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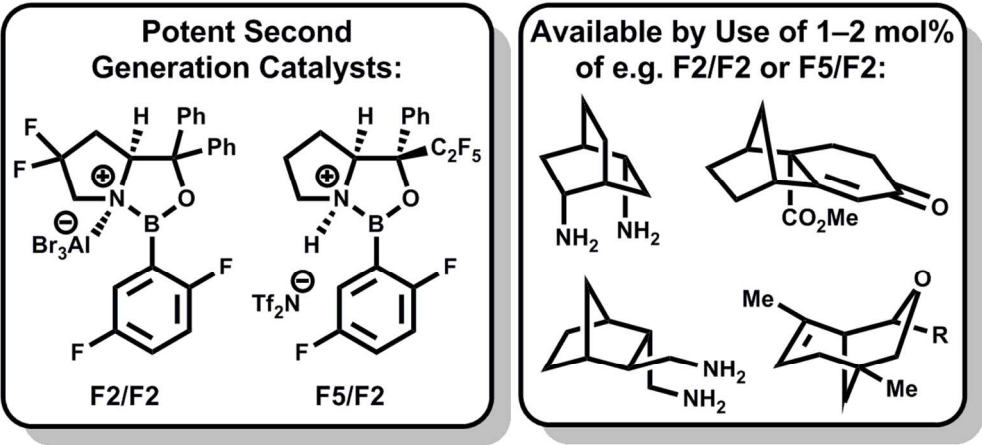
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Cationic Chiral Fluorinated Oxazaborolidines. More Potent, Second Generation Catalysts for Highly Enantioselective Cycloaddition Reactions

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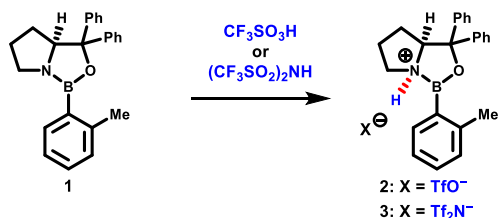
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ABSTRACT: The coordination of chiral ligands to Lewis acid metal derivatives, a useful strategy for enantioselective, electrophilic catalysis, generally leads to a lower level of catalytic activity than that of the original uncomplexed compound. Activation by further attachment of a proton or strong Lewis acid to the complex provides a way to overcome the deactivating effect of a chiral ligand. The research described herein has demonstrated that further enhancement of catalytic activity is possible by the judicious placement of fluorine substituents in the chiral ligand. This approach has led to a new, second generation family of chiral oxazaborolidinium cationic species which can be used to effect many Diels–Alder reactions in >95% yield and >95% ee using catalyst loadings at the 1–2 mol% level. The easy recovery of the chiral ligand makes the application of these new catalysts especially attractive for large scale synthesis.

INTRODUCTION

Ever since its discovery in the 1920's,^{1,2} the Diels–Alder reaction has achieved so much success that it occupies a unique position as a versatile and powerful construction in carbochemical synthesis. It is, in fact, a superfamily of (4+2)-cycloaddition reactions consisting of many variants, e.g. catalyzed and thermal, carbo- and heterocyclic, intra- and intermolecular, and normal and reverse polarity reactions. In recent years, the synthetic power of the Diels–Alder reaction has been further increased by the development of enantioselective approaches involving the use of either chiral controllers or chiral catalysts.³ The most versatile and electrophilic chiral catalysts so far developed are the chiral oxazaborolidinium cations,⁴ derived by protonation of the (*S*)-oxazaborolidine **1**, or the (*R*)-enantiomer, with either triflic acid or triflimide to form the proton-activated cations **2**,⁵ or **3**.⁶

Scheme 1. First Generation Oxazaborolidine Catalysts **2** and **3**



These catalysts are effective not only with a range of cyclic and acyclic 1,3-dienes, but also for a wide variety of dienophiles including conjugated aldehydes, ketones,

esters, lactones and 1,4-quinones, and lead to impressively high enantio- and diastereoselectivity in (4+2)-cycloadditions. In addition, **2** and **3** have proven useful in (2+2)-cycloadditions,⁸ (3+2)-cycloadditions,⁹ (2+1)-cycloadditions,¹⁰ C–H insertions,¹¹ Mukaiyama–Michael,¹² and cyanosilylation reactions.¹³ Enantioselective catalysis by **2** and **3** has also served as a key step for the enantioselective synthesis of many complex naturally occurring and/or bioactive structures, for example, estrone,¹⁴ desogestrel,¹⁴ oseltamivir,¹⁵ aflatoxin,⁹ cortisol,¹⁶ dendrobine,¹⁶ vitamin B₁₂,¹⁶ microcin C,¹⁶ various triquinanes,¹⁶ georgyone and arborone,¹⁷ and dolabellatrienone.¹⁸

Subsequent to the discovery of the proton-activated catalysts **2** and **3**, it was also found that AlBr_3 could be used to activate the oxazaborolidine **1** with the formation of **4**.⁷ Complexes **2**, **3** and **4** exhibited similar catalytic properties, although differences between their effectiveness were noted. Remarkably, AlBr_3 was the only Lewis acid among the many tried that generated a useful catalyst from **1**.⁷

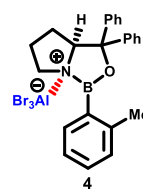


Figure 1. AlBr_3 -activated Oxazaborolidine Catalyst **4**

In previous work, catalysts **2**, **3** and **4** have usually been employed at loadings between 5 and 20 mol% of the sub-

strates. In this article, we describe recent systematic studies that addressed the following questions: (1) is it possible to design more potent versions of catalysts **2**, **3** and **4** that gave even greater acceleration of reaction rates (and therefore significantly shorter reactions times) and broader reaction scope; (2) is it possible to reduce the required amount of catalyst to the 1 mol% level and (3) is it possible to increase the stability of the catalyst so that reactions could routinely be carried out at ambient temperature, or above in the case of unreactive substrates. The achievement of these objectives would have important implications for synthetic practice – especially at the production level. Here it should be noted that the chiral ligand used to generate the precatalyst **1** can easily be recovered from the catalytic reaction mixtures. Finally, we hoped that a comprehensive study of a selected range of catalysts related to **2**, **3** and **4** would yield important information regarding both the limits of electrophilicity attainable in these systems and the finer details of the catalytic pathways. In the discussion that follows it should be recalled that all of our previous research gave results that could be interpreted in terms of just two types of pre-transitions state assembly, one for conjugated aldehydes (**5**) and one for α,β -unsaturated carbonyl compounds possessing an α -C–H bond (**6**). These models have received support from computational studies,¹⁹ as well as from their predictive success in numerous examples.

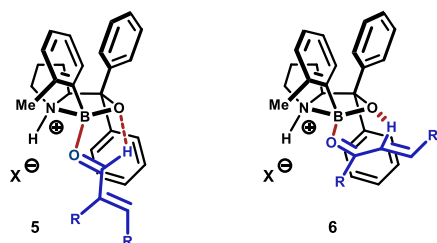


Figure 2. Pre-transition State Models for the Enantioselectivity in Diels–Alder Reactions of α,β -Enals (**5**) and other Dienophiles (**6**)

RESULTS

Second Generation Oxazaborolidines for Catalysis. Enantioselective catalysis involving electron-deficient main group- or transition-metal centers is generally accomplished by attachment of a chiral ligand to the electrophilic element. Therefore, the design of effective catalysts involves a balance between the requirement that the chiral ligand be sufficiently nucleophilic to bind completely to the catalytic center and the need to maximize its electron- deficiency. In the case of the precatalyst **1**, the boron center is already in place and activation requires a new coordination with either a proton or AlBr_3 . A logical possibility for increasing the electrophilicity of the activated catalyst thus requires modification of the chiral ligand in the precatalyst, specifically by reduction of its basicity. We chose to do so by judicious replacement of C–H subunits in precatalyst **1** by C–F. An obvious advantage to the use of fluorine substitution is its powerful electron affinity along with its non-coordinating property

and general unreactivity. In particular, we have investigated the synthesis and catalytic activity of catalysts, derived from the chiral fluorinated precatalysts **7**, **8**, **9** and **10**, having fluorine substituents at carbons β to either the prolinol nitrogen or oxygen.

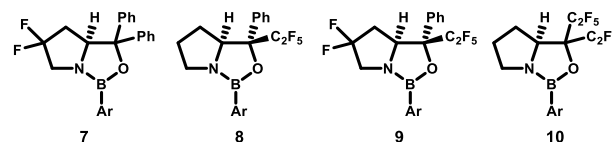
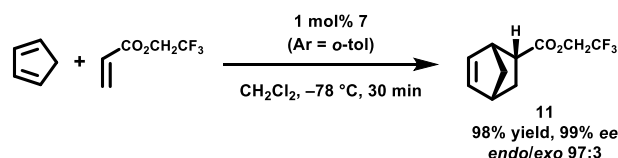


Figure 3. Second Generation Oxazaborolidines **7**, **8**, **9** and **10**

The powerful electron-withdrawing effect of the β -fluorine substituents is well known; for example the basicity of ethylamine is reduced by 1.5–1.7 pK_a units for each β -H/ β -F substitution, since the pK_a values for ethylamine and its β -mono-, di- and trifluoro analogs are 10.7, 9.0, 7.3 and 5.7, respectively.²⁰ Three different aryl substituents on boron of **7**, **8**, **9** and **10** were studied: *o*-tolyl, 2-fluorophenyl and 2,5-difluorophenyl. In the sections which follow, we compare the catalytic behaviour of the oxazaborolidinium catalysts of the various series, some preparative aspects of the most potent catalysts, the synthesis of the various ligands, precatalysts and catalysts and, finally, a number of practical applications.

Relative Catalytic Activity of 7 (Ar = *o*-tolyl). At the outset of this work, we compared triflimide- and AlBr_3 -activated catalysts based on **1**, i.e. **3** and **4**, respectively, in the test reaction of cyclopentadiene with trifluoroethyl acrylate. Whereas both catalysts afforded the Diels–Alder adduct **11** in 99% *ee* and 97–98% yield using CH_2Cl_2 as solvent, the reaction with **4** was 3–4 times as fast as that with **3** at -78°C . In the case of **7** (Ar = *o*-tolyl), the reaction was about an order of magnitude faster than with **3** or **4** as catalysts, and again, the AlBr_3 -activated version was more potent than the Tf_2NH -activated form. The enhanced potency of the difluoro-analog of **4** allowed the use of as little as 1 mol% of catalyst to obtain a 98% yield of adduct **11** in just 30 min at -78°C in CH_2Cl_2 as solvent as shown in Scheme 2.

Scheme 2. Test Reaction for Catalytic Activity



The initial experiments confirmed that the expected boost in catalytic potency could be realized by use of fluorine substituents and encouraged the in-depth study of fluorinated analogs of **3** and **4**. They also underscored the potential practical value of such catalysts, especially because (1) the chiral hydroxymethyl pyrrolidine precursor ligand can easily be recovered for reuse from the reaction mixtures, (2) smaller amounts of catalyst can be used, and (3) excellent yields and *ee*'s can be obtained.

For the ensuing discussion of the various fluorine-bearing analogs of **3** and **4**, we introduce for clarity the following

simple mnemonic nomenclature for the various precatalysts: **F2/Fo** will refer to **7** (Ar = *o*-tolyl); **F2/F2** will refer to **7** (Ar = 2,5-difluorophenyl); **F5/Fo** will refer to **8** (Ar = *o*-tolyl); **F5/F2** will refer to **8** (Ar = 2,5-difluorophenyl); **F7/Fo** will refer to **9** (Ar = *o*-tolyl) and **F10/Fo** will refer to **10** (Ar = *o*-tolyl), etc. This simplified system is exemplified in Figure 4.

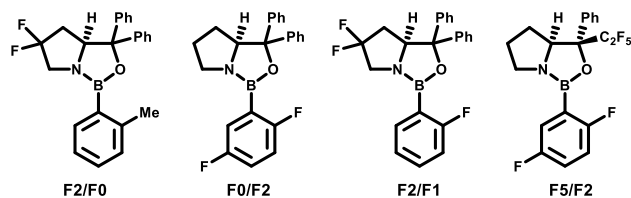


Figure 4. Examples for Nomenclature of the Precatalysts

The enhancement of catalytic potency by *gem*-difluorine substituents was clearly indicated by a study of the reaction of cyclopentadiene with the relatively less reactive dienophile ethyl crotonate under standard conditions – 5 mol% catalyst at –20 °C in CH₂Cl₂ for 8 hours. The results, which are shown in Table 1, further point to roughly an order of magnitude gain in catalytic power upon replacement of the β-CH₂ by CF₂ in the chiral catalyst. In this connection, it is important to note that the carbonyl group of the Diels–Alder product can also bind to the Lewis acid center of the catalyst. The resulting product inhibition can be expected to moderate the rate acceleration due to fluorine substituents in the **F2** systems versus **2**, **3** or **4** to a degree that depends on the relative strength of coordination of dienophile and product to the catalyst.

Table 1. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Ethyl But-2-enoate using Catalysts **3, **4** and **F2/Fo****

catalyst	% yield (<i>endo</i> / <i>exo</i>)	% ee
3	2 (91:9)	98
4	10 (92:8)	98
F2/F0 (Tf ₂ NH)	24 (95:5)	98
F2/F0 (AlBr ₃)	35 (98:2)	98

A comparison of the results obtained in a variety of Diels–Alder reactions catalyzed by the triflimide-activated **F2/Fo** catalyst with previously described findings using catalyst **2** or **3** in the *same reactions* is presented in Table 2. These data show that equally good outcomes in terms of yield and *ee* of product can be obtained with the **F2/Fo** catalyst in various combinations of (a) lower amounts of catalyst, (b) lower reaction time or (c) lower temperature.

Table 2. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles in the Presence of Catalyst **2, **3**, or Triflimide-activated **F2/Fo** catalyst**

Product	catalyst (mol%)	Conditions (°C, h)	% yield (<i>endo</i> / <i>exo</i>)	% ee
	2 ^{a,c} (20)	–20, 14	99 (95:5)	92
	F2/F0 (10)	–20, 2	98 (95:5)	92
	2 ^a (20)	–20, 16	97 (91:9)	93
	F2/F0 (10)	–20, 3	98 (95:5)	92
	2 ^a (20)	–20, 36	99 (91:9)	88
	F2/F0 (10)	–20, 16	99 (92:8)	92
	3 ^b (20)	+20, 40	78	88
	F2/F0 (10)	+20, 16	88	90
	N-Me ^d (20)	+23, 24	98	82
	F2/F0 (10)	+23, 8	97	85

^a see ref. 5b. ^b see ref. 6. ^c 3,5-dimethylphenyl replaced the phenyl groups of **3**. ^d see ref. 21.

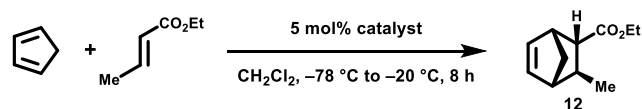
The AlBr₃-activated fluorinated **F2/Fo** catalyst is sufficiently powerful as a Lewis acid that it can be employed to advantage in just 1 mol% amounts, as supported by the evidence summarized in Table 3, in which previously obtained data with catalyst **4** are shown for comparison.⁷ The finding that this AlBr₃-activated **F2/Fo** catalyst can be used effectively at the 1 mol% level plus the fact that the difluorinated diphenylprolinol ligand can easily be recovered with >95% efficiency recommend this reagent for large scale enantioselective syntheses.

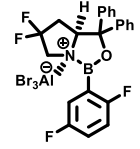
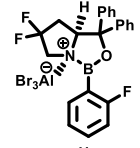
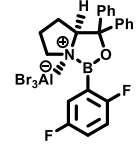
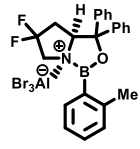
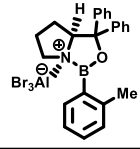
Table 3. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles in the Presence of AlBr₃-activated **F2/Fo Catalyst or **4****

Product	catalyst (mol%)	Conditions (°C, h)	% yield (<i>endo</i> / <i>exo</i>)	% ee
	4 ^a (4)	–40, 1	95 (93:7)	92
	F2/F0 (1)	–40, 6	92 (96:4)	92
	4 ^a (4)	–20, 6	99 (94:6)	95
	F2/F0 (1)	–20, 12	98 (95:5)	96
	F2/F0 (1)	–20, 16	90 (92:8)	93
	4 ^a (4)	–20, 48	71	97
	F2/F0 (1)	–20, 24	91	96
	4 ^a (8)	–40, 16	71	99
	F2/F0 (1)	–40, 24	65	96

^a see ref. 7.

Table 4. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Ethyl But-2-enoate using the F₂ Family of AlBr₃-activated Catalysts



catalyst	% yield (<i>endo</i> / <i>exo</i>)	% ee
 F2/F2 (AlBr ₃)	75 (97:3)	96
 F2/F1 (AlBr ₃)	50 (97:3)	96
 F0/F2 (AlBr ₃)	65 (97:3)	96
 F2/F0 (AlBr ₃)	35 (98:2)	98
 4	10 (92:8)	98

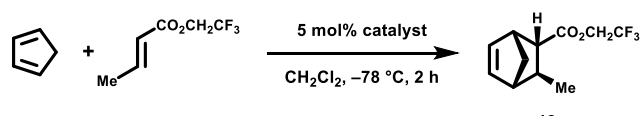
Encouraged by the finding that the AlBr₃-activated F₂/F₀ catalyst is a definite improvement over the first generation AlBr₃-activated catalyst **4**, we prepared the F₂/F₂ precatalyst **7** (Ar = 2,5-difluorophenyl) and the F₂/F₁ precatalyst **7** (Ar = *o*-fluorophenyl). The whole family of catalysts was compared using the reaction of cyclopentadiene and ethyl crotonate under identical conditions to determine relative effectiveness, with the results that are summarized in Table 4. We believe these data accurately reflect the relative potencies of the various catalysts, since considerable care was exercised to ensure that the experiments were all carried out under identical conditions starting with the pure (by ¹H-NMR analysis) precatalysts. In each case, the Diels–Alder adduct **12** was the sole product and the conversion was calculated from ¹H-NMR analysis to determine the ratio of **12** to ethyl crotonate. Interestingly, the increase in conversion to product by CF₂ replacement of CH₂ in the pair F₂/F₂ and F₀/F₂ is considerably less than for the pair F₂/F₀ and **4**. This fact may signal a limit to the increase in catalytic potency with additional fluorine substitution.

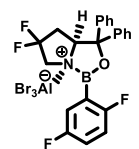
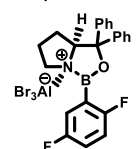
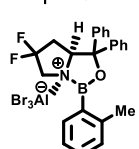
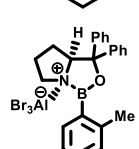
From the results shown in Table 4, it appears that the AlBr₃-activated F₂/F₂ catalyst is superior to the others. However, it is noteworthy that the AlBr₃-activated F₀/F₂ catalyst is surprisingly more powerful than **4**, and clearly

potentially very useful because it can be made from commercially available diphenylprolinol (e.g. Sigma-Aldrich, Fluorochem) and 2,5-difluorophenylboron dibromide, an excellent preparation of which is described in a later section.

A similar comparison of catalytic potencies was made using as test reaction the Diels–Alder addition of cyclopentadiene and trifluoroethyl crotonate, a somewhat more reactive dienophile than ethyl crotonate, with the results shown in Table 5. The relative catalytic activities were similar for the trifluoroethyl and ethyl esters, with the AlBr₃-activated F₂/F₂ catalyst clearly being the most powerful.

Table 5. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Trifluoroethyl But-2-enoate using the F₂ Family of AlBr₃-activated Catalysts



catalyst	% yield (<i>endo</i> / <i>exo</i>)	% ee
 F2/F2 (AlBr ₃)	95 (98:2)	94
 F0/F2 (AlBr ₃)	80 (97:3)	94
 F2/F0 (AlBr ₃)	50 (98:2)	92
 4	30 (98:2)	90

1,3-Cyclohexadiene, which is considerably less reactive than cyclopentadiene, was selected for further comparison of the catalysts used in the studies summarized in Tables 4 and 5. The relative potency of AlBr₃-activated catalysts in the reaction of this diene with trifluoroethyl acrylate under standard conditions were found to be in the order F₂/F₂ > F₂/F₀ > **4**, with the results shown in Table 6. Thus, relative catalytic activity is likely to be the same with a range of dienes.

The enhanced catalytic potency of the F₂/F₂ and F₂/F₀ catalysts in the series encompassed by the general formula **7** encouraged the exploration of their application to the enantioselective Diels–Alder reactions of a variety of dienes with a range of dienophiles at catalyst loadings of just 1 mol%. The results for several such test cases, as

summarized in Table 7, compare very favorably with those previously reported using 10–20 mol% of the first generation catalysts 2, 3 or 4.

Table 6. Comparison of Diels–Alder Reactions of Cyclohexadiene with (*E*)-Trifluoroethyl Acrylate using the F2 Family of AlBr₃-activated Catalysts and 4

catalyst	% yield (<i>endo/exo</i>)	% ee		
	F2/F2 (AlBr ₃)	74 (97:3)	96	
	F2/F0 (AlBr ₃)	40 (98:2)	94	
	4	13 (96:4)	94	

Table 7. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles using 1 mol% of the F2 Family of AlBr₃-activated Catalysts

Product	catalyst (mol%) ^a	Conditions (°C, h)	% yield (<i>endo/exo</i>)	% ee
	F2/F2 (0.5)	–78, 0.5	95 (96:4)	92
	F2/F2 (1)	–78, 0.3	96 (97:3)	97
	3 (20)	–78, 1.5	97	99
	F2/F2 (1)	–78, 1	95	98
	4 (4)	–78, 0.5	99	99
	F2/F2 (1)	–78, 0.3	95	98
	4 (4)	–78, 2	99 (8:92)	93
	F2/F2 (1)	–78, 0.5	97 (8:92)	91
	4 (4)	–78, 6	95	98
	F2/F2 (1)	–78, 4	93	96
	3 (20)	–78, 16	92	97
	F2/F2:HNTf ₂ (1)	–78, 12	96	93
	4 (4)	–78, 16	99	97
	F2/F0 (1)	–78, 24	92	93

^a AlBr₃ was used as activator unless otherwise noted.

These advantages of the F2/F0 and F2/F2 catalysts were also evident from a series of Diels–Alder experiments involving various furans as dienophiles. These heterocyclic dienes were of special interest to us because they allow access to a host of otherwise inaccessible structures, as detailed in a later section. The results with five different cases are outlined in Table 8. Again, excellent yields and enantioselectivities were observed with just 1 mol% of catalyst, which compares favorably to the first generation catalyst 4.⁷

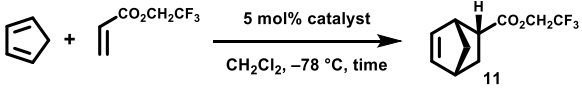
Table 8. Enantioselective Diels–Alder Reactions of Furans and Dienophiles using 1 mol% of the F2 Family of AlBr₃-activated Catalysts

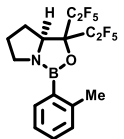
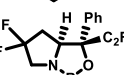
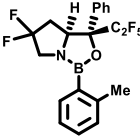
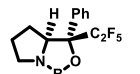
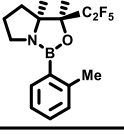
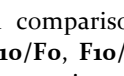
Product	catalyst (mol%) ^a	Conditions (°C, h)	% yield (<i>endo/exo</i>)	% ee
	4 (8)	–40, 16	71	99
	F2/F2 (1)	–40, 12	68	96
	4 (4)	–78, 8	99 (88:12)	99
	F2/F2 (1)	–78, 5	96 (90:10)	98
	F2/F2 (1)	–40, 7	75	95
	4 (8)	–40, 24	72 ^a	91
	F2/F2 (1)	–40, 16	68 ^a	90
	4 (4)	–78, 12	99 (90:10)	94
	F2/F2 (1)	–78, 7	92 (92:8)	94

^a yield determined after conversion to the hydrogenated product.

The series of precatalysts defined by structures 8, 9 and 10 were selected next for our comprehensive survey of second generation oxazaborolidine reagents. Efficient and stereocontrolled syntheses of 8, 9 and 10 are detailed in a later section. These precatalysts of the F5, F7 and F10 series were of special interest to determine whether the placement of fluorine substituents β/γ to the oxygen of the oxazaborolidine ring might have a superior effect on the potency of the corresponding oxazaborolidinium catalysts. The precatalysts 8, 9 and 10 (Ar = *o*-tol) led to fast, enantioselective and efficient (4+2)-cycloaddition after activation with Tf₂NH using cyclopentadiene and trifluoroethyl acrylate as test reactants, as shown in Table 9. However, when AlBr₃ was employed as activator of the F10/F0 precatalyst, the test reaction was surprisingly less enantioselective than with the F5/F0 or F7/F0 precatalysts. This result may be due to the presence of uncoordinated AlBr₃ in the case of the F10/F0 precatalyst, even though a 1.4-fold excess of precatalyst compared to the activator was used in the repeated experiments. It is possible that the presence of a bulky C₂F₅ substituent *cis* to the coordination site of AlBr₃ may disfavor complexation.

Table 9. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Trifluoroethyl Acrylate using the F5/Fo, F7/Fo and F10/Fo Catalysts



catalyst	time	% yield (endo/exo)	% ee
 F10/Fo (Tf ₂ NH)	1.5 h	95 (98:2)	96
 F10/Fo (AlBr ₃)	0.66 h	96 (98:2)	66
 F7/Fo (Tf ₂ NH)	0.75 h	97 (98:2)	98
 F7/Fo (AlBr ₃)	0.5 h	95 (98:2)	97
 F5/Fo (Tf ₂ NH)	1.0 h	95 (98:2)	98
 F5/Fo (AlBr ₃)	0.5 h	97 (98:2)	98

A comparison of the catalytic power of the activated **F10/Fo**, **F10/F2**, **F7/Fo**, **F7/F2**, **F5/Fo** and **F5/F2** precatalysts using the reaction of cyclopentadiene with ethyl crotonate under the standard conditions of the comparisons shown in Table 4 is outlined in Table 10. Again, the Tf₂NH-activated catalysts give good enantioselectivities in each case, but the **F10**-based catalyst did not when AlBr₃ was employed for activation. From the data in Table 9 and 10, we conclude that the **F10/Fo**·AlBr₃ catalyst is likely to be less useful as Diels–Alder catalyst than the other systems studied.

When all the data summarized in Table 4, 5, 6 and 10 are scrutinized carefully, it is clear that the **F2/F2** catalyst is the most potent of all those that are included in the present work, followed by the **F7/F2**- or **Fo/F2**-derived catalysts.

Aluminum Bromide Activation of Oxazaborolidines for (4+2)-Cycloaddition. As mentioned at the outset of this article, faster rates of (4+2)-cycloaddition are usually observed for AlBr₃-activated oxazaborolidine catalysts as compared to proton-activated equivalents. In addition, AlBr₃ was the only Lewis acid activator that was found to afford fast, clean and highly enantioselective Diels–Alder reactions. It occurred to us that the superior effectiveness of AlBr₃ activation might be due to an equilibrium between two aluminum (III)-complexed species, specifically **15** and **16** (Scheme 3). Of these, the later would be expected to be the more powerfully catalytic.

Scheme 3. Equilibrium of AlBr₃-activated Oxazaborolidinium Catalysts

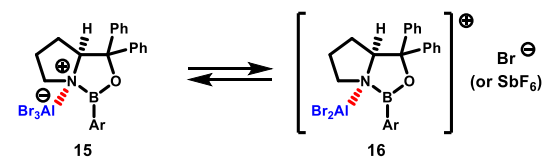
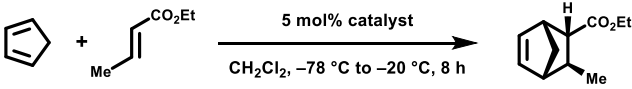
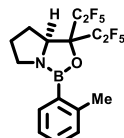
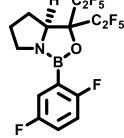
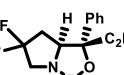
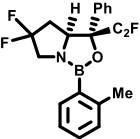
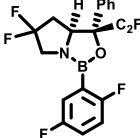
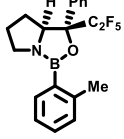
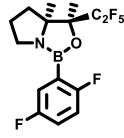


Table 10. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Ethyl But-2-enoate using the F5, F7 and F10 Family of Catalysts



catalyst	% yield (endo/exo)	% ee
 F10/Fo (Tf ₂ NH)	20 (98:2)	94
 F10/F2 (Tf ₂ NH)	30 (97:3)	90
 F10/F2 (AlBr ₃)	35 (96:4)	55
 F7/Fo (AlBr ₃)	50 (98:2)	90
 F7/F2 (AlBr ₃)	62 (98:2)	82
 F5/Fo (AlBr ₃)	50 (98:2)	95
 F5/F2 (AlBr ₃)	60 (98:2)	86

To test this idea, we measured the catalytic conversion of cyclopentadiene and ethyl crotonate to the Diels–Alder adduct in the presence or absence of AgSbF₆ (one equivalent based on the amount of **15** in CH₂Cl₂ solution). In this connection, it was observed that a precipitate of AgBr is rapidly formed upon addition of AgSbF₆ to the complex **15**. The results of these experiments with three different oxazaborolidines are shown in Table 11. The fact that there was acceleration as well as formation of AgBr indicate that the cationic pathway via **16** is at least partly responsible for the superior performance in oxazaborolidinium-catalyzed reactions that is seen with the use of AlBr₃-activation.

The possible formation of the cationic species **16** finds further support from ¹H-NMR measurements. Table 12 summarizes the NMR data for **1**, **4** and **16**. The H_a-proton, which is especially sensitive to complexation, undergoes a progressive downfield shift in the series **1**, **4** and **16**.

Table 11. Acceleration of AlBr_3 -activated Oxazaborolidinium Catalysts by AgSbF_6 .

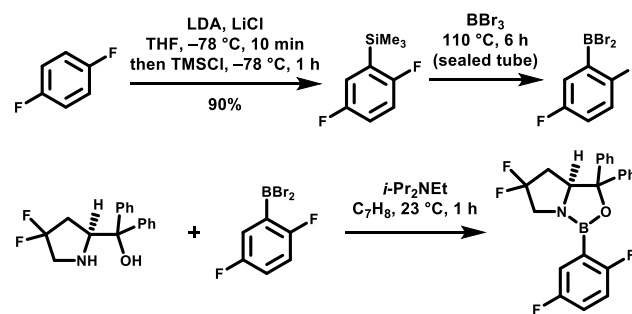
catalyst		additive	% yield (endo/exo)	% ee
	4 (AlBr_3)	—	10 (98:2)	98
	—	AgSbF_6	35 (97:3)	98
	F5/F0 (AlBr_3)	—	48 (98:2)	95
	—	AgSbF_6	62 (98:2)	95
	F7/F0 (AlBr_3)	—	50 (98:2)	90
	—	AgSbF_6	65 (98:2)	92

Table 12. Selected ^1H -NMR Data of Compounds 1, 4 and 16 in CD_2Cl_2

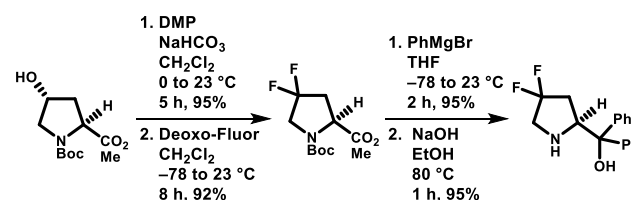
Proton	1 (ppm)	4 (ppm)	16 (ppm)
a	4.54	5.25	5.47
b	3.40, 3.24	3.98, 3.47	4.23, 3.49
c	1.78 (2H)	2.10 (2H)	2.17 (2H)
d	1.60, 0.95	1.90, 1.41	1.98, 1.52
e	2.63	2.85	2.88

Synthesis of Ligands and Precatalysts. The formation of the first-generation oxazaborolidine precatalyst can be accomplished efficiently and cleanly simply by heating the commercially available (*S*)-diphenylprolinol with either *o*-tolylboronic acid, the corresponding trimeric anhydride (boroxine) or dimethyl *o*-tolylborate with toluene (or benzene) at reflux with removal of H_2O or methanol (e.g. using an external extractor containing a mixture of NaH /celite, CaH_2 /celite or 4 Å molecular sieves). These procedures are unsuitable for the clean formation of the precatalysts in the series 7, 8, 9 and 10. Therefore, another approach had to be developed. Fortunately, we were able to solve the problem in every case by use of the appropriate aryl dibromoborane under the carefully controlled preparative conditions that are shown for the synthesis of the F_2/F_2 precatalyst in Scheme 4. This approach was also

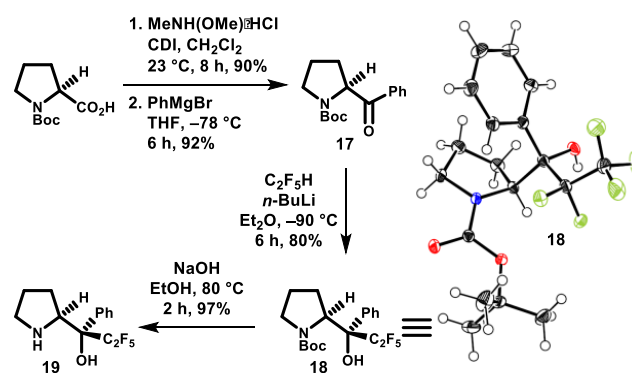
effective as a general process for formation of the other precatalysts mentioned in this paper of general formulas 8, 9 and 10.

Scheme 4. Synthesis of the F_2/F_2 Precatalyst

The synthesis of (*S*)-(4,4-difluoropyrrolidin-2-yl)diphenylmethanol, the amino alcohol required for the generation of F_2/F_0 , F_2/F_1 and F_2/F_2 catalysts, was accomplished efficiently by the process shown in Scheme 5. The ready availability of the starting (*S*)-4-hydroxyproline methyl ester, the efficiency of the route and the easy purification of the nicely crystalline F_2 amino alcohol are key to the value of the second generation catalysts such as F_2/F_0 and F_2/F_2 . The experimental details for the synthesis of the ligand and its conversion to the F_2/F_0 , F_2/F_1 and F_2/F_2 precatalysts are given in the Supporting Information.

Scheme 5. Synthetic Route to the Precursor of the F_2 precatalysts 7

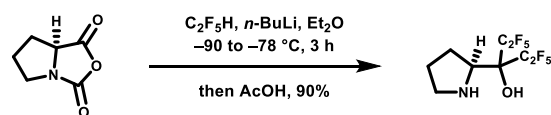
The synthetic pathway to the amino alcohol ligands of the family of precatalysts of general structure 8, (*S*)-2,2,3,3,3-pentafluoro-1-phenyl-1-((*S*)-pyrrolidin-2-yl)propan-1-ol, is summarized in Scheme 6. There are two notable aspects of this synthetic route. First, the use of the commercially available refrigerant pentafluoroethane (HFC-125) to generate $\text{CF}_3\text{CF}_2\text{Li}$ by reaction with *n*-BuLi in ether

Scheme 6. Synthetic Route to the Precursor of the F_5 precatalysts 8

at $-90\text{ }^{\circ}\text{C}$,²² and second, the remarkably high diastereoselectivity of the addition to the *N*-Boc-(*S*)-prolyl phenyl ketone **17** to form the crystalline fluorinated tertiary alcohol **18** (m.p. = $175\text{--}178\text{ }^{\circ}\text{C}$). This allows efficient and rapid access to the unusual amino alcohol **19**, which is the precursor for precatalyst family **8**. The structure of **18** was unambiguously demonstrated by X-ray crystallographic analysis.

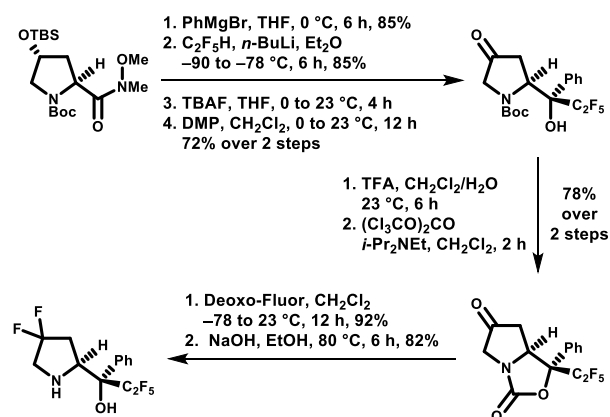
The synthesis of (*S*)-1,1,1,2,2,4,4,5,5,5-decafluoro-3-(pyrrolidin-2-yl)pentan-3-ol, the amino alcohol precursor of precatalyst **10**, was accomplished simply by addition of pentafluoroethyl lithium to the Leuchs anhydride of (*S*)-proline, as shown in Scheme 7.

Scheme 7. Synthetic Route to the Precursor of the F10 precatalysts **10**



Finally, it should be mentioned that the methodology just described can also be extended to the heptafluoro (*S*)-prolinol shown in Scheme 8. This interesting ligand is the precursor to the precatalyst **9** which was found to be highly effective (see Tables 9 and 10).

Scheme 8. Synthetic Route to the Precursor of the F7 precatalysts **9**



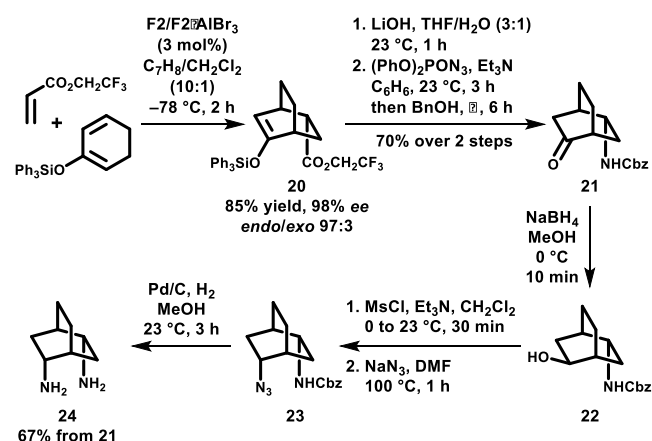
Expanding the Utility of Second-Generation Catalysts through New Synthetic Applications. The development of new and very potent chiral oxazaborolidinium cationic catalysts, e.g. the **F2/Fo**, **F2/F2** and **F7/Fo** structures described above, provides major opportunities for practical new applications. A high diversity of such very useful processes is possible because of the synthetic versatility of Diels–Alder adducts and the wide variety of chiral structures which have become readily accessible. A range of such practical applications is presented in this section.

1. Synthesis of Optically Active Diamines

The C_2 -symmetric diamine **24** has recently been shown by J. D. White and S. Shaw to be a valuable precursor to effective salen catalysts for asymmetric nitro-aldol, allylation, cycloaddition, cyclopropanation and Michael reactions.²³ The chiral diamine **24** was obtained by a multistep synthesis *via* a diacid which was resolved inefficiently

using a brucine salt. Consequently, its availability and utilization in synthesis is limited. We therefore applied the methodology described above to a solution of this problem, with the results outlined in Scheme 9.

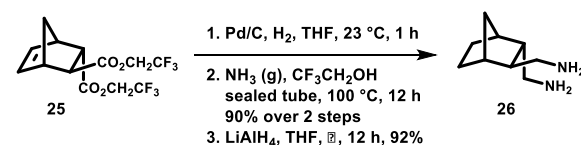
Scheme 9. Synthesis of (–)-*cis*-2,5-Diaminobicyclo[2.2.2]octane (**24**)



The initial Diels–Alder step using the AlBr_3 -activated **F2/F2** catalyst provides the adduct **20** cleanly in 98% ee. Ester hydrolysis and Schmidt rearrangement followed by reaction of the resulting keto isocyanate with benzyl alcohol *in situ* forms the keto amide **21**. The following sequence of (1) ketone reduction, (2) mesylation, (3) $\text{S}_{\text{N}}2$ displacement of the mesylate with azide to **23**, and (4) catalytic reduction with H_2 – Pd/C gives the target diamine **24** in 67% yield over four steps from **21**. It should be noted that the ketone reduction proceeds with complete diastereoselectivity to afford the *exo*-alcohol **22**. The same facial selectivity was also observed in attempted imine reduction under either reductive amination or hydrogenation conditions. Reaction of diamine **24** with 3,5-di-*tert*-butylsalicylaldehyde afforded the crystalline salen ligand that is spectroscopically identical with the known compound.²³ We believe that this method of synthesis is superior to the route previously employed.

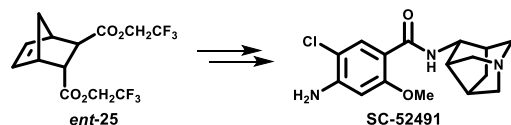
There are many other 1,4-diamines which are of possible value as ligands that are readily accessible by the use of the enantioselective (4+2)-cycloaddition methodology reported herein. As a further example, the 1,4-diamine **26**, was readily prepared from the chiral diester **25**, as shown in Scheme 10. Reaction of diamine **26** with 3,5-dichlorosalicylaldehyde gave the corresponding crystalline Schiff base cleanly (m.p. = $115\text{ }^{\circ}\text{C}$).

Scheme 10. Synthesis of (+)-*trans*-2,3-Diaminomethylbicyclo[2.2.1]heptane (**26**)



Chiral diester *ent*-**25** also effectively opens a catalytic enantioselective route to the dual 5-HT₄/5-HT₃ serotonergic agonist/antagonist SC-52491 (Scheme 11).²⁴

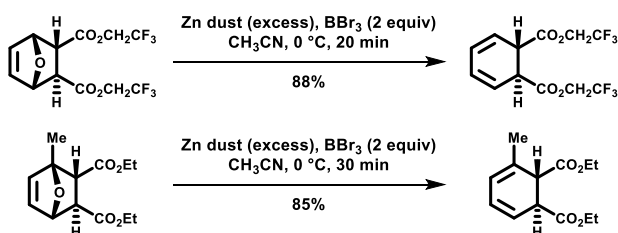
Scheme 11. Diester *ent*-25 as Intermediate in the Enantioselective Synthesis of SC-52491²⁴



2. Diels–Alder Adducts of Furans as Key Synthetic Intermediates

The (4+2)-cycloaddition reactions of furans and various dienophiles have hardly been exploited in the synthetic literature, despite the fact that such processes generate a new six-membered ring which is functionalized at all six carbons and offer useful handles for derivatization. Herein, we describe 1,4-deoxygenation as one such useful post-cycloaddition transformation that exemplifies the synthetic potential of furan–Diels–Alder products, a number of which are listed in Table 8 above. We have found that these various adducts undergo smooth 1,4-deoxygenation to form 1,3-cyclohexadienes upon exposure to a mixture of zinc powder (excess) and BBr_3 (2 equiv) in CH_3CN at 0 °C in 20–30 min, as shown in Scheme 12. Further examples are presented in the Supporting Information. It should be noted that the products shown, which correspond to Diels–Alder adducts with the unavailable dehydro-1,3-butadiene-1,4-diyl, can potentially be used for a large number of further transformations. An earlier publication from our group described another type of application of furan Diels–Alder adducts, specifically, to the synthesis of the HIF-1 inhibitor laurenditerpenol.²⁵

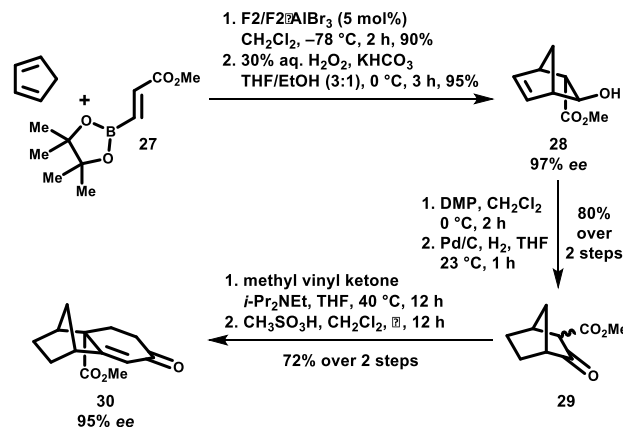
Scheme 12. Efficient 1,4-Deoxygenation of Furan–Diels–Alder Adducts



3. A Tactical Combination: Diels–Alder – Robinson Annulation Sequence

Concatenation of two or more powerful synthetic constructions generally provides the most effective access to complex structure. An example of the value of this approach using enantioselective (4+2)-cycloaddition methodology enabled by the potent catalysts described above is illustrated here by the synthesis of **30** as shown in Scheme 13. The reaction of the *E*-boronate ester **27** with cyclopentadiene gave, after work-up with H_2O_2 – KHCO_3 – H_2O , the *trans*- β -hydroxy ester **28** in excellent yield and enantioselectivity.²⁶ The tactical combination of (4+2)-cycloaddition and Robinson annulation between readily available ketoester **29**, obtained after Dess–Martin periodinane oxidation and olefin hydrogenation, and methyl vinyl ketone then afforded the tricyclic ester enone **30** efficiently and conveniently.

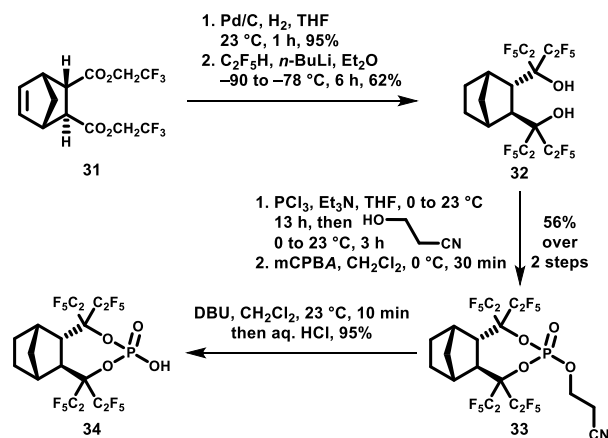
Scheme 13. Tactical Combination of Diels–Alder and Robinson Annulation Reactions



4. Synthesis of Highly Acidic Novel Brønsted Acids

The rigid bicyclic structures provided by the Diels–Alder reaction between cyclic dienes and disubstituted dienophiles provide novel scaffolds for asymmetric catalysis (e.g. as shown in Scheme 9 above). As representative examples, we demonstrate the synthesis of the highly acidic eicosafuorodiol **32** and its corresponding phosphoric acid diester **34** (Scheme 14).

Scheme 14. Synthesis of Chiral Brønsted Acids

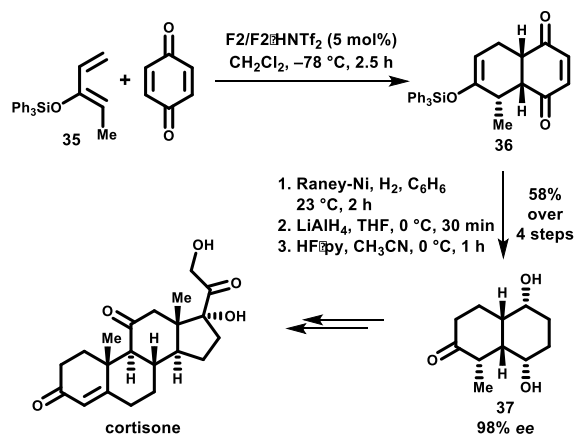


Hydrogenation and exhaustive pentafluoroethylation of the esters in adduct **31** afforded the intriguing diol **32**. Tartaric acid-derived perfluorodiols similar to **32** have been shown by Berkessel to be highly acidic with pK_a -values as low as 2.4 in DMSO,²⁷ and diols based on bicyclo[2.2.1]heptanes have been successfully applied to enantioselective catalysis.²⁸ The strongly electron-withdrawing effect exerted by the perfluoroalkyl substituents also leads to a large enhancement of acidity of the phosphoric acid diester **34** as estimated from relative rates of intramolecular Prins cyclization in comparison with standards of known pK_a (see Supporting Information for details). The acidity of **34** is between picric acid (pK_a in MeCN = 11.0) and methanesulfonic acid (pK_a in MeCN = 9.97). This represents an increase in reactivity of three orders of magnitude as compared to BINOL-derived chiral phosphoric acids.²⁹ The ready availability of the chiral diol **32** and acid **34** open new avenues for Brønsted acid catalysis.

5. Enantioselective Route for the Synthesis of Cortisone via the Sarett–Merck Approach^{30,31}

The reaction of the 1,3-diene **35** with benzoquinone in the presence of 5 mol% of the triflimide-activated **F2/F2** catalyst proceeded to completion in 2.5 h in CH_2Cl_2 at -78°C to give the adduct **36** in 98% *ee* and 98% yield by quantitative ^1H -NMR analysis (Scheme 15). Hydrogenation of the conjugated double bond in benzene followed by reduction with LiAlH_4 in THF at 0°C and enol deprotection provided the pure crystalline keto diol **37** in high yield. In the original Sarett–Merck synthesis this intermediate was obtained in racemic form and resolution could only be performed with a later tricyclic intermediate which represented a serious drawback to the use of this route for production.^{30,31} Although we did not pursue the use of even less of the **F2/F2** catalyst for the Diels–Alder step, that is certainly a likely possibility if a somewhat longer reaction time is allowed.

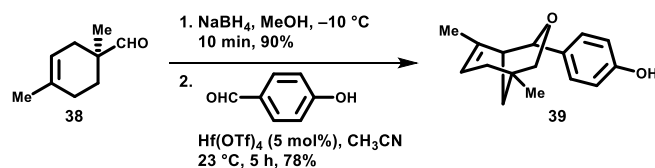
Scheme 15. An Enantioselective Form of the Early Stage of the Sarett–Merck Synthesis of Cortisone



6. Access to Enantioenriched Heterobicycles

The adducts available from acyclic dienes with dienophiles also offer an entry into complex heterobicyclic systems, as exemplified by the synthesis of the 3-oxabicyclo[3.3.1]non-6-ene **39** from aldehyde **38** by reduction and Prins cyclization (Scheme 16). This heterobicyclic motif has been identified as a potent estrogen receptor ligand.³²

Scheme 16. Example for the Elaboration of Diels–Alder Adducts to 3-Oxabicyclo[3.3.1]non-6-enes



DISCUSSION

A major objective of this study was the development of more potent chiral, cationic oxazaborolidinium catalysts for enantioselective reactions, such as Diels–Alder cycloadditions. Specifically, it was hoped that sufficiently active catalysts could be found to allow the routine use at

the 1–2 mol% level. We have achieved this target level of catalytic efficiency in several different series by the judicious use of fluorine substituents on the prolinol scaffold of the chiral ligand and on the aryl substituent attached to boron. Catalysts derived from the **F2**, **F5** and **F7** ligands described above were found to function at the desired level of Lewis acidity and afford excellent yields and enantioselectivities in a number of test Diels–Alder reactions even at the 1 mol% catalyst level. The high potency of these catalysts coupled with the extremely easy recovery of the chiral ligand during product isolation combine to make these second generation chiral reagents ideal for larger scale use.

The absolute configuration of the cycloaddition products resulting from the use of the fluorine-substituted catalysts **F2/Fo**, **Fo/F2**, **F2/F1**, **F2/F2**, **F5/Fo**, **F5/F2**, **F7/Fo** and **F7/F2** was the same as for the non-fluorine bearing, first generation catalysts **2**, **3** and **4**, and as predicted by the pre-transition state models **5** and **6**. All these catalysts contain the neighboring π -aromatic substituent on the oxazaborolidine ring that favors dienophile binding as shown in structures **5** and **6**.

As mentioned in an earlier section, the successive introduction of fluorine substituents into the oxazaborolidine system results in increased catalytic activity. However, the incremental increase diminishes as fluorines are added and activity tends towards a limit (e.g. see Table 10). Clearly, if the basicity at nitrogen in the precatalyst were to be decreased to the point that Tf_2NH or AlBr_3 are not sufficiently electrophilic to coordinate, there would be no activation, and hence a limit. Nonetheless, the results reported herein demonstrate the value of judicious introduction of a limited number of fluorine atoms to boost the performance of a chiral electrophilic catalyst. This approach merits wider use in the design of chiral catalytic systems.

The interesting finding that AlBr_3 is usually somewhat more effective for precatalyst activation than Tf_2NH , along with the fact that other strong Lewis acids (e.g. BF_3 , BCl_3 , BBR_3) are far inferior to AlBr_3 , prompted the experiments shown in Table 11 to probe a possible reason for these facts. The further rate enhancements produced by the use of a combination of AlBr_3 and AgSbF_6 as compared to AlBr_3 alone support the idea that the reactive complex may be cationic, for example as shown in structure **40** or **41** (Figure 5, diene component omitted).

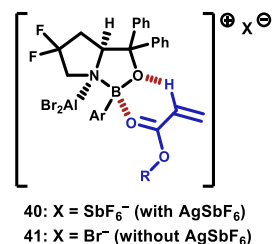


Figure 5. Possible Reactive Complexes between an AlBr_3 -activated Catalyst and an α,β -Unsaturated Dienophile

CONCLUSION

Enhancement of enantioselective catalysis of Diels–Alder reactions by introduction of fluorine substituents in oxazaborolidinium cations has been demonstrated as both significant and useful. Specifically, the objective of achieving excellent reaction rates, product yields and enantioselectivities has been realized using 1–2 mol% of several catalysts e.g. **F2/Fo**, **F2/F2** and **F7/Fo** structures. The chiral prolinols used for catalysis are readily prepared and easily recovered for reuse (see Supporting Information). A variety of specific examples document some of the many ways in which readily available chiral Diels–Alder adducts can be used either for general synthesis or for the production of chiral ligands and reagents that are useful for asymmetric catalysis. Efficient synthetic procedures have been presented for each of the new second generation chiral ligands and precatalysts (see Supporting Information).

ASSOCIATED CONTENT

Experimental procedures and characterization data for all reactions and products including copies of ^1H and ^{13}C NMR spectra. 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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