JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Subscriber access provided by Northern Illinois University

Communication

Acceleration of Enantioselective Cycloadditions Catalyzed by Second-Generation Chiral Oxazaborolidinium Triflimidates by Bis-Coordinating Lewis Acids.

Barla Thirupathi, Simon Breitler, Karla Mahender Reddy, and E. J. Corey

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b08018 • Publication Date (Web): 16 Aug 2016

Downloaded from http://pubs.acs.org on August 17, 2016

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036
Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Acceleration of Enantioselective Cycloadditions Catalyzed by Second-Generation Chiral Oxazaborolidinium Triflimidates by Bis-Coordinating Lewis Acids.

Barla Thirupathi,‡ Simon Breitler,‡ Karla Mahender Reddy,‡ and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information Placeholder

ABSTRACT: The activation of second-generation fluorinated oxazaborolidines by the strong acid triflimide in CH_2Cl_2 solution leads to highly active chiral Lewis acids which are very effective catalysts for (4+2)-cycloaddition. We report herein that this catalytic activity can be further enhanced by the use of triflimide (Tf_2NH) in combination with the bis-coordinating Lewis acid $TiCl_4$ or $SnCl_4$ as co-activator. The effective increase in acidity of an exceedingly strong protic acid is greater for the bis-coordinating $TiCl_4$ and $SnCl_4$ than for mono-coordinating salts, even the strong Lewis acids $AlBr_3$ or BBr_3 in CH_2Cl_2 or CH_2Cl_2–toluene. The increase in effective acidity of triflimide 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]

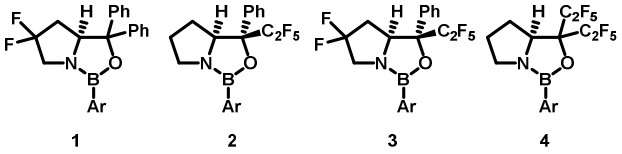


Figure 1. Second Generation Oxazaborolidines **1**–**4**

Very powerful cationic catalysts are available from **1**–**4** by activation using one equivalent 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 pre-catalysts **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 dienophile in which the coordinating group on nitrogen is actually the equivalent of the unknown mono-coordinated cation $AlBr_2^+$ – for instance structure **5** (Figure 2) in the case of an acrylate ester as dienophile.

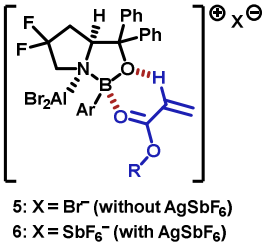
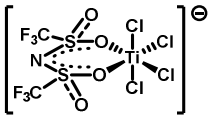


Figure 2. Possible Reactive Complexes between an $AlBr_3$-activated Catalyst **1** and an α,β-Unsaturated Dienophile

Strong evidence in favor of this possibility was obtained from experiments which demonstrated that the rates of the $AlBr_3$-oxazaborolidine catalyzed (4+2)-cycloaddition could be considerably enhanced by the further addition of one equivalent of $AgSbF_6$ per $AlBr_3$ which led to the precipitation of AgBr and generation of $AlBr_2^+$-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 the 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 not unreasonable because the reaction medium for catalytic cycloadditions is generally non-polar – specifically CH_2Cl_2 or CH_2Cl_2–toluene mixtures. It was thought that a bis-coordinating 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 the complex **7** (Figure 3), in which the negative charge is far more delocalized than in the triflimidate ion.



7

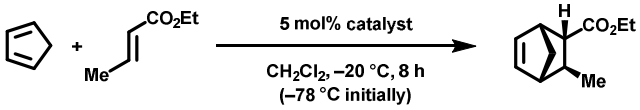
Figure 3. Possible $Tf_2N/TiCl_4$-ate complex **7**

We were gratified to find by experiment that triflimide activation of various oxazaborolidines could in fact be markedly enhanced simply by the use of $TiCl_4$ as co-activator (1:1 $Tf_2NH/TiCl_4$ ratio, 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 experiments were conducted under exactly the same reaction conditions and so the % 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 co-activator. There is only a modest further acceleration of these cycloadditions by increasing the $TiCl_4/Tf_2NH$ ratio from 1 to 2.

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 not as effective as $TiCl_4$. On the other hand, it is notworthy that the mono-coordinating 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 ^{1}H-NMR spectroscopy. Shown in Tables 2A and 2B are ^{1}H-NMR chemical shift data for the **F0/F3** (**8**) and the **F10/F0** (**12**) oxazaborolidines alone and in the presence of one equivalent of Tf_2NH or one equivalent each of Tf_2NH and $TiCl_4$. As expected, the protons attached alpha to the pyrrolidine nitrogen, which are shifted downfield by one equivalent 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 thought of as a contact ion pair and the $TiCl_4$-enhanced species as a solvent-separated oxazaborolidiniuim triflimidate-$TiCl_4$ complex.

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



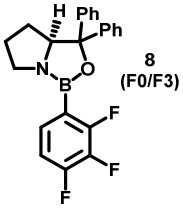
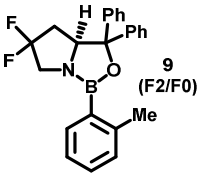
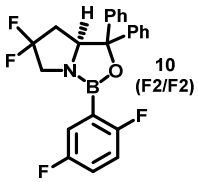
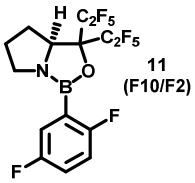
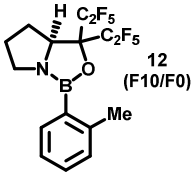
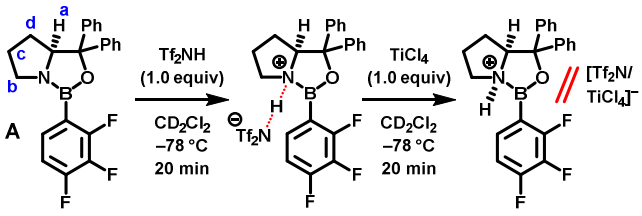
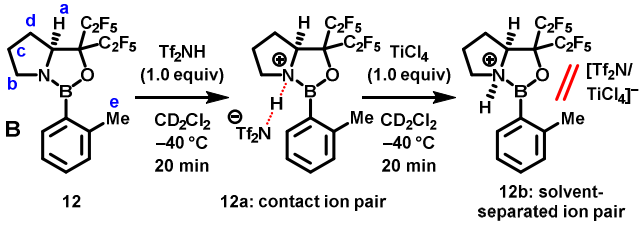
precatalyst	activator (0.7 equiv)	% yield (*endo*/*exo*)	% *ee*
 **8** (F0/F3)	Tf_2NH	5% (97:3)	99
	$Tf_2NH/TiCl_4$ (1:1)	36% (97:3)	99
	$Tf_2NH/SnCl_4$ (1:1)	28% (97:3)	98
 **9** (F2/F0)	Tf_2NH	24% (98:3)	99
	$Tf_2NH/TiCl_4$ (1:1)	70% (98:2)	99
 **10** (F2/F2)	Tf_2NH	42% (98:2)	99
	$Tf_2NH/TiCl_4$ (1:1)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

Table 2A and 2B. ^{1}H-NMR Data for Two Oxazaborolidines without and 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

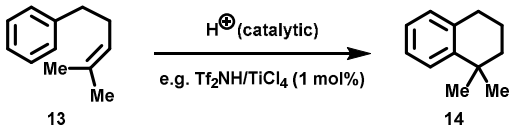


12 12a: contact ion pair 12b: solvent-separated ion pair

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

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, for example the Tf_2NH-catalyzed cyclization of **13** to **14** (Scheme 1) which proceeds very rapidly in CH_2Cl_2 solution (0.05 M) at –40 °C using 1 mol% of Tf_2NH.

Scheme 1. Proton-Catalyzed Cyclization of 13 to 14

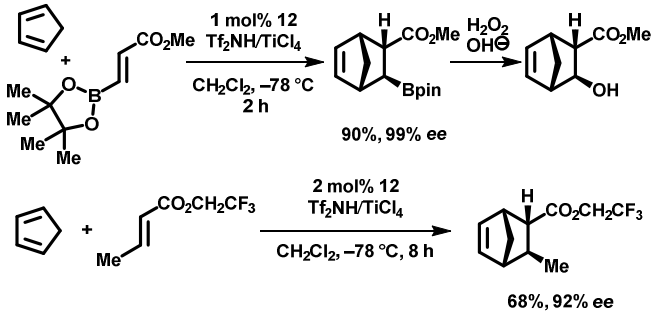


The rate of the strictly pseudo-first order reaction was followed by gas chromatography.[4] The first order rate constant was determined to be 7.1×10^{-4} s^{-1} for Tf_2NH alone versus 1.2×10^{-2} s^{-1} for 1:1 $Tf_2NH/TiCl_4$, which corresponds to a 17-fold acceleration due to $TiCl_4$. There is no cyclization under these conditions with $TiCl_4$. In a similar experiment comparing Tf_2NH and 1:1 $Tf_2NH/SnCl_4$, an acceleration of 13-fold 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 1 mol% if a 1:1 mixture of $Tf_2NH/TiCl_4$ which normally require much larger amounts of more conventional Brønsted acids such as H_2SO_4, HCl, CH_3SO_3H or CF_3CO_2H, with obvious advantages operationally.[5]

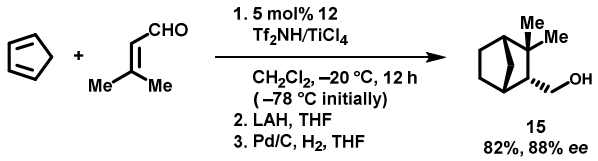
The beneficial effect of $TiCl_4$ as co-activator together with Tf_2NH is especially pronounced with **F10**-oxazaborolidines (**4**, Figure 1). These are easy to make,[2] use and recover for reuse. Furthermore, their use can be effective even at the 1–2 mol% level, as illustrated by the following examples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

Scheme 2. Diels–Alder Cycloaddition using 1–2 mol% of F10/Fo·$Tf_2NH/TiCl_4$ Catalyst



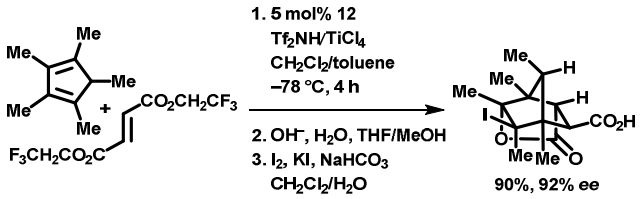
β,*β*-Disubstitution in an *α*,*β*-unsaturated carbonyl substrate is well-known to prevent (4+2)-cycloaddition reactions with 1,3-dienes. Indeed, *β*,*β*-dimethyl acrolein was found to be unreactive even with cyclopentadiene using first-generation oxazaborolidine catalysts,[1b] and even several of the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

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



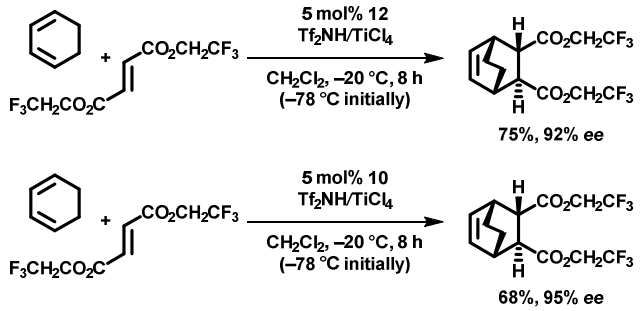
The rapid enantioselective construction of a product with seven contiguous stereocenters was also accomplished efficiently using a polysubstituted diene, as shown in Scheme 4.

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



Direct comparison of the **F10/Fo** 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/Fo** oxazaborolidine is simpler to make than the **F2/F2** compound.

Scheme 5. Comparison of F10/Fo and F2/F2 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 due to two unfavorable factors: (1) the intrinsically high reactivity and non-catalyzed cycloaddition rates and (2) the lower carbonyl electron-density which translated into poorer binding to the catalyst.[7] Recently, we have discovered a dramatic effectiveness of the **F10/Fo**·Tf2NH/TiCl4 catalytic system with *α*,*β*-unsaturated acid chlorides that has allowed access to the highly reactive and useful products shown in Figure 4 with the use of just 5 mol% of catalyst in CH_2Cl_2 at –78 °C.[8]

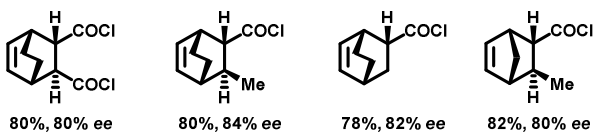


Figure 4. Acid chlorides available using 5 mol% of the **F10/Fo**·Tf2NH/TiCl4 catalyst

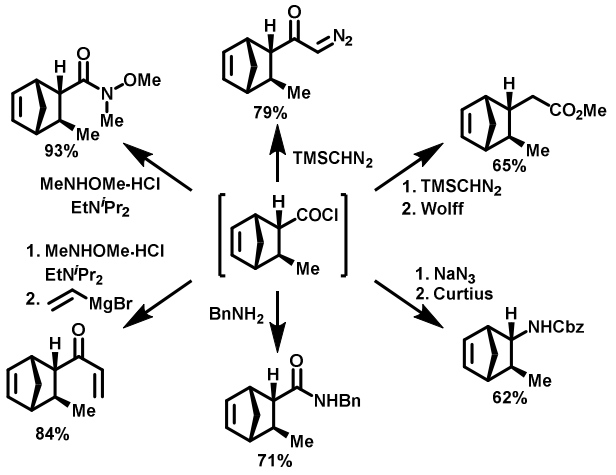
We also found that these same products could be prepared with approximately the same yields and enantioselectivities using the **F2/F2** catalyst **10** and the $Tf_2NH/TiCl_4$ activator combination. This combination appeared to be superior to the **F10/F0** precatalyst **12** for the $Tf_2NH/TiCl_4$-promoted reactions of acid chlorides and *acyclic* dienes (see 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 ^{1}H-NMR and ^{19}F-NMR analysis of the total reaction product. Moreover, no catalytic reaction occurred between cyclopentadiene and acryloyl fluoride 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**·Tf2NH/TiCl4 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 to 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 diazoketone 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 is driven by the greater stability of complex **7** in comparison with Tf_2N^-.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for novel reactions and products including copies of ^{1}H- and ^{13}C-NMR spectra and chiral HPLC traces. This material is available free of charge via the In-ternet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*corey@chemistry.harvard.edu

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to the following for research grants: Pfizer, Gilead and Bristol-Myers Squibb. S. B. acknowledges a postdoctoral fellowship from the Swiss National Science Foundation.

REFERENCES

(1) (a) Corey, E. J. *Angew. Chem. In. Ed.* **2002**, *41*, 1650-1667. (b) Corey, E. J. *Angew. Chem. In. Ed.* **2009**, *48*, 2100-2117.

(2) Reddy, K. M.; 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 results in Table 1 see Supporting Information.

(4) For full details see Supporting Information.

(5) A reviewer has 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.

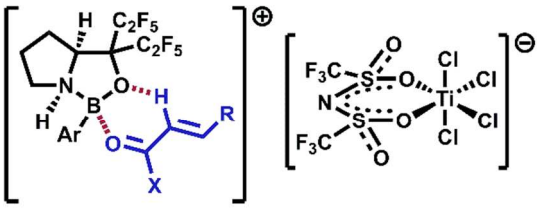
(6) The bicyclic alcohol **15** was prepared for comparison from camphene by hydroboration-oxidation, see Biellmann, J.-F.; d'Orchymont, H. *J. Org. Chem*. **1982**, *47*, 2882-2886.

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

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

For Table of Contents Only



Reactive Complex for (4+2)-Cycloaddition Reactions