JOC Perspective

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Complexity-Building Annulations of Strained Cycloalkanes and C=O π Bonds

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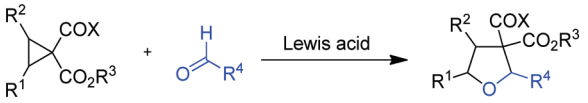
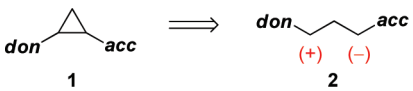


This Perspective details a developing research program that emerged from simple plans for achieving the synthesis of tetrahydrofurans from cyclopropanes and C=O π bonds. Lewis acid catalyzed annulations of malonate-derived donor−acceptor cyclopropanes with aldehydes are unusually broad in scope and lead to the synthesis of structurally diverse tetrahydrofurans. The reactions are stereospecific, with inversion observed at the cyclopropane donor site. Substituent effects on the aldehyde suggest that it acts as a nucleophile in the reaction. An unusual mechanism emerges in which the aldehyde traps a configurationally stable intimate ion pair to stereospecifically construct the C−O bond. In addition to the stereospecific conversion of enantiomerically enriched cyclopropanes into nonracemic heterocycles, we have also demonstrated that racemic cyclopropane 1,1-diesters can undergo dynamic kinetic asymmetric annulations catalyzed by (pybox)MgI_2 complexes. Asymmetric syntheses of (+)-polyanthellin A and (+)-virgatusin have been achieved; both rely upon cyclopropane/aldehyde annulation for construction of the core tetrahydrofurans.

Introduction

Ring strain engenders thermodynamic destabilization in organic molecules that can be parlayed into interesting reactivity with the proper kinetic trigger. This notion has been well-recognized and extensively exploited in the chemistry of strained rings. Cyclopropanes are the most strained simple cycloalkane, and there exist many excellent methods for their preparation. This situation offers the synthetic chemist ample opportunities for reaction discovery. Kinetic lability in the σ-framework can be further accentuated through introduction of groups capable of stabilizing incipient negative and positive charge at vicinal carbons. Donor−acceptor cyclopropanes such as **1** are commonly viewed as the synthetic equivalent to the all-carbon 1,3-zwitterionic synthon **2** (Scheme 1).[1−4] Nucleophilic substitution involving donor−acceptor cyclopropanes was established in multiple cases as proceeding with inversion at the donor site,[5−9] but annulation reactions appeared to be a hodgepodge of mechanistic types[10,11] or mechanistically undefined. In this Perspective, we provide a description of research activities that focus on the development of new heterocycle-forming reactions between strained donor−acceptor cycloalkanes and aldehydes.

SCHEME 1



The reactions, particularly for cyclopropane/aldehyde combinations, are unusually broad in scope and proceed stereospecifically and with predictable diastereoselectivity.

Results and Discussion

Entrée. Our interest in this area initially centered on the Lewis acid-catalyzed generation of reactive intermediates from donor−acceptor aziridines. We were able to achieve the first productive cycloadditions of azomethine ylides obtained from Lewis acid-promoted carbon−carbon bond cleavage of aziridines (Scheme 2).[12] We assumed, without any corroborating evidence, that these reactions occurred via the Lewis acid bound azomethine ylide. While the reactions were conceptually interesting, there existed several obstacles that we were never able to overcome. The aziridine starting materials were not trivial to synthesize, nor were they particularly stable. Hydrolysis to the aminomalonate and

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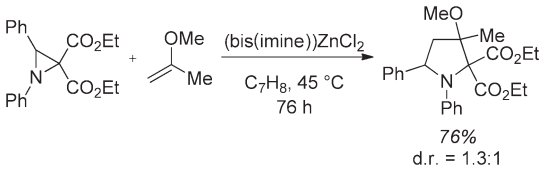
SCHEME 2



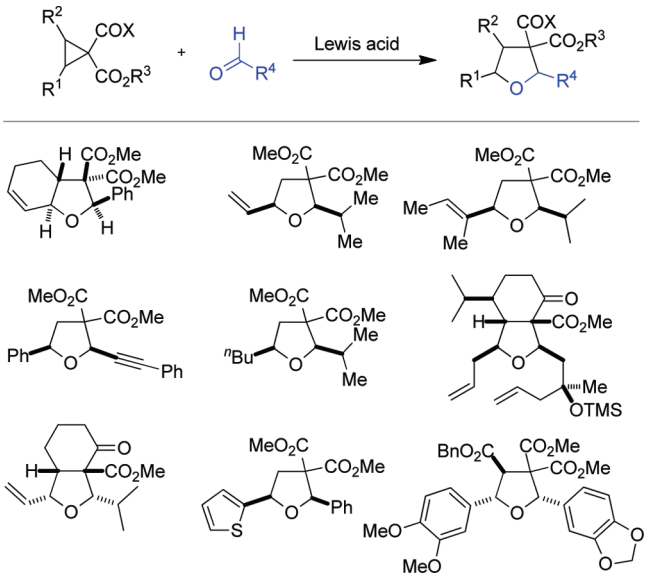
aldehyde occurred spontaneously on silica gel. Our efforts at enantioselective catalysis were largely unsuccessful, and the scope of the racemic reaction was rather narrow. As a synthetic method, the aziridine/enol ether cycloaddition left much to be desired.

Transition. The notion of employing ring strain as an enabling tool in reaction development, particularly for the synthesis of five-membered heterocycles, remained attractive to us; however, it was clear that a change of tactic was required. Predating our aziridine work, the Kerr group at Western Ontario had reported an interesting annulation between malonate-derived cyclopropanes and nitrones, a reaction they termed a "homo [3 + 2] dipolar cycloaddition".[13] Interest in these reagents for ring formation has only grown in the intervening years.[14−37]

The similarity between the aziridine and cyclopropane reagents, especially in the identity of the malonate activating group, provided the impetus for us to examine annulation[38] chemistry with aldehydes. The selection of aldehydes (to give tetrahydrofurans) rather than aldimines (to give pyrrolidines) was guided by simple pragmatism: as an entry point into the chemistry, we perceived that there were fewer variables to manage with aldehyde "dipolarophiles". In contrast to the aziridines, the cyclopropane 1,1-diesters were trivial to synthesize on scale (Knoevenagel condensation followed by Corey−Chaykovsky cyclopropanation) and exhibited good stability. Gratifyingly, we discovered that a number of Lewis acids were successful in catalyzing the desired cyclopropane/aldehyde annulation, with $Sn(OTf)_2$ providing excellent yields and diastereocontrol for the 2,5-*cis*-tetrahydrofuran.[39−41] In contrast to the aziridine-based cycloadditions, the preparations of the tetrahydrofurans were exceptionally clean, regularly providing >90% yield of analytically pure material. The reactions worked best when the donor was sp^2-hybridized, but even simple alkyl groups provided the product with reasonable yields. Of the synthetic methods developed in our laboratory, this one comes closest to being "general", and has much to recommend for it. Scheme 3 illustrates a small subset of tetrahydrofurans synthesized by this method; those selected are designed to illustrate the structural diversity that can arise through the application of this method.

A brief comment on the activating group is in order. Overall, the role of the β-dicarbonyl is reminiscent of that played in the classic malonic acid and acetoacetic acid syntheses: (1) The malonate greatly simplifies the synthesis of the substrates, typically rendering them accessible under mild conditions and from inexpensive starting materials. (2) The β-dicarbonyl provides potent electronic activation by installing a second contact point for Lewis acid coordination through chelation with divalent metal ions. The chelated complex in turn delivers a highly ordered transition structure. (3) The β-dicarbonyl delivers a valuable functional

SCHEME 3



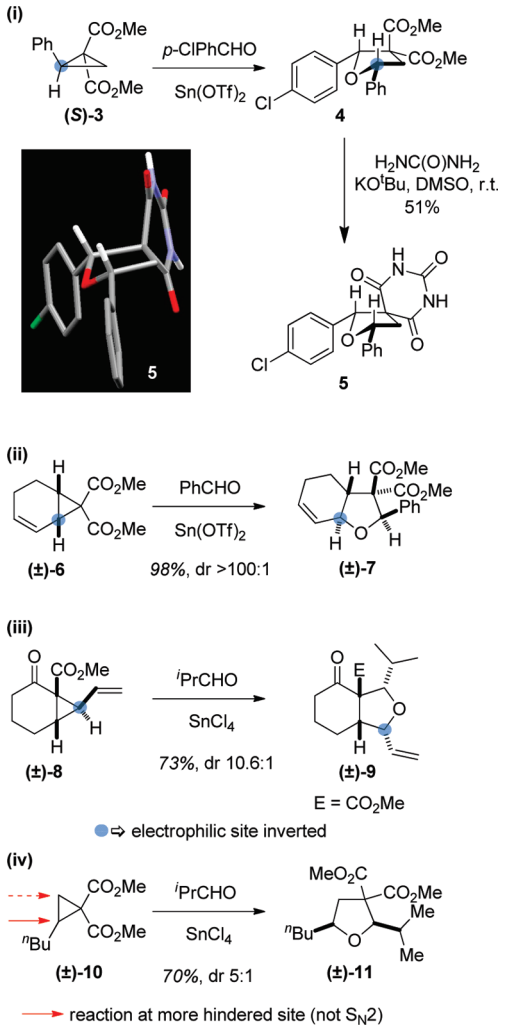
group in the product. Decarboxylation occurs simply and often with good diastereocontrol.[40,42,43] Other manipulations could be envisioned based on precedent.[35] Because of the attractive attributes conferred, there exists in our view no strong driving force to examine monoactivated cyclopropane substrates.

Mechanism.[41] The stereochemical course of this reaction could be evaluated in several ways. Using an enantiopure cyclopropane starting material with one stereogenic center (**3**), we determined the fate of the stereocenter by X-ray diffraction analysis of the annulation product's barbituric acid (**5**) (Scheme 4). Alternatively, those substrates having an additional chiral center that was not changed during the reaction (**6**, **8**) contained a stereochemical "reference point" that allowed the outcome at the donor site to be evaluated through NMR experiments. The analyses were internally consistent and revealed inversion at the electrophilic site.

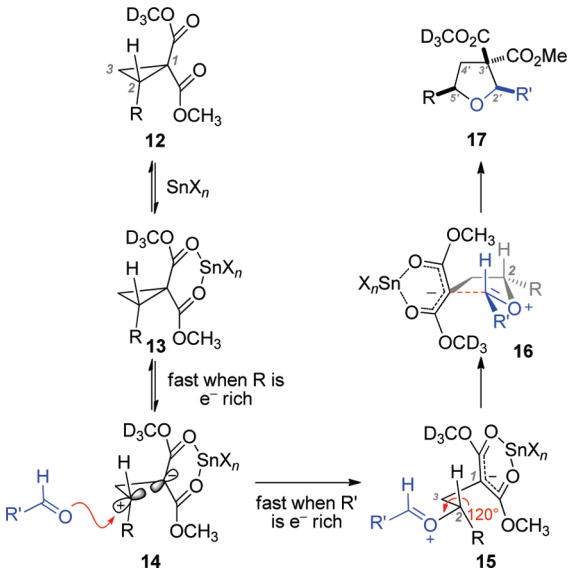
Electron-rich aldehydes reacted faster than electron-poor aldehydes in direct competition experiments, pointing to the aldehyde's role as a nucleophile in the annulation. The observed reaction at the methine carbon in preference to the methylene carbon in cyclopropane **10** ruled out an S_N2 reaction. To give nucleophilic attack at the more substituted carbon (in the absence of mitigating electronic effects, e.g., benzylic carbon), the electrophilic carbon must have significant carbenium ion character. We have proposed that the most likely identity of the electrophile is the intimate ion pair **14** wherein the nucleofugal malonate is unable to progress to the solvent separated ion pair or completely dissociated ion pair because of the constraints of the methylene bridge (Scheme 5). The other possible fate for the intimate ion pair **14** is racemization through bond rotation and recombination. This scrambling does occur, but unless the donor group is extremely electron-rich or the aldehyde is particularly electron-poor, its rate is typically not competitive with annulation.

This stereochemical behavior is related to seminal work from Cram involving solvolytic ring-opening of cyanoacetate-derived donor−acceptor cyclopropanes (e.g., **18**).[5] A similar carbenium/carbanion pair was invoked to account

SCHEME 4

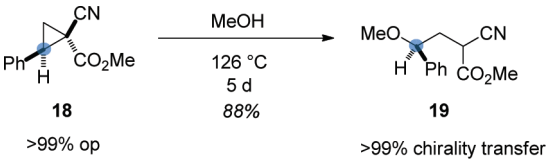


SCHEME 5

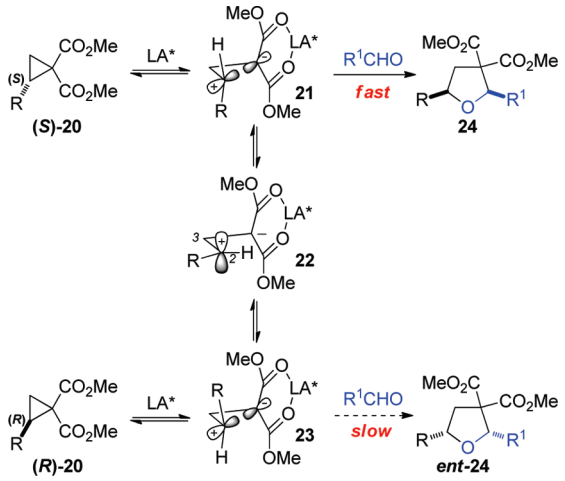


for the observed inversion. What is remarkable about the cyclopropane/aldehyde annulation reactions in comparison

SCHEME 6



SCHEME 7

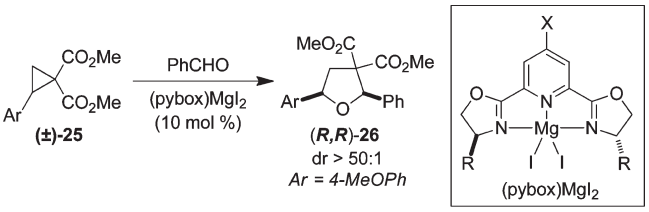


to the solvolyses are the mildness of the conditions and the magnitude of the rate enhancement one accrues by employing Lewis acid catalysis. While solvolysis of **18** in neat MeOH required 5 d at 126 °C (Scheme 6), *the cyclopropane/aldehyde annulations typically proceed at ambient temperature over the course of ca. 1−5 h with a much poorer nucleophile*.

Asymmetric Catalysis.[44] What drove this project from the beginning (back to the aziridine work) was the idea that chiral Lewis acid catalysis could be employed to convert racemic starting materials to enantiomerically enriched heterocycles. In the case of aziridines, this would involve a Lewis acid coordinated azomethine ylide. Our mechanistic studies revealed that the situation with cyclopropanes would be somewhat more complex insofar as the reactions occur via a chiral intermediate rather than an achiral one (cf. azomethine ylide). What would be required then, is a type I dynamic kinetic asymmetric transformation[45] wherein the role of the Lewis acid is twofold: (1) catalyze the racemization of the starting cyclopropane ((***S***)-**20** ⇆ (***R***)-**20**) and (2) catalyze the selective annulation of one enantiomer of the interconverting pair ((***S***)-**20** → **24**) (Scheme 7). The former would need to occur in the manner proposed by Cram.[46] The latter has been achieved for *noninterconverting* enantiomers (i.e., simple kinetic resolution).[15,19] The configurational stability of the cyclopropane starting material is an asset in the stereospecific conversion of enantiopure cyclopropanes to enantiopure tetrahydrofurans but would be a barrier to the development of a dynamic kinetic asymmetric annulation. To accelerate the enantiomer interconversion, we have focused on cyclopropanes bearing electron-releasing donor groups since they undergo racemization at an elevated rate.

A broad screen of chiral ligands and Lewis acids revealed that MgI_2 in combination with *tert*-butyl pybox provided promising results (Table 1). MgI_2 is a Lewis acid that appears

TABLE 1. Optimal DYKAT Reaction Conditions



solvent	X	R	yield (%)	er
CH_2Cl_2	H	Bn	<5	nd
CH_2Cl_2	H	Ph	<5	nd
CH_2Cl_2	H	^{i}Pr	18	nd
CH_2Cl_2	H	^{t}Bu	30	80:20
Et_2O	H	^{t}Bu	43	84:16
$CHCl_3$	H	^{t}Bu	68	84:16
CCl_4	H	^{t}Bu	64	92.5:7.5
CCl_4	OMe	^{t}Bu	5	Nd
CCl_4	CF_3	^{t}Bu	57	96.5:3.5
CCl_4	**Cl**	**^{t}Bu**	**74**	**96:4**
CH_2Cl_2	Cl	^{t}Bu	16	82.5:17.5
PhMe	Cl	^{t}Bu	40	96:4

prominently in the literature associated with cyclopropane ring-opening,[47−55] so its emergence as a top candidate was perhaps not surprising. Other Mg(II) salts were ineffective. The use of the *tert*-butyl pybox is essential for both yield and enantioselection. Pybox ligands derived from other amino acids give poorer results. Varying the substituents at the pyridine 4-position[56,57] revealed a rate and yield benefit conferred by electronegative groups. Variations at that position are a useful way to modulate reactivity and selectivity when changes in the oxazoline substituent are not tolerated. Solvent effects are not well understood in this reaction, with CCl_4 offering both the optimal enantioselectivity and reaction efficiency.

As long as the C2-donor group on the cyclopropane is electron-rich, the efficiency of the reaction is quite good for a range of substrates. Reactions with enantiomerically pure, noninterconverting cyclopropanes (***S*)-3** and (***R*)-3** revealed that the inversion mechanism was still operative and that the (*S*)-enantiomer was the fast reacting antipode. By corollary, reaction with the racemate (±)**-3** provided a result consistent with a simple kinetic resolution. It might be tempting to invoke participation of a nucleophilic iodide in the mechanism to account for the unique effectiveness of MgI_2, but the stereochemical results in Scheme 8 argue convincingly against iodide acting on the productive pathway.

When the enantiomeric composition of a "dynamic" cyclopropane was measured as a function of conversion in a catalytic reaction, a buildup of the slow-reacting enantiomer ($((R)/(S))_{max} \approx 70{:}30$) was observed (Chart 1). An ideal DYKAT or DKR maintains a (*R*)/(*S*) ratio of 50:50 throughout the reaction by rapid racemization. The divergence from this ideal makes the high observed enantioselectivity, in the face of a rising effective concentration of the slow reacting enantiomer, even more impressive.

Stereochemical Model. What accounts for the preferred reaction of the (*S*)-enantiomer of the cyclopropane with the (*S*,*S*)-(^{t}Bupybox)MgI_2 catalyst? In the absence of a crystal structure of the complex or its derivatives, we have constructed our working model based on an X-ray structure of a $(terpy)Mg(OH_2)(HOMe)_2]^{2+}$ complex (**28**).[58] Not surprisingly, this complex displays octahedral geometry. To accommodate a chelating substrate, the (pybox)MgI_2 complex **29** must be transformed to a cationic catalyst−substrate complex (**30**), and the combination of the chiral cyclopropane with the chiral complex means that four diastereomeric octahedral complexes are possible (Scheme 9). We have discounted two of these diastereomers on the basis of what we believe are debilitating steric interactions with the proximal *tert*-butyl group, leaving **30a** and **30b** as candidate reactive complexes. The product's stereochemical identity points to **30a** as the productive complex, an interesting finding considering the instability that one might presume

SCHEME 8

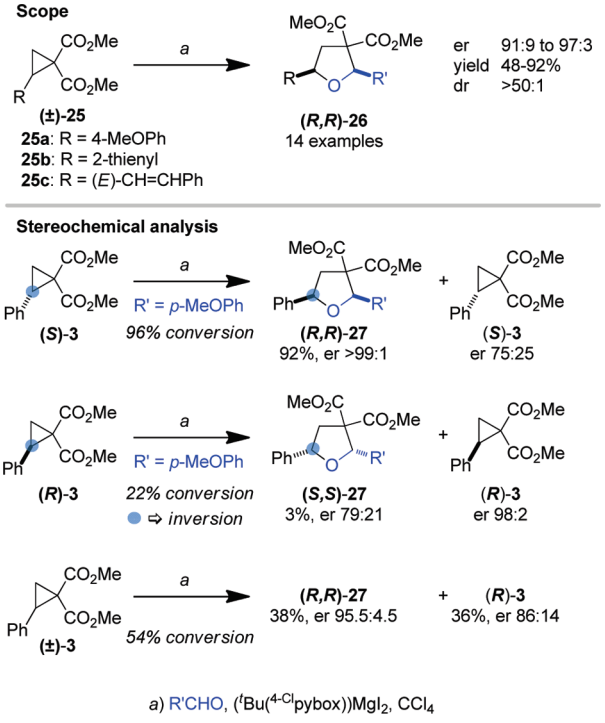
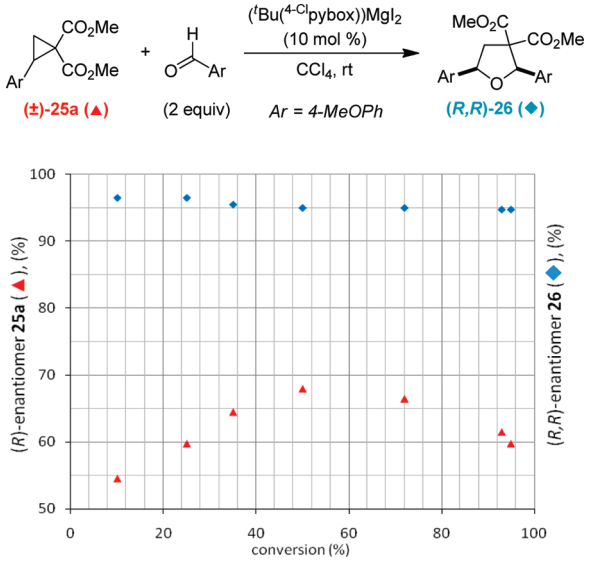
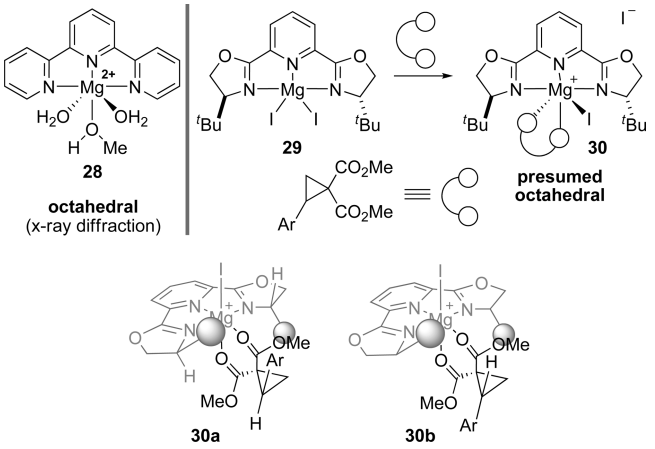


CHART 1. Enantiomeric Composition of 25a and 26 as a Function of Conversion



SCHEME 9

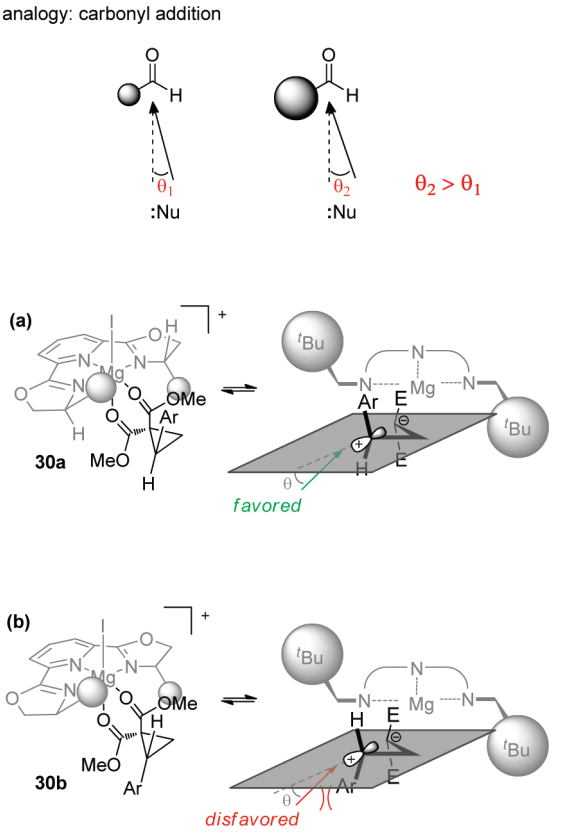


to arise via interactions between the illustrated Ar and *tert*-butyl group. In rationalizing this somewhat surprising finding, we have found two concepts useful in our analysis: (1) modified nucleophile attack trajectories and (2) creation of stereoselection via destabilization of reactive intermediates.

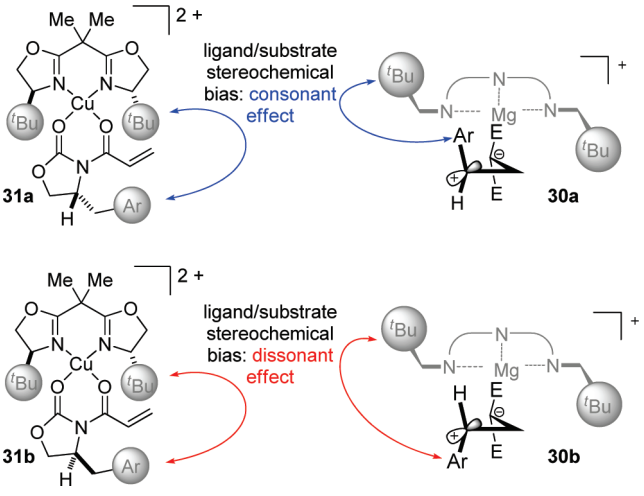
In 1983, Heathcock formalized the idea that ideal reaction trajectories in stereoselective reactions are perturbed by steric bulk.[59,60] For carbonyl addition, "drift" from a trajectory that gives optimal overlap with $\pi^*_{C=O}$ occurs when substituents on the carbonyl are sterically demanding (Scheme 10). How does this fit in the present case? In Scheme 10, the dashed lines associated with complexes **30a** and **30b** represent optimal approach trajectories for overlap of the oxygen lone pair with the empty p orbital of the carbenium ion. To the extent that the *tert*-butyl group of the ligand causes the aldehyde's approach to change from this ideal, interactions with the proton (**30a**) or aryl group (**30b**) will become manifest. Complex **30b** should suffer a slower reaction rate because of unfavorable interactions with the substrate. By contrast, ligand-induced trajectory drift in the fast reacting complex **30a** only brings the nucleophilic aldehyde into proximity with the cyclopropane methine proton, not the C2 aryl group. This interaction presumably carries a lesser energetic (and thus rate) penalty.

A second concept that may work in concert with the trajectory drift hypothesis is linked to double-stereodifferentiating experiments performed by Evans in bis(oxazoline)-Cu(II)-catalyzed Diels–Alder reactions with chiral dienophiles.[61] That work revealed that substrate and ligand chirality working together can have a dramatic effect on reaction rates of diastereomeric complexes. While **31a** is nominally less stable than **31b** due to the spatial proximity of the dienophile (benzyl) and ligand (*tert*-butyl) substituents, the complex **31a** is conferred with significantly greater reactivity than **31b**, either by virtue of its destabilization or its "clean" access to one diastereoface of the dienophile. It appears appropriate (or at least reasonable) to invoke this precedent in the present case, since **30a** clearly positions the substrate and ligand substituents in closer proximity than in the diastereomeric complex **30b** (Scheme 11). The preferred reaction via complex **30a**, which confines all of the steric bulk in one quadrant of the catalyst–substrate complex, could be a consequence of either ground-state destabilization or relatively unfettered access for the nucleophilic aldehyde.[62]

SCHEME 10

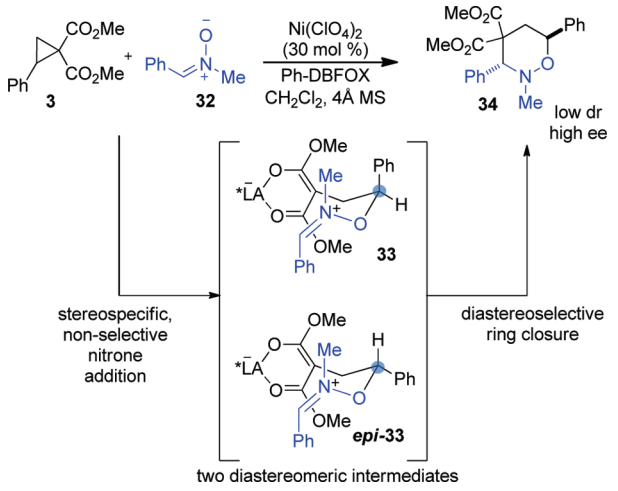


SCHEME 11



Before concluding this section on asymmetric catalysis, it should be noted that, because of the mechanistic nuances of cyclopropane-based annulations, it is still possible in principle to obtain high product enantioselectivity in reactions where there exists minimal rate difference for the enantiomeric cyclopropane starting materials. To illustrate this point, we consider an example of an asymmetric nitrone/cyclopropane annulation that was described by Sibi and coworkers. As reported by Kerr, the reaction between cyclopropane **3** and nitrone **32** catalyzed by an achiral Lewis acid ($Yb(OTf)_3$) gives exclusive formation of the *cis*-tetrahydro-1,2-oxazine **34** (Scheme 12).[13] Conversely, a chiral Ni(II)

SCHEME 12

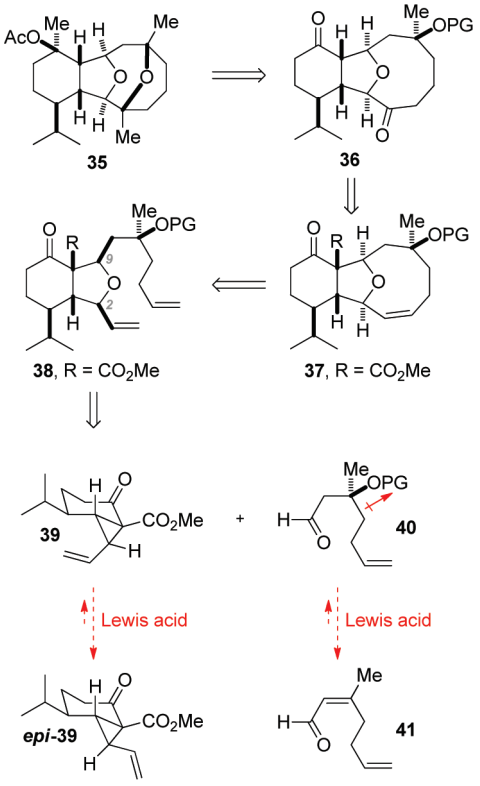


complex provides a ~1:1 mixture of the *cis* and *trans* isomers, but both are obtained with high enantioselectivity.[15] It appears that, in contrast to the (pybox)MgI_2 system, the (DBFOX)$Ni(ClO_4)_2$ catalyst exerts no enantiomeric preference in the stereospecific C−O bond formation (giving both **33** and ***epi*-33**). Instead, the chiral metal complex (acting as a chiral malonate) exhibits high facial selectivity in the intramolecular addition to the iminium intermediates. This phenomenon has been termed "enantiodifferentiation after the first irreversible step".[63] The divergent results seen in the literature highlight the difficulty in achieving useful stereochemical recognition in enantioselective reactions of this particular family of chiral substrates.

Natural Product Synthesis.[3] Given the frequent occurrence of tetrahydrofurans in natural products, it was reasonable to explore whether the cyclopropane/aldehyde annulation might be applicable in more complex settings. We endeavored to be aggressive in our target selection. Choosing molecules where the annulation had a high or obvious probability of success ("showcasing the method") seemed unlikely to yield much in the way of useful information. Instead, we chose molecules that would permit us to ask some questions that remained unanswered from our scope studies.

(a) Polyanthellin A. Cladiellin diterpenes are structurally interesting polycyclic natural products that exhibit a variety of biological activities and have been attractive targets for synthesis.[64] Polyanthellin A (**35**)[65,66] is a constituent member first synthesized by Kim;[67] it contains both a tetrahydrofuran and tetrahydropyran ring. Our retrosynthetic plan for polyanthellin A hinged on the implementation of an annulation fragment coupling in a manner that would maximize convergency. Retrosynthetic excision of two C−O bonds via etherification and hydration transforms, along with Wittig transforms led to the oxonanone **36** (Scheme 13). If the precursor to **36** was alkene **37**, a ring-closing metathesis could be considered for the oxonene synthesis. The functionality present in ring-closing metathesis precursor **38** collectively comprises a retron for a cyclopropane/aldehyde (3 + 2) annulation. This rather aggressive coupling presented us with two potentially significant obstacles. First, the requisite aldehyde appeared to be both fragile (due to the possibility of β-elimination under acidic conditions, **40** → **41**) and poorly nucleophilic (due to the full substitution at the β-carbon

SCHEME 13



together with an electronegative substituent). We already knew from our scope studies that α-silyloxy aldehydes were not viable in the annulation. Second, the mechanism of the annulation dictated the requisite stereochemistry at the cyclopropane donor site. The bicyclo[4.1.0]heptanone **39** presents the donor group on the hindered concave (*endo*) surface. It seemed reasonable to fear preannulation epimerization to what was presumably the more stable isomer ***epi*-39**. Such an isomerization would thwart the synthesis from a stereochemical standpoint, since we already knew that the *exo*-vinyl isomer would lead to the incorrect C2/C9 isomer (cf. **8** → **9**). Determining the feasibility of the **39** + **40** → **38** conversion would help define the limits of the method and engage two reactants that might otherwise be unlikely to appear in a substrate table.

Concerns of cyclopropane epimerization were unfounded, but our suspicions regarding the fragility and poor nucleophilicity of **40** were confirmed. With those Lewis acids that had been found to be broadly effective for a range of annulation partners, model aldehyde β-silyloxy aldehydes decomposed, leaving unreacted cyclopropane behind. At this point, we might have contemplated "packaging" the tertiary hydroxyl group in some latent form that would engender a more efficient annulation, but we were adamant that unnecessary refunctionalization should be minimized. Accordingly, a new Lewis acid screen was undertaken to identify promising candidates with challenging reaction partners. Al(III) emerged as a prospect when it successfully promoted THF formation between **42** and **43**; however, when the nucleophilicity of the aldehyde was attenuated through both steric and electronic effects (**44**), ring-opening by the chloride counterion to give **46** became competitive

SCHEME 14

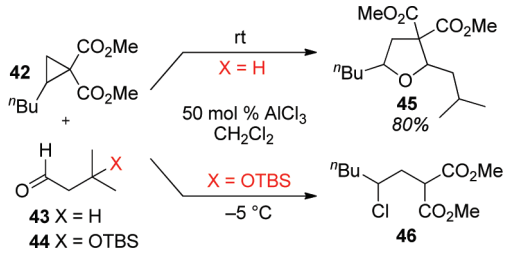
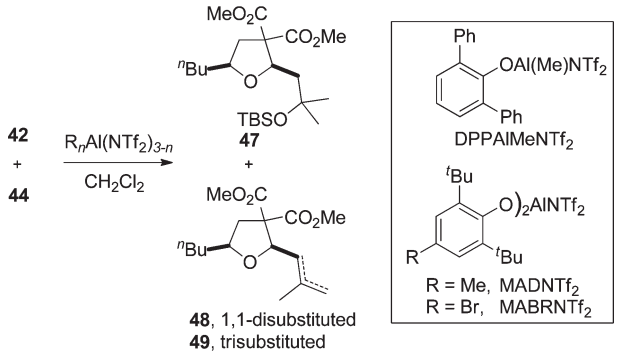


TABLE 2. Catalyst Optimization for a Challenging Annulation

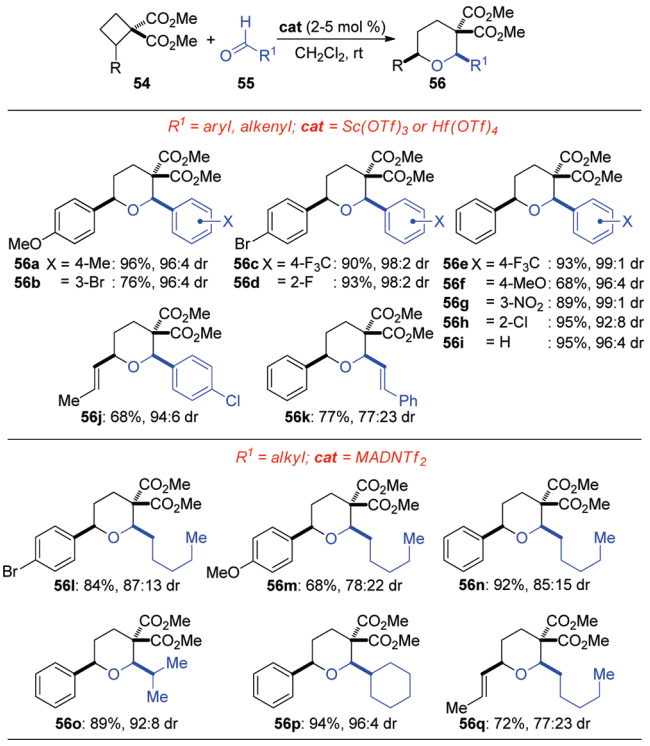


entry	Lewis acid	T (°C)	yield (%)	**47**:**48**:**49**	**47** (*cis*/*trans*)
1	$Al(NTf_2)_3$	−70	0	NA	NA
2	$MeAl(NTf_2)_2$	0	28	< 5: < 5: > 95	NA
3		−20	< 5	< 5: < 5: > 95	NA
4		−35	0	NA	NA
5	Me_2AlNTf_2	0	63	50:25:25	85:15
6		−20	72	66:17:17	85:15
7		−35	0	NA	NA
8	$^tBuOAlMeNTf_2$	rt	78	50:38:12	87:13
9	$DPPAlMeNTf_2$	rt	39	97:3: < 1	84:16
10	$MABRNTf_2$	rt	55	> 95: < 5: < 5	89:11
11	$MADNTf_2$	rt	71	99:1: < 1	86:14

(Scheme 14). Taking these two findings together, the Al(III) center was modified to (1) remove nucleophilic counterions and (2) change the steric environment around the Lewis acid to discourage coordination of the silyloxy group (Table 2). With respect to the former point, bis(triflimide) was found to be superior to triflate. The latter requirement was satisfied by the application of variants of Yamamoto's MAD catalysts.[68] Thus, $MADNTf_2$ was identified as a catalyst with sufficient Lewis acidity to induce the annulation while possessing the correct properties to short-circuit pre- or postannulation elimination.

Gratifyingly, when $MADNTf_2$ was applied in catalytic quantities to the annulation of **50** and **39**, clean formation of

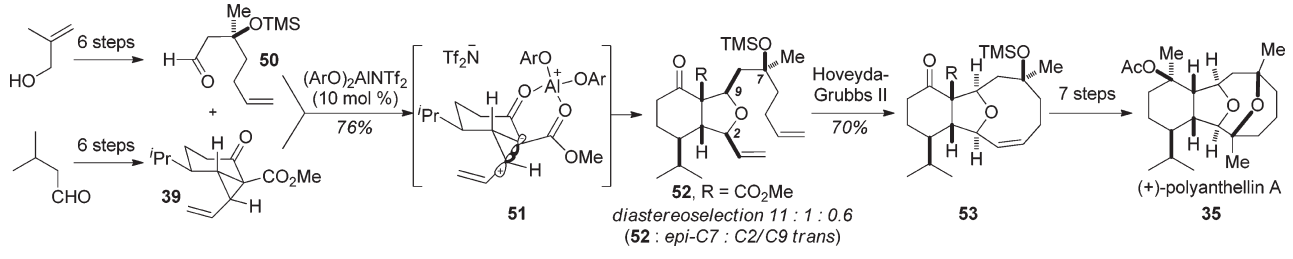
SCHEME 16



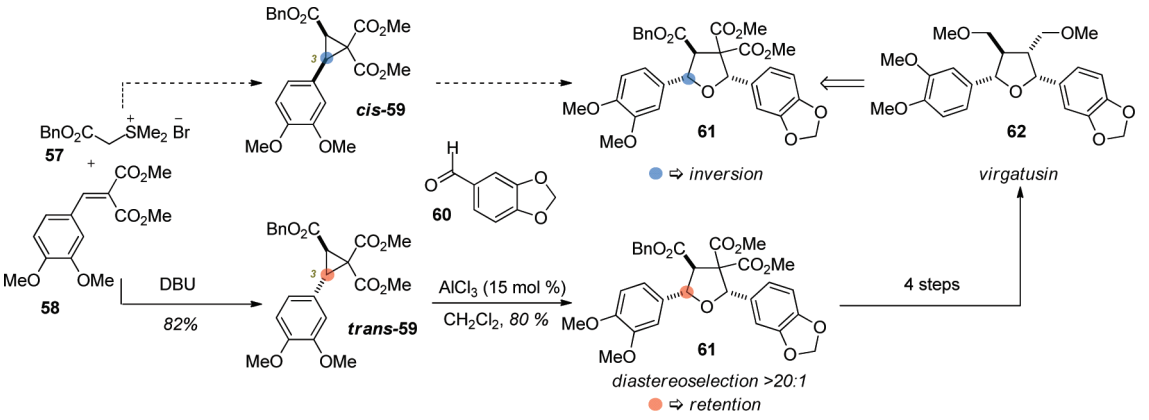
the desired bicyclic tetrahydrofuran **52** was observed, presumably by way of the chelated cationic complex **51** (Scheme 15).[69] As expected and needed, the reaction occurred with inversion at the vinyl bearing stereogenic center and the requisite C2/C9 *cis* relationship was obtained. Our adherence to a synthetic plan predicated on minimizing functional group manipulation paid immediate dividends: the annulation reaction directly delivered the functionality required to execute the oxonene-forming ring-closing metathesis in the next step (**52** → **53**). Seven additional steps yielded polyanthellin A (**35**).[42]

At this juncture, it is instructive to note an unanticipated benefit that arose from the polyanthellin study. Parallel investigations had revealed that (4 + 2) annulation between donor−acceptor cyclobutanes and aldehydes was viable for the synthesis of tetrahydropyrans (e.g., **54** + **55** → **56**, Scheme 16).[70] The Lewis acid of choice in our initial studies was $Sc(OTf)_3$, but the application of this and other Lewis acids to aliphatic aldehydes was unsuccessful. A synergy between the total synthesis studies and the reaction development work was realized upon the application of the $(ArO)_2AlNTf_2$ catalyst to this problem: the

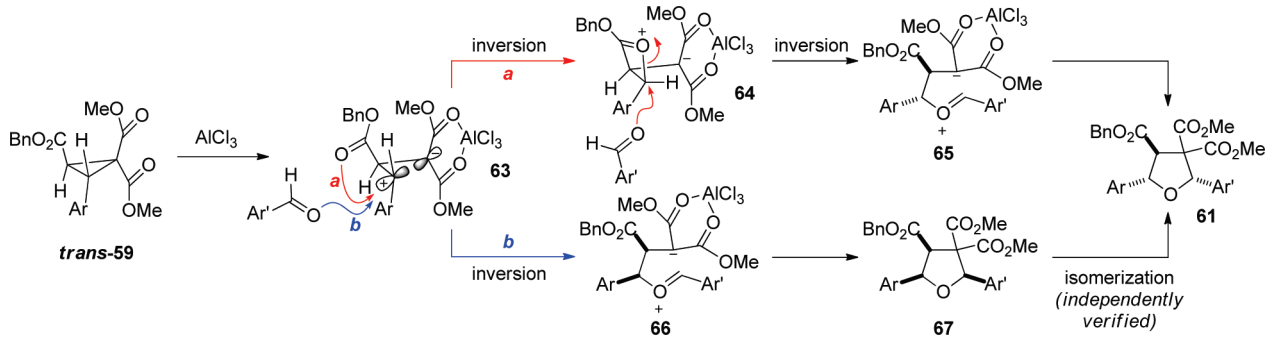
SCHEME 15



SCHEME 17



SCHEME 18



Yamamoto-based catalyst was uniquely effective for annulation with aliphatic aldehydes. As a consequence, the substrate scope (still under exploration) was considerably wider than it might otherwise have been.

(**b**) **Virgatusin.**[71−75] The synthesis of the furanolignan virgatusin (**62**)[76] provided us with a mechanistic surprise. Based on our understanding of the aldehyde/cyclopropane annulation mechanism, we projected that in order to arrive at the indicated stereochemical array in **61**, cyclopropane ***cis*-59** would be required. In the course of attempting to synthesize **59**, we had occasion to examine the Corey−Chaykovsky cyclopropanation reaction between sulfonium salt **57** and benzylidene malonate **58** (the product of a Knoevenagel condensation) (Scheme 17). We were initially disappointed to find that this high-yielding cyclopropanation (82% on ca. 7 g scale) provided exclusively the *trans* isomer (***trans*-59**). What follows constitutes a useful lesson in not hewing too closely to one's assumptions: we proceeded to attempt the annulation with the "wrong" stereoisomer just to "see what happened". The result also exposed by corollary one of the joys of chemistry and one that pervades this project; to wit, the discovery of the unexpected. Annulation of ***trans*-59** and piperonal (**60**) was catalyzed by $AlCl_3$ and unexpectedly yielded the needed virgatusin framework with >20:1 diastereoselection (80% yield, 10 g scale). Four additional steps yielded virgatusin. An enantioselective synthesis of cyclopropane ***trans*-59** allowed us to achieve an asymmetric synthesis.[43]

What is the source of this anomaly? The net retention that is observed could arise by at least two mechanisms. Neighboring group participation by the C2 benzyl ester (path a) could provide the first inversion that gives the secondary electrophile **64** (Scheme 18). Nucleophilic attack by the aldehyde would give a second inversion and thus net retention at the donor site. Alternatively, the established nucleophilic substitution mechanism (path b) could give the *all-cis* diastereomer **67** that undergoes Lewis acid catalyzed isomerization to the thermodynamically preferred diastereomer **61**. The viability of path b was confirmed when independently synthesized **67** gave **61** upon exposure to $AlCl_3$, a result that is consistent with known acid-catalyzed isomerizations of tetrahydrofurans.[72,77−80] The present case is apparently an extreme one, since we have found that this type of isomerization, even in very electron-rich systems, is only problematic if the reactions are not quenched promptly upon cyclopropane consumption.[41] In any event, we were indeed fortunate that the diastereoselectivity for the thermodynamic product **61** was so high in this reaction.

Conclusion

This phase of our investigation into the chemistry of activated strained rings has yielded valuable information and reactions. A superficially simple tetrahydrofuran synthesis breaks down into a mechanistically unique reaction wherein a malonate acts as a nucleofuge in concert with an aldehyde nucleophile. The β-dicarbonyl group plays a role analogous to that seen in the classic acetoacetate or malonic acid syntheses: it facilitates substrate synthesis, enables mild activation protocols, and provides functionality that is readily removed and/or manipulated. An understanding of the mechanistic principles underlying the annulation permitted

us to develop the enantioselective conversion of racemic donor−acceptor cyclopropanes to enantiomerically enriched tetrahydrofurans. Interrogating the limits of the reaction scope in the context of natural product synthesis led to the development of new catalysts for the annulation, which in turn enabled improvement of another new reaction, the cyclobutane/aldehyde tetrahydropyran synthesis. Investigating new substitution patterns in the building blocks revealed cases where the mechanistic framework can break down, albeit in an understandable way. Collectively, these reactions provide a general and useful tool for the preparation of stereochemically defined tetrahydrofurans, structural subunits that remain prominent in organic chemistry.

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