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Acceleration of Enantioselective Cycloadditions Catalyzed by Second-Generation Chiral Oxazaborolidinium Triflimidates by Biscoordinating Lewis Acids

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Supporting Information

ABSTRACT: The activation of second-generation fluorinated oxazaborolidines by the strong acid triflimide (Tf_2NH) in CH_2Cl_2 solution leads to highly active chiral Lewis acids that are very effective catalysts for (4 + 2) cycloaddition. We report herein that this catalytic activity can be further enhanced by the use of Tf_2NH in combination with the biscoordinating Lewis acid $TiCl_4$ or $SnCl_4$ as a coactivator. The effective increase in acidity of an exceedingly strong protic acid is greater for biscoordinating $TiCl_4$ and $SnCl_4$ than for monocoordinating salts, even the strong Lewis acids $AlBr_3$ and BBr_3 in CH_2Cl_2 or CH_2Cl_2/toluene. The increase in the effective acidity of Tf_2NH can be understood in terms of a stabilized cyclic anionic complex of Tf_2N^- and $TiCl_4$, which implies a broader utility than that described here. The utility of Tf_2NH–$TiCl_4$ activation of fluorinated oxazaborolidines is documented by examples including the first enantioselective (4 + 2) cycloaddition to α,β-unsaturated acid chlorides.

The introduction of chiral oxazaborolidinium ions has greatly broadened the scope and utility of catalytic enantioselective (4 + 2) cycloaddition reactions,[1] especially with the advent of second-generation fluorine-enhanced oxazaborolidines such as **1**–**4** (Figure 1).[2]

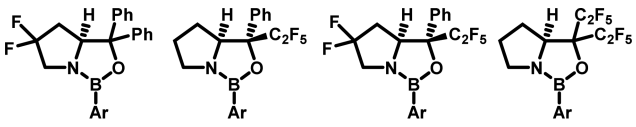

Figure 1. Second-generation oxazaborolidines **1**–**4**.

Very powerful cationic catalysts are available from **1**–**4** by activation using 1 equiv of the strong protic acid triflimide (Tf_2NH) but not from weaker acids such as CH_3SO_3H. Aluminum tribromide is also an effective activator of **1**–**4**, but other (weaker) Lewis acids are not. The fluorine substituents in the precatalysts **1**–**4** strongly decrease the electron density of the donor nitrogen and enhance the electrophilic power of the activated catalysts. Triflic acid activation is not quite as effective as triflimide activation, whereas $AlBr_3$ coordination to **1**–**3** leads to distinctly higher catalytic power than protonation by Tf_2NH.[2] These facts led us to entertain the idea that the reactive species in the case of aluminum bromide activation is a cationic complex with the dienophile in which the coordinating group on nitrogen is actually the equivalent of the unknown monocoordinated cation $AlBr_2^+$, e.g., structure **5** (Figure 2) in the case of an acrylate ester as the dienophile.

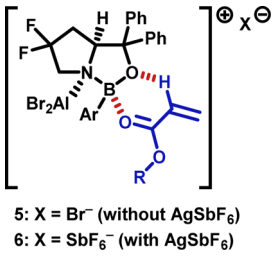

Figure 2. Possible reactive complexes between $AlBr_3$-activated catalyst **1** and an α,β-unsaturated dienophile.

Strong evidence in favor of this possibility was obtained from experiments demonstrating that the rate of the $AlBr_3$–oxazaborolidine-catalyzed (4 + 2) cycloaddition could be considerably enhanced by the further addition of 1 equiv of $AgSbF_6$ per $AlBr_3$, which led to precipitation of AgBr and generation of the $AlBr_2^+$-coordinated oxazaborolidine, which in turn can complex with, e.g., an acrylate ester to generate the super-reactive species **6**.[2]

Although a reaction pathway via cationic species such as **6** can explain the effectiveness of $AlBr_3$ activation, it remained unclear why protic acid activation (which also could generate a cation) was less effective than the $AlBr_3$ or $AlBr_3/AgSbF_6$ process. This concern led us to surmise that the proton-activated oxazaborolidine catalyst might be either a hydrogen-bonded complex of triflimide and **1**, **2**, **3**, or **4** or a contact ion pair. That possibility seemed reasonable because the reaction medium for catalytic cycloadditions is generally nonpolar—specifically CH_2Cl_2 or CH_2Cl_2/toluene mixtures. It was thought that a biscoordinating Lewis acid such as $TiCl_4$ or $SnCl_4$ might be especially effective in separating triflimidate ion from a protonated oxazaborolidine because of coordination to form complex **7** (Figure 3), in which the negative charge is far more delocalized than in the triflimidate ion.

We were gratified to find by experiment that triflimide activation of various oxazaborolidines could in fact be markedly

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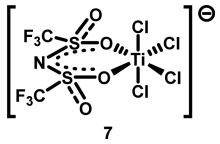
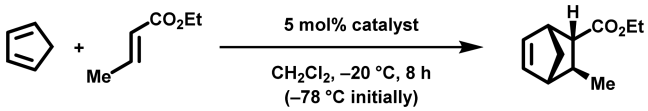


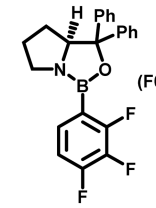
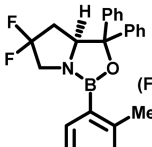
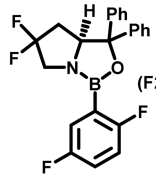
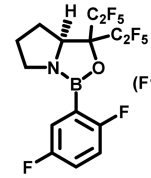
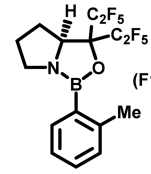
7

Figure 3. Possible $Tf_2N/TiCl_4$-ate complex 7.

enhanced simply by the use of $TiCl_4$ as a coactivator (Tf_2NH:$TiCl_4$ ratio of 1:1, 0.7 equiv based on oxazaborolidine). The experimental results for the (4 + 2) cycloaddition of cyclopentadiene to the relatively unreactive dienophile ethyl crotonate using five different oxazaborolidines are summarized in Table 1. All of the experiments were conducted under exactly the same reaction conditions, so the percent conversion to product is an unambiguous indicator of the potency of the catalytic mixture. It is clear from Table 1 that $TiCl_4$ is a very useful coactivator. There is only a modest further acceleration of these cycloadditions when the $TiCl_4$:Tf_2NH ratio is increased from 1:1 to 2:1.

Table 1. Acceleration of (4 + 2) Cycloaddition Using Various Oxazaborolidines with Tf_2NH and $TiCl_4$ or $SnCl_4$ as Coactivators

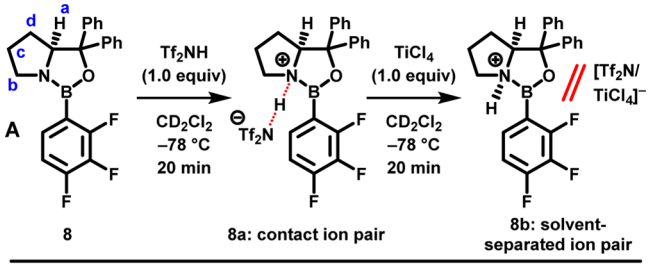


precatalyst	activator (0.7 equiv)	% yield (*endo*/*exo*)	% *ee*
 8 (F0/F3)	Tf_2NH	5% (97:3)	99
	$Tf_2NH/TiCl_4$ (1:1)	36% (97:3)	99
	$Tf_2NH/SnCl_4$ (1:1)	28% (97:3)	98
 9 (F2/F0)	Tf_2NH	24% (98:3)	99
	$Tf_2NH/TiCl_4$ (1:1)	70% (98:2)	99
 10 (F2/F2)	Tf_2NH	42% (98:2)	99
	$Tf_2NH/TiCl_4$ (1:1)	95% (98:2)	99
 11 (F10/F2)	Tf_2NH	30% (98:2)	90
	$Tf_2NH/TiCl_4$ (1:1)	85% (98:2)	90
 12 (F10/F0)	Tf_2NH	30% (98:2)	99
	$Tf_2NH/TiCl_4$ (1:1)	100% (98:2)	99
	$Tf_2NH/SnCl_4$ (1:1)	100% (98:2)	95

In this reaction, $TiCl_4$ alone is not an effective activator of oxazaborolidines such as **8**–**12**. The combination of Tf_2NH and $TiCl_4$ is especially beneficial with the **F10**/**F0** catalyst **12**. The weaker Lewis acid $SnCl_4$ can also accelerate the reaction, although it is not as effective as $TiCl_4$. On the other hand, it is notworthy that the monocoordinating Lewis acids $AlBr_3$ and $SbCl_5$ are considerably less effective coactivators, although they are very strong Lewis acids.[3]

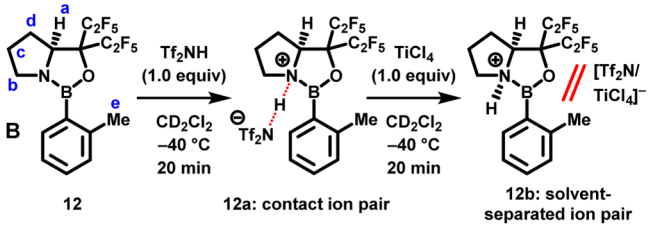
The interaction between oxazaborolidinium triflimidates and $TiCl_4$ could also be detected by ^1H NMR spectroscopy. Shown in Table 2 are ^1H NMR chemical shift data for **F0**/**F3**

Table 2. ^1H NMR Data for Oxazaborolidines (A) 8 and (B) 12 without or with Tf_2NH or $Tf_2NH/TiCl_4$



8 8a: contact ion pair 8b: solvent-separated ion pair

Proton	8 (ppm)	8a (ppm)	8b (ppm)
a	4.68	5.26	5.50
b	3.47, 3.33	3.75, 3.11	4.23, 3.49
c	1.92, 1.86	1.97 (2H)	2.20 (2H)
d	1.78, 0.99	1.70, 1.40	1.87, 1.72



12 12a: contact ion pair 12b: solvent-separated ion pair

Proton	12 (ppm)	12a (ppm)	12b (ppm)
a	4.42	4.93	5.10
b	3.41, 3.27	4.04, 3.46	4.25, 3.53
c	2.15–2.08 (2H)	2.42–2.28 (4H)	2.52–2.39 (4H)
d	2.07–2.01 (2H)		
e	2.46	2.52	2.58

oxazaborolidine **8** and **F10**/**F0** oxazaborolidine **12** alone or in the presence of 1 equiv of Tf_2NH or 1 equiv each of Tf_2NH and $TiCl_4$. As expected, the protons attached α to the pyrrolidine nitrogen, which are shifted downfield by 1 equiv of Tf_2NH, are further shifted downfield by the 1:1 $Tf_2NH/TiCl_4$ combination. As a working hypothesis, we suggest that the oxazaborolidinium triflimidate can be considered as a contact ion pair and the $TiCl_4$-enhanced species as a solvent-separated oxazaborolidiniuim triflimidate–$TiCl_4$ complex.

The augmented catalytic potency shown by 1:1 mixtures of triflimide and $TiCl_4$ in (4 + 2) cycloadditions mediated by chiral oxazaborolidines could also be observed in entirely different chemical reactions, e.g., the Tf_2NH-catalyzed cycliza-

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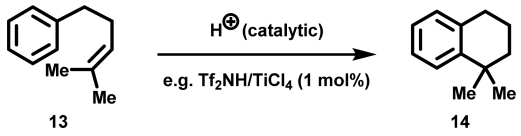
tion of **13** to **14** (Scheme 1), which proceeds very rapidly in CH_2Cl_2 solution (0.05 M) at −40 °C using 1 mol % Tf_2NH.

Scheme 1. Proton-Catalyzed Cyclization of 13 to 14

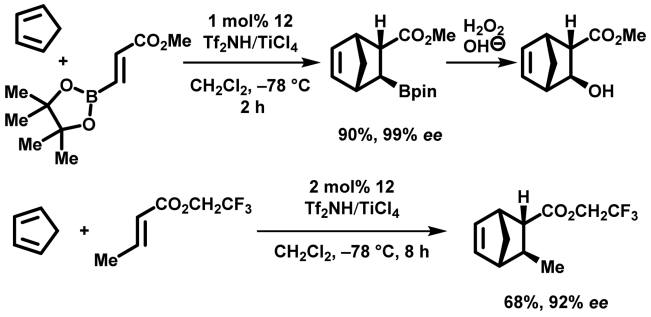


The rate of the strictly pseudo-first-order reaction was followed by gas chromatography.[4] The first-order rate constant was determined to be 7.1×10^{-4} s^{-1} for Tf_2NH alone versus 1.2×10^{-2} s^{-1} for 1:1 $Tf_2NH/TiCl_4$, which corresponds to a 17-fold acceleration due to $TiCl_4$. There was no cyclization under these conditions with $TiCl_4$. In a similar experiment comparing Tf_2NH and 1:1 $Tf_2NH/SnCl_4$, a 13-fold acceleration was measured for the latter cyclization reaction. It seems reasonable to think of the accelerated cyclization of **13** to **14** as involving (1) H-bonded π complexation of Tf_2NH and the olefinic linkage of **13** and (2) reaction of this olefin−Tf_2NH complex with $TiCl_4$ (or $SnCl_4$), which leads to accelerated generation of the product **14**.

We propose that many reactions can be effected by using a 1 mol % loading of a 1:1 $Tf_2NH/TiCl_4$ mixture that normally require much larger amounts of a more conventional Brønsted acid such as H_2SO_4, HCl, CH_3SO_3H, or CF_3CO_2H, with obvious advantages operationally.[5]

The beneficial effect of $TiCl_4$ as a coactivator together with Tf_2NH is especially pronounced with **F10** oxazaborolidines **4** (Figure 1). These are easy to make,[2] use, and recover for reuse. Furthermore, their use can be effective even at the 1−2 mol % level, as illustrated by the examples shown in Scheme 2.

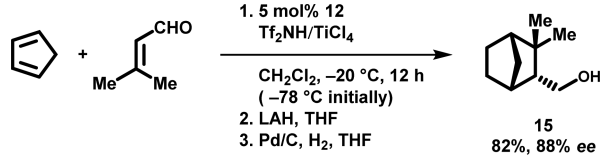
Scheme 2. Diels−Alder Cycloaddition Using 1−2 mol % F10/F0·$Tf_2NH/TiCl_4$ Catalyst



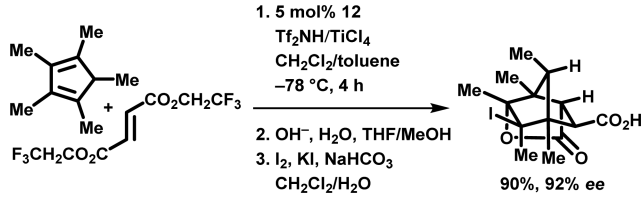
β,β-Disubstitution in an α,β-unsaturated carbonyl substrate is well-known to prevent (4 + 2) cycloaddition reactions with 1,3-dienes. Indeed, β,β-dimethylacrolein was found to be unreactive even with cyclopentadiene using first-generation oxazaborolidine catalysts[1b] and even several of the second-generation catalysts. Nonetheless, smooth (4 + 2) cycloaddition of cyclopentadiene to β,β-dimethylacrolein was observed using just 5 mol % **F10/F0** catalyst **12** together with $Tf_2NH/TiCl_4$ for activation at −78 °C, allowing an efficient route to bicyclic alcohol **15** (Scheme 3).[6]

The rapid enantioselective construction of a product with seven contiguous stereocenters was also accomplished efficiently using a polysubstituted diene, as shown in Scheme 4.

Scheme 3. Enantioselective (4 + 2) Cycloaddition of Cyclopentadiene to β,β-Dimethylacrolein

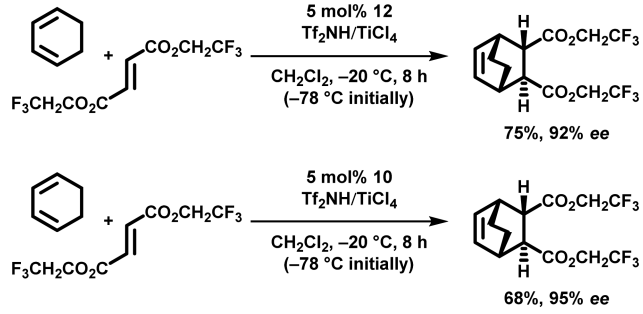


Scheme 4. Enantioselective (4 + 2) Cycloaddition with a Heavily Substituted Diene



Direct comparison of the **F10/F0** catalyst **12** with the **F2/F2** catalyst **10** showed these two oxazaborolidines to be comparably effective, e.g., in the addition of the less reactive 1,3-cyclohexadiene to trifluoroethyl fumarate, as shown in Scheme 5. It is important to note that the **F10/F0** oxazaborolidine is simpler to make than the **F2/F2** compound.

Scheme 5. Comparison of F10/F0 and F2/F2 Catalysts in the (4 + 2) Cycloaddition of 1,3-Cyclohexadiene to Trifluoroethyl Fumarate



In earlier research we found that the use of the first-generation oxazaborolidines for (4 + 2) cycloaddition of acryloyl chloride or other acid chlorides to dienes proceeded with poor (or no) enantioselectivity because of two unfavorable factors: (1) the intrinsically high reactivity and noncatalyzed cycloaddition rates and (2) the lower carbonyl electron density, which translated into poorer binding to the catalyst.[7] We recently discovered a dramatic effectiveness of the **F10/F0**·$Tf_2NH/TiCl_4$ catalytic system with α,β-unsaturated acid chlorides that allows access to the highly reactive and useful products shown in Figure 4 using just 5 mol % catalyst in CH_2Cl_2 at −78 °C.[8] We also found that these same products could be prepared in approximately the same yields and

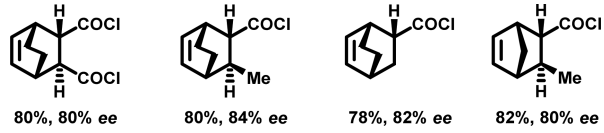


Figure 4. Acid chlorides available using 5 mol % **F10/F0**·$Tf_2NH/TiCl_4$ catalyst.

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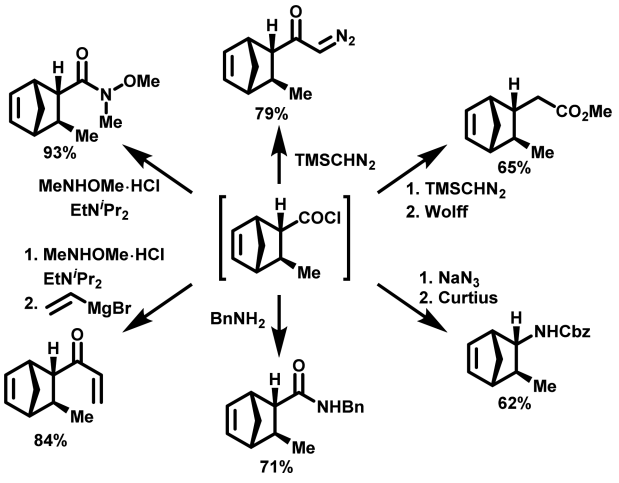
enantioselectivities using the **F2**/**F2** catalyst **10** and the $Tf_2NH/TiCl_4$ activator combination. This combination appeared to be superior to the **F10**/**F0** precatalyst **12** for the $Tf_2NH/TiCl_4$-promoted reactions of acid chlorides and *acyclic* dienes (see the Supporting Information).

Acid fluorides are much less reactive than acid chlorides in oxazaborolidinium-catalyzed (4 + 2) cycloadditions and in fact seem to be surprisingly inert. A 1:1 mixture of acryloyl chloride and fluoride with the **F10**/**F0** catalyst and excess cyclopentadiene at −78 °C formed exclusively the acid chloride adduct as determined by ^1H and ^{19}F NMR analyses of the total reaction product. Moreover, no catalytic reaction between cyclopentadiene and acryloyl fluoride occurred even at 0 °C over several hours. It is possible that acryloyl fluoride does not coordinate to the catalyst.

α,β-Unsaturated acid chlorides were found to be the most reactive dienophiles that we have studied using the **F10**/**F0**·$Tf_2NH/TiCl_4$ catalytic system. A comparison of the catalytic (4 + 2) cycloaddition of cyclopentadiene with several crotonate derivatives ($CH_3CH{=}CHCOX$) showed the following times to completion at −78 °C: X = Cl, 0.7 h; X = CF_3CH_2O, 2 h; X = $ClCH_2O$, 3 h; X = $NCCH_2O$, 4.5 h; X = C_2H_5O, ca. 8 h at −20 °C.[9]

One advantage of the use of acid chlorides as dienophiles is the possibility of using the reactive Diels−Alder adducts directly for conversion into a wide range of useful compounds, e.g., amides, Wolff rearrangement products via diazoketones, or Curtius rearrangement products via acyl azides (Scheme 6). Such compounds cannot be obtained directly from Diels−Alder reactions of the corresponding dienophiles.

Scheme 6. Derivatizations of Acid Chloride Diels−Alder Adducts



In summary, this research has demonstrated an unprecedented increase in the activation of chiral oxazaborolidines by triflimide combined with an equimolar amount of $TiCl_4$. The $Tf_2NH/TiCl_4$ reagent would appear to have considerable potential for other applications in CH_2Cl_2 or CH_2Cl_2/toluene requiring strong protic acid catalysis. We suggest that the effectiveness of the $Tf_2NH/TiCl_4$ combination derives from the greater stability of complex **7** in comparison with Tf_2N^-.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08018.

Experimental procedures and characterization data for novel reactions and products, including copies of ^1H and ^{13}C NMR spectra and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(2) Mahender Reddy, K.; Bhimireddy, E.; Thirupathi, B.; Breitler, S.; Yu, S.; Corey, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 2443−2453.

(3) For a complete list of the results in Table 1, see the Supporting Information.

(4) For full details, see the Supporting Information.

(5) A reviewer suggested the citation of a paper on acceleration of Mukayama aldol reactions by reagents such as Me_3SiOTf/Et_2AlCl. See: Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271−8272.

(6) For comparison, bicyclic alcohol **15** was prepared from camphene by hydroboration−oxidation. See: Biellmann, J.-F.; d'Orchymont, H. *J. Org. Chem.* **1982**, *47*, 2882−2886.

(7) Ryu, D. H.; Zhou, G.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1633−1636.

(8) For the determination of yields and enantioselectivities after in situ quenching with various reagents, see the Supporting Information.

(9) The reactivity of the various esters in the series $CH_3CH{=}CHCOX$ with dienes and $Tf_2NH/TiCl_4$-acitvated oxazaborolidines parallels the IR stretching frequencies (cm^{-1}) of the C=O group (COCl = 1758, 1740; $COOCH_2CF_3$ = 1736; $COOCH_2Cl$ = 1737; $COOCH_2CN$ = 1727; $COOCH_2CH_3$ = 1716). On the other hand, it was observed that the hexafluoroisopropyl and 2,6-dichlorophenyl esters were quite unreactive, possibly because of steric deceleration. For details, see the Supporting Information.

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