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Diels−Alder Reactions of Cyclic Isoimidium Salts

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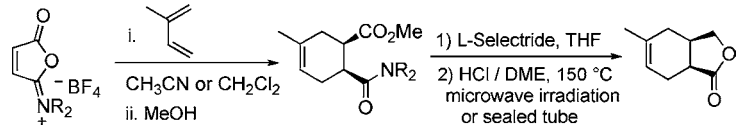
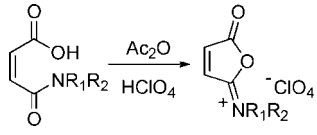
ABSTRACT



Diels−Alder reactions of cyclic isoimidium salts are described. The corresponding cycloadducts are obtained with high regio- and stereoselectivity. The use of homochiral cyclic isoimidium salts delivers cycloadducts with excellent diastereoselectivity (>99:1) that can be efficiently converted to enantiomerically pure lactones.

The treatment of a variety of N-substituted amic acids with acetic anhydride and aqueous perchloric acid has been shown by Boyd and co-workers to result in the formation of cyclic isoimidium salts (eq 1).[1] These salts are typically isolable, air-stable materials that display a distinctive, high-frequency IR absorption around 1860 cm^{-1}, similar to that of an acid chloride.



(1)

R_1 = H or Alkyl, R_2 = Alkyl or Aryl

The Boyd group had explored the reactivity of these compounds. In particular, they found that amine, alcohol, and azide nucleophiles added to the carbonyl group in a regiospecific fashion to give the corresponding ring-opened products in good yields. Friedel−Crafts acylation products were also obtained in moderate yields when isoimidium salts were treated with aromatic compounds.[1]

Although Diels−Alder reactions of isoimidium salts had not been described in the literature, we became interested in the synthetic potential of these salts as dienophiles. We reasoned that such compounds should behave as highly activated unsymmetrical dienophiles affording predictably high regioselectivity in cycloadditions with unsymmetrical dienes owing to our expectation that polarization of the olefin would be enhanced by the iminium moiety [the largest LUMO coefficient resides on the carbon β to the iminium moiety ($\beta = -0.488$, $\alpha = 0.363$ by AM1)]. Thus, these species would not require Lewis acid activation and should be more compatible with Lewis acid and thermally sensitive dienes.

Simple elaboration of the adducts could potentially regio-, stereo-, and enantioselectively lead to unsymmetrical γ-butyrolactones bearing multiple chiral centers. Although such enantiomerically pure γ-lactones have been previously prepared by enantioselective reduction of *meso*-anhydrides,[2a] methanolysis of *meso*-anhydrides followed by reduction,[2b] or oxidation of *meso*-diols,[2c] those methods require a *meso*-precursor that precludes synthesis of unsymmetrical systems. Direct Diels−Alder reactions of 2(5*H*)-furanone with dienes promoted by achiral Lewis acids have also been reported but afford mixtures of regioisomers.[3]

(1) (a) Boyd, G. V. *Chem. Commun.* **1969**, 1147–1148. (b) Boyd, G. V.; Monteil, R. L. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1338–1350. (c) Baydar, A. E.; Boyd, G. V. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1360–1366. (d) Baydar, A. E.; Boyd, G. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2871–2877. (e) Baydar, A. E.; Boyd, G. V.; Aupers, J.; Lindley, P. F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2890–2894. (f) Balaban, A. R.; Balaban, T. S.; Boyd, G. V. *Synthesis* **1987**, 577–578.

(2) (a) Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* **1993**, *34*, 1167–1170. (b) Okamatsu, T.; Irie, R.; Katsuki, T. *Synlett* **2007**, *10*, 1569–1572. (c) Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521–2526.

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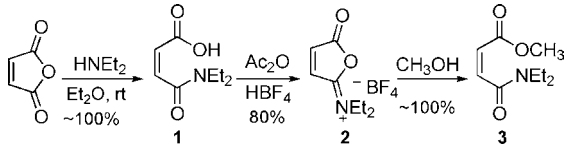
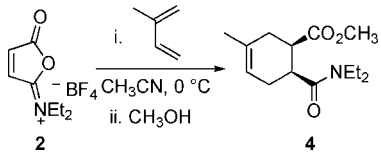
When we initiated our studies, only one partially characterized example of an isoimidium tetrafluoroborate salt could be found in the literature.[1b] Nevertheless, we felt it was highly desirable to employ isoimidium tetrafluoroborate salts rather than the related perchlorate salts[1] to avoid the preparation and handling of potentially explosive intermediates on scale. Thus, amic acid **1** derived from maleic anhyride and diethylamine was treated with acetic anhydride and tetrafluoroboric acid to afford the desired isoimidium tetrafluoroborate salt **2** in good yield (Scheme 1). As an additional benefit, we also found that tetrafluoroborate salts such as **2** exhibited improved solubility in nonpolar organic solvents relative to the corresponding perchlorates. Formation of the isoimidium salt **2** was confirmed by observation of the diagnostic IR peak at 1828 cm^{-1} and the downfield shift of the olefinic signals (^1H NMR/$CDCl_3$) from 6.41 and 6.60 to 8.41 and 7.49 ppm, respectively.[1] This increase in the chemical shift ($\Delta\delta = 2$ ppm for the proton β to the amide) was in accord with our postulate regarding differential polarization of the olefin in **2**. Moreover, treatment of the salt with methanol gave a quantitative yield of the known methyl ester **3**.[1] Isoimidium salt **2** could also be generated by treatment of the potassium salt of **1** with oxalyl chloride followed by exposure to $AgBF_4$ or in situ by exposure of the acid to TFAA in CH_2Cl_2, the latter affording the analogous trifluoroacetate salt.

Scheme 1. Formation of Cyclic Isoimidium Salt **2** with Tetrafluoroboric Acid



We then examined the reactivity of isoimidium salt **2** toward dienes. Upon treatment with isoprene in CH_3CN at 0 °C, we were pleased to find rapid formation of a single cycloadduct **4** (>98% dr by ^1H NMR) in high yield that was isolated after methanolysis to the ester (eq 2). The structure of **4** confirmed our expectation that the regioselectivity would be high and dominated by the iminium moiety in **2**. The observed high selectivity can be contrasted with the related acyclic fumaric and maleic acid derived amide-ester substrates, which have been reported to give mixtures of regioisomers when reacted with isoprene (~5:1, ~1:1 *endo*/*exo*).[4]

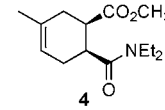
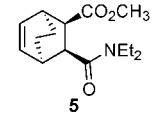
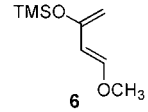
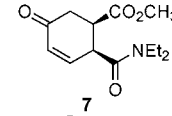
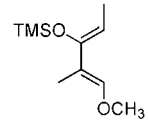
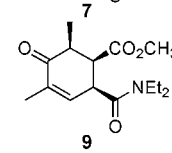
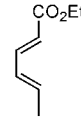
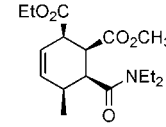
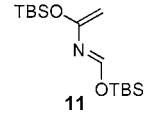
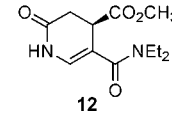


(2)

Initial results in hand, we explored the scope of the reaction with a panel of dienes chosen to illustrate the pertinent features of the reaction (Table 1). The *endo* selectivity was notably high as demonstrated by reaction with 1,3-cyclohexadiene providing **5** as a single diastereomer whose relative stereochemistry was assigned based upon NOE measurements (entry 2). The degree of stereoselectivity observed in the formation of **5** was also significantly improved relative to that reported for related acyclic dienophiles.[4] Sensitive electron-rich oxygenated dienes **6** and **8**[5] worked well (entries 3 and 4), each affording a single enone diastereoisomer after hydrolysis/elimination. Even ethyl sorbate, an electron-poor diene, afforded a moderate yield of the expected cycloadduct **10** as a single regioisomer (entry 5). The sensitive heterodiene **11** also reacted smoothly with the isoimidium salt **2** affording a single regioisomer (entry 6) to yield enamide **12** in high yield (85%) after elimination of TBSOH.[6]

Heartened by the high regio- and stereoselectivity of the cycloadditions of isoimidium salt **2**, we then explored use of a chiral isoimidium salt that could potentially provide access to enantiomerically enriched products.

Table 1. Reactions of Cyclic Isoimidium Salt **2**

entry[a]	diene	*t* (°C)	product[b]	yield (%)[c]
1		0 °C	 **4**	91
2		0 °C	 **5**	95
3	 **6**	-30 °C	 **7**	80
4	 **8**	-30 °C	 **9**	85
5		40 °C	 **10**	43
6	 **11**	rt	 **12**	85

[a] All reactions conducted in CH_3CN. [b] Determined by ^1H NMR spectroscopy (>98% dr). [c] Isolated product after purification.

(3) (a) Saito, A.; Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2004**, *45*, 9439–9442. (b) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539–7556.

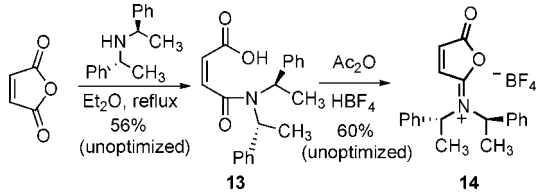
(4) (a) Bienayme, H.; Longeau, A. *Tetrahedron* **1997**, *53*, 9637–9646. (b) Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 8579–8586.

(5) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808. (b) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001–7008. (c) Danishefsky, S.; Chao, K. H.; Schulte, G. *J. Org. Chem.* **1985**, *50*, 4650–4652.

(6) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428–1430.

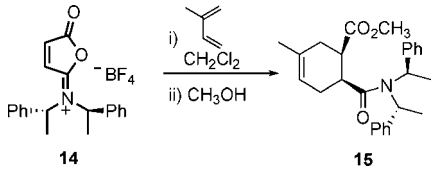
(+)-Bis[(*R*)-1-phenylethyl]amine, which is both C_2 symmetric and sterically demanding, was selected for our initial studies owing to its commercial availability and relatively low cost. Ring opening of maleic anhydride with (+)-bis[(*R*)-1-phenylethyl]amine afforded chiral acid **13**, followed by treatment with acetic anhydride and tetrafluoroboric acid at 10 °C which provided the somewhat less stable chiral isoimidium salt **14** (Scheme 2).

Scheme 2. Formation of Chiral Cyclic Isoimidium Salt **14**



Cycloaddition of isoimidium salt **14** was initially conducted with isoprene at 0 °C in CH_2Cl_2 affording **15** (Table 2 entry 1); however, the observed diastereomeric ratio (dr)

Table 2. Temperature Effect on Cycloaddition of Cyclic Isoimidium Salt **14** with Isoprene



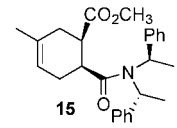
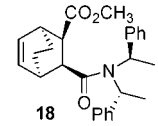
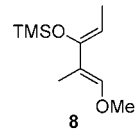
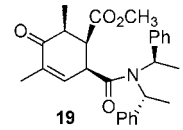
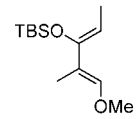
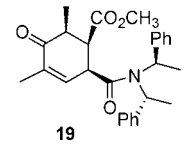
entry	t (°C)	time (h)	yield (%)[a]	dr[b]
1	0 °C	3	91	1:1
2	−30 °C	6	89	4:1
3	−45 °C	8	89	8:1
4	−60 °C	18	62	8:1
5	−78 °C	24	0	−

[a] Based on isolated yields after chromatography. [b] Determined by ^{1}H NMR spectroscopy.

was minimal (~1:1). Thus, we examined the effect of temperature on diastereoselectivity (Table 2). As expected when the cycloaddition was performed at lower temperatures, the dr increased with decreasing temperature. The optimal temperature proved to be ~−45 °C, affording an 8:1 dr (entry 3). Further decrease in the reaction temperature to −60 °C or below slowed significantly or stopped the reaction but provided no further increase in dr (entries 4 and 5).

Having optimized the temperature (−45 °C), we next explored the reaction scope of isoimidium salt **14** with a variety of dienes (Table 3). Cycloadducts of isoprene and cyclohexadiene gave high yield and promising diastereoselectivity (entries 1 and 2). Danishefsky dienes **8** and **16**[5] gave lower yields and diastereoselectivity owing to the higher reactivity of these dienes

Table 3. Reactions of Cyclic Isoimidium Salt **14**

entry[a]	diene	product	yield(%)[b]	dr[c]
1		 **15**	89	8:1
2		 **18**	90	8:1
3	 **8**	 **19**	49	3:1
4	 **16**	 **19**	58	3:1

[a] All reactions conducted in CH_2Cl_2 at −45 °C. [b] Based on isolated yields after chromatography. [c] Determined by ^{1}H NMR spectroscopy.

(entries 3 and 4). Less stable, highly reactive dienes **6**,[3] **11**, and **17**[7] afforded no cycloadduct at −45 °C supporting this conclusion.

X-ray crystallographic analysis of the Diels−Alder adducts **15** and **19** revealed both the relative and absolute stereochemistry of these adducts and defined the geometry of the most favorable cycloaddition transition state (see Supporting Information for crystallographic details). A combination of secondary orbital interactions[8] and differential nonbonded interactions between the phenyl and methyl groups, in the transition state arising from the conformation minimizing $A_{1,2}$ strain, account for the observed relative and absolute stereochemistry of **15** and **19**. As depicted (Figure 1), phenyl groups in isoimidium salt **14** block the bottom face of **14** leading to preferential top face attack.

These results led us to consider modification of the chiral auxiliary. We postulated that changing the reactive conformation of the auxiliary would increase the differential stereofacially defining steric interactions between the diene and dienophile (phenyl vs hydrogen). We chose to examine the rigid chiral isoimidium salt **20** that we expected would render the *endo* top face approach even more favorable and provide significantly improved diastereoselectivity.

Isoimidium salt **20** was prepared in analogous fashion to **14** from maleic anhydride and the known chiral auxiliary (2*R*,5*R*)-2,5-diphenylpyrrolidine in 60% overall yield (Scheme 2).[9] Gratifyingly, cycloaddition reactions of isoimidium salt **20** at −45 °C afforded both excellent regioselectivity and diastereoselectivity (Table 4).

(7) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627.

(8) Arrieta, A.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 6178–6180.

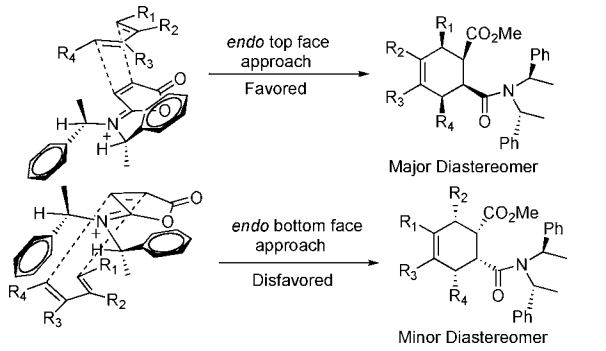
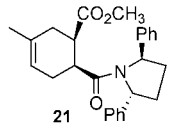
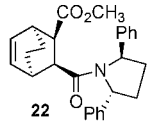
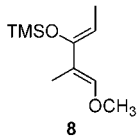
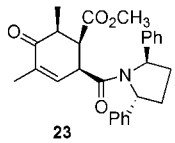
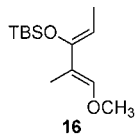
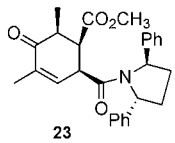


Figure 1. *Endo* top/bottom face approach for cycloaddition of isoimidium salt **14** with a diene.

Table 4. Reactions of Cyclic Isoimidium Salt **20**

entry[a]	diene	product	yield(%)[b]	dr[c]
1		 **21**	90	> 99:1
2		 **22**	90	> 99:1
3	 **8**	 **23**	56	> 99:1
4	 **16**	 **23**	65	> 99:1

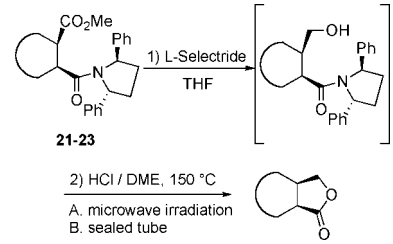
[a] All reactions conducted in CH_2Cl_2 at −45 °C. [b] Based on isolated yields after chromatography. [c] Determined by ^1H NMR spectroscopy.

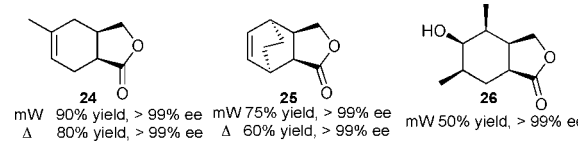
Cycloaddition with isoprene and 1,3-cyclohexadiene provided adducts **21** and **22** in high yield (90%) and excellent dr (>99:1) (entries 1 and 2). It is especially noteworthy that excellent *endo* selectivity is also observed in the formation of adduct **22**, whose stereochemistry was confirmed by X-ray crystallographic analysis. Cycloaddition with Danishefsky dienes **8** and **16**[3] also proceeded cleanly to afford Diels−Alder adduct **23** in 56−65% yields, again with >99:1 dr (entries 3 and 4).

Limitations in the scope of reactions of **20** with dienes still exist. Less stable dienes **6** and **17** failed to undergo Diels−Alder reaction under standard conditions, and less reactive azadiene **11** required higher temperatures to effect cycloaddition leading to low observed dr.

Cleavage of the hindered amide chiral auxiliary moiety proved to be challenging since **21**−**23** are remarkably robust to a variety of mild acidic, basic, and oxidative reaction conditions.[10] Cleavage of the amide alcohols derived from reduction of amide esters **21**−**23**, which was observed to occur under strongly acidic conditions, must be rapid owing to competing addition of the hydroxyl group to the proximal olefin affording bicyclic ethers. Recently, Scheidt and co-workers reported efficient cleavage of a similar hindered amide chiral auxiliary without epimerization using HCl under microwave irradiation at 150 °C.[11] Accordingly, L-Selectride reduction of cycloadducts **21**−**23** to the corresponding alcohol, followed by microwave-mediated ring closure, afforded the enantiomerically pure lactones **24**−**26** in very good to excellent yields. Preparative scale reactions can be conducted at 150 °C (preheated oil bath) using a sealed tube (Scheme 3) in similar yields (unoptimized).

Scheme 3. Cleavage of the Chiral Auxiliary





The foregoing studies demonstrate that isoimidium salts serve as reactive dienophiles toward a variety of dienes. Chiral analogues afford excellent regio- and diastereoselectivity providing a useful, reasonably general route to prepare differentially functionalized, enantiomerically pure bicyclic γ-lactones while permitting efficient recovery of the chiral amine auxiliary.

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Supporting Information Available: General experimental procedures and characterization data for compounds **4**, **5**, **7**, **9**, **10**, **12**−**15**, and **18**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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