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Cycloadditions of chiral anthracenes: effect of the trifluoromethyl group☆

Matthew S. Corbett, Xiang Liu, Amitav Sanyal and John K. Snyder*

Boston University, Department of Chemistry, Boston, MA 02215, USA

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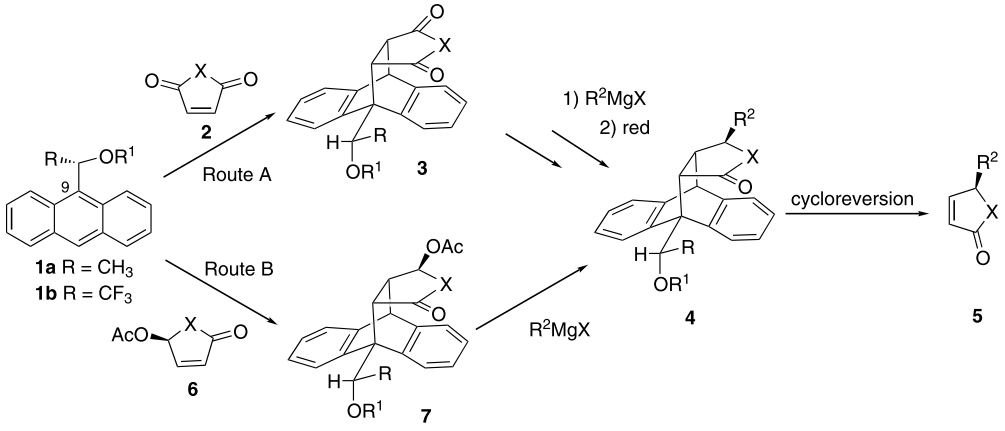
Abstract—Chiral anthracene template, 10-methyl-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene undergoes highly diastereoselective cycloadditions with maleic anhydride and 5-acetoxy-2(5*H*)-furanone. Subsequent regioselective and stereoselective manipulations demonstrate the synthetic utility in conversions to enantioenriched butenolides, and elucidate the origin of diastereoselection.

Anthracenes are viable diene templates in organic syntheses employing a Diels–Alder/retro Diels–Alder strategy.[2] As such, we were intrigued by the possibility of using chiral, non-racemic anthracene templates as stereocontrolling elements in the preparation of butenolides, α,β-unsaturated lactams and related compounds from achiral dienophiles. Recently we reported highly diastereoselective cycloadditions of chiral anthracenes **1** (R = CH_3, CF_3, $R^1 \neq H$) with C_{2v}-symmetric dienophiles such as maleic anhydride and maleimides as part of these efforts to design anthracene-based templates for asymmetric Diels–Alder/retro Diels–Alder strategies (Scheme 1).[3,4]

Although excellent levels of diastereoselection in the cycloaddition is a crucial requirement in this approach, successful application in asymmetric synthesis will also depend upon the ability to manipulate the cycloadducts with high regio- and stereoselectivity in subsequent steps. Thus, the original anthracene C-9 substituent must act as an effective regio- and stereocontrolling element in subsequent chemistry of the cycloadducts. Strategically, chiral lactones **4** (X = O) upon cycloreversion will lead to chiral γ-butyrolactones **5**. The diastereoselective Diels–Alder cycloaddition of maleic anhydride with a chiral anthracene **1** followed by regioselective carbonyl transformation through addition



Scheme 1.

☆ Taken from: Sanyal, A. Ph.D. Dissertation, Boston University, 2002.

* Corresponding author. Tel.: 617/353-2621; fax: 617/353-6466; e-mail: jsnyder@chem.bu.edu

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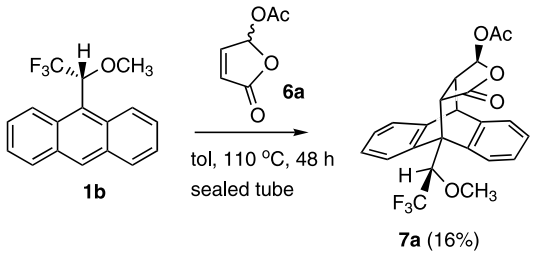
of a nucleophile, such as an alkyl Grignard reagent, followed by reduction (Scheme 1, Route A), or a cycloaddition with an unsymmetric dienophile such as furanone **6a** (X=O, Scheme 1, Route B) followed by Grignard addition will lead to chiral lactone **4**. The success of this strategy therefore depends upon selectivity in the carbonyl differentiation in the reaction with the Grignard reagent in the former approach, and upon both the regioselectivity and diastereoselectivity in the cycloaddition in latter approach. Herein is described preliminary work examining the potential synthetic utility of the cycloadditions of chiral anthracenes with unsymmetric dienophile **6a** (X=O), and establishes the proof of concept in using a new chiral anthracene as a template for the cycloaddition/cycloreversion strategy in the preparation of chiral, non-racemic butenolides.

As the anthracene becomes increasingly electron rich, its reactivity in cycloadditions increases but at the cost of its stability toward oxygen.[5] This is a problem with the methyl carbinol derived template **1a** which showed limited benchtop stability due to its slow reaction with oxygen (over several days). While the trifluoromethyl derivative **1b** was more stable, it was also eight times less reactive than the methyl derivative **1a**, and only half as reactive as anthracene, towards cycloadditions with maleic anhydride as shown by competition experiments in refluxing benzene.[1]

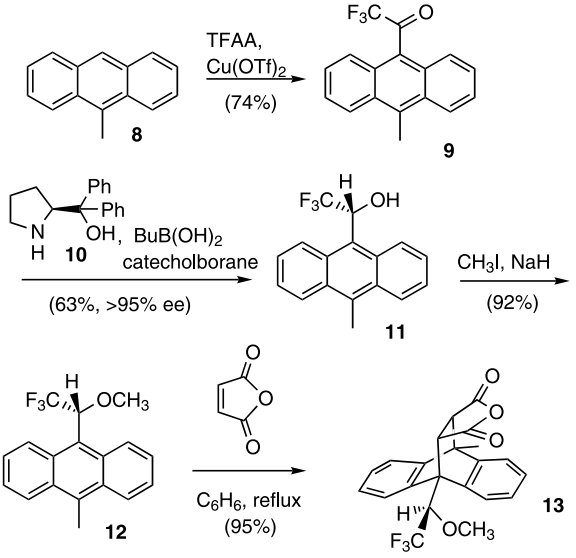
Difficulties with the lower reactivity of Pirkle's alcohol **1b** were encountered in the cycloadditions with 5-acetoxyfuranone **6a**.[6] The cycloaddition of **6a** with anthracene **1b** in toluene in a sealed tube at 110°C furnished the cycloadduct **7a** as the sole product detected, though the presence of the minor regioisomer could not be completely ruled out due to the low conversion (16%) (Scheme 2).[7]

It is well established that electron donating substituents substantially increase the reactivity of dienes in normal Diels–Alder reactions. Thus, 9-methyl anthracene (**8**) is 15.9 times more reactive than anthracene in cycloadditions with maleic anhydride.[8] It was therefore considered that substituting the 10-position of anthracene **1b** with a methyl group would increase its reactivity while retaining the observed excellent diastereoselectivity since this would still be controlled by the stereocenter. This new anthracene template should also be of relatively higher stability toward oxygen in comparison to its methyl counterpart **1a** due to the electron withdrawal of the trifluoromethyl group. The main concern would be the regioselectivity in the cycloaddition with the unsymmetric dienophiles such as **6a**.

10-Methyl-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (**12**) was prepared as illustrated in Scheme 3. Trifluoroacetylation of 9-methylanthracene (**8**) catalyzed by $Cu(OTf)_2$, as previously reported for the acetylation of toluene with acetic anhydride,[9] yielded **9** in 74% yield in a clean conversion. This procedure proved superior to trifluoroacetylation using trifluoroacetic anhydride, DMAP, and $AlCl_3$,[10] which after extensive optimization gave at best only a 41% yield.



Scheme 2.



Scheme 3.

With the ketone **9** in hand, asymmetric reduction to obtain the chiral alcohol **11** in high enantiopurity was explored (Scheme 3). Enantioselective reductions of trifluoromethylaryl ketones have been reported by Corey.[11] Corey's catechol borane system (20 mol% ligand **10**) furnished crude **11** which was recrystallized from hexanes to provide **11** in 63% yield, and >95% ee.[12] Comparison of the sign of optical rotation of Pirkle's alcohol **1b** with **11** led the absolute configuration assignment of the stereocenter as *R*.[13] The absolute configuration of this newly formed chiral center is in agreement with that observed in the reductions of similar trifluoromethylaryl ketones studied by Corey.[11] Subsequent methylation of anthryl alcohol **11** provided the chiral anthracene template **12**.[14]

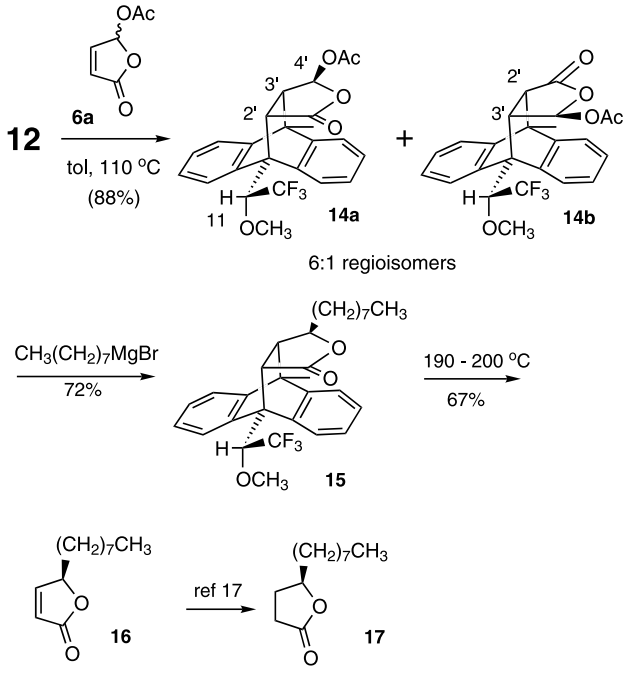
In a preliminary experiment, anthracene **12** was subjected to a cycloaddition with maleic anhydride in refluxing benzene. Not only did the cycloaddition proceed with complete diastereoselectivity to give only **13** (>98% de), one of two possible diastereomers, but also with excellent yield (95%). A competition experiment was performed by refluxing equimolar amounts of anthracene, the newly synthesized anthracene **12**, and maleic anhydride in benzene. The ^1H NMR spectrum of the product mixture indicated that **12** is five times more reactive than anthracene. Thus, the 10-methyl substitution improved the reactivity by a factor of 10 in com-

parison to anthracene **1b**. Furthermore, no decomposition of **12** was observed during routine handling and chromatography under ambient conditions.

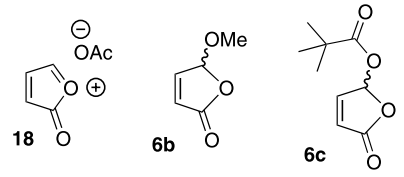
The cycloaddition of unsymmetric dienophile **6a** with 10-methyl substituted anthracene **12** in toluene in a sealed tube at 110°C gave cycloadduct **14a** and its regioisomer **14b** (6:1, **14a**:**14b**) in a combined yield of 88% (Scheme 4). The regioisomers were distinguished by NOE studies.[15] Thus, C-10 methyl substitution did indeed improve the reactivity of the anthracene in cycloadditions relative to **1b**, but at the expense of regioselectivity. Due to the difficult separation of the regioisomers, and their instability on prolonged exposure to SiO_2, the cycloadduct mixture was used in the subsequent step, after passing through a short SiO_2 plug to remove unreacted dienophile.

Reaction of the mixture of cycloadducts **14a** and **14b** with octyl magnesium bromide, produced the octyl substituted lactones which could be separated, yielding **15** in 72% isolated yield (based on **14a**). Octyl substituted lactone **15** was then subjected to cycloreversion by heating to ca. 200°C, neat, under vacuum, furnishing the chiral butenolide **16** (67% yield), a precursor of the rove beetle pheromone **17**,[16,17] after chromatography. Comparison of the optical rotation of lactone **16** with that reported in the literature[17,18] indicated that the absolute configuration of the chiral center was (*R*). Butenolide **16** was shown to be enantiomerically pure within the limits of detection by ^1H NMR employing $Eu(hfc)_3$ as a chiral shift reagent.[17]

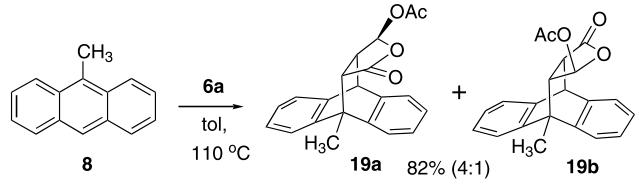
The diastereomeric purity of regioisomers **14a** and **14b** may result from a cycloaddition between **12** and intermediate oxonium ion pair **18**, followed by acetate addition to the oxonium cycloadduct from the top face. Alternatively, a kinetic resolution of the dienophile **6a** may be occurring through the cycloaddition. No reaction occurred under the same conditions with methoxyfuranone **6b**, which is less likely to form an ion pair analogous to **18**. In addition, pivaloxyfuranone **6c** also participated in cycloadditions with **12** to produce a mixture of diastereomerically pure regioisomers in a 3.3:1 ratio (50% yield) as observed with **6a**. Finally, 9-methylanthracene (**8**) also under went cycloadditions with **6a** to produce a mixture of diastereomerically pure cycloadduct regioisomers (**19a** and **19b**) in a 4:1 ratio (Scheme 5); **8** also failed to react with methoxyfuranone **6b**. Attempts to catalyze the cycloaddition between **6a** and **12** with Lewis acids not unexpectedly led only to dienophile decomposition.



Scheme 4.



The preparation of (*R*)-**16** enabled the assignment of the absolute configuration of the cycloadduct **14** and thus provided insight into the transition state for the cycloaddition. Four possible approaches of the dienophile **6a** to diene **12** which lead to the observed **14a** are presented in Figure 1. Model **D**, which presents a 'minimum sterics rationale' can be disregarded since it cannot explain the high level of dienophile facial selectivity observed. Models **B** and **C** are also considered unlikely since they have relatively low σ*-orbitals aligned with the anthracene HOMO, which would thereby retard the cycloaddition. Furthermore, model **C** also suffers from repulsive electrostatic interactions between the carbonyl oxygen of the incoming dienophile and the trifluoromethyl group on the anthracene stereocenter, which would lead to the opposite facial selectivity to that observed. Model **A**, which is analogous to that used to rationalize the stereoselectiv-



Scheme 5.

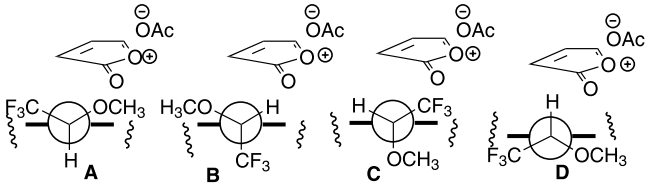


Figure 1. Possible approaches of dienophile **6a** to anthracene **12**.

ity in the cycloadditions of **1a**,[3] aligns the relatively acidic C–H bond of the stereogenic center with the anthracene orbitals, thereby allowing for maximum σ-donation and enhanced reactivity in the cycloaddition by raising the $HOMO_{diene}$.

The incoming dienophile would approach the anthracene from the top face, *anti* to the hydrogen atom, and *syn* to the methoxy or the trifluoromethyl substituents. The lone electron pairs on the oxygen atom of the carbonyl group of the incoming dienophile will experience repulsive electrostatic interactions with both the highly electronegative fluorine atoms of the trifluoromethyl group and the lone electron pairs on the oxygen of the methoxy group. It is well known that the effective negative charge for a trifluoromethyl group is very large,[19] and that this effective charge is responsible for the seemingly abnormal 'steric' effects often associated with the CF_3 group,[20] which are perhaps better described as electrostatic repulsions. Thus, higher electron density around the trifluoromethyl group would force the dienophile to approach with the carbonyl pointed away from it (Fig. 2), to produce the observed diastereoisomer. Similar electrostatic control of facial selectivity by a perfluoroalkyl group (CF_3CF_2) dominating over a methoxyl group has been reported by Wipf in the addition of methyllithium to the carbonyl group of 4,4-disubstituted cross-conjugated dienones.[21] Kraus has also established the role of electrostatic repulsions in controlling facial selectivity in cycloadditions.[22]

These studies indicate that C-10 methylated chiral anthracene **12** is a promising template for asymmetric synthesis. Subsequent manipulations of the cycloadducts elucidated the role played by the trifluoromethyl group on the origin of diastereoselection. Further tuning of this template, required to increase the regioselectivity in cycloaddition with nonsymmetrical dienophiles, is currently underway.

Acknowledgements

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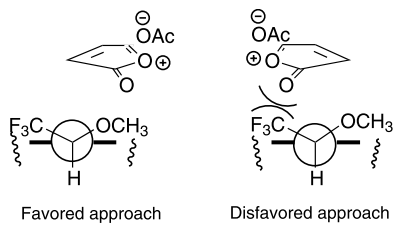

Figure 2. Facial selectivity control by CF_3 electrostatic repulsion.

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