(OCH_2CF_3)_3$

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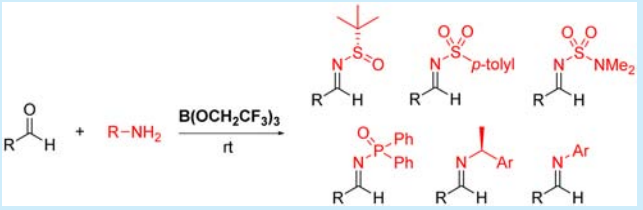
Supporting Information

ABSTRACT: Tris(2,2,2-trifluoroethyl)borate [$B(OCH_2CF_3)_3$] was found to be a mild and general reagent for the formation of a variety of imines by condensation of amides or amines with carbonyl compounds. *N*-Sulfinyl, *N*-toluenesulfonyl, *N*-(dimethylamino)sulfamoyl, *N*-diphenylphosphinoyl, *N*-(α-methylbenzyl), and *N*-(4-methoxyphenyl) aldimines are all accessible using this reagent at room temperature. The reactions are operationally simple, and the products are obtained without special workup or isolation procedures.



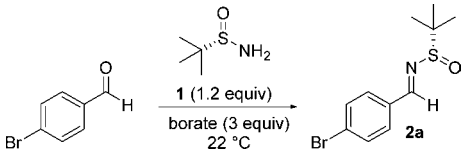
The imine or azomethine functional group is exceptionally useful in organic synthesis.[1] Chiral *N*-sulfinyl imines in particular have emerged in the past two decades as practical and selective auxiliaries.[2] *N*-*tert*-Butanesulfinyl imines, developed by Ellman and co-workers, are the most versatile and well-explored class of *N*-sulfinyl imines.[2b,c] 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.[3] The initial conditions developed for the condensation employed either $MgSO_4$ or $CuSO_4$.[3a−c] Ellman and co-workers later reported the use of $Ti(OEt)_4$ for the condensation of ketones with **1** and showed this reagent was also effective for the condensation of all types of aldehydes.[3b−d] Importantly, $Ti(OEt)_4$ enabled conversion of aldehydes not amenable to the $MgSO_4$ or $CuSO_4$ conditions. The $Ti(OEt)_4$ procedure has the drawback of requiring the removal of insoluble TiO_2 waste during the workup, however. The filtration of TiO_2 is often extremely slow and can become prohibitive on large scale.[4,5] Numerous other reagents have been developed for condensation of **1** with aldehydes, such as Cs_2CO_3,[6] NaOH or KO*t*-Bu,[7] $Yb(OTf)_3$,[8] and $KHSO_4$.[9] Recently, Ruano and Cid reported a general protocol for imine formation using catalytic pyrrolidine and 4 Å MS in CH_2Cl_2 at 60 °C.[10] As part of our continuing work on nucleophilic additions to *N*-sulfinyl imines, we required a scalable procedure for preparation of a variety of *N*-sulfinyl imines. We employed Ellman's $Ti(OEt)_4$ procedure for a wide variety of *N*-sulfinyl aldimines and ketimines with excellent results, but the postreaction filtration and disposal of large amounts of TiO_2 waste often proved tedious, especially for large scale reactions. The use of $Ti(OEt)_4$ also necessitated extensive reactor cleaning protocols to ensure complete removal of Ti residue. The heterogeneous nature of many of the alternative reagents was not desirable, as these systems could lead to etching of reactor walls. We thus searched for an alternative reagent system which would ideally (1) require no filtration of insoluble materials postreaction; (2) be homogeneous; (3) be amenable to aldehydes of diverse electronic and steric properties; and (4) use benign and commercially available materials. Herein we report that tris(2,2,2-trifluoroethyl)borate is an effective reagent for promoting the condensation of **1** with aldehydes and even ketones, and also for the preparation of several other valuable types of aldimines.

In previous work on making *N*-acetyl enamides, we found that trialkyl borates were effective reagents to promote the condensation of ammonia with ketones, being surpassed in performance only by titanium alkoxides.[5] Borates have the advantage of giving aqueous soluble boric acid as a byproduct upon hydrolysis and, consequently, help avoid the workup issues encountered with titanium alkoxides. A screen of various trialkyl borates as promotors for *N*-sulfinyl imine formation was therefore initiated. 4-Bromobenzaldehyde was reacted with (*S*)-*tert*-butanesulfinamide **1** (1.2 equiv) and trialkyl borate (3 equiv) (Table 1). In most cases the trialkyl borate was employed as both the condensation reagent and the solvent. The reactions employing trialkyl borates (entries 1−5) at ambient temperature (22 °C) proceeded slowly but cleanly to give 48−94% conversion to **2a** after 72 h. Among these reagents, triisopropyl borate (entry 3) gave the highest conversion of 94%. The use of triphenyl borate (entry 6) resulted in a significant increase in rate, giving full conversion to **2a** after 8 h. An even more dramatic acceleration occurred when tris(2,2,2-trifluoroethyl)borate [$B(OCH_2CF_3)_3$] was used (entry 7), as full conversion was achieved in only 1 h. When the amount of $B(OCH_2CF_3)_3$ was reduced to 1 equiv and THF was used as solvent (entry 8), full conversion was reached after 4 h. The use of a substoichiometric amount of $B(OCH_2CF_3)_3$ (0.5 equiv) was possible, but resulted in an increased reaction time (entry 9). Sheppard and co-workers have pioneered the use of $B(OCH_2CF_3)_3$ as a highly effective reagent for amide bond

Received: April 1, 2015
Published: April 23, 2015

DOI: 10.1021/acs.orglett.5b00949
Org. Lett. 2015, 17, 2442−2445

Table 1. Reagent Screening Results



entry	borate	time (h)	conversion (%)[a]
1	$B(OMe)_3$	72	71
2	$B(OEt)_3$	72	85
3	$B(O\textit{i}\text{-}Pr)_3$	72	94
4	$B(O\textit{t}\text{-}Bu)_3$	72	48
5	*i*-PrOB(pin)	72	67
6	$B(OPh)_3$[b]	8	100
7	$B(OCH_2CF_3)_3$	1	100
8	$B(OCH_2CF_3)_3$ (1 equiv)[c]	4	100
9	$B(OCH_2CF_3)_3$ (0.5 equiv)[c]	16	97
10	$Si(OEt)_4$	72	28
11	$Si(OCH_2CF_3)_4$	72	91

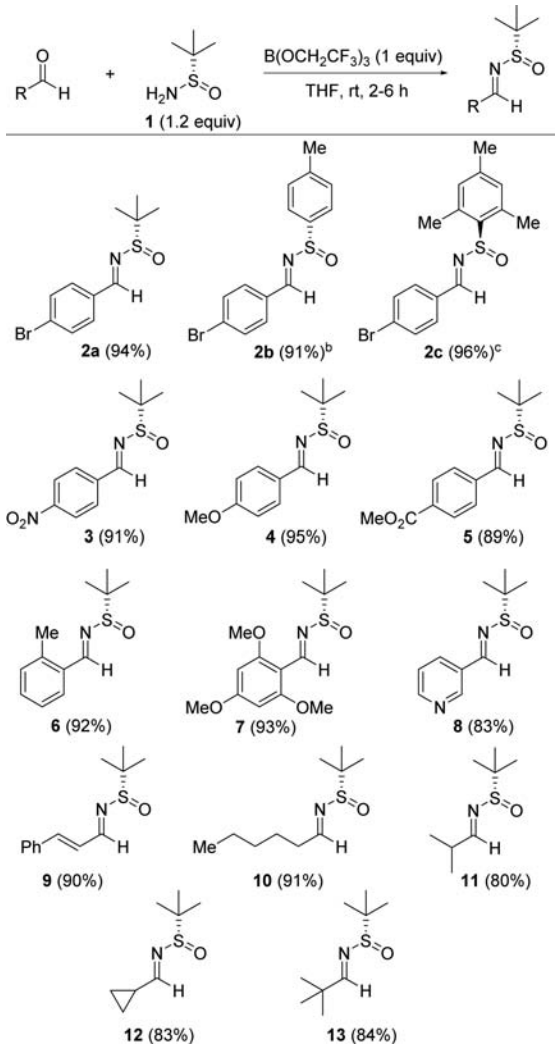
[a]Conversion of 4-bromobenzaldehyde to **2a** as measured by HPLC analysis. [b]CH_2Cl_2 was employed as solvent since $B(OPh)_3$ is a solid. [c]THF was used as solvent.

formation.[11] While the use of tetraethyl orthosilicate (entry 10) gave a low conversion of 28% after 72 h, the trifluoroethyl variant $Si(OCH_2CF_3)_4$ gave a 91% conversion after the same reaction time (entry 11).[12]

The scope of *N*-sulfinyl aldimine formation using $B(OCH_2CF_3)_3$ was next explored (Scheme 1). In addition to **1**, the condensation was also effective for 4-*p*-tolylsulfinamide and 2,4,6-triisopropylphenylsulfinamide, providing the corresponding imines **2b** and **2c** in high yields. The reaction was amenable to both electron-poor (products **2a**−**c**, **3**, and **5**) and electron-rich aromatic aldehydes (products **4** and **7**). Aldehydes bearing one (product **6**) or two (product **7**) ortho substituents were converted smoothly to *N*-sulfinyl imines. It is noteworthy that the previously reported synthesis of the 2,4,6-trimethoxyphenyl sulfinimine **7** required the use of $Ti(OEt)_4$ in THF at reflux.[13] Heterocyclic (product **8**) and α,β-unsaturated (product **9**) substrates could be employed. Finally, the $B(OCH_2CF_3)_3$ mediated condensation was also effective for alkyl aldehydes, as aldehydes with two, one, or zero α-protons reacted to give *N*-sulfinyl imines **10**−**13** in good yields. Notably the hindered trimethylacetaldehyde derived imine **13**, which previously was accessible only through the use of $Ti(OEt)_4$, was formed without difficulty. The reactions were conveniently worked up by addition of saturated aqueous $NaHCO_3$ solution and EtOAc. This resulted in two clear phases; no insoluble materials required filtration. Importantly, no epimerization of the sulfur stereocenter was observed, since **1** of >99.5% ee gave **2a** of >99.5% ee.[14]

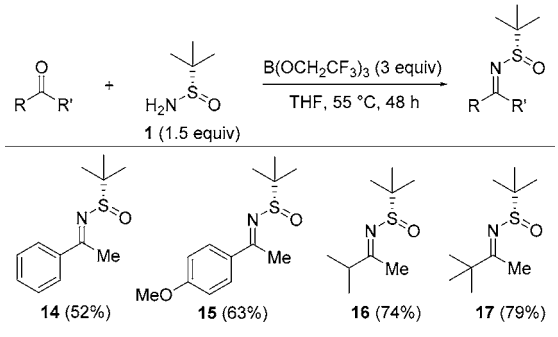
Given the facility of the reaction with a broad spectrum of aldehydes, we explored the extension to ketones. After some optimization, it was found that the condensation with ketones could be effected using 1.5 equiv of sulfinamide **1** and 3 equiv of $B(OCH_2CF_3)_3$ in THF at 55 °C for 48 h (Scheme 2). Under these conditions, acetophenone and 4-methoxyacetophenone gave ketimines **14** and **15** in modest yields. Aldol-derived byproducts were observed by LC-MS analysis of these reaction mixtures and constituted the main detractors to product yield. The use of dialkyl ketones proceeded more cleanly, as isopropyl methyl ketone and pinacolone reacted to give ketimines **16** and **17** in 71% and 79% yields, respectively. The more electron-rich dialkyl ketones may be less prone to enolization and aldol side reactions than the aryl alkyl ketones. It is noteworthy that *N*-sulfinyl ketimines have previously required $Ti(OEt)_4$ for their preparation.[3b−d]

Scheme 1. Scope of *N*-Sulfinyl Aldimine Formation[a]



[a]Reaction conditions: 2.0 mmol of aldehyde, 2.4 mmol of **1**, 2.0 mmol of $B(OCH_2CF_3)_3$, 2 mL of THF, rt, 2−6 h. Isolated yields. [b](*S*)-4-Methylphenylsulfinamide used instead of **1**. [c](*R*)-2,4,6-Triisopropylphenylsulfinamide used instead of **1**.

Scheme 2. Scope of *N*-Sulfinyl Ketimine Formation[a]

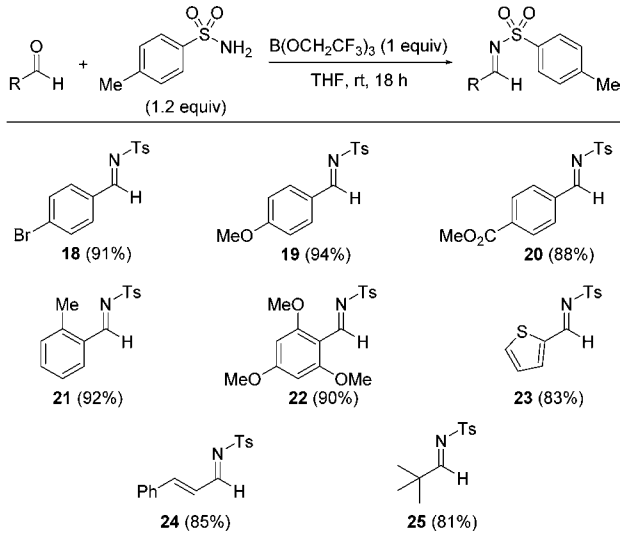


[a]Isolated yields.

DOI: 10.1021/acs.orglett.5b00949
Org. Lett. 2015, 17, 2442−2445

We next extended the reaction to the preparation of *N*-toluenesulfonyl aldimines (Scheme 3). This type of imine has found utility in several catalytic asymmetric additions[15] and has been prepared either by the acid catalyzed condensation of aldehydes and *p*-toluenesulfonamide in refluxing toluene with azeotropic removal of water[16] or by the action of $TiCl_4/Et_3N$.[17] The pyrrolidine catalyzed method of Ruano and Cid is also effective for the preparation of *N*-toluenesulfonyl aldimines.[10] The reaction conditions developed for *N*-sulfinyl aldimine formation using $B(OCH_2CF_3)_3$ were directly applicable to *N*-toluenesulfonyl aldimine formation, with the exception of the reaction time, which was increased to 18 h. A variety of aryl aldehydes underwent the condensation, including electron-poor and -rich substrates, giving products **18**–**23** in high isolated yields. As observed for the reaction with *tert*-butanesulfinamide **1** to give **7**, condensation of the sterically hindered and electron-rich 2,4,6-trimethoxybenzaldehyde with *p*-toluenesulfonamide proceeded smoothly to give imine **22** in 90% yield. The reaction of cinnamaldehyde gave *α,β*-unsaturated imine **24** in 85% yield. The sterically hindered trimethylacetaldehyde derived alkyl imine **25** was accessible in good yield as well (81%).

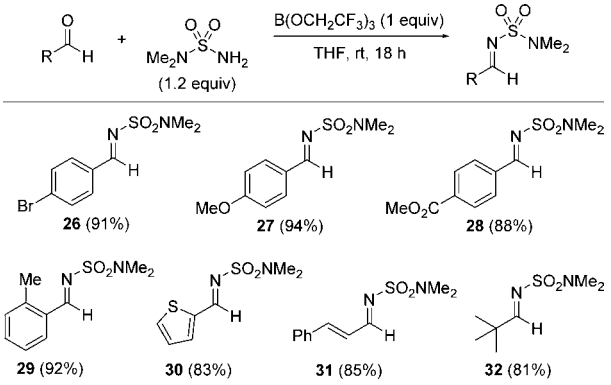
Scheme 3. Scope of *N*-Toluenesulfonyl Aldimine Formation[a]



[a]Isolated yields.

N-Dimethylsulfamoyl aldimines were first prepared by van Leusen and co-workers in 1997.[18] Their synthesis was accomplished by refluxing a mixture of aldehyde and *N*-(dimethylsulfamoyl)amide in toluene with azeotropic removal of water. After nucleophilic addition to the imine, the *N*-dimethylsulfamoyl group may be cleaved under either acidic[19] or basic[20] reaction conditions. Application of the B-$(OCH_2CF_3)_3$ mediated imine formation conditions to the condensation with *N*-(dimethylsulfamoyl)amide was effective and provided a mild avenue to the corresponding imines (Scheme 4). As with the *N*-toluenesulfonyl imines, a reaction time of 18 h was employed to ensure complete conversion. Both electron-rich and -poor aryl aldehydes provided the corresponding imines **26**–**29** in high yields. The heterocyclic substrate 2-thienyl carbaldehyde furnished *N*-dimethylsulfamoyl imine **30** in good yield. Cinnamaldehyde and trimethylacetaldehyde also reacted smoothly to give imines **31** and **32**.

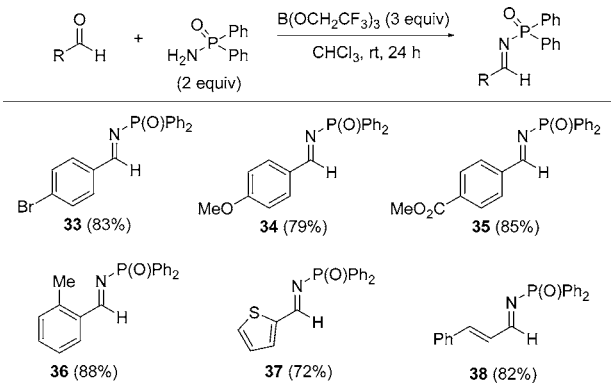
Scheme 4. Scope of *N*-Dimethylsulfamoyl Aldimine Formation[a]



[a]Isolated yields.

The $B(OCH_2CF_3)_3$ mediated imine formation was also applicable to *N*-(diphenylphosphinoyl)imines (Scheme 5). As with *N*-toluenesulfonyl imines, this class of imines has found significant utility for a variety of catalytic asymmetric addition reactions.[21] The diphenylphosphinoyl group often confers high crystallinity to products and can be cleaved under mildly acidic conditions.[22] The traditional methods for making *N*-(diphenylphosphinoyl)imines require either $TiCl_4/Et_3N$ mediated condensation of diphenylphosphinamide with aldehydes,[17] the reaction of oximes with Ph_2PCl,[23] or the Kresze reaction of aldehydes with diphenyl-*N*-sulfinylphosphoramidate.[24] Alternatively, the sulfinate adduct of the phosphinoyl imine may be prepared and the imine released *in situ* with a base.[22] Ruono and Cid's recently reported pyrrolidine catalyzed imine formation was demonstrated for *N*-(diphenylphosphinoyl)-imine formation for three aryl aldehydes.[10] To achieve the condensation using $B(OCH_2CF_3)_3$, it was necessary to increase the stoichiometry of diphenylphosphinamide and B-$(OCH_2CF_3)_3$ to 2 and 3 equiv, respectively. It was also found that the use of $CHCl_3$ as solvent was critical, as it was the only solvent which solubilized $Ph_2P(O)NH_2$. Under these conditions, the condensation occurred at rt within 24 h for electronically diverse aryl aldehydes (**33**–**36**) as well as for a heterocyclic (**37**) and an *α,β*-unsaturated (**38**) substrate.

Scheme 5. Scope of *N*-Diphenylphosphinoyl Aldimine Formation[a]



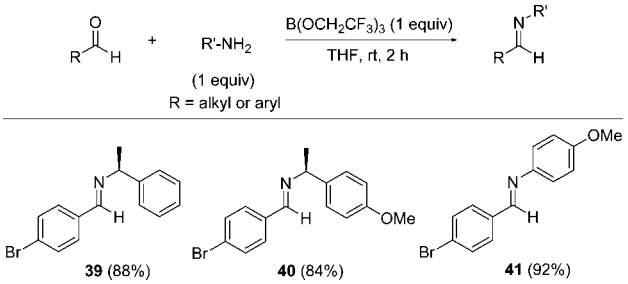
[a]Isolated yields.

Finally, we briefly examined the utility of the $B(OCH_2CF_3)_3$ procedure for the formation of *N*-alkyl and *N*-aryl imines.

DOI: 10.1021/acs.orglett.5b00949
Org. Lett. 2015, 17, 2442–2445

Among various *N*-alkyl imines, *N*-(α-methylbenzyl)imines have been well explored as chiral electrophiles for an assortment of reactions.[25] The preparation of these *N*-alkyl imines occurred under the standard conditions developed for *N*-sulfinyl imine formation, except that a 1:1 stoichiometry of aldehyde and amine was used (Scheme 6).

Scheme 6. Scope of *N*-Alkyl or *N*-Aryl Aldimine Formation[a]



[a]Isolated yields.

The products **39** and **40** were isolated in excellent yields. The condensation was also amenable to *N*-aryl imines, as the reaction of *p*-anisidine with 4-bromobenzaldehyde furnished imine **41** in 92% yield.

In summary, $B(OCH_2CF_3)_3$ was shown to be an effective and general reagent for the formation of a variety of synthetically useful imines via condensation of amides or amines with aldehydes. The reactions proceed at room temperature. Upon aqueous workup, the reagent $B(OCH_2CF_3)_3$ is hydrolyzed to give aqueous-soluble boric acid, and no filtration of insoluble reagents or byproducts is required. The formation of *N*-sulfinyl ketimines was also possible at elevated temperature and represents the first alternative to $Ti(OEt)_4$ for preparation of this type of ketimine. Notably, $B(OCH_2CF_3)_3$ is commercially available and may also be prepared on large scale in one step from boric anhydride and trifluoroethanol as described by Sheppard and co-workers.[11b]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^1H and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.orglett.5b00949
Org. Lett. 2015, 17, 2442−2445