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

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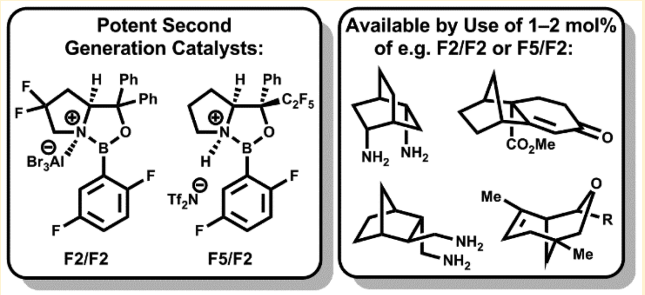
Supporting Information

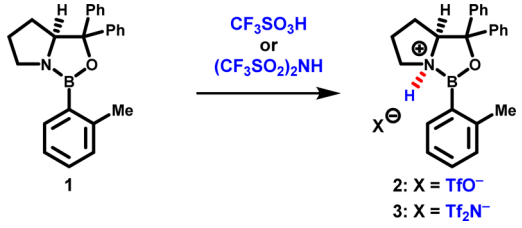
ABSTRACT: The coordination of chiral ligands to Lewis acid metal derivatives, a useful strategy for enantioselective, electrophilic catalysis, generally leads to a lower level of catalytic activity than that of the original uncomplexed compound. Activation by further attachment of a proton or strong 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 1920s,[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 superfamiliy of (4+2)-cycloaddition reactions consisting of many variants, for example, 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).

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 B_{12},[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** (Figure 1).[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]

In previous work, catalysts **2**–**4** have usually been employed at loadings between 5 and 20 mol % of the substrates. In this article, we describe recent systematic studies that addressed the following questions: (1) Is it possible to design more potent

Received: January 5, 2016
Published: January 26, 2016

DOI: 10.1021/jacs.6b00100
J. Am. Chem. Soc. 2016, 138, 2443–2453

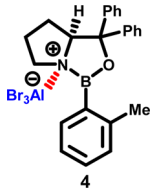


Figure 1. $AlBr_3$-activated oxazaborolidine catalyst **4**.

versions of catalysts **2**−**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**−**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 pretransition state assembly: one for conjugated aldehydes (**5**) and one for α,β-unsaturated carbonyl compounds possessing an α-C−H bond (**6**) (Figure 2). These models have received support from computational studies[19] as well as from their predictive success in numerous examples.

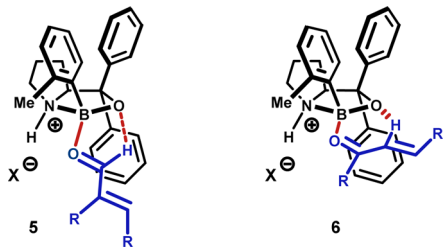


Figure 2. Pretransition-state models for the enantioselectivity in Diels−Alder reactions of α,β-enals (**5**) and other dienophiles (**6**).

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 noncoordinating 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).

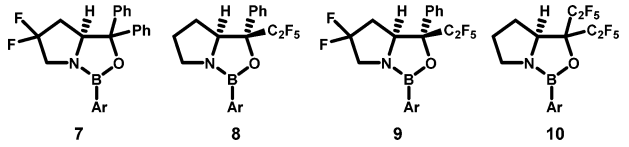
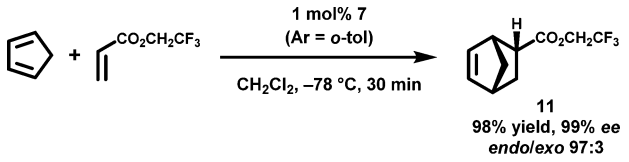


Figure 3. Second-generation oxazaborolidines **7**−**10**.

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**−**10** were studied: *o*-tolyl, 2-fluorophenyl, and 2,5-difluorophenyl. In the following sections, we compare the catalytic behavior 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/F0** will refer to **7** (Ar = *o*-tolyl); **F2/F2** will refer to **7** (Ar = 2,5-difluorophenyl); **F5/F0** will refer to **8** (Ar = *o*-tolyl); **F5/F2**

DOI: 10.1021/jacs.6b00100
J. Am. Chem. Soc. 2016, 138, 2443−2453

will refer to **8** (Ar = 2,5-difluorophenyl); **F7/F0** will refer to **9** (Ar = *o*-tolyl); and **F10/F0** will refer to **10** (Ar = *o*-tolyl), etc. This simplified system is exemplified in Figure 4.

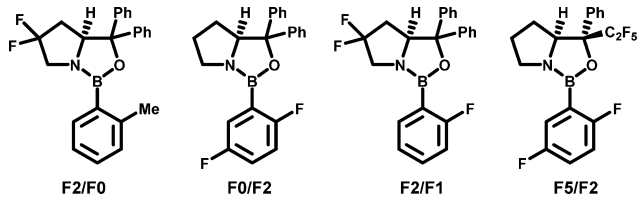
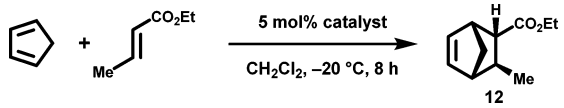


Figure 4. Examples for nomenclature of the precatalysts.

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 CH_2Cl_2 for 8 h). The results, which are shown in Table 1, further point to roughly an order of magnitude gain in

Table 1. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Ethyl But-2-enoate using Catalysts 3, 4, and F2/F0



catalyst	% yield (*endo*/*exo*)	% ee
3	2 (91:9)	98
4	10 (92:8)	98
F2/F0 (Tf_2NH)	24 (95:5)	98
F2/F0 ($AlBr_3$)	35 (98:2)	98

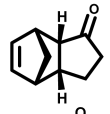
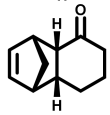
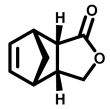
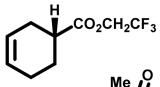
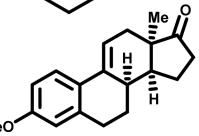
catalytic power upon replacement of the β-CH_2 by CF_2 in the chiral catalyst. In this connection, it is important to note that the carbonyl group of the Diels–Alder product can also bind to the Lewis acid center of the catalyst. The resulting product inhibition can be expected to moderate the rate acceleration 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.

A comparison of the results obtained in a variety of Diels–Alder reactions catalyzed by the triflimide-activated **F2/F0** 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/F0** catalyst in various combinations of (1) lower amounts of catalyst, (2) lower reaction time, or (3) lower temperature.

The $AlBr_3$-activated fluorinated **F2/F0** 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 $AlBr_3$-activated **F2/F0** 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.

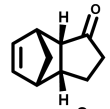
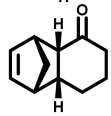
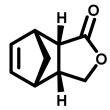
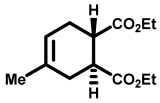
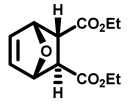
Encouraged by the finding that the $AlBr_3$-activated **F2/F0** catalyst is a definite improvement over the first-generation $AlBr_3$-activated catalyst **4**, we prepared the **F2/F2** precatalyst **7**

Table 2. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles in the Presence of Catalyst 2, 3, or Triflimide-Activated F2/F0 Catalyst

Product	catalyst (mol%)	Conditions (°C, h)	% yield (*endo*/*exo*)	% 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.

Table 3. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles in the Presence of $AlBr_3$-Activated F2/F0 Catalyst or 4

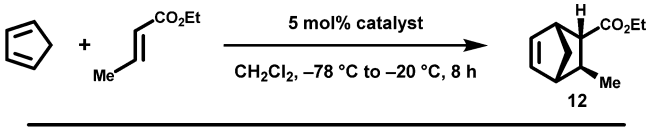
Product	catalyst (mol%)	Conditions (°C, h)	% yield (*endo*/*exo*)	% ee
	**4**[a] (4)	–40, 1	95 (93:7)	92
	F2/F0 (1)	–40, 6	92 (96:4)	92
	**4**[a] (4)	–20, 6	99 (94:6)	95
	F2/F0 (1)	–20, 12	98 (95:5)	96
	**F2/F0** (1)	–20, 16	90 (92:8)	93
	**4**[a] (4)	–20, 48	71	97
	F2/F0 (1)	–20, 24	91	96
	**4**[a]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

[a] see ref. 7.

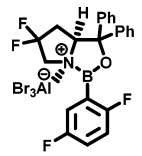
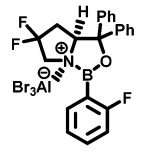
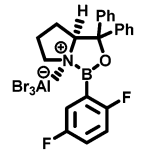
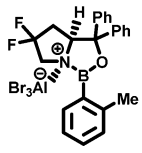
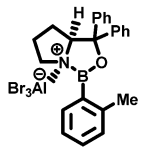
(Ar = 2,5-difluorophenyl) and the **F2/F1** precatalyst **7** (Ar = *o*-fluorophenyl). The whole family of catalysts was compared using the reaction of cyclopentadiene and ethyl crotonate under identical conditions to determine relative effectiveness, with the results that are summarized in Table 4. 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 ^{1}H-NMR analysis) precatalysts. In

DOI: 10.1021/jacs.6b00100
J. Am. Chem. Soc. 2016, 138, 2443–2453

Table 4. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Ethyl But-2-enoate Using the F2 Family of $AlBr_3$-Activated Catalysts



12

catalyst	% yield (*endo*/*exo*)	% *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

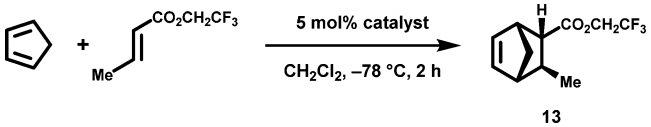
each case, the Diels–Alder adduct **12** was the sole product, and the conversion was calculated from ^{1}H-NMR analysis to determine the ratio of **12** to ethyl crotonate. Interestingly, the increase in conversion to product by CF_2 replacement of CH_2 in the pair **F2**/**F2** and **F0**/**F2** is 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 $AlBr_3$-activated **F2**/**F2** catalyst is superior to the others. However, it is noteworthy that the $AlBr_3$-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.

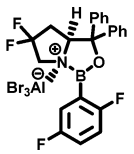
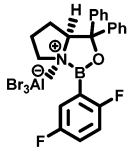
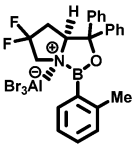
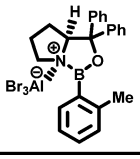
A similar comparison of catalytic potencies was made using as test reaction the Diels–Alder addition of cyclopentadiene and trifluoroethyl crotonate, a somewhat more reactive dienophile than ethyl crotonate, with the results shown in Table 5. The relative catalytic activities were similar for the trifluoroethyl and ethyl esters, with the $AlBr_3$-activated **F2**/**F2** catalyst clearly being the most powerful.

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 $AlBr_3$-activated catalysts in the reaction of

Table 5. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Trifluoroethyl But-2-enoate Using the F2 Family of $AlBr_3$-Activated Catalysts



13

catalyst	% yield (*endo*/*exo*)	% *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

this diene with trifluoroethyl acrylate under standard conditions was 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**.

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]

The series of precatalysts defined by structures **8**–**10** were selected next for our comprehensive survey of second-generation oxazaborolidine reagents. Efficient and stereocontrolled syntheses of **8**–**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

DOI: 10.1021/jacs.6b00100
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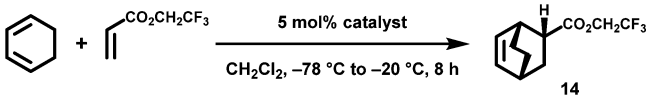
Table 6. Comparison of Diels–Alder Reactions of Cyclohexadiene with (*E*)-Trifluoroethyl Acrylate Using the F2 Family of $AlBr_3$-Activated Catalysts and 4



14

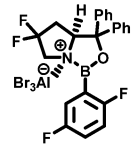
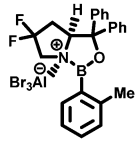
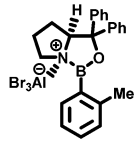
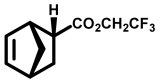
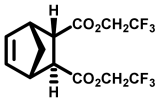
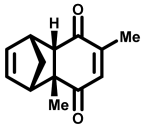
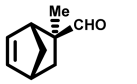
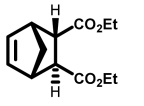
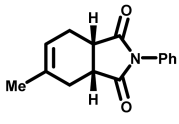
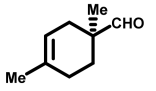
catalyst	% yield (*endo*/*exo*)	% *ee*
 F2/F2 ($AlBr_3$)	74 (97:3)	96
 F2/F0 ($AlBr_3$)	40 (98:2)	94
 4	13 (96:4)	94

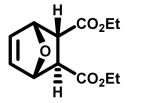
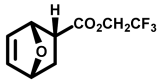
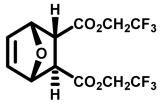
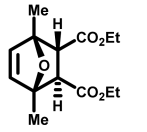
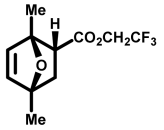
Table 7. Enantioselective Diels–Alder Reactions of Various Dienes and Dienophiles Using 1 mol % of the F2 Family of $AlBr_3$-Activated Catalysts

Product	catalyst (mol%)[a]	Conditions (°C, h)	% yield (*endo*/*exo*)	% *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] $AlBr_3$ was used as activator unless otherwise noted.

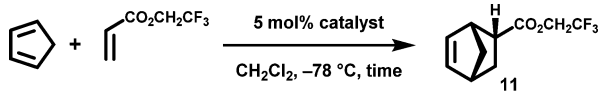
8–10 (Ar = *o*-tol) led to fast, enantioselective, and efficient (4+2)-cycloaddition after activation with Tf_2NH using cyclopentadiene and trifluoroethyl acrylate as test reactants, as shown in Table 9. However, when $AlBr_3$ was employed as activator of the **F10/F0** precatalyst, the test reaction was surprisingly less enantioselective than with the **F5/F0** or **F7/F0** precatalysts. This result may be due to the presence of uncoordinated $AlBr_3$ 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

Table 8. Enantioselective Diels–Alder Reactions of Furans and Dienophiles Using 1 mol % of the F2 Family of $AlBr_3$-Activated Catalysts

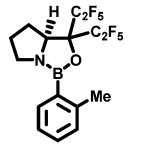
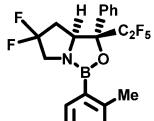
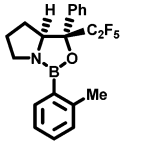
Product	catalyst (mol%)[a]	Conditions (°C, h)	% yield (*endo*/*exo*)	% *ee*
	4 (8)	–40, 16	71	99
	F2/F2 (1)	–40, 12	68	96
	4 (4)	–78, 8	99 (88:12)	99
	F2/F2 (1)	–78, 5	96 (90:10)	98
	F2/F2 (1)	–40, 7	75	95
	4 (8)	–40, 24	72[a]	91
	F2/F2 (1)	–40, 16	68[a]	90
	4 (4)	–78, 12	99 (90:10)	94
	F2/F2 (1)	–78,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

[a] yield determined after conversion to the hydrogenated product.

Table 9. Comparison of Diels–Alder Reactions of Cyclopentadiene with (*E*)-Trifluoroethyl Acrylate Using the F5/F0, F7/F0, and F10/F0 Catalysts



11

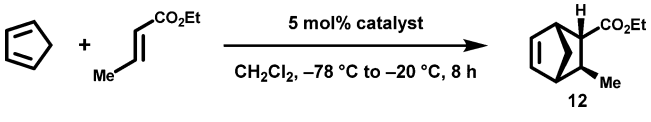
catalyst	time	% yield (*endo*/*exo*)	% *ee*
 F10/F0 (Tf_2NH)	1.5 h	95 (98:2)	96
F10/F0 ($AlBr_3$)	0.66 h	96 (98:2)	66
 F7/F0 (Tf_2NH)	0.75 h	97 (98:2)	98
F7/F0 ($AlBr_3$)	0.5 h	95 (98:2)	97
 F5/F0 (Tf_2NH)	1.0 h	95 (98:2)	98
F5/F0 ($AlBr_3$)	0.5 h	97 (98:2)	98

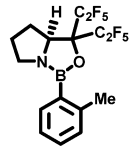
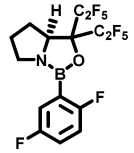
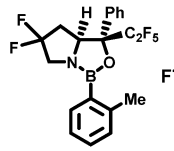
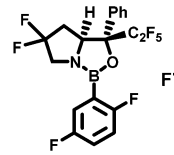
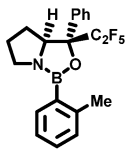
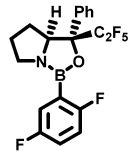
DOI: 10.1021/jacs.6b00100
J. Am. Chem. Soc. 2016, 138, 2443–2453

that the presence of a bulky C_2F_5 substituent *cis* to the coordination site of $AlBr_3$ may disfavor complexation.

A comparison of the catalytic power of the activated **F10/F0**, **F10/F2**, **F7/F0**, **F7/F2**, **F5/F0**, 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 Tf_2NH-activated catalysts give

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



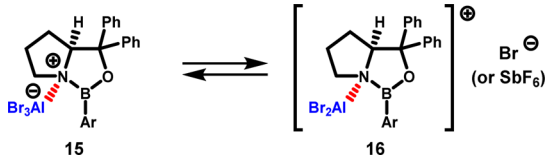
catalyst	% yield (*endo*/*exo*)	% *ee*
 F10/F0 (Tf_2NH)	20 (98:2)	94
 F10/F2 (Tf_2NH)	30 (97:3)	90
F10/F2 ($AlBr_3$)	35 (96:4)	55
 F7/F0 ($AlBr_3$)	50 (98:2)	90
 F7/F2 ($AlBr_3$)	62 (98:2)	82
 F5/F0 ($AlBr_3$)	50 (98:2)	95
 F5/F2 ($AlBr_3$)	60 (98:2)	86

good enantioselectivities in each case, but the **F10**-based catalyst did not when $AlBr_3$ was employed for activation. From the data in Tables 9 and 10, we conclude that the **F10/F0**·$AlBr_3$ catalyst is likely to be less useful as a Diels–Alder catalyst than the other systems studied.

When all the data summarized in Tables 4–6 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**-, **F0/F2**- and **F2/F0**-derived catalysts.

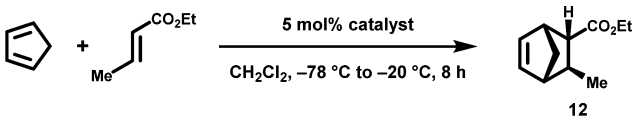
Aluminum Bromide Activation of Oxazaborolidines for (4+2)-Cycloaddition. As mentioned at the outset of this article, faster rates of (4+2)-cycloaddition are usually observed for $AlBr_3$-activated oxazaborolidine catalysts as compared to proton-activated equivalents. In addition, $AlBr_3$ was the only 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 $AlBr_3$ activation might be due to an equilibrium between two aluminum(III)-complexed species, specifically **15** and **16** (Scheme 3). Of these, the latter would be expected to be the more powerfully catalytic.

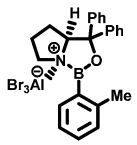
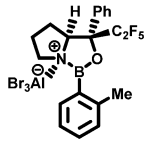
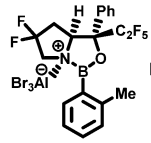
Scheme 3. Equilibrium of $AlBr_3$-Activated Oxazaborolidinium Catalysts



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 $AgSbF_6$ (1 equiv based on the amount of **15** in CH_2Cl_2 solution). In this connection, it was observed that a precipitate of AgBr is rapidly formed upon addition of $AgSbF_6$ 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

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

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 $AlBr_3$-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**.

DOI: 10.1021/jacs.6b00100
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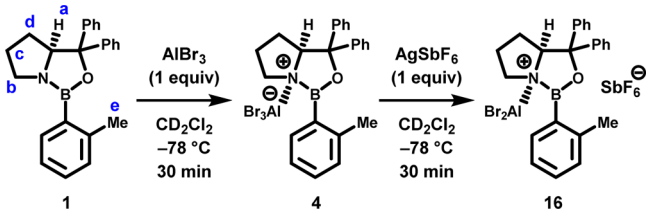
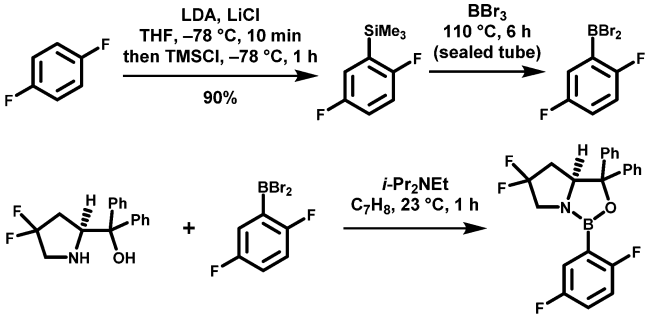
Table 12. Selected ^{1}H-NMR Data of Compounds 1, 4, and 16 in CD_2Cl_2



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**–**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 **F2/F2** 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**–**10**.

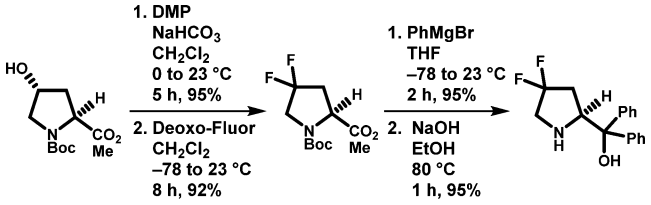
Scheme 4. Synthesis of the F2/F2 Precatalyst



The synthesis of (*S*)-(4,4-difluoropyrrolidin-2-yl)-diphenylmethanol, the amino alcohol required for the generation of **F2/F0**, **F2/F1**, and **F2/F2** 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 **F2** amino alcohol are key to the value of the second-generation catalysts such as **F2/F0** and **F2/F2**. The experimental details for the synthesis of the ligand and its conversion to the **F2/F0**, **F2/F1**, and **F2/F2** precatalysts are given in the Supporting Information.

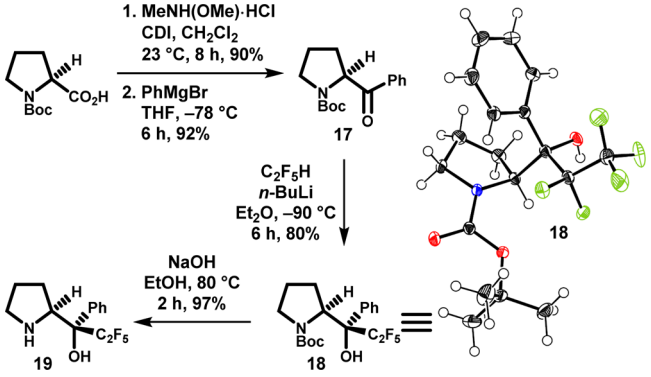
The synthetic pathway to the amino alcohol ligands of the family of precatalysts of general structure **8**, (*S*)-2,2,3,3,3-pentafluoro-1-phenyl-1-((*S*)-pyrrolidin-2-yl)propan-1-ol, is

Scheme 5. Synthetic Route to the Precursor of the F2 precatalysts 7



summarized in Scheme 6. There are two notable aspects of this synthetic route. First, the use of the commercially available

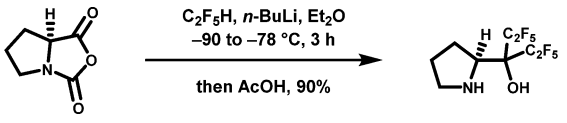
Scheme 6. Synthetic Route to the Precursor of the F5 Precatalysts 8



refrigerant pentafluoroethane (HFC-125) to generate CF_3CF_2Li by reaction with *n*-BuLi in ether at −90 °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** (mp = 175–178 °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-decaafluoro-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).

Expanding the Utility of Second-Generation Catalysts through New Synthetic Applications. The development of new and very potent chiral oxazaborolidinium cationic catalysts, for example, the **F2/F0**, **F2/F2**, and **F7/F0** structures described above, provides major opportunities for practical

DOI: 10.1021/jacs.6b00100
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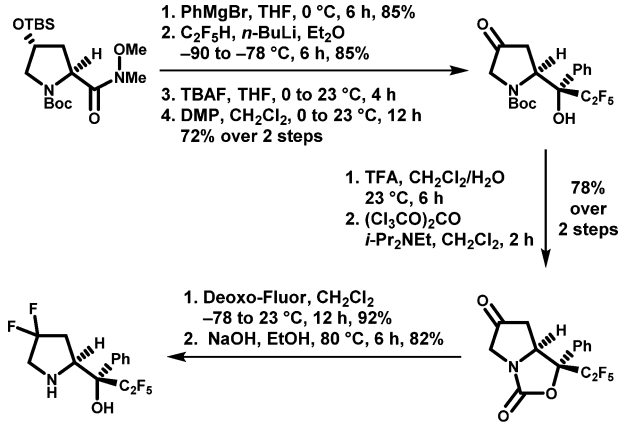
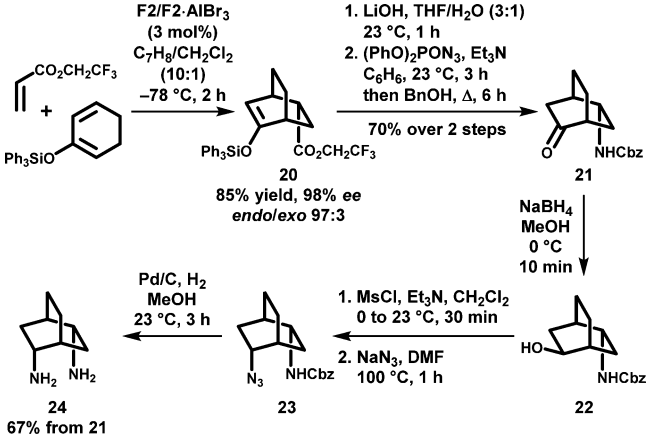
Scheme 8. Synthetic Route to the Precursor of the F7 Precatalysts 9



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.

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.

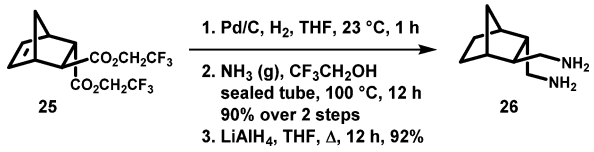
Scheme 9. Synthesis of (−)-*cis*-2,5-Diaminobicyclo[2.2.2]octane (24)



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* form the keto amide **21**. The following sequence of (1) ketone reduction, (2) mesylation, (3) S_N2 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.

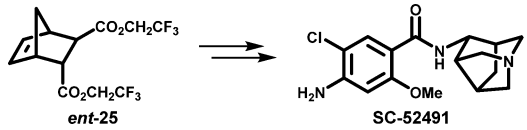
There are many other 1,4-diamines which are of possible value as ligands that are readily accessible by the use of the enantioselective (4+2)-cycloaddition methodology reported herein. As a further example, the 1,4-diamine **26**, was readily prepared from the chiral diester **25**, as shown in Scheme 10. Reaction of diamine **26** with 3,5-dichlorosalicylaldehyde gave the corresponding crystalline Schiff base cleanly (mp = 115 °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-HT_4/5-HT_3 serotonergic agonist/antagonist SC-52491 (Scheme 11).[24]

Scheme 11. Diester *ent*-25 as Intermediate in the Enantioselective Synthesis of SC-52491[24]



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 offers useful handles for derivatization. Herein, we describe 1,4-deoxygenation as one such useful postcycloaddition 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]

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 method-

DOI: 10.1021/jacs.6b00100
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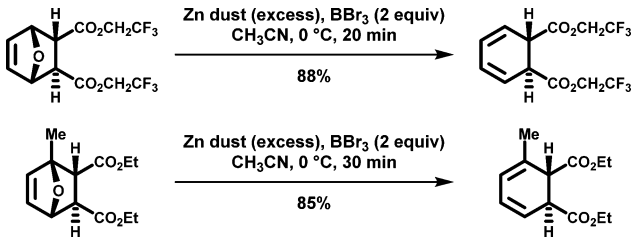
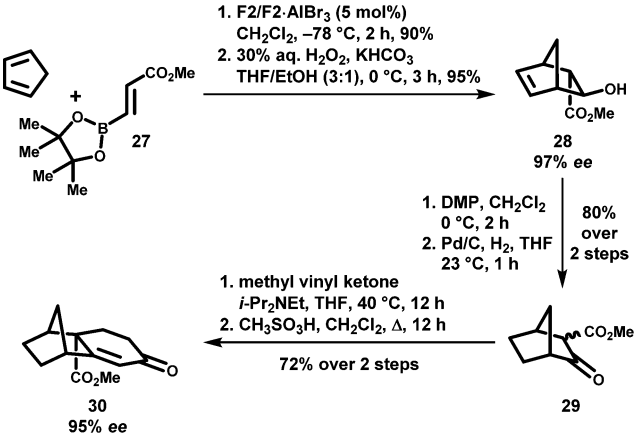
Scheme 12. Efficient 1,4-Deoxygenation of Furan Diels–Alder Adducts



ology enabled by the potent catalysts described above is illustrated here by the synthesis of **30**, as shown in Scheme 13.

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

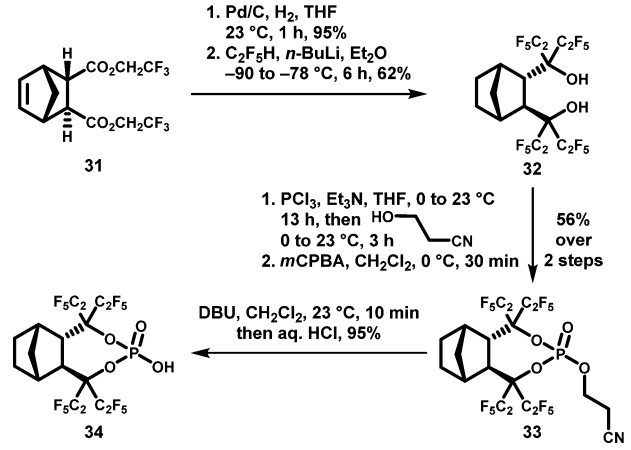


The reaction of the *E*-boronate ester **27** with cyclopentadiene gave, after workup with H_2O_2-$KHCO_3$-H_2O, the *trans*-β-hydroxy ester **28** in excellent yield and enantioselectivity.[26] The tactical combination of (4+2)-cycloaddition and Robinson annulation between readily available ketoester **29**, obtained after Dess–Martin periodinane oxidation and olefin hydrogenation, and methyl vinyl ketone then afforded the tricyclic ester enone **30** efficiently and conveniently.

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 eicosafluorodiol **32** and its corresponding phosphoric acid diester **34** (Scheme 14).

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 3 orders of magnitude as compared to BINOL-derived chiral phosphoric acids.[29] The

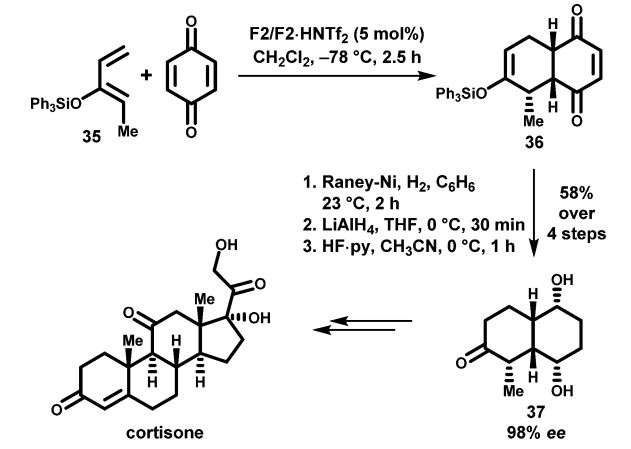
Scheme 14. Synthesis of Chiral Brønsted Acids



ready availability of the chiral diol **32** and acid **34** opens new avenues for Brønsted acid catalysis.

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).

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



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.

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]

DOI: 10.1021/jacs.6b00100
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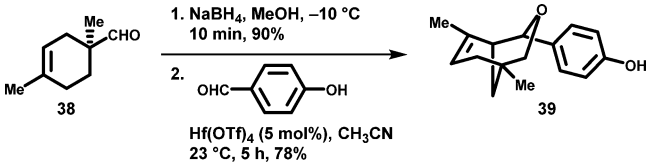
Scheme 16. Example for the Elaboration of Diels–Alder Adducts to 3-Oxabicyclo[3.3.1]non-6-enes



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 substitutents 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.

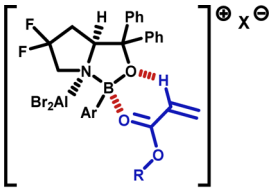
The absolute configuration of the cycloaddition products resulting from the use of the fluorine-substituted catalysts **F2/F0**, **F0/F2**, **F2/F1**, **F2/F2**, **F5/F0**, **F5/F2**, **F7/F0**, and **F7/F2** was the same as for the nonfluorine bearing, first-generation catalysts **2**–**4**, and as predicted by the pretransition 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 toward a limit (e.g., see Table 10). Clearly, if the basicity at nitrogen in the precatalyst was decreased to the point that Tf_2NH or $AlBr_3$ is 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).

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, for example, **F2/F0**, **F2/F2**, and **F7/F0** 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).



40: X = SbF_6^- (with $AgSbF_6$)
41: X = Br^- (without $AgSbF_6$)

Figure 5. Possible reactive complexes between an $AlBr_3$-activated catalyst and an α,β-unsaturated dienophile.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00100.

Structure report (PDF)
Crystallographic data (CIF)
Experimental procedures and characterization data for all reactions and products including copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the following for research grants: Pfizer, Gilead, Bristol-Myers Squibb, and Strategic Science and Technology. S.B. acknowledges a postdoctoral fellowship from the Swiss National Science Foundation. We were generously supplied with Deoxo–Fluor by Airgas Co. and pentafluoroethane by DuPont/Chemours. We thank Dr. Shao-Liang Zheng for his help with the X-ray data collection and structure determination. Sigma-Aldrich Corporation assisted this research with a chemical supply grant.

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DOI: 10.1021/jacs.6b00100
J. Am. Chem. Soc. 2016, 138, 2443−2453