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Chiral anthracene and anthrone templates as stereocontrolling elements in Diels–Alder/retro Diels–Alder sequences

Kerrie L. Burgess, Matthew S. Corbett, Paul Eugenio, Neil J. Lajkiewicz, Xiang Liu, Amitav Sanyal, Wanlin Yan, Qian Yuan and John K. Snyder*

Department of Chemistry and the Center for Methodology and Library Development, Boston University, 590 Commonwealth Ave., Boston, MA 02215, USA

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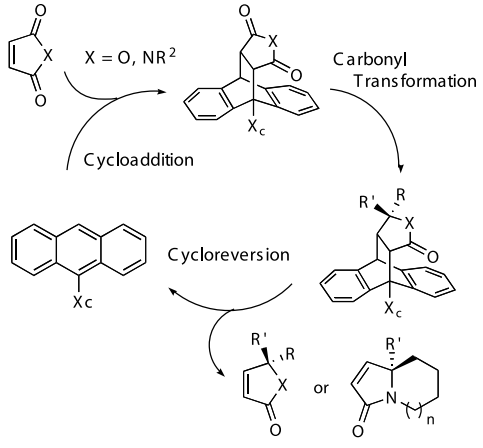
Abstract—The development of chiral anthracene templates for use in Diels–Alder/retro Diels–Alder sequences is described. A summary of past results and new progress is reported.

1. Introduction

Over the past few years, we have been developing chiral anthracene templates as recyclable stereocontrolling elements in the preparation of butenolides, α,β-unsaturated γ-lactams, and polycyclic alkaloidal core structures (Scheme 1).[1] Our intent was to apply these chiral auxiliaries in Diels–Alder/retro Diels–Alder sequences for library development,[2] an application that was originally inspired by Thebtaranonth's anthracene-templated Diels–Alder/retro Diels–Alder sequence to racemic and achiral cyclopentenones.[3] Success in this endeavor requires not only high diastereoselectivity in the cycloaddition but also high regioselectivity in subsequent transformations of the carbonyls of the mounted dienophile. Subsequent cycloreversion,[4] which must proceed without racemization, then produces the target lactams or lactones and regenerates the chiral anthracene template. In this article, we summarize our work and also describe new work using chiral anthrone templates.



Scheme 1.

2. Enantioselectivity in the cycloadditions of 1,5-disubstituted anthracenes

Our initial efforts focused on the discovery of homochiral catalysts to promote the enantioselective cycloaddition of achiral 1,5-disubstituted anthracenes with maleic anhydride (MA) and *N*-alkyl maleimides.[5] Despite screening of numerous catalysts known to engineer highly enantioselective Diels–Alder reactions with other reactants,[6] these efforts were basically unsuccessful. The best results (50% ee, enantiomer not assigned) were obtained in the cycloaddition of *N*-methylmaleimide (NMM) with 1,5-diphenylanthracene (**1**) using (*S*)-BINOL/Me_2AlCl as the catalytic system[7] (Scheme 2, Eq. 1). Further experimentation established that carbonyl differentiation in the MA cycloadducts of **1** was also

* Corresponding author. Tel.: +1 617 353 2621; fax: +1 617 353 6466; e-mail: jsnyder@bu.edu

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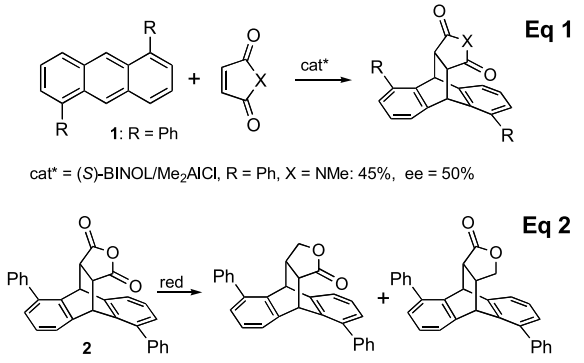


Scheme 2.

not synthetically valuable. For example, the highest level of regioselectivity in the reduction of MA cycloadduct **2** was 3:1 with L-selectride but in <10% yield. Higher yield was obtained with $NaBH_4$ (55%) but the regioselectivity dropped to 2:1 (regioselectivity not assigned; Scheme 2, Eq. 2).

3. Chiral anthracene templates

With the disappointing enantioselectivity in the cycloadditions of 1,5-disubstituted anthracenes, we then turned to homochiral anthracenes with stereogenic centers located in C-9 substituents. Two types of anthracenes were examined (Fig. 1): Type A with alkyl substituents (**3**–**6**) and Type B with heteroatom substituents (**7** and **8**). All of the Type A anthracenes (**3a**–**6**) underwent cycloadditions with maleic anhydride and *N*-alkylmaleimides with complete diastereoselectivity, producing single products in high yield (75–99%), thereby accomplishing the first step in the sequence depicted in Scheme 1 with the illustrated diastereoselectivity.

The structural requirements for high diastereoselectivity in the cycloadditions of the chiral anthracenes were also probed. With the unprotected alcohols **3b** and **4b**, the cycloadditions with NMM showed poor diastereoselectivity (1:1.7 and 1:1.9, respectively, Scheme 3). Furthermore, the minor product in both these cycloadditions corresponded to the sole diastereomers produced with the methyl ethers **3a** and **4a** with regard to the sense

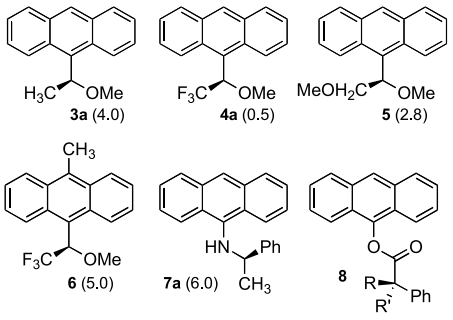
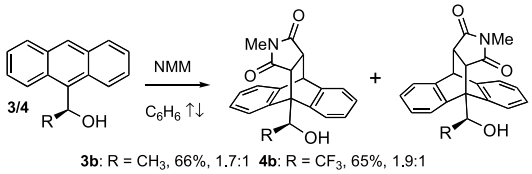


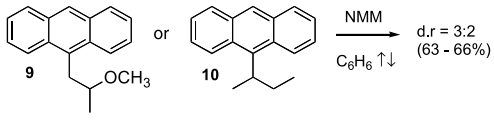
Figure 1. Chiral anthracene templates; the number in parentheses is relative rate of cycloadditions with NMM relative to unsubstituted anthracene from competition experiments.



Scheme 3.

of diastereoselection. Similar observations were also reported by Jones with **3b** who also studied the solvent dependency of the diastereoselection.[8,9] In addition, moving the stereogenic center one atom away from the anthracene ring (**9**) or removing the oxygen from the stereogenic center (**10**) led to near complete losses in diastereoselection (dr = 3:2 in both cases in cycloadditions with NMM, major diastereomers not assigned; Scheme 4).

These observations led us to propose a transition state that accounts for the observed diastereoselection. This explanation for the diastereoselection requires kinetic control in the cycloaddition, that was confirmed using anthracene **5**.[1c] In this model, the methoxymethyl group of **5** (or the methyl group in **3a**, not shown) is oriented antiperiplanar to the approaching dienophile with facial selectivity established by minimization of electrostatic repulsion between the anthracene C-9 methoxyl oxygen and the dienophile carbonyl oxygen (**A** vs **B**, Fig. 2). This rationale, which derives from Houk's inside alkoxide effect[10] can also be applied to the trifluoromethyl analogues **4a** and **6** wherein the electrostatic repulsion between the trifluoromethyl group (**D**) is greater than that suffered with the methoxyl oxygen (**C**),[1b] also giving rise to the observed diastereoselection. Finally, with the free alcohol in **3b**, hydrogen bonding (in **F**) helps to stabilize the alternative approach that now competes effectively with the transition state **E**, giving rise to the



Scheme 4.

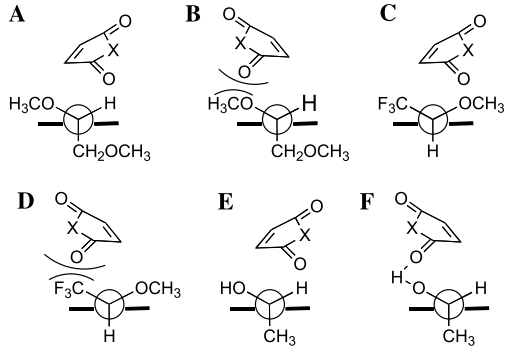


Figure 2. Proposed transition states for the cycloadditions of **5** (**A/B**), **4a/6** (**C/D**), and **3b** (**E/F**).

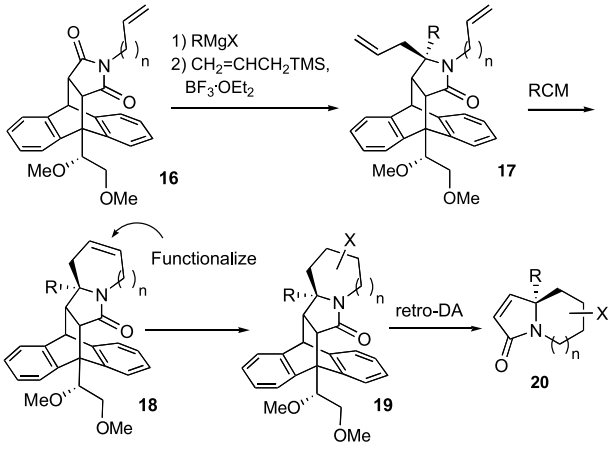
observed mixture of diastereomeric cycloadducts depicted in Scheme 3.[8,10a,11]

From these preliminary studies, **5** emerged as our leading chiral anthracene for use as a template in Diels–Alder/retro Diels–Alder sequences. Dimethoxyethylanthracene **5** was easy to prepare in a very high ee[12] and was quite stable to storage under ambient conditions, though we still stored **5** under nitrogen. Despite this stability, **5** was also more reactive than anthracene itself in competition experiments in cycloadditions with NMM. Indeed, competition experiments established the relative rates (Fig. 1), with the lower reactivity of **4a** proving to be the main drawback in the use of this commercially available chiral anthracene (Pirkle's alcohol[13]).

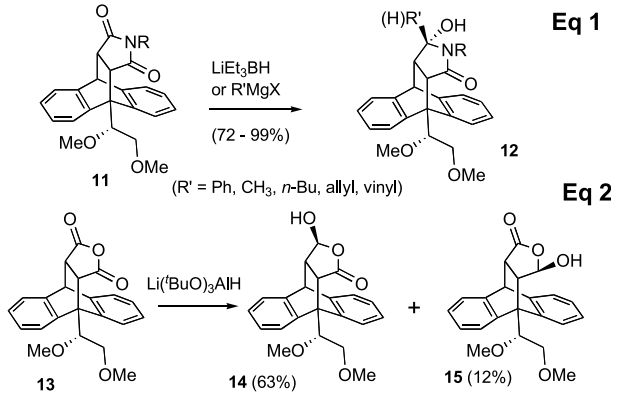
With the excellent diastereoselection in the cycloadditions of chiral anthracenes **3**–**6** established, regioselective transformations of the original dienophilic subunits, now mounted on the anthracene templates, were probed using cycloadducts **11** and **13** formed from template **5**. Reductions with superhydride and additions of Grignard reagents showed excellent regioselectivity, occurring exclusively at the carbonyl remote to the original C-9 anthracene substituent with the maleimide cycloadducts **11** (Scheme 5, Eq. 1).[1c] Only nucleophilic addition from the top face of the carbonyl, the anthracene template blocking the approach to the bottom face, were observed. We attributed the regioselectivity to developing repulsive interactions between the chiral substituent and the carbonyl oxygen in the transition state resulting from addition to the near carbonyl group as this group changes from sp^2 to sp^3 hybridization. In contrast, Li(*t*-BuO)$_3$AlH reduction of the anhydride **13** gave a mixture of regioisomers **14** and **15** (63% and 12% isolated yields, respectively; Scheme 5, Eq. 2), with the hydroxyl group β-oriented.[5] Presumably, top face reduction still occurred, with isomerization to the more stable anomers resulting during workup. With the more electrophilic anhydride, in comparison to imides **11**, the lower regioselectivity in the reduction may be the result of an earlier transition state, with correspondingly less sp^3 character developed in the transforming carbonyl, and therefore less repulsion with the stereogenic anthracene substituent. Addition of Grignard reagents to **13** invariably led to γ,γ-dialkyl lactones as the major or sole products (not shown).

With the high regio- and stereoselectivity of Grignard reagent additions to the maleimides mounted on the anthracene templates established, a divergent strategy emerged to prepare alkaloidal core structures enantioselectively by annulating rings of varying sizes onto the mounted pyrrolidinone. In this approach, cycloadducts **16** formed from a maleimide substituted on the nitrogen with terminal alkenyl groups can be subjected to one of the two procedures. In the first sequence (Scheme 6), reduction or Grignard reagent addition followed by allylation and ring closing metathesis (RCM) yields the lactam **18**, with cycloreversion producing the target bicyclic alkaloidal system **20**.[14] The ring size of the annulation can be systematically varied by changing '*n*' in the maleimides. Transformation of the metathesis-formed alkene lends further diversification to the chemistry. Cycloreversion then produces the bicyclic targets.

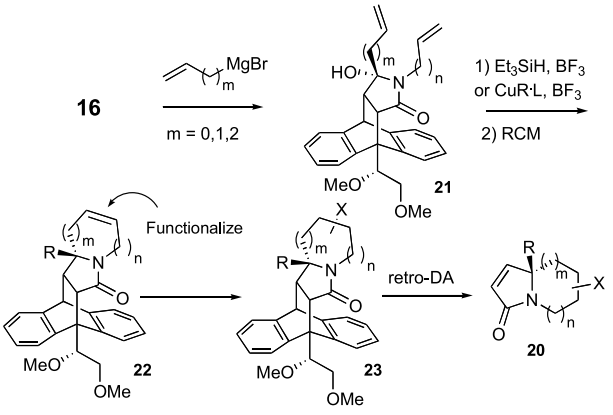
An alternative sequence can also be envisioned (Scheme 7) wherein addition of a Grignard reagent bearing a terminal alkenyl group, followed by silane reduction or addition of a second alkyl nucleophile, then RCM produces the same system **20** but with the stereogenic center inverted in comparison to the first route leading to **18**



Scheme 6.



Scheme 5.



Scheme 7.

illustrated in Scheme 6. Thus, both enantiomers of **20** can in principle be produced from the same chiral anthracene template. Furthermore, in this latter strategy, the location of the double bond following RCM can also be systematically altered by changing '*m*' and '*n*', but keeping '*m* + *n*' as constant.

We successfully probed the suitability of the first alternative of this strategy in the synthesis of indolizidone and pyrroloazepinone core structures.[1c] *N*-Vinyl-, *N*-allyl-, and *N*-(3-butenyl)maleimide cycloadducts **16** (Scheme 6 above, $n = 0$, 1, and 2, respectively) were prepared, and all underwent highly regio- and stereoselective addition of phenyl or methyl Grignard reagents, or superhydride reduction in excellent yields. Allylations also were successful (72–94%) with the transformed *N*-allyl and *N*-butenyl cycloadducts, but not with the *N*-vinyl analogue. Following ring closure with Grubbs' I catalyst,[15] hydrogenation, and cycloreversion using flash vacuum pyrolysis[16] (FVP, 400 °C, 4 min) produced bicyclic lactams **20a**–**e** (Fig. 3).

Chiral anthracene **5** was fully recovered in all cases. Attempts to prepare pyrrolizidone scaffolds from the *N*-allylmaleimide cycloadduct by vinyl Grignard reagent addition, reduction, and RCM failed. Thus, attempts to reduce vinyl adduct **21a** led only to **24**, and **21a** proved to be resistant to RCM with the Grubbs I catalyst,[14b] producing only **25** in low yield with loss of the stereogenic center at C-8 after chromatography on silica gel (Scheme 8).

α-Substituted cycloadducts **26** were also readily obtained beginning with 2-substituted maleic anhydrides or maleimides. In the limited cases examined to date, the cycloaddition invariably proceeded with excellent stereo- and regioselectivity, providing only those regioisomers with the dienophile C-2 substituent remote to the anthracene C-9 stereogenic substituent (Scheme 9).

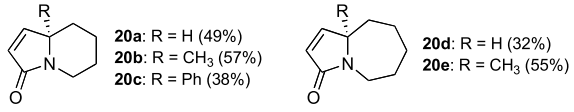
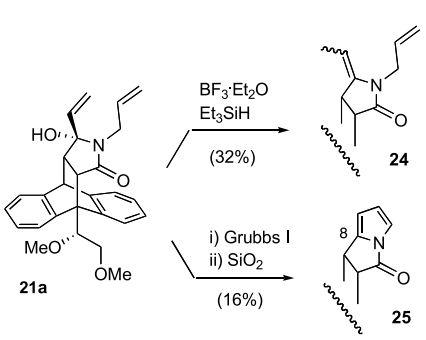
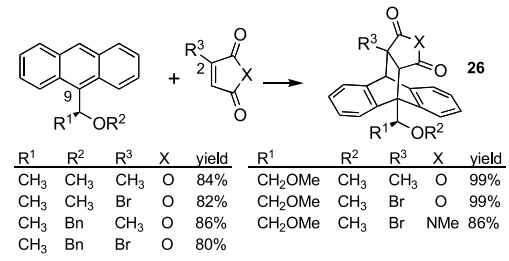


Figure 3. Indolizidones and pyrroloazepinones prepared from the general sequence shown in Scheme 6. Numbers in parentheses are overall yields including the cycloaddition to form **16** (six steps).

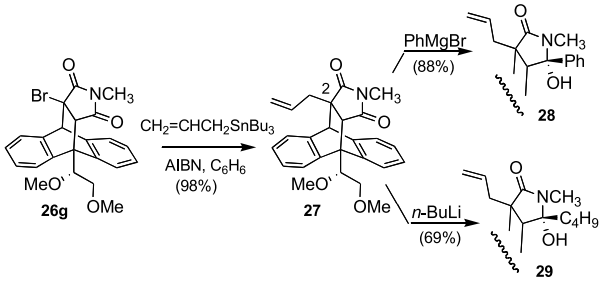


Scheme 8.

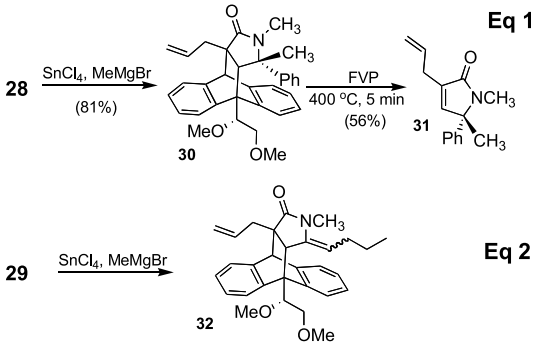


Scheme 9.

Furthermore, the chemoselectivity of subsequent carbonyl transformations of the mounted dienophile through reduction or Grignard reagent addition were now controlled by the dienophilic C-2 substituent while the anthracene template provided the stereocontrol, yielding solely additions to the carbonyl remote to the C-2 substituent from the top face away from the aryl rings. For example, radical allylation[17] of **26g** followed by the addition of PhMgBr or *n*-BuLi gave the corresponding adducts **28** and **29**, respectively (Scheme 10) in good yields as the sole isomers. Subsequent treatment of **28** with $SnCl_4$, followed by the addition of MeMgBr to the generated acyliminium ion[18] produced γ,γ-disubstituted lactam **30** (Scheme 11, Eq. 1, 81%). Cycloreversion via FVP then yielded the desired α,β-unsaturated lactam **31**. Attempts to apply the same sequence to butyl adduct **29**, however, led only to elimination (Scheme 11, Eq. 2). This proved to be a general problem with those acyliminium ions capable of dehydrating into the side chain as further described below.



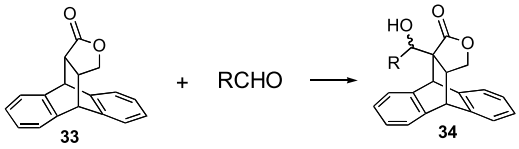
Scheme 10.



Scheme 11.

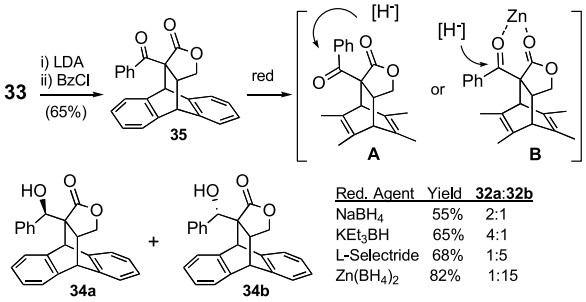
Stereoselectivity in the enolate chemistry of racemic lactone **33** prepared from the $NaBH_4$ reduction of the anthracene/maleic anhydride cycloadduct was also examined as a model prior to using chiral anthracenes in similar chemistry. Reactions of the enolate with aldehydes proceeded only in poor yields[19] and with stereoselectivity that proved to be acceptable only with the most sterically encumbered electrophile, pivaldehyde (Scheme 12). With sterically less demanding aldehydes, the stereoselectivity was unsatisfactory ($\leqslant$3.5:1). Benzoylation of the enolate of **33** was slightly more successful, however, leading to β′-ketolactone **35** (Scheme 13). With nonchelating reducing agents such as $NaBH_4$ and $KBHEt_3$, **35** underwent hydride reduction with opposite facial selectivity in comparison with chelation controlled reductions with L-selectride, or even better $Zn(BH_4)_2$. In these reactions, the anthracene template blocked the 'bottom' face of the carbonyl, requiring a 'top' face approach by the reducing agent. Without chelation, the favored *anti*-orientation of the carbonyl oxygens of **35(A)** exposes the opposite face of the carbonyl in comparison with the *syn*-orientation (**B**) maintained by chelation (here with Zn).

This enolate approach to β′-alcohols was subsequently applied to the synthesis of the natural acyl-CoA:cholesterol transferase inhibitor acaterin.[20] Thus, treatment of **14**, whose preparation was described earlier by the reduction of maleic anhydride adduct **13** (Scheme 5), with excess MeMgBr (2.2 equiv) gave lactone **36** (Scheme 14). This lactone was also prepared by the cycloaddition of **5** with acetoxyfuranone **37**



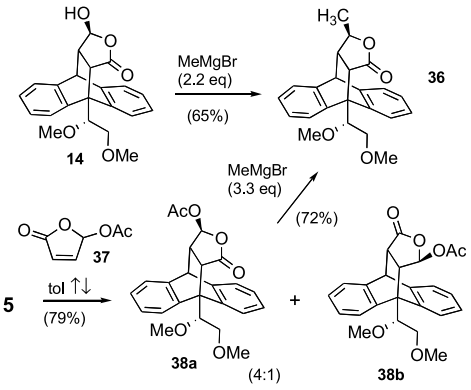
R	Yield (%)	d.r.
^{t}Bu	31%	33:1
^{i}Pr	38%	2:1
Ph	49%	2:1
	40%	3.5:1

Scheme 12.



Red. Agent	Yield	32a:32b
$NaBH_4$	55%	2:1
KEt_3BH	65%	4:1
L-Selectride	68%	1:5
$Zn(BH_4)_2$	82%	1:15

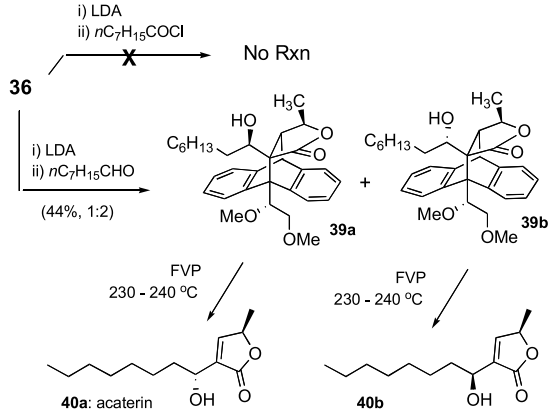
Scheme 13.



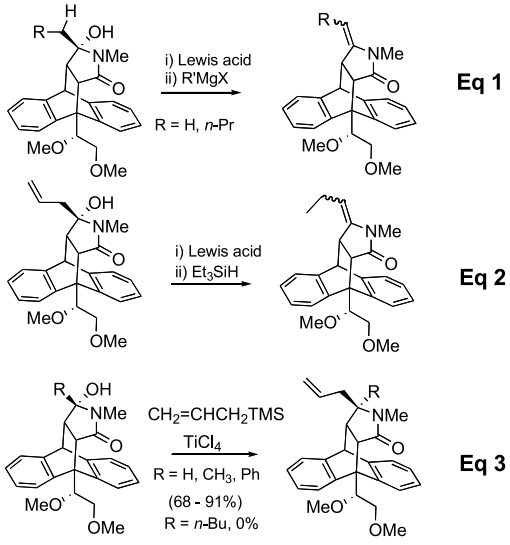
Scheme 14.

that produced separable cycloadducts **38a** and **b** in a 4:1 ratio, each as a single diastereomer, followed by MeMgBr addition to **38a**. Acylation of the enolate of **36** with octanoyl chloride failed to produce the expected β′-ketolactone (Scheme 15). Presumably the added steric encumberance of the anthracene C-9 substituent further reduces the reactivity at this site in comparison with **33** (Scheme 13). Reaction of the lithio enolate of **36** with octanal, however, did proceed in a modest 44% yield to give separable hydroxylactones **39a** and **b** in an unattractive 2:1 ratio, unfortunately with the unnatural diastereomer **39b** as the major product. Cycloreversion (FVP, 230–240 °C, 15 min) then produced acaterin **40a** and its diastereomer **40b**. This work pointed out the somewhat disappointing regioselectivity in the cycloadditions of **5** with nonsymmetric dienophiles such as **37** (Scheme 14), as well as the relatively poor yields in working with the enolates of the lactones derived from the cycloadducts of maleic anhydride.

In addition to the poor enolate chemistry of the lactones described above, other limitations in these anthracene templates were found. First, attempts to capture the acyliminium ion, generated upon treatment of the γ-hydroxylactams with a Lewis acid, using organometallic reagents (such as Grignard reagents, organolithium reagents, cuprates, or even Et_3SiH), led to dehydration



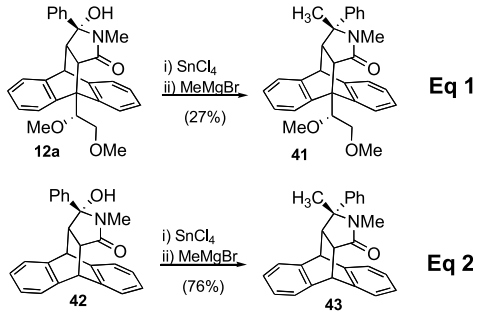
Scheme 15.



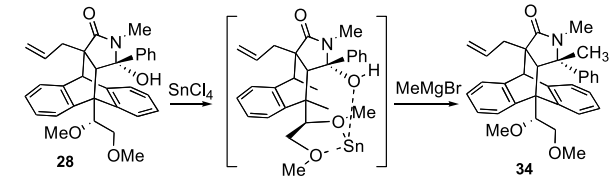
Scheme 16.

or rearrangement in those cases with alkyl side chains (Scheme 16, Eqs. 1 and 2, respectively, also see Scheme 11, Eq. 2). This stood in contrast to the success with the Lewis acid catalyzed allylations (Schemes 6 and Scheme 16, Eq. 3), as well as the MeMgBr addition to the acyliminium ion generated from **28** (Scheme 11, Eq. 1) illustrated earlier. Similar results were also obtained with analogous adducts capable of undergoing dehydration, which were prepared from unsubstituted anthracenes, suggesting that the limited ability to generate and synthetically exploit the acyliminium may be an inherent problem with the anthracene system.

With acyliminium ions that cannot rearrange or undergo elimination (Scheme 17, Eq. 1), Grignard reagent addition did succeed, though often only in poor yield (e.g., **41**, 27%). By comparison, the unsubstituted anthracene analogue **42** underwent the same MeMgBr addition in 76% yield (Scheme 17, Eq. 2). The lower yield with the chiral template **12a** in these examples was thought to be due to complexation of the Lewis acid between the lactam carbonyl oxygen and the auxiliary methoxy groups, which inhibits formation of the desired acyliminium ion. Supporting this suggestion was the earlier observation that Sn(IV) promoted acyliminium ion formation followed by MeMgBr addition to **28** (Scheme



Scheme 17.



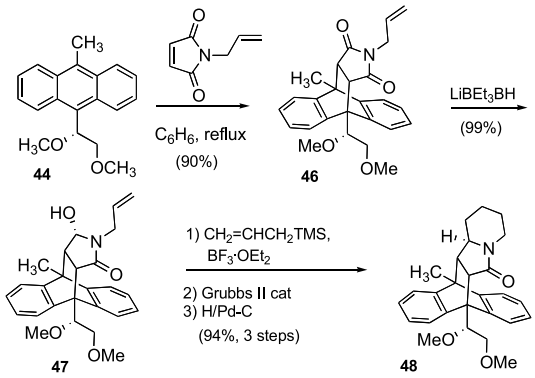
Scheme 18.

11, Eq. 1) was also successful. In this example, complexation of the Lewis acid between the methoxy groups as well as the hydroxyl oxygen of **28** would position the Sn(IV) optimally for acyliminium ion formation (Scheme 18). Thus, with the cycloadducts of 2-substituted maleimides, which direct additions to the carbonyl above the stereogenic C-9 substituent, the dimethoxy element also assists in further transformations through the corresponding acyliminium ion, as long as dehydration cannot compete.

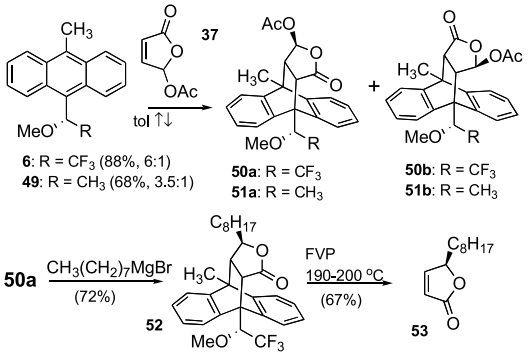
A second limitation was the relatively high temperatures necessary to achieve the retro Diels–Alder reactions. We initially addressed the issue of more facile cycloreversions by preparation of 9,10-disubstituted chiral anthracenes **6**, **44**, and later, **49** (see below). Kirby and co-workers[21] and Keck and co-workers[22] had also used a 9,10-disubstituted anthracene (9,10-dimethylanthracene) to trap and subsequently release highly reactive acylnitroso reagents and thioaldehydes, and Kirby had noted that cycloreversions with 9,10-dimethylanthracene were slightly faster than with anthracene itself.[21c] Another purpose in using **6** was enhanced reactivity relative to **4a** by substituting C-10 with a methyl group. This latter effect was indeed observed as the relative reactivities of **4a**:**6** was 1:10 in competition experiments with NMM.

Cycloadditions of **6**, **44**, and **49** with maleic anhydride, *N*-alkylmaleimides, and 2-bromomaleic anhydride were all completely diastereoselective. Regioselectivities in subsequent carbonyl transformations were also excellent, as illustrated for **44** (Scheme 19).

Unfortunately, there was insufficient moderation in the conditions for the cycloreversion with 9,10-disubstituted anthracene templates. For example, cycloadditions of



Scheme 19.



Scheme 20.

the unsymmetric dienophile **37** with **6** and **49** were investigated for comparison with the results described earlier with anthracene **5** (see Scheme 14). The regioselectivity observed with these 9,10-disubstituted anthracenes (Scheme 20) was comparable to that obtained with **5**. Cycloadduct **50a**, the major regioisomer in the cycloaddition with **6**, was subsequently transformed into the butenolide **53**, a precursor to a rove beetle pheromone,[23] as previously reported.[1b] Thus, the addition of *n*-octyl Grignard reagent to **50a** gave **52**, which was followed by FVP, now at 190–200 °C, to yield **53**. While the temperature required for cycloreversion with this 9,10-disubstituted anthracene template was reduced in comparison to those with **3a** and **5**, high temperatures were still necessary. Some cycloreversions could be achieved in refluxing xylenes or by FVP at 190–200 °C, but typically the best yields still required FVP at 400 °C (4 min).

From this work, anthracene **5** emerged as the preferred template due to its ease of preparation, stability to storage, and greater range of chemistry toleration with excellent regioselectivity in carbonyl transformations subsequent to the cycloaddition. Considerable effort was therefore expended to accomplish the cycloreversion under microwave irradiation[24] using this template with adducts **19** (Fig. 4). Various conditions were examined including irradiation neat at ambient atmosphere, under vacuum, and adsorbed on silica gel, Montmorillonite KSF, Montmorillonite K10, and graphite, all with and without Lewis acids present. Best results for

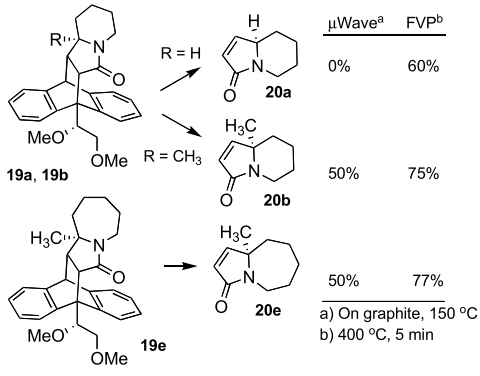


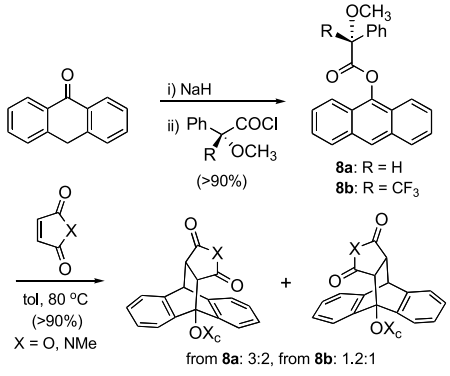
Figure 4. Comparison of FVP with microwave-induced cycloreversion.

microwave promoted cycloreversion were observed with graphite as a support with **19b** and **e**, while with **19a**, no indolizidinone **20a** was isolated, which was not stable to microwave conditions. In all cases, however, the yields of the lactams were higher with FVP (400 °C, 4–5 min). Moreover, with FVP the chiral anthracene template was fully recovered, but was completely lost with microwave irradiation.

These relatively harsh cycloreversion conditions stimulated further research into other chiral anthracene templates. We turned to type B chiral anthracenes **7a** and **8** substituted at C-9 with lone pair donors (nitrogen and oxygen) in an effort to develop a more reactive template for both the original cycloaddition and the cycloreversion. Czarnik has demonstrated that electron donating substituents at anthracene's C-9 (and C-10) position accelerate the cycloreversion,[25] though they also increase the susceptibility of the anthracene to oxidation.[26]

Initially, we examined 9-acyloxyanthracenes **8a** and **b**, both easily prepared from anthrone (Scheme 21). Trost et al.,[27] Siegel and Thornton,[28] and others[29] had shown that the corresponding mandelate-type 1-acyloxybutadienes can participate in Diels–Alder cycloadditions with excellent diastereoselectivities. Furthermore, oxyanion promoted cycloreversions should be easily achieved, following desired transformations of the mounted dienophiles, by basic hydrolysis of the esters, analogous to the work of Knapp et al.[30] and Bunnage and Nicolaou.[31] Unfortunately, the cycloadditions of **8a** and **b** with maleic anhydride and NMM proceeded with poor diastereoselectivity, presumably due to the temperatures necessary to achieve acceptable yields of cycloadduct in a reasonable amount of time. Lewis acid catalysis did not improve the results.

Aminoanthracene **7a** was then prepared via Pd-catalyzed aryl amination[32] beginning with 9-bromoanthracene.[1d] This anthracene was considered a good candidate to serve as a chiral stereocontrolling template based on the work of Rawal who has shown the effectiveness of homochiral 1-aminobutadienes in controlling the stereochemistry of cycloadditions.[33] As anticipated, **7a** proved to be sensitive to oxygen, producing anthraquinone upon standing under ambient conditions.

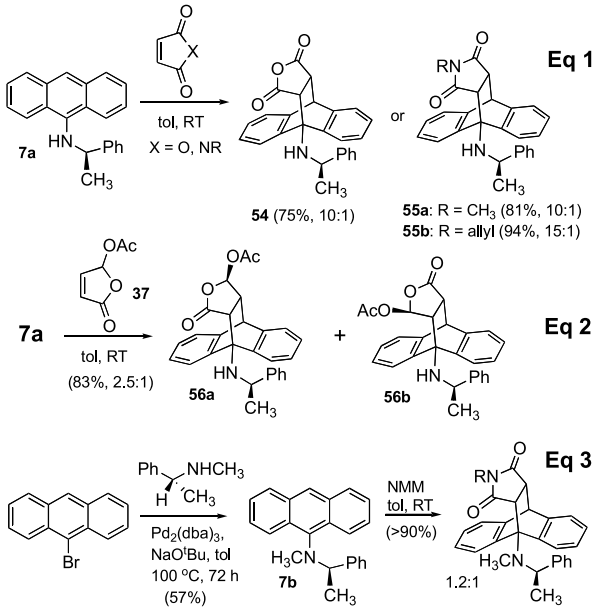


Scheme 21.

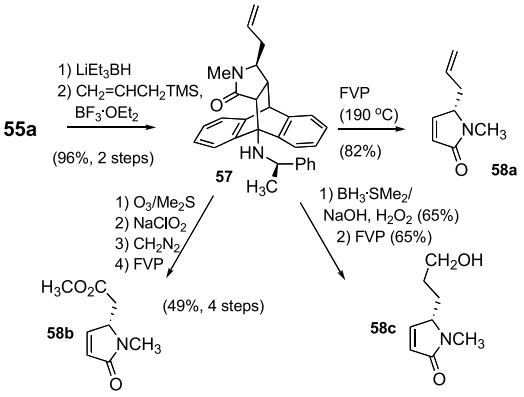
Storage under nitrogen at 0 °C was adequate, but it was found to be easier to simply proceed to the cycloaddition with maleic anhydride or an *N*-alkylmaleimide (Scheme 22); the cycloadducts were stable under ambient conditions for extended periods of time. The cycloadditions proceeded at room temperature (rt) over 48 h, a significantly lower temperature than achieved with other chiral anthracenes. Unlike the cycloadditions of other chiral anthracenes **3**–**6**, however, trace amounts of the minor, stereoisomeric cycloadduct could be detected in the NMR spectra of the reaction mixture. Increasing the reaction temperature to accelerate the cycloaddition unfortunately led to increasing amounts of the minor diastereomer. For example, the diastereoselectivity of the cycloaddition of **7a** with NMM dropped from 10:1 at rt to 6:1 at 60 °C. The cycloaddition with acetoxyfuranone **37** was also not very selective, producing a 2.5:1 ratio of **56a** and **b** at rt (Scheme 22, Eq. 2). The corresponding *N*-methylaminoanthracene **7b**, also prepared by Pd-catalyzed aryl amination, gave poor diastereoselectiviy in the cycloaddition with NMM at rt (1.2:1, Scheme 21, Eq. 3).[34]

As with anthracenes **3**–**6**, reductions or the additions of Grignard reagents to adducts **55** occurred with exclusive stereoselectivity at the carbonyl group remote to the anthracene stereogenic substituent. However, Grignard reagent additions were accompanied by some unwanted cycloreversion, resulting in lower yields (57–78% for methyl and phenyl Grignard reagents) in comparison with the additions to the adducts of template **5** (83 – 99+%). Subsequent allylation, alkene transformations, and FVP, now at 190 °C (10 min), yielded the target butenolides and α,β-unsaturated γ-lactams as illustrated for **58a**–**c** (Scheme 23).[1d]

While the amino substituent facilitated the cycloreversion, FVP was still required for optimal yield, albeit at lower temperatures. Aminoanthracene **7a** could be



Scheme 22.

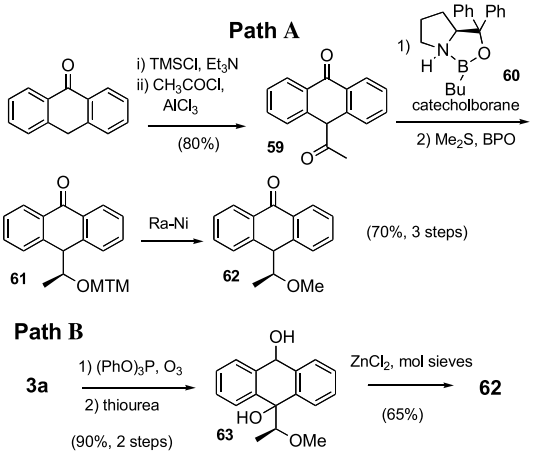


Scheme 23.

recovered by trapping as the NMM (or other maleimide) cycloadduct in a minimum 70% yield, less than the recovery of **5**, that was essentially quantitative. Given the greater stability of **5**, its greater recovery from the cycloreversion, and greater versatility in Grignard reagent additions to its cycloadducts, and the fact that FVP was still required for optimal cycloreversion using **7a**, **5** remains as the chiral anthracene template with which we are pursuing other synthetic goals. In further efforts to achieve cycloreversions under milder conditions, we examined chiral anthrone templates as described in the following section.

4. Chiral anthrone templates

Rickborn's extensive investigation into the cycloadditions of anthrone,[35] coupled with Knapp's et al.[30] and Bunnage and Nicolaou's,[31] demonstrated success with the oxyanion promoted cycloreversions of 9-hydroxyanthracene cycloadducts led us to prepare and investigate the cycloadditions of chiral anthrones. Effort to date has focused primarily on anthrone **62**, since the 1-methoxyethyl stereogenic substituent had proven effective in exerting excellent stereocontrol over the cycloadditions of anthracene **3a**. The preparation of **62** was accomplished in two ways. In the first route, anthrone was



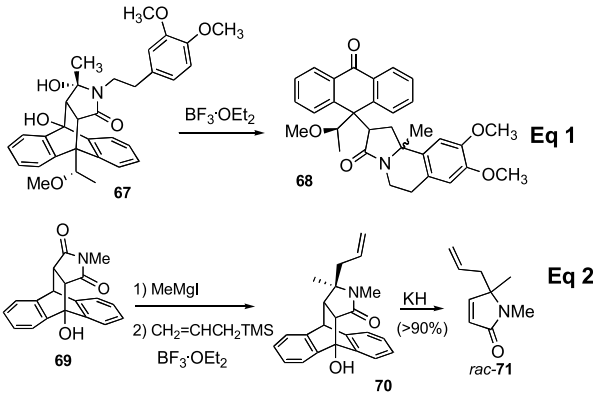
Scheme 24.

acylated via its in situ generated TMS ether, giving anthronyl ketone **59** (Scheme 24, Path A).[36] Asymmetric reduction following Corey's procedure[37] reported for similar substrates proceeded with excellent enantioselectivity (>95% ee by HPLC). Selective methylation of the alcohol proved troublesome due to competing methylation of the anthrone carbonyl oxygen. Indirect methylation to give **62** finally succeeded by formation of the methylthiomethyl ether **61**[38] followed by Raney-Ni reduction.

Alternatively, **62** was also prepared from **3a** by singlet oxygen cycloaddition,[39] followed by reduction of the resultant cyclic peroxide and dehydration of **63** catalyzed by $ZnCl_2$ adsorbed onto molecular sieves (Scheme 24, Path B). This latter route was more practical on a larger scale.

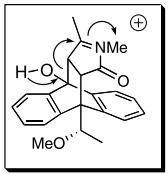
Cycloadditions of **62** with maleimides such as NMM proceeded in quantitative yields and complete diastereoselectivity under Rickborn conditions[40] to give adducts **64** (Scheme 25). Reactions with maleic anhydride were not successful due to the instability of this dienophile to the reaction conditions. Though the highly hindered tertiary alcohol of **64** could not be protected (Rickborn previously noted the lack of reactivity of this alcohol,[40]) **64** smoothly underwent the addition of Grignard reagents to the top face of the cycloadduct at the carbonyl remote to the chiral substituent with complete regioselectivity. Surprisingly, no trace of cycloreversion product could be detected. Since both Knapp and Nicolaou had triggered their cycloreversions from anthrone cycloadducts via oxygen anion generation with KH, we reasoned that a cation effect may account for the lack of cycloreversion from the magnesium alkoxides produced in the Grignard reagent additions. Treatment of adducts **65** with KH did indeed result in rapid cycloreversion (at rt) but resulted in racemic lactams **66**. Presumably, the oxyanion-triggered cycloreversion is sensitive to the degree of covalency of the alkoxide 'salt,' with the less covalent K^+ salt allowing for the facile retro Diels–Alder reaction. Unfortunately, the basic conditions of the cycloreversion also led to rapid racemization of the hydroxylactams **66**.

Attempts to utilize acyliminium ion chemistry, as was successful with the chiral anthracene adducts derived from **5**, were not successful with adducts related to **65**. For example, attempted cyclization of **67** led only to

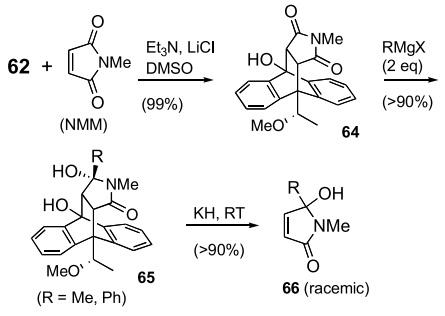


Scheme 26.

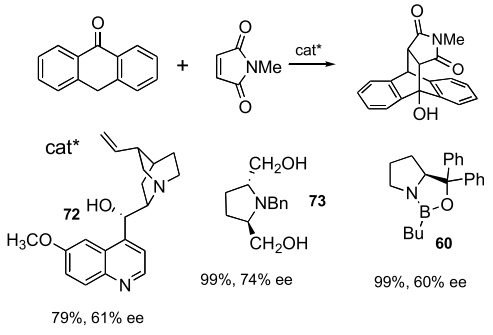
ring-opened product **68** as a diastereomeric mixture (Scheme 26, Eq. 1), parallelling observations previously recorded by both Rickborn[34,39] and Kagan and coworkers.[41] Allylation of model anthrone adduct **70** formed after MeMgBr addition to **69**, however, was successful with cycloreversion then producing racemic lactam **71** (Scheme 26, Eq. 2). Therefore, it was concluded that the difficulty in working with the acyliminium ions from **65** to **67** was a consequence of the conjugative continuum extending from the alcohol oxygen lone pair through the sigma framework to the acyliminium ion (inset). With the acyliminium ion generated at the alternative carbonyl group as from **69**, this continuum does not exist, and ring opening is not a competitive pathway. Therefore, we have turned our attention to the asymmetric cycloaddition between anthrone itself and *N*-alkylmaleimides.



Both Kagan and co-workers[41,42] and Yamamoto and coworkers,[43] have reported sufficiently intriguing enantioselectivities in the cycloadditions of anthrones with *N*-alkylmaleimides to warrant further investigation (Scheme 27). Kagan observed a maximum 61% ee using quinidine (**72**) as the basic catalyst to promote the cyclo-



Scheme 25.



Scheme 27.

addition, while Yamamoto achieved 74% ee in the same reaction using diol **73** as the catalyst with NMM as the dienophile. In our own efforts, we have obtained a 60% ee using Corey's ligand **60** as the catalyst in the reaction with NMM. Given the excellent diastereo- and regioselectivity in the carbonyl transformations of the dienophile mounted on the anthrone, along with the extremely facile oxyanion-initiated cycloreversions as illustrated in Schemes 25 and 26, we are continuing efforts to optimize the enantioselectivity in this cycloaddition.

5. Conclusions

Chiral anthracenes have shown great promise as stereocontrolling templates in the Diels–Alder/retro Diels–Alder sequence. The applications with maleimide dienophiles have shown success in the synthesis of alkaloidal core structures, such as indolizidinones and pyrroloazepinones, as well as in the preparation of α, β-unsaturated γ-lactams. The chiral anthracene that has currently emerged for applications in synthesis is dimethoxyethylanthracene **5**. This anthracene has shown the widest range of compatibility with carbonyl transformations subsequent to the cycloaddition and is also benchtop stable. The main drawback with **5** is the requirement for FVP for the cycloreversion. To overcome this drawback, current efforts are also devoted to develop the asymmetric cycloadditions of anthrone. The anthrone template holds high potential due to the facile cycloadditions, the high regioselectivity in subsequent carbonyl transformations including Grignard reagent additions, and facile cycloreversion upon oxyanion generation.

Dedication

This manuscript is dedicated to Prof. Koji Nakanishi of Columbia University, not only on the occasion of the awarding of the well-deserved *Tetrahedron* prize, but also for his exceptional mentorship and inspiration he has provided since we first met more than 20 years ago. J.K.S. is eternally grateful for the opportunities Professor Nakanishi has afforded him to begin his research career, which remains one of the most stimulating experiences of his life.

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