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Useful Applications of Enantioselective (4 + 2)-Cycloaddition Reactions to the Synthesis of Chiral 1,2-Amino Alcohols, 1,2-Diamines, and β-Amino Acids

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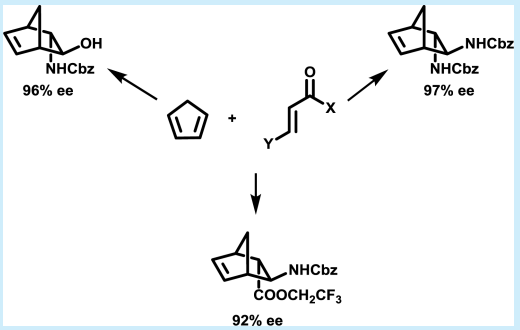
Supporting Information

ABSTRACT: The scope of enantioselective (4 + 2)-cycloaddition reactions has been expanded to include reactive olefinic components that are equivalents of three inoperable and unstable ethylene derivatives: 1-hydroxy-2-aminoethylene, 1,2-diaminoethylene, and β-aminoacrylic acid. In this way, a variety of otherwise unavailable functionalized (4 + 2)-cycloadducts have been synthesized from 1,3-dienes with high enantioselectivity (92−98%) and in good yields. The research leading up to this synthetic advance has also produced some surprising insights on reactivity and positional selectivity in catalytic enantioselective (4 + 2)-cycloaddition.



The chiral oxazaborolidine **1** (Figure 1) has been shown to catalyze a wide range of valuable (4 + 2)-cycloaddition

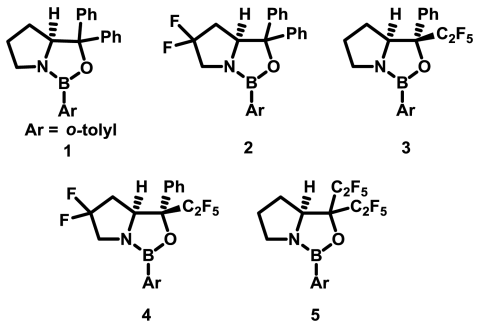


Figure 1. Precatalysts for enantioselective cycloadditions.

reactions after activation by triflic acid (TfOH), triflimide (Tf_2NH), or $AlBr_3$.[1] More recently, a series of even more powerful second-generation catalyst systems based on **2**, **3**, **4**, and **5** have been introduced. These chiral oxazaborolidines afford even more effective cationic Lewis acid catalysts after activation by Tf_2NH or $AlBr_3$ and as a result can be used at lower molar ratios, generally in the range of 1−3 mol %.[2] In addition, it has been discovered that still greater rate acceleration can be achieved by the use of Tf_2NH and $TiCl_4$ in a 1:1 ratio (Figure 2).[3] This additional increase in catalytic power was ascribed to formation of the complex anion **6**, which facilitates solvent separation from the oxazaborolidinium cation contact ion pair in the reaction medium, CH_2Cl_2 or toluene. Solvent separation of the ion pair enhances the power of the second-generation oxazaborolidinium catalysts so much that previously inoperable dienophiles can become good substrates

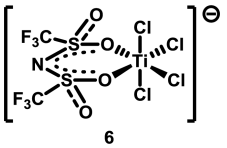


Figure 2. Triflimide−$TiCl_4$ complex ion.

for enantioselective (4 + 2)-cycloaddition reactions. A striking example of such an expansion of scope in (4 + 2)-cycloaddition is the case of α,β-unsaturated acid chlorides, which had not previously been employed successfully in enantioselective Diels−Alder reactions, even with catalysts formed from oxazaborolidine **1** using TfOH, Tf_2NH, or $AlBr_3$ for activation. This lack of success, e.g., with the simplest dienophile, acrylyl chloride, is due to two factors: (1) the rates of uncatalyzed (4 + 2)-cycloaddition are high relative to those for other acrylyl derivatives and (2) the catalysts based on **1** are simply not powerful enough to produce strong rate acceleration. The second of these can be ascribed to the very low affinity of the oxygen of acrylyl chloride for a Lewis acid. In contrast, the adducts **7**−**10** (Figure 3) were readily formed with various α,β-unsaturated acid chlorides using the *B*-*o*-tolyl derivative of oxazaborolidine **5** (F10/F0 precatalyst, **11**) with 1:1 Tf_2NH−$TiCl_4$ for activation at −78 °C in CH_2Cl_2.

The ready availability of (4 + 2)-cycloaddition products from acid chlorides suggested that these compounds might allow quick access to products of cycloaddition to equivalents of the hypothetical dienophiles **12**−**14** (Figure 4), which can neither be made nor used directly.

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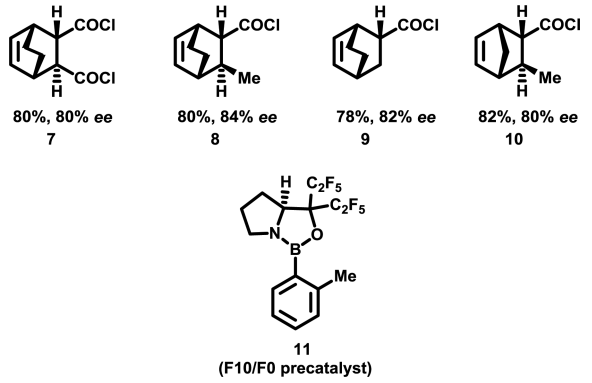


Figure 3. Diels–Alder products from α,β-unsaturated acid chlorides.

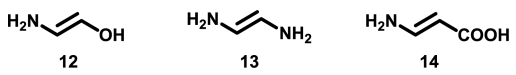
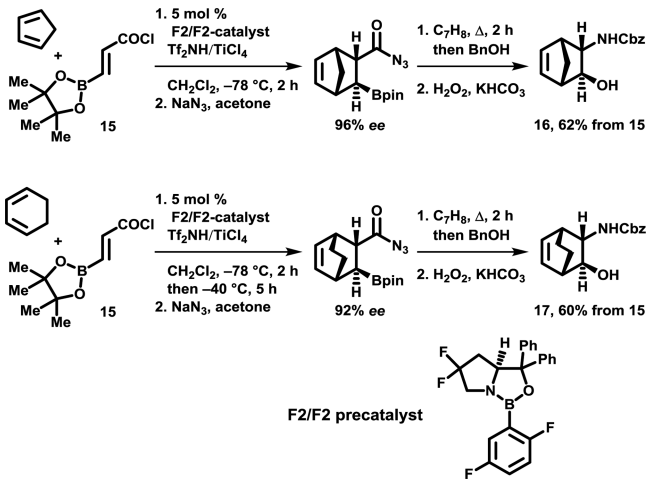


Figure 4. Useless but replaceable dienophiles.

A specific method for the enantioselective synthesis of two different *N*-protected chiral 1,2-amino alcohols is shown in Scheme 1 using catalyst **2** with Ar = 2,4-difluorophenyl (F2/F2 catalyst) and (*E*)-β-boroacrylyl chloride **15** with either cyclopentadiene or 1,3-cyclohexadiene. Acid chloride **15** is readily available from the known ester[4] by hydrolysis to the acid using LiOH and reaction with oxalyl chloride. The dienophile **15** is potentially quite versatile as a precursor of chiral (4 + 2)-cycloaddition adducts since the boron is also a replaceable group. The boron in the adduct **18** from cyclopentadiene and **15** was readily converted to the more reactive boronic acid equivalents **19** and **20** (R = COOMe) (Figure 5).

Scheme 1. Synthetic Route to 1,2-Amino Alcohols



Fumaryl chloride is a readily available and reactive dienophile that undergoes enantioselective (4 + 2)-cycloaddition with the second-generation F2/F2 catalyst/Tf_2NH–$TiCl_4$ combination but not with the original first-generation oxazaborolidines. We find it to be a very useful and practical equivalent of *N*-protected 1,2-diaminoethylenes. This approach is exemplified for three common dienes in Scheme 2. In each case, excellent enantioselection (>95:5) resulted along with good overall yield. The method is also flexible with regard to the choice of the group used for *N*-protection as well as for the diene component for the (4 + 2)-cycloaddition reaction.

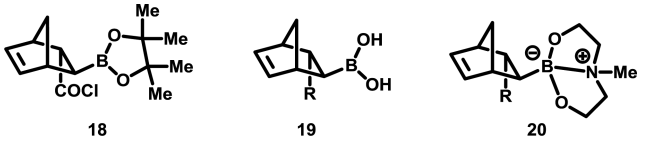
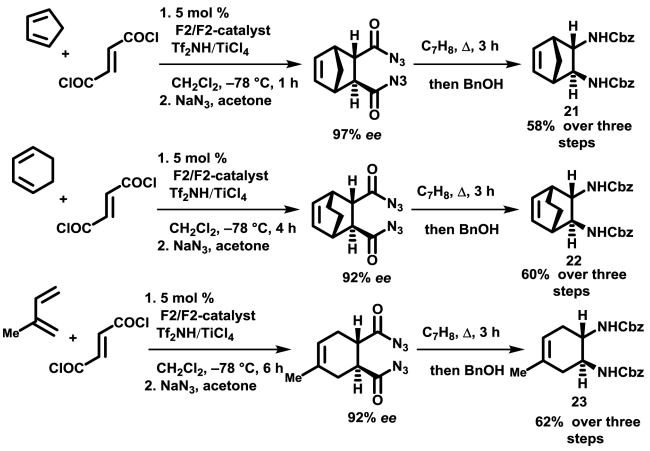


Figure 5. Some boronic acid derivatives from **18**.

Scheme 2. Fumaryl Chloride as a Useful Equivalent of *N*-Protected (*E*)-1,2-Diaminoethylene



In contrast, the development of a dienophilic equivalent of (*E*)-3-aminoacrylic acid (**14**) turned out to be unexpectedly challenging despite the availability of multiple precatalysts (based on core structures **1**–**5**) and four different modes of activation (TfOH, Tf_2NH, Tf_2NH–$TiCl_4$, and $AlBr_3$).[2,3] The (4 + 2)-cycloaddition reactions of 1,3-cyclopentadiene with a variety of (*E*)-fumaryl monoacid chloride monoesters and a range of catalysts was found to be surprising non-regioselective. The *endo*-ester/*exo*-acid chloride generally predominated but only by 1.5:1 to 2.5:1 with methyl, *tert*-butyl, or trifluoroethyl esters. This result is noteworthy in view of results from earlier work demonstrating, for example, that trifluoroethyl acrylate undergoes much slower (4 + 2)-cycloaddition than methyl acrylate even though the latter coordinates more strongly to the catalytic boron,[5] and the same is true for the corresponding symmetrical fumarate esters.[5] This divergence of binding affinity and reaction rate appears to manifest itself in the case of unsymmetrical fumarate esters as diminished regioselectivity, which is clearly shown by the results summarized in Scheme 3.

As mentioned in the introduction, previous research[5] with the first-generation precatalyst **1** showed that the reaction of acrylyl chloride with cyclopentadiene gave only racemic adduct, indicating that the uncatalyzed reaction was very fast. Acrylyl chloride also did not retard the reaction of cyclopentadiene with methyl acrylate.[5] Thus, it is clear that protonated **1** is not sufficiently strong as a Lewis acid to bind or activate α,β-unsaturated acid chlorides, which must therefore be much less basic than, for example, the corresponding esters. In contrast, the second-generation catalysts based on **2**–**5** are capable of binding to and activating acid chlorides. Acrylyl fluoride is even less basic than acrylyl chloride and does not react with cyclopentadiene even with second-generation activated oxazaborolidines such as **2**–**5**. Thus, it is of great interest that the reaction of fumaryl methyl ester fluoride (**26**) with cyclopentadiene using Tf_2NH–$TiCl_4$ or Tf_2NH-activated F2/F2

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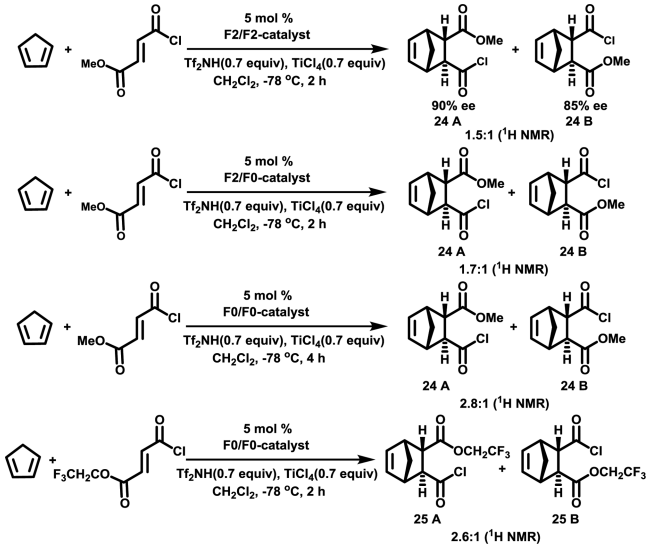
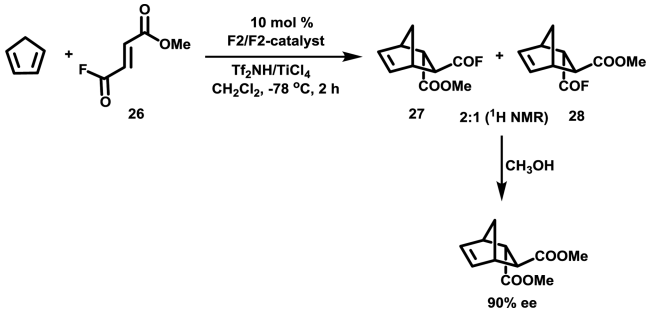
Scheme 3. Lack of Position Selectivity in (4 + 2)-Cycloadditions with Fumarate Ester/Acid Chloride



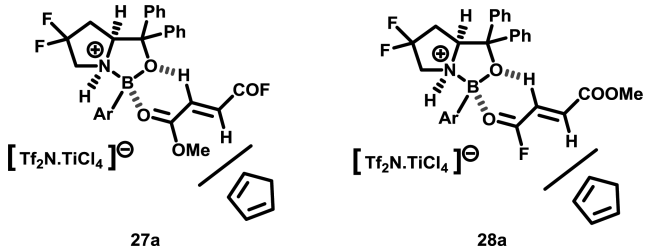
catalyst is not position-selective, although it is highly (95:5) enantioselective, as indicated by the results summarized in Scheme 4. Fluoride **26** was prepared from fumaryl methyl ester

Scheme 4. Unexpected Lack of Position Selectivity with a Fumaryl Monoester Monoacid Fluoride



acid using HF·Py and DCC.[6] The production of **27** and **28** from **26** and cyclopentadiene most likely occurs via the pre-transition-state assemblies **27a** and **28a**, respectively, on the basis of a large body of earlier results[1b,2,3,4,5] (see Scheme 5). We surmise that although the binding of acyl fluoride to the catalyst as shown in **28a** is very weak and the concentration of **28a** may be very low, the reactivity of the complex versus cyclopentadiene is sufficiently great to allow this pathway to compete significantly with that leading to *endo*-methyl ester **27**. It is apparent that this subtle aspect of catalysis of (4 + 2)-

Scheme 5. Transient Structures on the Pathway from 26 to 27 and 28

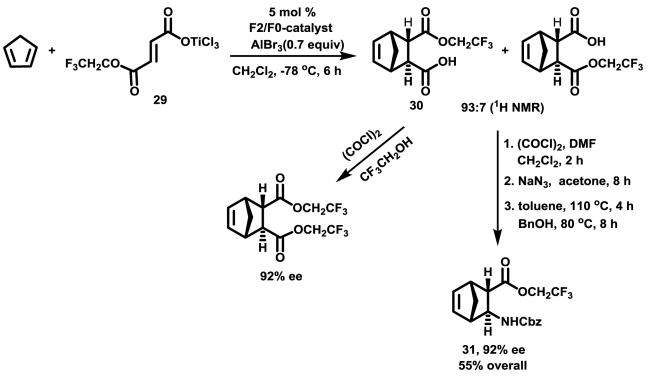


cycloaddition, which is intriguing from a structure/reactivity perspective, deserves further study.

From the above results it appears possible that in the case of unsymmetrical fumarate derivatives the basicity of each of the carbonyl functions may be influenced by the other in a way that leads to smaller differences in catalyst affinity.[7] Furthermore, it is likely that the fumarate LUMO is sufficiently low in energy to promote a synchronous (4 + 2)-cycloaddition pathway. Thus, for the reaction shown in Scheme 4, only weak binding by the COF group is sufficient for fast reaction. The carbonyl group that is attached to the catalytic boron center adopts the *endo* orientation in the product.

Despite the complications just described, we have been able to develop a novel fumarate derivative that effectively serves as an equivalent of methyl (*E*)-*β*-aminoacrylate. As shown in Scheme 6, we found that the mixed ester trifluoroethyl

Scheme 6. Use of Trifluoroethyl Trichlorotitanium Fumarate as an Effective Dienophilic Equivalent of Trifluoroethyl *β*-Amino Fumarate



trichlorotitanium fumarate (**29**) (prepared in situ from monotrifluoroethyl fumarate and $TiCl_4$) undergoes (4 + 2)-cycloaddition to cyclopentadiene to give as the major product *endo*-trifluoroethyl ester **30** with 93:7 selectivity and high (96:4) enantioselectivity. The adduct **30** was transformed into the Cbz-*β*-amino acid ester **31** with 92% ee in good overall yield, thus demonstrating a simple and practical solution to the problem of finding a *β*-amino acid ester equivalent for enantioselective (4 + 2)-cycloaddition to 1,3-dienes. It is of interest that $AlBr_3$ activation afforded better results than protic activation. To the best of our knowledge, the use of trichlorotitanium esters in enantioselective Diels–Alder reactions has not previously been reported.

The results described above open up a practical synthetic approach to chiral Diels–Alder products that cannot be produced by direct (4 + 2)-cycloaddition reactions. In addition, very high levels of enantioselectivity and position selectivity have been demonstrated in the formation of difunctionalized adducts bearing hydroxyl, amino, and carboxylic acid subunits.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02437.

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

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Notes

The authors declare no competing financial interest.

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(7) For example, it is very possible that the COF group in **26** reduces the basicity of the COOMe carbonyl subunit.

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