

## Benzotrifluoride: A Useful Alternative Solvent for Organic Reactions Currently Conducted in Dichloromethane and Related Solvents

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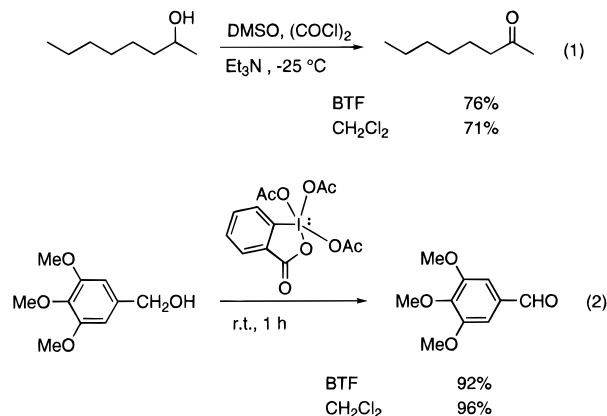
Dichloromethane is one of the most popular solvents in organic synthesis<sup>1</sup> because of its good dissolving power for organic molecules, its favorable physical properties, and its inertness toward many types of reagents and reaction conditions.<sup>2</sup> Its weak Lewis basicity makes it especially attractive for organometallic and Lewis acid reactions,<sup>3</sup> and it is also commonly used in oxidations<sup>4</sup> and functional group interconversions.<sup>5</sup> However, the toxicity of dichloromethane coupled with its low boiling point (40 °C) can pose problems.<sup>6</sup> Thus, the development of other solvents that can substitute for dichloromethane is a useful goal. In this paper, we report that benzotrifluoride<sup>7</sup> (C<sub>6</sub>H<sub>5</sub>CF<sub>3</sub>, BTF, **1**) is a potentially valuable alternative solvent to CH<sub>2</sub>Cl<sub>2</sub>.

BTF is a clear, free-flowing liquid with a boiling point of 102 °C, a melting point of –29 °C, and a density of 1.2 g/mL (25 °C). It is a robust compound with a relatively low toxicity and price.<sup>8</sup> Judging from empirical measures of solvent polarity,<sup>2b,c</sup> BTF is slightly more polar than fluorobenzene, THF, and ethyl acetate, very similar to pentafluorobenzene, and slightly less polar than chloroform, pyridine, and dichloromethane.<sup>7b</sup> Despite these favorable properties, BTF is not used as a solvent in organic synthesis. Our recent success in using BTF as a hybrid organic/fluorous solvent<sup>9</sup> showed that it is capable of dissolving a wide variety of organic compounds. This suggested that the potential of BTF as a solvent for standard organic synthesis was unappreciated. To evaluate this potential, we selected a series of representative transformations from the literature and conducted pairs of reactions differing only in the substitution of benzotrifluoride for dichloromethane. The

results suggest that benzotrifluoride shows good potential as a solvent for many types of organic reactions.<sup>8c</sup>

We first examined some common derivatization reactions of alcohols. Standard acylation,<sup>10,11</sup> tosylation,<sup>12</sup> and silylation<sup>13</sup> reactions all occur in BTF in comparable yields and reaction times to their counterparts in CH<sub>2</sub>Cl<sub>2</sub>. The results of these experiments are described in the Supporting Information.

We next checked some representative procedures for the oxidation of alcohols. The Swern oxidation is a well-known method for the conversion of alcohols to aldehydes or ketones, and it is typically performed below –60 °C in order to avoid the decomposition of unstable intermediates.<sup>14</sup> However, Swern and co-workers reported that the use of excess amounts of reagents enables the oxidation at higher temperatures. Thus, we examined the Swern oxidation of a secondary alcohol in BTF at –27 °C. Vigorous gas evolution (presumably CO and CO<sub>2</sub>) occurred when dimethyl sulfoxide (DMSO) was added to the BTF solution of oxalyl chloride (1.3 equiv to the alcohol) at –27 °C. Immediately, 2-octanol was added to the mixture at –27 °C. Subsequent addition of Et<sub>3</sub>N and workup provided a 76% yield of 2-octanone (eq 1). The oxidation of 2-octanol in CH<sub>2</sub>Cl<sub>2</sub> under similar conditions gave rise to 2-octanone in 71% yield.



The Dess–Martin oxidation is another mild and convenient method for the oxidation of alcohols to aldehydes.<sup>15</sup> The oxidation of a benzylic alcohol with Dess–Martin reagent (1.1 equiv) was performed by using BTF and CH<sub>2</sub>Cl<sub>2</sub> at room temperature. As shown in eq 2, this oxidation proceeded smoothly in both solvents to yield the corresponding aromatic aldehyde in 92% and 96% yield, respectively.

Hydrogen peroxide/dichloromethane (H<sub>2</sub>O<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>) is one of the most used oxidation systems, and it is therefore important to learn whether hydrogen peroxide can be used in BTF. For this purpose, we selected the selenoxide elimination reaction from an  $\alpha$ -seleno ketone. Upon treatment of  $\alpha$ -(phenylseleno)butyrophenone with 30% H<sub>2</sub>O<sub>2</sub> in BTF in the presence of pyridine, the corresponding  $\alpha,\beta$ -unsaturated ketone was produced in almost quantitative yield (eq 3).<sup>16</sup>

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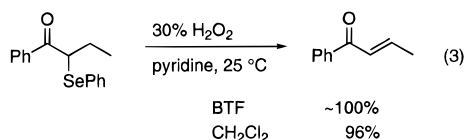
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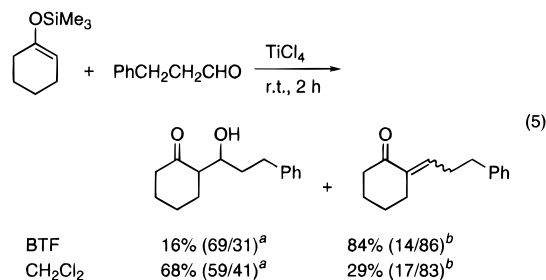
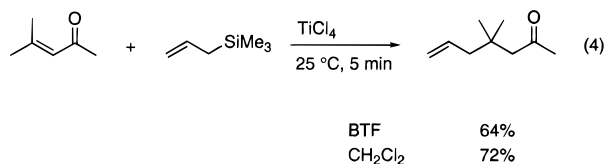
(7) (a) The IUPAC name of benzotrifluoride is (trifluoromethyl)benzene, and it is also called  $\alpha,\alpha,\alpha$ -trifluorotoluene. We use the name benzotrifluoride because it is prevalent in the organofluorine literature. (b) The dipole moment and dielectric constant of BTF are 2.86 D and 9.18 (at 30 °C), respectively. (c) Commercial BTF was purified by refluxing over phosphorus pentoxide for a few hours followed by distillation.

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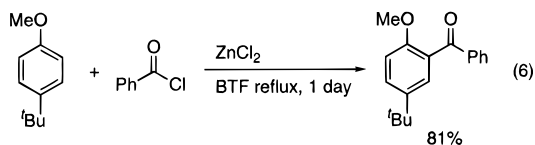
To extend the utility of BTF to carbon–carbon bond-forming reactions, we investigated some important Lewis acid-assisted reactions including the Sakurai and Mukaiyama reactions. The reaction of mesityl oxide with a slight excess allyltrimethylsilane (1.2 equiv) in BTF was performed in the presence of  $\text{TiCl}_4$  (1 equiv). This mixture was heterogeneous (a white precipitate was formed when  $\text{TiCl}_4$  was added to a solution of mesityl oxide in BTF), but the desired reaction took place at room temperature, affording 4,4-dimethyl-6-hepten-2-one in 64% yield (eq 4).<sup>17</sup> In contrast, the parallel reaction in  $\text{CH}_2\text{Cl}_2$  was homogeneous, and the yield of the allylation product was a little bit higher (72%).



<sup>a</sup> The ratio of erythro / threo. <sup>b</sup> The ratio of trans / cis.

In the standard Mukaiyama reaction between silyl enol ethers and aldehydes,  $\beta$ -hydroxy ketones are formed as major products with the formation of  $\alpha,\beta$ -unsaturated ketones as byproducts. The  $\text{TiCl}_4$ -induced reaction of a silyl enol ether of cyclohexanone with 2-phenylpropionaldehyde in  $\text{CH}_2\text{Cl}_2$  afforded the aldol product (68%) and the  $\alpha,\beta$ -unsaturated ketone (29%) (eq 5).<sup>18</sup> In contrast, a similar reaction in BTF gave rise to  $\alpha,\beta$ -unsaturated ketone as the major product (84%). Stereoselectivities (syn/anti, *E/Z*) in both products were roughly comparable.

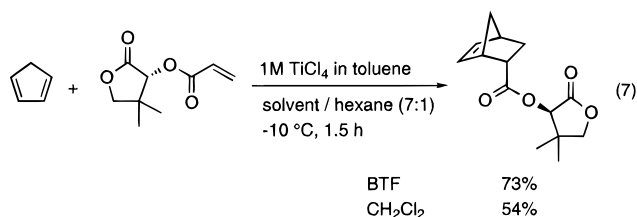
Aluminum chloride ( $\text{AlCl}_3$ ) is typically used for Friedel–Crafts reactions; however, it is known that BTF reacts with  $\text{AlCl}_3$  at ambient temperature.<sup>19</sup> With this limitation in mind, we examined the zinc chloride-catalyzed Friedel–Crafts reaction between 4-*tert*-butylanisole and benzoyl chloride (eq 6).<sup>20</sup> In the literature, the  $\text{ZnCl}_2$ -



catalyzed benzoylation of 4-*tert*-butylanisole was performed at 138 °C for 2 days by employing *sym*-tetrachlo-

roethane as the solvent. This gave 2-benzoyl-4-*tert*-butylanisole in 66% yield. In contrast, an equimolar reaction of 4-*tert*-butylanisole and benzoyl chloride in a refluxing BTF (102 °C) was complete after 1 day, and 2-benzoyl-4-*tert*-butylanisole was isolated in 81% yield.

A Lewis acid-induced Diels–Alder reaction was also conducted, as shown in eq 7. According to the litera-



ture,<sup>21</sup> a mixed solvent consisting of  $\text{CH}_2\text{Cl}_2$  and hexane (7:1) was used for this reaction. When the reaction of the pantolactone acrylate with cyclopentadiene (1.1 equiv) in the presence of  $\text{TiCl}_4$  (10 mol %) was carried out at  $-10$  °C using a BTF/hexane mixture, the desired Diels–Alder adduct was produced as a single isomer in 73% yield. A similar reaction in  $\text{CH}_2\text{Cl}_2$ /hexane also proceeded stereoselectively, but the yield of the adduct was lower in comparison with BTF.

The results suggest that benzotrifluoride has the potential to become a generally useful solvent. It can be considered as a replacement not only for dichloromethane, but also for other chloro- and chlorofluorocarbon solvents and for hydrocarbon solvents like benzene, toluene, hexane, etc. However, at least three limitations are already evident with benzotrifluoride. First, the freezing point ( $-29$  °C) is too high for certain applications (this problem can presumably be solved by using cosolvents to depress the freezing temperature). Second, benzotrifluoride will certainly be sensitive to some kinds of reducing conditions. While things like hydride reductions and hydrometalations may succeed, reactions occurring by electron transfer (for example, dissolving metal reductions) will probably fail because benzotrifluoride will be reduced. In this respect, benzotrifluoride resembles dichloromethane, not benzene and toluene. Third, in addition to its reaction with  $\text{AlCl}_3$ ,<sup>19</sup> benzotrifluoride is hydrolyzed by aqueous acid at high temperatures.<sup>8</sup>

It is clearly inappropriate to draw sweeping conclusions about the scope and limitations of benzotrifluoride as a solvent on the basis of the results of a dozen or so pairs of reactions. However, it already appears that BTF may be an interesting solvent for small-scale applications, and the results suggest that further investigation of the short and long term toxicity profile, the cost and environmental impact of disposal, and the potential for recycling of BTF are worthwhile with an eye toward larger scale applications.

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**Supporting Information Available:** Contains details of the acylation, tosylation, and silylation reactions of alcohols (2 pages).

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