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(1*R*)-(+)-Camphor and Acetone Derived α′-Hydroxy Enones in Asymmetric Diels−Alder Reaction: Catalytic Activation by Lewis and Brønsted Acids, Substrate Scope, Applications in Syntheses, and Mechanistic Studies

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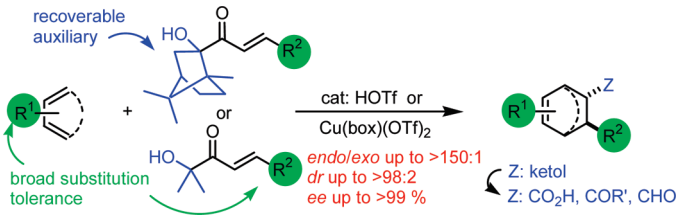

The Diels−Alder reaction constitutes one of the most powerful and convergent C−C bond-forming transformations and continues to be the privileged route to access cyclohexene substructures, which are widespread within natural products and bioactive constituents. Over the recent years, asymmetric catalytic Diels−Alder methodologies have experienced a tremendous advance, but still inherently difficult diene-dienophile combinations prevail, such as those involving dienes less reactive than cyclopentadiene or dienophiles like *β*-substituted acrylates and equivalents. Here the main features of α′-hydroxy enones as reaction partners of the Diels−Alder reaction are shown, with especial focus on their potentials and limitations in solving the above difficult cases. α′-Hydroxy enones are able to bind reversibly to both Lewis acids and Brønsted acids, forming 1,4-coordinated species that are shown to efficiently engage in these inherently difficult Diels−Alder reactions. On these bases, a convenient control of the reaction stereocontrol can be achieved using a camphor-derived chiral α′-hydroxy enone model (substrate-controlled asymmetric induction) and either Lewis acid or Brønsted acid catalysis. Complementing this approach, highly enantio- and diastereoselective Diels−Alder reactions can also be carried out by using simple achiral α′-hydroxy enones in combination with Evans' chiral Cu(II)-BOX complexes (catalyst-controlled asymmetric induction). Of importance, α′-hydroxy enones showed improved reactivity profiles and levels of stereoselectivity (*endo*/*exo* and facial selectivity) as compared with other prototypical dienophiles in the reactions involving dienes less reactive than cyclopentadiene. A rationale of some of these results is provided based on both kinetic experiments and quantum calculations. Thus, kinetic measurements of Brønsted acid promoted Diels−Alder reactions of α′-hydroxy enones show a first-order rate with respect to both enone and Brønsted acid promoter. Quantum calculations also support this trend and provide a rational explanation of the observed stereochemical outcome of the reactions. Finally, these fundamental studies are complemented with applications in natural products synthesis. More specifically, a nonracemic synthesis of (−)-nicolaioidesin C is described wherein a Brønsted acid catalyzed Diels−Alder reaction involving a α′-hydroxy enone substrate is the key step toward the hitherto challenging trisubstituted cyclohexene subunit.

Introduction

The Diels−Alder reaction, that is, the [4 + 2] cycloaddition involving a diene and an alkene (the dienophile component), is among the most powerful bond construction processes in organic synthesis.[1] Not only does this transformation establish two new carbon−carbon bonds in a single

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synthetic operation and provide functionalized cyclohexenes with up to four new stereogenic centers, it also plays a pivotal strategic role in the synthesis of numerous complex natural products.[2] Its relevance and versatility in synthesis is due in part to the wide variety of both diene and dienophile components that nicely engage in the cycloaddition process. As a logical consequence, both activation of the reaction and control of its stereochemical outcome have been and continue to be the subjects of intensive research activity, and to date a number of effective chiral reagents as well as catalysts have been demonstrated to be effective for the purpose.[3,4]

For years, the dominant strategy for substrate activation has relied on lowering the energy of LUMO of the dienophile component by coordination with a Lewis acid. Concomitant stereocontrol can be effected by either a covalently bound chiral auxiliary (stoichiometric amount of chiral inductor) or chiral ligands coordinated to the Lewis acid metal center (substoichiometric amount of chiral inductor). As a result several Lewis acid catalyzed diastereo-[1,3] and enantioselective[2,4] Diels–Alder methodologies have been developed.[5] Complementing Lewis acid mediated methods, organocatalytic methods have recently emerged as a plausible strategy, with chiral amines and Brønsted acids being the most useful organocatalysts. Amines can act by LUMO-lowering of the respective unsaturated aldehyde or ketone dienophile through iminium ion formation,[6] whereas Brønsted acids activate the dienophile by hydrogen bonding.[7,8]

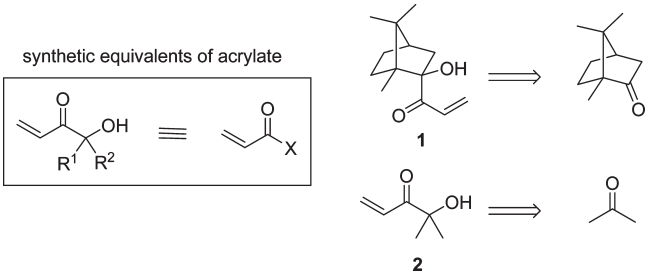

FIGURE 1. α-Hydroxy enone templates derived from camphor and acetone as acrylate equivalents.

All of these tools combined offer a powerful platform for carrying out many individual Diels–Alder reactions with remarkable levels of efficiency and selectivity. The fact is, however, that difficult diene-dienophile combinations persist for which known methods are not suitable or perform less satisfactorily, a notable deficiency that hampers a more general use of this reaction. In particular, dienes less reactive than cyclopentadiene, which has become the benchmark diene in the field, require more forcing conditions that lead to diminished stereoselectivity in most cases. Similarly, β-substituted enoyl derivatives are often less competent dienophiles than the corresponding β-unsubstituted (acryloyl) counterparts. Accordingly, the search for new methodologies (chiral reagents, catalysts, and templates) to address these persistent limitations is of considerable current interest.

Recently our laboratory introduced two new subtypes of α′-hydroxy enones as acrylate equivalents, Figure 1, showing their potential as dienophile components of the Diels–Alder reaction. On the one hand, chiral α′-hydroxy enone **1**, readily accessible from commodity chemicals, nicely engages in Brønsted acid promoted Diels–Alder reactions with a variety of dienes.[9] On the other hand, simple achiral α′-hydroxy enone **2** behaves remarkably as dienophile in enantioselective Diels–Alder reactions catalyzed by Cu-bis(oxazoline) chiral complexes.[10] From these preliminary results it was apparent that the α′-hydroxy carbonyl moiety played a key role for the Diels–Alder reactions to proceed satisfactorily. The present investigation provides full details of our studies

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(8) For organocatalytic asymmetric Diels–Alder reactions involving a bifunctional activation mechanism, see the following. Cinchona alkaloid catalyst: (a) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422–2423. Cinchona-thiourea catalyst: (b) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236–9239. Pyrrolidine-pyridine catalyst in seawater: (c) Xu, D.-a.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821–3824.

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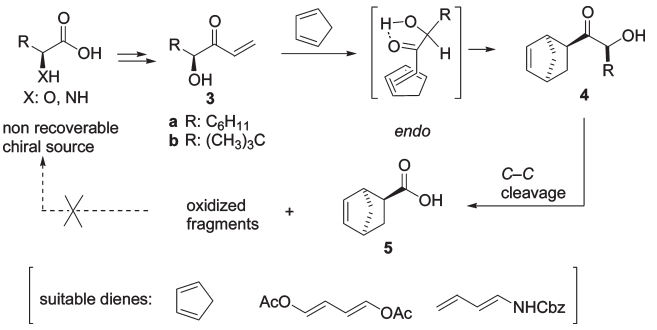
SCHEME 1. Masamune's Self-Immolative Chiral Dienophile Approach for Asymmetric Diels–Alder Reactions[11]



in this area that reveal α′-hydroxy enones as robust bidentate substrates, well-suited for appropriate activation/chirality transfer events that might also be applicable beyond the confines of the Diels–Alder reaction.

Results and Discussion

Early α′-Hydroxy Enone Models in Asymmetric Diels–Alder Reactions. The first illustration of the potential of α′-hydroxy enones in Diels–Alder reactions was reported by Masamune and co-workers,[11] who have documented the capability of these templates to react with cyclopentadiene without the need of external catalysts or promoters. Both the high reactivity and selectivity of enones **3**, Scheme 1, were attributed to the formation of an internal hydrogen bond between hydroxyl and carbonyl group, which freezes the free rotation along the bond that links the carbonyl and the carbinol carbons. The same group subsequently found that some Lewis acids, particularly $ZnCl_2$ and $BF_3 \cdot OEt_2$, enhance the reaction speed and also selectivity, although these studies were essentially limited to reactive dienes such as cyclopentadiene, the very active diacetoxybutadiene, and Cbz-protected aminobutadiene. Chemical elaboration of the resulting cycloadducts **4**, to furnish the corresponding carboxylic acid **5**, implies oxidative scission of the ketol C–C bond by treatment with sodium metaperiodate, a step that causes destruction of the source of chiral information (stoichiometric) that cannot be recovered and reused.

Background and Working Hypothesis. Prior reports from our laboratories[12] have documented the utility of methyl ketone reagent **6**, derived from (1*R*)-(+)-camphor and acetylene, two raw materials available in bulk, for the asymmetric lithium enolate mediated "acetate" aldol and Mannich reactions (Scheme 2). The high level of diastereofacial control imparted during the reactions was explained on the basis of formation of lithium-centered chelate **7**, which shows strongly biased front and rear faces with respect to the enolate π plane. Interestingly, oxidative removal of the chiral auxiliary from the reaction adducts (**8**) affords the products along with camphor, the stoichiometric source of chiral information that can be reused without loss of efficiency. Of practical and conceptual significance, all carbon atoms employed in the entire process, including acetylene as the source of acetyl, are integrated in the final products **9**.

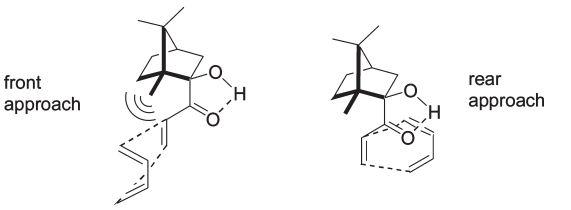
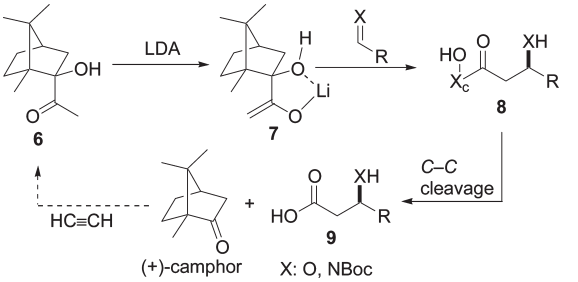


FIGURE 2. Proposed stereomodels showing the shielding capacity of the camphor skeleton in α′-hydroxy enone **1**.

SCHEME 2. "Acetate" Aldol and Mannich Reactions from Camphor-Based Methyl Ketone Reagent 6



On the basis of these results, we were intrigued by the possibility of using camphor-derived α′-hydroxy enone **1** as a new non-self-inmolative dienophile reagent in asymmetric Diels–Alder reactions. For this concept to be successful, the new enone model represented by **1** needed to fulfill the requirements of chemical and stereochemical efficiency. The subjacent hypothesis was that **1** might adopt a rigid enough coplanar cisoid conformation, as in Figure 2, with strongly biased front and rear half spaces while still eliciting proper reactivity against dienes. Accordingly, the preparation of **1** and of the β-substituted congeners needed for the study was pursued.

A convenient route for preparing gram quantities of compound **1** in a straightforward manner from (1*R*)-(+)-camphor was developed, which consists of the addition of lithium methoxyallene to the camphor carbonyl followed by mild acid hydrolysis (workup) of the resulting intermediate **10** (Scheme 3). The overall process took place in 75% yield at a 10 g scale, after chromatographic purification of the solid product. For comparative purposes, enone **11** was also prepared via methylation reaction of **10** using NaH and iodomethane in DMF and subsequent acid hydrolysis with 5% H_2SO_4. In their turn, several alternate protocols for the preparation of β-substituted analogs **12** from either **6** or **1** were also established. Thus Heck reaction or olefin metathesis applied to **1** provided the corresponding enones **12** with β-aryl or β-alkyl substituents, respectively, in good yields. Optionally, direct aldol condensation of methyl ketone **6** with aromatic aldehydes also led to the desired enones **12**. Using these procedures, one may routinely obtain β-aryl- and alkyl-substituted α′-hydroxy enones in yields ranging

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SCHEME 3. Preparation of Camphor-Derived α′-Hydroxy Enones 1, 11, and 12

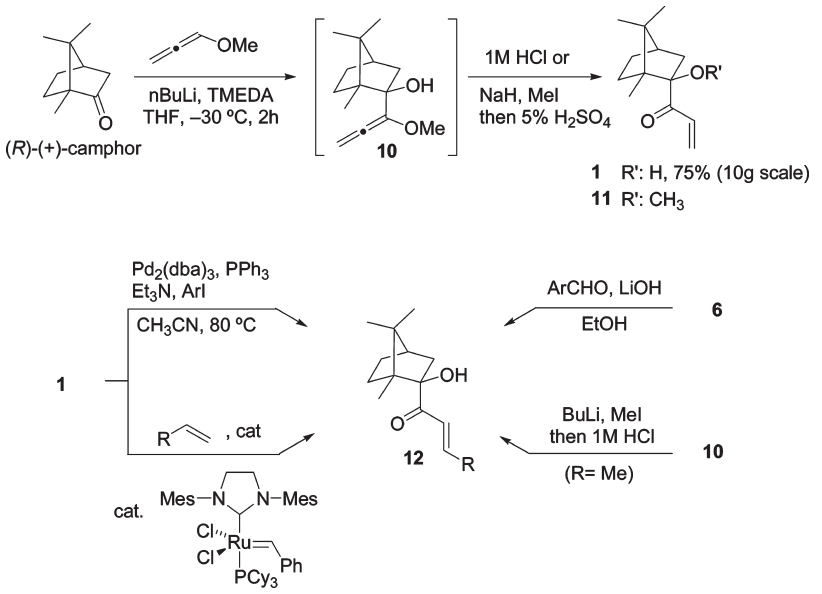
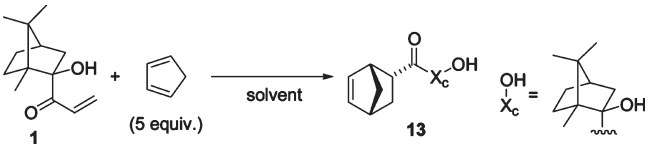


TABLE 1. Uncatalyzed Diels–Alder Reaction of Enone 1 with Cyclopentadiene[a]



entry	solvent	*T*, °C	*t*, h	conv, %	yield, %	*endo*:*exo*	dr
1	CH_2Cl_2	20	12	>99	90	92:8	96:4
2	CH_2Cl_2	0	12	>99	82	93:7	97:3
3	CH_2Cl_2	−25	24	>99	90	94:6	98:2
4	$CHCl_3$	0	12	>99	80	90:10	96:4
5	toluene	0	12	>99	94	90:10	94:6
6	Et_2O	0	12	50	ND	90:10	83:17
7	THF	20	12	>99	95	88:12	84:16
8	EtOH	−25	24	>99	87	91:9	73:27

[a]Yields after purification of the crude reaction mixture. ND: not determined.

from 80% to 90%. It is worth noting that all of these enones are bench-stable compounds and could be safely stored for weeks at room temperature or even months at −30 °C without detectable decomposition.

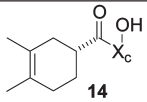
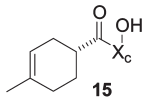
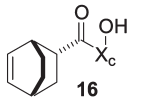
Uncatalyzed and Lewis Acid Catalyzed Diels–Alder Reactions. For initial evaluation of the capability of enone **1** as a dienophile, its reaction with cyclopentadiene was studied first. The results in Table 1 correspond to the uncatalyzed reaction between **1** and cyclopentadiene carried out in different solvents and temperatures. In most of the cases full conversion was obtained after 12 h at 0 °C (24 h at −25 °C, entry 3) regardless of the solvent employed. The *endo*/*exo* selectivity also was quite invariant (around 90:10 in favor of the *endo* isomer) with respect to the nature of the solvent or temperature used. Facial selectivity (dr) was the most dependent parameter. The highest dr values (equal or higher than 95:5) were attained with poorly coordinating solvents such as CH_2Cl_2, $CHCl_3$, or toluene (entries 1–5), whereas lower dr values were obtained in more polar solvents such as Et_2O, THF, or alcohols (entries 6–8).

Concomitant with the above experiments, attempted uncatalyzed reaction of enone **11** with cyclopentadiene failed, the unreacted starting materials being recovered. The lack of reactivity of enone **11**, which presents its hydroxyl group blocked in the form of its methyl ether, strongly supports the internal hydrogen bonding activation model, previously disclosed by Masamune for enones **3**.

As expected, the uncatalyzed D–A reaction of enone **1** with dienes less reactive than cyclopentadiene proceeded much more slowly. For instance, with 2,3-dimethylbutadiene (Table 2, entry 1), 3 days at room temperature were required for substantial (96%) conversion, and the reaction turned impractical at 0 °C. Accordingly, the reaction between **1** and 2,3-dimethylbutadiene was selected as convenient case study in order to evaluate the effect of added Lewis acids on the reaction outcome. Among others, $Mg(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $(CuOTf)_2 \cdot Tol$, $SnCl_4$, and $SnCl_2$ salts were tested for the reaction at 0 °C using a 10 mol % loading of the catalyst. From the survey, $Cu(OTf)_2$ clearly arose as the most effective Lewis acid catalyst for this reaction.[13] Other Cu(II) and Cu(I) species also demonstrated acceleration of the reaction but to a lesser extent, whereas $Mg(OTf)_2$, $Zn(OTf)_2$, or Sn species showed almost no appreciable catalytic effect. Encouraged by these observations, the reactivity of **1** against other dienes with attenuated reactivity under $Cu(OTf)_2$ catalysis was examined, and the results are summarized in Table 2. The catalytic effect by added 10 mol % $Cu(OTf)_2$ was observed in all cases studied. Importantly, this Lewis acid also improved the selectivity. For example, the reaction of **1** with 2,3-dimethylbutadiene at 0 °C was complete after 16 h, with an increase of the diastereoselectivity from 96:4 to greater than 98:2 (entries 1 and 2). A similar trend was observed in the reactions with isoprene and cyclohexadiene, respectively, in this latter case with more pronounced catalytic effect. Thus, while no reaction was observed between **1** and cyclohexadiene at 20 °C in the absence of

(13) For a review on copper-catalyzed Diels–Alder reactions, see: Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359–5406.

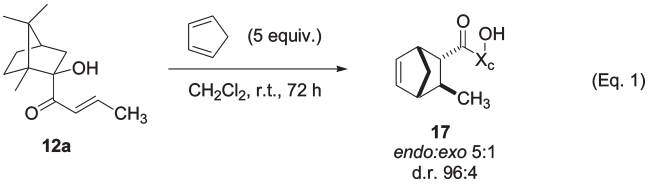
TABLE 2. Diene Survey for the $Cu(OTf)_2$-Catalyzed Diels–Alder Reaction with Enone 1[a]

entry	diene	catalyst	T (°C)	t (h)	conv (%)	yield (%)	product	isomer ratio[b]	d.r.[c]
1		none	20	72	96	90	 **14**	--	96:4
2		$Cu(OTf)_2$	0	16	>99	95		--	98:2
3		none	20	48	>99		 **15**	70:30	>98:2
4		$Cu(OTf)_2$	0	17	>99			>98:2	>98:2
5		none	20	72	<5		 **16**	--	--
6		$Cu(OTf)_2$	20	1	>99			98:2	>98:2

[a]Reactions conducted at 1 mmol scale in CH_2Cl_2. Molar ratio of diene/enone = 5:1, and 10 mol % of $Cu(OTf)_2$ was used. [b]*endo*:*exo* or regioisomer ratio, as applicable, determined by HPLC or ^{13}C NMR. [c]Diastereomeric ratio of the *endo* or major regioisomer (as applicable) determined by ^{13}C NMR.

catalyst (entry 5), full conversion of starting material and formation of cycloadduct with excellent yield, *endo*/*exo* selectivity, and diastereoselectivity was observed in its presence (entry 6). These representative examples demonstrate that enone **1** in combination with $Cu(OTf)_2$ constitutes a powerful dienophile-catalyst combination set, suitable for highly stereoselective Diels–Alder reactions involving less reactive diene counterparts.

Next, we turned our attention to the Diels–Alder reaction involving the corresponding β-substituted α'-hydroxy enones **12**, which expectedly resulted to be more challenging substrates. Indeed, camphor-derived enones **12** in combination with $Cu(OTf)_2$ were essentially unreactive toward dienes less reactive than cyclopentadiene. However, with cyclopentadiene useful reactivity and selectivity could be attained even in the absence of catalyst. As eq 1 illustrates, the reaction between **12a** and cyclopentadiene provided adduct **17** in good *endo*:*exo* and diastereomeric ratio.



(Eq. 1)

Brønsted Acid Catalyzed Diels–Alder Reactions. While catalysis of the Diels–Alder reaction has largely relied on the use of Lewis acids, less attention has been paid to the complementary Brønsted acid catalyzed Diels–Alder methodologies. In the late 1940s pioneering work by Wassermann[14] underscored the ability of Brønsted acids to accelerate Diels–Alder reactions in organic solvents, thus setting the principles of a metal-free Diels–Alder methodology. However, despite the elapsed time since then, only a few reports that have appeared relatively recently have documented diastereo- and enantioselective Diels–Alder reactions mediated by Brønsted acid catalysts.[7,8] Given the inherent reactivity demonstrated by α'-hydroxy enone **1** and the fact that the most plausible activation model involves an internal hydrogen bond, it was argued that external Brønsted acids might engage in hydrogen bonding networks and hence contribute to both acceleration of the reaction and enhancement of the stereochemical control. Accordingly, the effect of a series of Brønsted acids on the reaction between **1** and some representative dienes was surveyed in CH_2Cl_2 as solvent (Table 3). The studies revealed that both triflic acid (TfOH) and trifluoroacetic acid (TFA) did indeed promote the reactions to completion, affording the cycloadducts with high regio- and stereoselectivity. In general, TfOH was more active than TFA, allowing for shorter reaction times[15,16] and smaller catalyst loading. However, TfOH required lower temperatures (−78 °C) for clean reaction, since at temperatures higher than about −25 °C increasing amounts of decomposition products were detectable. For instance, the reaction of **1** and 2,3-dimethylbutadiene was over after 3 h of stirring at −78 °C with 10 mol % TfOH (16 h at −25 °C with 30 mol % TFA), and the product **14** was obtained as a single isomer in 98% isolated yield (75% for the TFA-catalyzed reaction, entries 3, 4). Other acids tested, among them CH_3CO_2H, $BrCH_2CO_2H$, Br_2CHCO_2H, Cl_2CHCO_2H, and HCO_2H, led to inferior results regardless of the temperature applied. On the other hand, while essentially the same trend was observed when toluene was employed as solvent, in solvents such as Et_2O or THF the unchanged starting materials were recovered whatever was the acid employed. The poor results obtained with ethereal solvents might be ascribed to competition for protons because of the Lewis basicity of the ether oxygen.

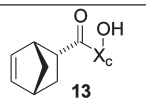
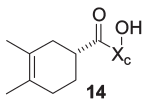
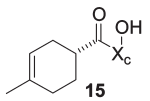
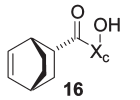
We next investigated the suitability and scope of the TfOH-catalyzed Diels–Alder reaction for the more challenging β-substituted acrylate substrates **12a–g**. As the results in Table 4 show, the reaction tolerates substrates with β-alkyl substituents of variable size (entries 1–10), as well as β-aryl substituents of electron-neutral (entries 11–13), electron-rich (entries 14, 15), or electron-poor (entry 16) character, which reacted smoothly with cyclopentadiene, and with less reactive dienes such as cyclohexadiene, isoprene, and 2,3-dimethylbutadiene, giving excellent stereoselectivity (*endo*/*exo* ≥ 150:1; facial selectivity ≥98:2). Under the above

(14) (a) Wassermann, A. *J. Chem. Soc.* **1942**, 618–622. (b) Wassermann, A. *J. Chem. Soc.* **1942**, 623–627.

(15) The relationship between the pK_a of the added acid and the reaction acceleration has been previously documented for the case of Diels–Alder reaction between several acrylates or methyl vinyl ketone and cyclopentadiene using a series of acetic acids: (a) Kasper, F.; Zobel, H. *J. Prak. Chem.* **1975**, *317*, 510–514. (b) Kasper, F.; Bischoff, St. *J. Prak. Chem.* **1986**, *328*, 449–453.

(16) For Diels–Alder reactions catalyzed by trimethylsilyl bis(trifluoromethanesulfonyl)imide, see: Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219–8226.

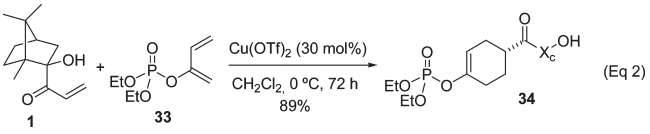
TABLE 3. Brønsted Acid Catalyzed Diels–Alder Reactions of Acrylate Equivalent 1[a]

entry	diene	product	acid (equiv.)	T (°C)	t (h)	yield[b] (%)	*endo:exo*[c]	d.r.[d]
1		 **13**	--	25	24	95	16:1	98:2
2			TfOH (0.1)	–78	2-3	98	49:1	>98:2
3		 **14**	TFA (0.3)	–25	16	75	--	>98:2
4			TfOH (0.1)	–78	2-3	98	--	>98:2
5		 **15**	TFA (0.3)	–25	16	91	--	>98:2
6		 **16**	TfOH (0.1)	–78	2-3	95	>150:1	>98:2

[a]Reactions conducted on a 1 mmol scale in CH_2Cl_2; ratio diene/**1** = 5:1. [b]Yield of isolated pure major diastereomer after column chromatography. [c]Determined by HPLC. [d]Diastereomeric ratio of the *endo* or major regioisomer (as applicable) determined by ^{13}C NMR.

conditions, β-aryl-substituted acrylate equivalents usually took longer reaction times, which could be consistently reduced by slightly increasing catalyst loading. Remarkably, even enones bearing bulky substitution at β-position, such as cyclohexyl- and *tert*-butyl-substituted enones **12b** (entries 5–8) and **12c** (entries 9, 10), were able to react with these representative less reactive dienes to furnish the corresponding adducts **22**–**24** and **26**, respectively, in acceptable yields and with essentially total stereocontrol.

From this study it becomes clear that Brønsted acid catalysis of the Diels–Alder reaction involving α′-hydroxy enones is more efficient than Cu(II) Lewis acid catalysis[17] and provides an efficient entry to nontrivial substituted cyclohexene systems, such as those often encountered in natural products, *vide infra*. A significant exception to the above preference is the Diels–Alder reaction involving acid-sensitive diene or dienophile counterparts, a reaction subtype where the utility of strong Brønsted acids, e.g., TfOH, may be somewhat limited. For example (eq 2), dienyl phosphates constitute an attractive class of dienes for Diels–Alder reactions owing to the synthetic possibilities of the resulting vinyl phosphate products.[18] In addition, they have been shown to be more stable than the corresponding silyloxy and alkoxy dienes.[19] However, treatment of dienyl phosphate **33** with TfOH and **1** led to polymeric products only. In cases like this, the alternative $Cu(OTf)_2$-catalyzed reaction provided a useful compromise. Thus, treatment of **1** with **33** under the presence of 30 mol % $Cu(OTf)_2$ gave rise to adduct **34** in 89% yield and essentially complete diastereoselectivity. This is so far the first reported asymmetric Diels–Alder reaction involving dienyl phosphates as dienes.[19,20]



(Eq 2)

Catalyst-Controlled Enantioselective Diels–Alder Reactions with Achiral α′-Hydroxy Enones. The above results based on the camphor-derived α′-hydroxy enones **1** and **12** could be ascribed to the capability of these dienophiles for acting as bidentate substrates susceptible to coordination to either selected Lewis acids, particularly Cu(II) salts, or hydrogen donors (Brønsted acid). Under the reported conditions, the formed complexes apparently are rigid enough to allow the camphor skeleton to impart efficient steric shielding in the transition state, thus resulting in almost perfect transfer of chiral information to the forming cycloadducts. At this stage, the question was whether development of an enantioselective, catalyst-controlled variant of the reaction would be feasible. The realization of this objective would involve simple achiral α′-hydroxy enones and a chiral catalyst acting in a concerted manner.[21] However, at the outset it

(17) A reversal in chemical efficiency has been observed in the reaction of azachalcone dienophiles with cyclopentadiene. See: Mubofu, E. B.; Engberts, J. B. F. N. *J. Phys. Org. Chem.* **2004**, *17*, 180–186.

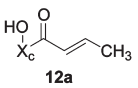
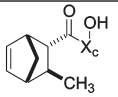
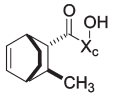
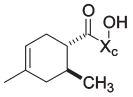
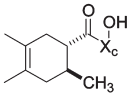
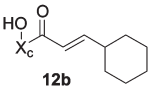
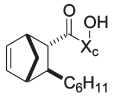
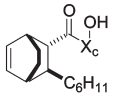
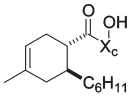
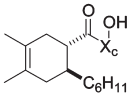
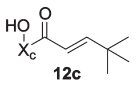
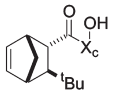
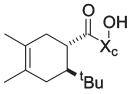
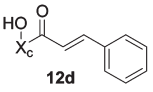
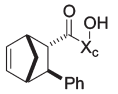
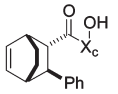
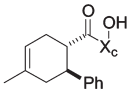
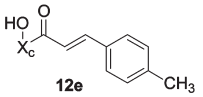
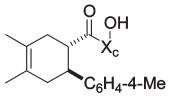
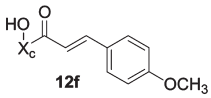
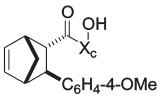
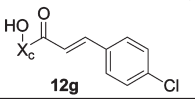
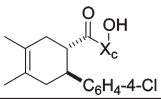
(18) Review on the chemistry of enol phosphates: Linchtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607–649. Enol phosphates in cross-coupling reactions: (a) Miller, J. A. *Tetrahedron Lett.* **2002**, *43*, 7111–7114. (b) Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, 2636–2644. (c) Guo, J.; Harling, J. D.; Steel, P. G.; Woods, T. M. *Org. Biomol. Chem.* **2008**, *6*, 4053–4058. Also, see:. (d) Skowrońska, A.; Koprowski, M.; Krawczyk, E. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1877–1880. In α-hydroxyl ketone synthesis: (e) Krawczyk, E.; Koprowski, M.; Skowrońska, A.; Luczak, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2599–2602.

(19) Liu, H. J.; Feng, W. M.; Kim, J. B.; Browne, E. N. C. *Can. J. Chem.* **1994**, *72*, 2163–2175.

(20) For non-asymmetric Diels–Alder reactions involving *O*-dienyl phosphate esters, see: (a) Skowronska, A.; Dybowsky, P.; Koprowski, M.; Crawczyc, E. *Tetrahedron Lett.* **1995**, *36*, 8133–8136. (b) Tatsuta, K.; Inukai, T.; Itoh, S.; Kawarasaki, M.; Nakano, Y. *J. Antibiot.* **2002**, *55*, 1076–1080. (c) Koprowski, M.; Skowornska, A.; Glowka, M. L.; Fruzunski, A. *Tetrahedron* **2007**, *63*, 1211–1228.

(21) For selected examples of bidentate dienophiles, see the following. *N*-Hydroxyacrylamides: (a) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735–1738. α,β-Unsaturated 2-acylimidazoles: (b) Evans, D. A.; Fandrick, K. R.; Soug, H. J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (c) Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Org. Lett.* **2007**, *9*, 3647–3650. (d) Ishihara, K.; Fushimi, M. *Org. Lett.* **2006**, *8*, 1921–1924. α,β-Unsaturated *N*-acylpyrazolidinones: (e) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395–405. (f) Zhou, J.; Tang, Y. *Org. Biomol. Chem.* **2004**, *2*, 429–433. Alkylidenemalonates: (g) Yamauchi, M.; Aoki, T.; Li, M.-Z.; Honda, Y. *Tetrahedron Asymmetry* **2001**, *12*, 3113–3118. α′-Arylsulfonyl enones: (h) Barroso, S.; Blay, G.; Al-Midfa, L.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2007**, *129*, 395–405 and also ref 13.

TABLE 4. Diels−Alder Reaction of Representative β-Alkyl- and β-Aryl-Substituted Acrylate Equivalents 12 with Dienes Catalyzed by TfOH[a]

entry	dienophile	diene	t (h)	major diastereomer[b]	prod.	yield (%)
1	 **12a**		1		**17**	95
2			1.5		**18**	90
3			0.5		**19**	93
4			1		**20**	95
5	 **12b**		18		**21**	63
6			60		**22**	67
7			55		**23**	57
8			72		**24**	60
9	 **12c**		18		**25**	53
10			72		**26**	53
11	 **12d**		3[c]		**27**	87
12			16[c,d]		**28**	93
13			2[c]		**29**	85
14	 **12e**		1.5[c]		**30**	90
15	 **12f**		1[c]		**31**	84
16	 **12g**		1		**32**	95

[a]Reactions conducted at 1 mmol scale in CH_2Cl_2 at −78 °C. Molar ratio of diene/enone/TfOH = 5:1:0.1, except for branched chain enones **12b**, **12c**, which was 5:1:0.5. [b]In every applicable single cases, *endo*:*exo* ratio of ≥150:1, determined by ^{13}C NMR and/or HPLC. In every case dr ≥98:2. [c]Reaction performed with 30 mol % TfOH. [d]Reaction performed at −50 °C.

was not clear whether chirality transfer from the catalyst chiral structure would be effective as the intramolecular chirality transfer involved in the Diels−Alder reactions described in the previous section. In pursuing this idea we found inspiration from the previous seminal work by Evans, who developed *N*-acyl oxazolidinones as efficient dienophile components of

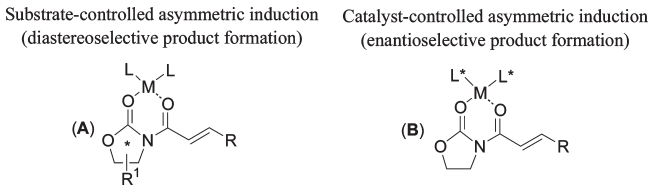


FIGURE 3. *N*-Enoyl oxazolidinones and their 1,5-metal binding complexes as useful dienophiles for Diels–Alder reactions developed by the Evans group. Active complex **A** formed from chiral oxazolidinone and achiral ML_2 catalyst; active complex **B** formed from achiral oxazolidinone and chiral ML^*_2 catalyst.

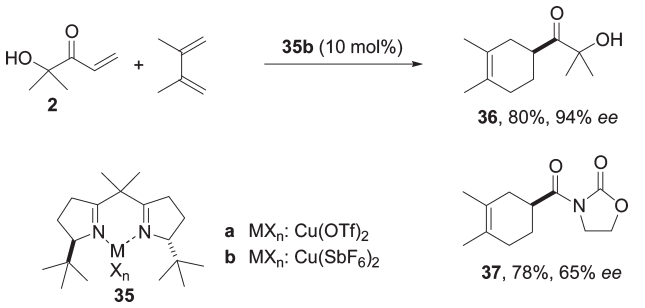
the Diels–Alder reaction in its substrate-controlled, diastereoselective version,[22] first, and the catalyst-controlled, enantioselective version later (Figure 3).[5a–c,23,24]

Since previous observations indicated $Cu(OTf)_2$ as the best-suited Lewis acid catalyst for the D–A reaction with camphor-derived enones **1** and **12**, we set out to test the behavior of achiral α′-hydroxy enone **2** in combination with Evans' Cu(II)-bis(oxazoline) chiral catalysts.[5a,b,23] Initial experiments with this enone/catalyst system proved instructive. For example, Scheme 4, the reaction of **2** with 2,3-dimethyl butadiene in the presence of 10 mol % **35b** at −20 °C provided **36** with 80% yield and remarkable enantioselectivity (94% ee), whereas the parent reaction using *N*-acryloyl oxazolidinone afforded the respective adduct **37** in 78% yield, but only 65% ee.[5b]

The results from the reaction of **2** with a range of dienes, Table 5, demonstrated that $(Cu(BOX))(OTf)_2$ **35a** and the related complex **35b** are indeed excellent catalysts for these transformations. Adducts **38** and **39**, from cyclopentadiene and cyclohexadiene, were formed in high yield and almost perfect enantiocontrol (entries 1, 2). Although piperylene provided **40** as an isomeric *cis*/*trans* mixture, the major *cis* isomer was also formed with essentially complete enantioselectivity (entry 4). Again, enone **2** reacted with isoprene in the presence of catalyst **35b** to afford the expected adduct **41** with good yield and 94% ee (entry 5), while the analogous reaction with *N*-acryloyl oxazolidinone provided the corresponding cycloadduct in only 59% ee.[5b]

As previously observed in the context of the camphor-derived enones, substitution at Cβ position of the α′-hydroxy enone with alkyl or aryl groups diminished their reactivity considerably. In fact, enones **42**–**45** resulted unsuitable dienophiles for the D–A reaction involving challenging dienes under the conditions tested. Still, such enones[25] reacted satisfactorily with cyclopentadiene, affording adducts **46**–**49** in almost complete enantioselectivity (Table 6).

SCHEME 4. Performance of Acrylate Equivalents Based on the Ketol and the *N*-Acyloxazolidinone Template, Respectively, in 35-Catalyzed Diels–Alder Reaction with 2,3-Dimethylbutadiene



Oxidative Cleavage of Ketol Moiety in Adducts. Access to aldehydes, ketones, and carboxylic acids. After determination of the most favorable conditions for Diels–Alder reactions with a survey of representative diene/dienophile combinations, reliable protocols were established for the removal of the auxiliary group from the adducts. It was found that by following standard methods for the oxidative C–C bond scission of ketols, the corresponding aldehydes, ketones, and carboxylic acids can be obtained in good yields and without compromising the configurational integrity of the products. The alternate paths shown in Scheme 5 represent two of such well-established protocols, which furnish, respectively, the corresponding carboxylic acid or ketone products. For instance, treatment of adducts **13**/**27** with ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water smoothly afforded the corresponding carboxylic acids **50**/**51** in high yield and in essentially enantiopure form. For adducts with limited solubility in acetonitrile/water, the oxidation could be carried out with equal efficiency by treatment with either periodic acid in THF (or diethyl ether) or sodium metaperiodate in a mixture of methanol and water. It is important to note that camphor, the accompanying byproduct delivered in these reactions, could be almost fully recovered and reused without loss of efficiency. As a consequence, all carbon atoms employed in the cycloaddition reaction are integrated in the final target compounds, an aspect of the approach that bears practical interest. Likewise, when the same conditions were applied to adducts such as **38** and **47**, which arise from the catalyst-controlled enantioselective Diels–Alder reaction, carboxylic acids such as **52** and **53** were afforded in high yield along with acetone, the accompanying organic byproduct concomitantly formed during these reactions. As evidenced by the opposite absolute configuration of products **50**/**51** with respect to **52**/**53**, either enantiomer of the final carboxylic acid is accessible by proper choice among the two optional approaches, namely, the camphor-based (substrate-controlled) approach or the catalyst-controlled enantioselective approach.

Complementing the direct oxidative scission of adducts to carboxylic acids, a two-step process involving initial treatment with an alkyllithium and subsequent oxidation of the resulting carbonyl addition intermediate with CAN[26] gave rise to the corresponding ketones, such as **54**–**57**.

(22) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1985**, *106*, 4261–4263. (c) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

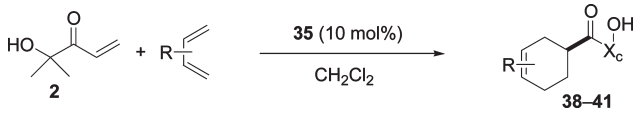
(23) (a) Evans, D. A.; Miller, S. J.; Lectka, T *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461. (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 798–800. Reaction scope and applications to synthesis: (c) Evans, D. A.; Ripin, D. H. B.; Johnson, J. S.; Shaugnessy, E. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2119–2121. (d) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, T.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

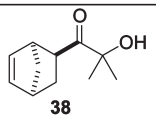
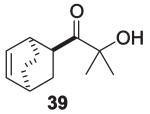
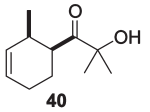
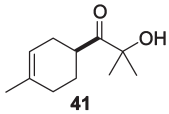
(24) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. For a recent review on bis(oxazolidine) ligands, see: (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.

(25) The starting enones may be easily prepared in multigram quantity from commercially available materials in a manner similar to that employed for camphor-based enones **12**. For details, see Supporting Information.

(26) For adducts bearing acid-sensitive groups, like acetals, or showing limited solubility in the acetonitrile/water system, the scission step could be carried out with improved results by using alternative oxidants like lead tetraacetate in benzene or sodium periodate in diethyl ether.

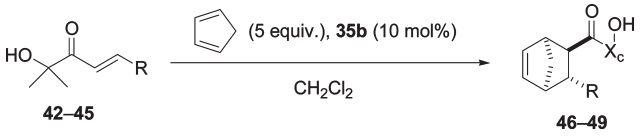
TABLE 5. Reactions of Acrylate Equivalent 2 with Representative Dienes Catalyzed by 35a and 35b[a]



entry	diene	catalyst	T (°C)	t (h)	isomer ratio[b]	*endo*:*exo* c	product	yield (%)	ee (%)[d]
1		**35a**	–78	2.5	--	>99:1	 **38**	99	>99
2		**35a**	25	2	--	>99:1	 **39**	93	≥98
3		**35a**	25	8	50:50	--	 **40**	--	--
4		**35b**	–10	15	88:12	--		95	>99
5		**35b**	–20	14	>99:1	--	 **41**	85	94

[a]Reactions conducted at 0.5 mmol scale in CH_2Cl_2. Molar ratio of enone/diene/catalyst = 1:5:0.1. [b]Ratio of regio- or *cis*/*trans* isomers, as applicable, determined by ^{13}C NMR. [c]Determined by ^{13}C NMR. [d]Enantiomeric excess of the major regio- or diastereoisomer, as applicable, determined by HPLC.

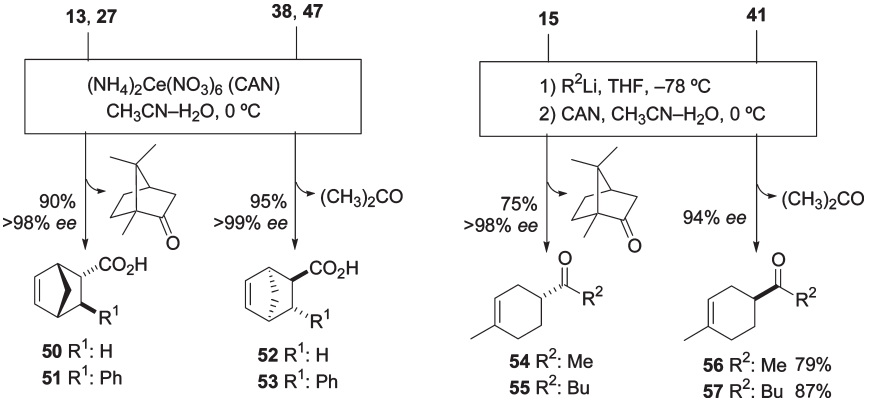
TABLE 6. Diels–Alder Reaction of β-Substituted Acrylate Equivalents 42–45 with Cyclopentadiene Catalyzed by 35b



entry	enone	R	*T* (°C)	*t* (h)	*endo*:*exo*[a]	product	yield (%)	ee (%)[b]
1	**42**	Et	−78	21	>98:2	**46**	90	>99
2	**43**	Ph	0	14	94:6	**47**	86	>99
3	**44**	4-ClC_6H_4	0	2.5	95:5	**48**	85	>99
4	**45**	4-$MeOC_6H_4$[c]	0	24	94:6	**49**	94	>99

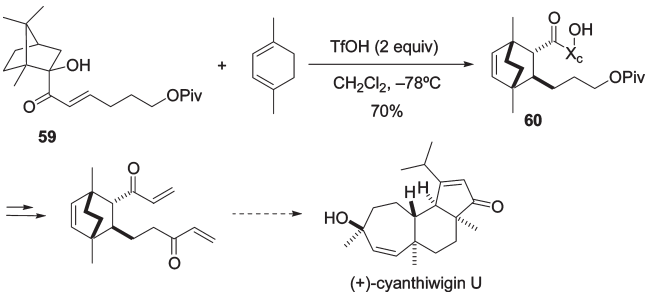
[a]Determined by ^{13}C NMR. [b]Determined by HPLC. [c]Using 10 equiv of diene.

SCHEME 5. Ketol C–C Bond Scission with Liberation of the Auxiliary



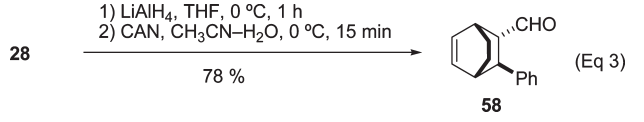
Again, the product ketones with preserved stereochemistry were obtained in yields from good to excellent, with liberation of camphor or acetone as the only organic side product formed, which could easily be separated and recycled. By this two-step sequence, cyclohexenes formally derived from a Diels–Alder reaction of simple monodentate

SCHEME 6. TfOH-Promoted Asymmetric Diels−Alder Reaction of α′-Hydroxy Enone 59 Documented by Philips in His Synthesis of (+)-Cyanthiwigin U



enones are obtained, a process that also bears considerable challenge.[27]

Alternatively, a two-step sequence for the removal of the auxiliary group from the cycloadducts can yield the corresponding aldehyde products. For instance, aldehyde **58** was smoothly obtained from the corresponding cycloadduct **28** by reduction with $LiAlH_4$ and subsequent oxidation with CAN in 78% overall yield. It should be noted that attempted Diels−Alder reaction of cinnamaldehyde and cyclohexanediene to afford **58** using MacMillan's iminium activation methodology under a variety of conditions failed, and unreacted materials were recovered.[28]



Application to the Synthesis of Natural and Bioactive Products. Given the outstanding position the Diels−Alder reaction holds as a tool for creating carbocycles of varying degree of skeletal complexity, the present methodology may prove to be useful in the synthesis of relatively complex target molecules, where a difficult Diels−Alder reaction is key for success. An illustrative example has recently been described by Philips and Pfeiffer within the context of an elegant total synthesis of (+)-cyanthiwigin U (Scheme 6). After unfruitful results using other alternate protocols to construct the required building-block **60**, the authors found that the reaction between camphor-based α′-hydroxy enone **59** and 1,4-dimethyl cyclohexadiene with the assistance of TfOH was the only best suited protocol.[29]

Our efforts in this direction focused on the "condensed" chalcone structure **A**, Figure 4, which represents an interesting target present in several bioactive constituents, such as the panduratins, nicolaioidesins, crinatusins, and fissistins

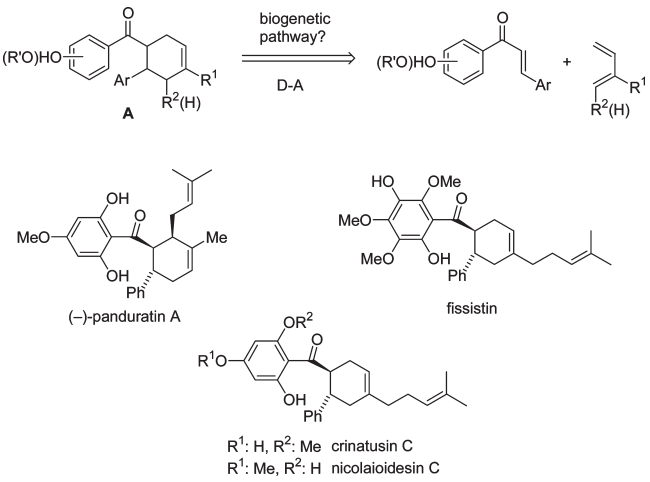


FIGURE 4. Representative "condensed" chalcones isolated from natural sources and the hypothetical Diels−Alder pathway for their biogenesis. Absolute configuration of (−)-panduratin A according to the assignment by Yoshikawa.[33]

families, isolated from natural sources.[30] Despite the wide variety of biological activities displayed by extracts of these constituents, data for most of these substances about the specific activity of each enantiomeric form remain awaited. On the other hand, while **A** can be considered to be biogenetically derived from a Diels−Alder-type cyclization between the respective chalcone and monoterpenoid diene, realization of this transformation in the laboratory has been demonstrated to be challenging.[31] In this context unsuccessful Diels−Alder cycloadditions toward the central trisubstituted cyclohexene core using Lewis acid promoted ("LUMO" lowering) conditions have been documented,[31a] whereas in the absence of any promoter rather harsh conditions (benzene, sealed tube, 220 °C, 24 h) are required to give regioisomeric mixtures of the respective cycloadducts.[31b] We decided to test our Brønsted acid promoted Diels−Alder methodology in this endeavor and pursued the first asymmetric synthesis of nicolaioidesin C,[32] a natural product isolated by Kinghorn and co-workers in racemic form from the roots of *Renealmia nicolaioides*.[30c]

We were delighted to observe that the reaction of enone **12d** with myrcene **61** (**12d**:**61** ratio 1:5) in the presence of 10 mol % TfOH at −78 °C in CH_2Cl_2 proceeded smoothly to afford the corresponding cycloadduct **62** as a single

(27) For advances in metal-catalyzed enantioselective Diels−Alder reactions involving monodentate ketone dienophiles (single-point binding activation), see refs 5c−f (cationic oxazaborolidine catalysts); ref 5h (monomeric Schiff base-Cr^{III} catalysts). For asymmetric organocatalytic methods mainly involving enals, see refs 6 and 7.

(28) (a) For detailed information on the experimental procedures employed and conditions variation, see Supporting Information. For substrate dependence in Diels−Alder reactions via iminium activation, see: (b) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120–14125.

(29) For detailed information, see: (a) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334–5335. For a recent case of α′-hydroxy dienones as diene components of asymmetric Diels−Alder cycloadditions in the context of biomimetic natural products synthesis, see: (b) Dong, S.; Hamel, E.; Bai, R.; Covell, D. G.; Beutler, J. A.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2009**, *48*, 1494 –1497.

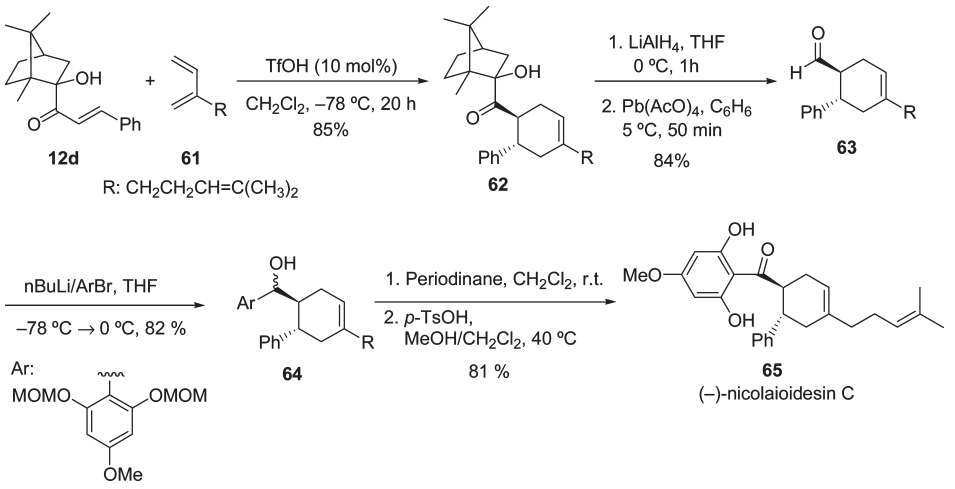
(30) (a) Tuntiwachwuttikul, P.; Pancharoen, O.; Reutrakul, V.; Byrne, L. T. *Aust. J. Chem.* **1984**, *37*, 449–453. (b) Alias, Y.; Awang, K.; Hadi, A. H. A. *J. Nat. Prod.* **1995**, *58*, 1160–1166. (f) Shibata, K.; Tatsukawa, A.; Umeoka, K.-i.; Lee, H. S.; Ochi, M. *Tetrahedron* **2000**, *56*, 8821–8824. (c) Gu, J.-Q.; Park, E. J.; Vigo, J. S.; Graham, J. G.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 1616–1620. (d) Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtrakul, S. *Bioorg. Med. Chem.* **2006**, *14*, 1710–1714. (e) Win, N. N.; Awale, S.; Esumi, H.; Tezuka, Y.; Kadota, S. *J. Nat. Prod.* **2007**, *70*, 1582–1587.

(31) (a) Cong, H.; Ledbetter, D.; Rowe, G. T.; Caradonna, J. P.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2008**, *130*, 9214–9215. (b) Jung, E. M.; Lee, Y. R. *Bull. Korean Chem. Soc.* **2008**, *29*, 1199–1204.

(32) For racemic syntheses of nicolaioidesin C based on an electron-transfer-initiated Diels−Alder cycloaddition and thermal Diels−Alder reaction, respectively, of 2′-hydroxychalcones, see refs 31a and 31b.

(33) Absolute configuration of several extracted prenylchalcones, including (+) and (−)-panduratin A, has recently been determined by CD: Yoshikawa, M.; Morikawa, T.; Funakoshi, K.; Ochi, M.; Pongpiriyadacha, Y.; Matsuda, H. *Heterocycles* **2008**, *75*, 1639–1650. Note that these determinations are in conflict with the structures of (−)-panduratin A depicted in refs 30e and 31a.

SCHEME 7. Total Synthesis of (−)-Nicolaioidesin C Relying on Our Brønsted Acid Catalyzed Diels−Alder Reaction As a Key Step



diastereomer in 85% yield, Scheme 7. It is important to note that, in agreement with difficulties previously encountered by other authors in similar transformations, the Lewis acid promoted Diels−Alder reaction between enone **43** and myrcene did not work at all, extensive polymerization of myrcene being the major detectable product instead. We believe that the remarkable performance of the Brønsted acid promoted reaction is primarily due to the efficient activation of the hydroxy enone even at quite low temperatures (−78 °C).[34] With **62** at hand, next the two-step transformation of **62** into **65**, consisting of the nucleophilic addition of the corresponding aryl-lithium reagent to **62** and oxidative cleavage of the expected diol adduct, was attempted unsuccessfully. As a matter of fact, the addition step under several reaction conditions failed, a result that may be due to the high steric demand of both the ketone **62** and the 2,4,6-trisubstituted aryl-lithium reagent. Finally, the synthesis continued through reduction of the carbonyl group in **62** with $LiAlH_4$ and oxidative cleavage of the resulting diol with $Pb(AcO)_4$,[35] which provided aldehyde **63** in 84% overall yield. Again, attempts to access this aldehyde adduct directly from cinnamaldehyde and myrcene via iminium ion activation were completely unfruitful and mainly unchanged starting materials were observed.[28]

Once the trisubstituted cyclohexene is built with the appropriate configuration, addition reaction of the lithium anion of di-MOM-protected methoxyresorcinol to the carbaldehyde afforded epimeric alcohol **64** in 82% yield. Oxidation of **64** with periodinane in dichloromethane and subsequent deprotection of the MOM group gave the (−)-enantiomer of nicolaioidesin C (**65**) in 81% yield (two steps). It is worth mentioning that the absolute configuration and optical rotation sign determined for product **65** are in good agreement with recent determinations by CD for related compounds.[33] Clearly, this approach offers an attractive way to construct prenylflavonoid natural products whose absolute and relative configuration still need to be established.

Mechanistic Insights into the Brønsted Acid Catalyzed Diels−Alder Reaction of α′-Hydroxy Enones. The above results demonstrate that α′-hydroxy enone **1** and its β-substituted congeners **12** can be conveniently activated upon addition of substoichiometric quantities of Brønsted acids and thus effectively participate in D−A reactions that normally do not perform well with other protocols. In order to get a better understanding of this activation mechanism, identify plausible reactive intermediate species, and provide a rationale for the stereochemical outcome of the reaction, some additional experimental and theoretical studies were carried out.

An important parameter that would help to characterize the structure of the formed substrate−catalyst complex is the actual stoichiometry of such complexes, and relevant information in this respect could be obtained from kinetic measurements. Accordingly, the reaction order with regard to enone and catalyst (TFA) for the aforementioned reaction between enone **1** and 2,3-dimethylbutadiene was determined as follows. In a set of experiments using a large excess of the diene, variations of $\ln([\mathbf{1}]/[\mathbf{1}]_0)$, with [**1**] and $[\mathbf{1}]_0$ being the actual and the initial concentration of enone **1**, respectively, were determined as a function of time for four different catalyst concentrations. Plots (see the Supporting Information for details) showed a linear behavior and thus first-order dependence of reaction rate with respect to enone **1** in either of the four conditions tested. Additionally, plotting the four apparent rate constants (k_{obs}) thus obtained versus catalyst concentration (Figure 5) fits well to a straight line ($R^2 = 0.9836$), which indicates a first-order reaction also with respect to the added Brønsted acid (TFA). The conclusion from these experiments is that a 1:1 hydroxy enone−Brønsted acid complex is the most likely active species participating in the rate-limiting step of these Diels−Alder reactions.

Quantum Calculations. Complementing these experimental data, some DFT-computing work[36] was undertaken to

(34) Under our optimized conditions (10 mol% TfOH, 5 equiv of myrcene, −78 °C, 20 h) a minute amount of polymer formation was detected. However, an increase of the reaction temperature up to about −30 °C or the loading of the promoter TfOH up to about 30 mol% led to extensive production of the undesired polymer.

(35) The use of the CAN/acetonitrile/water oxidation system was not practical in this particular case due to the poor solubility of the substrate diol in the polar media.

(36) DFT has been shown to reliably predict the results of Diels−Alder cycloaddition reactions; see: (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036. (b) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378. (c) García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415. (d) Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917.

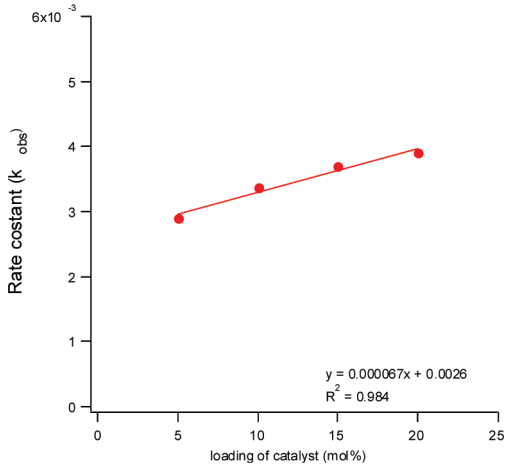


FIGURE 5. Observed rate constants (20 °C) as a function of catalyst loading.

get more information about the structure and energetic profiles of the activated complexes and the transition states involved in the Diels−Alder reaction of α′-hydroxy enone **1**[37] with cyclopentadiene promoted by Brønsted acids. We compared the reactions in the absence of an external acid and in the presence of one molecule of TFA or TfOH. All structures were optimized using the functional B3LYP[38] and the 6-311+G** basis set as implemented in Gaussian 03.[39,40] The activation energies ($\Delta G^{\ddagger}$*) reported in this work refer to the energy difference computed for the transition states and the corresponding H-bonded initial complexes.

Given the presence of various sites with H-bond donor/acceptor character in both the hydroxy-ketone substrate and the added acid, several complexes involving both components and each with a distinct H-bond network can be conceived. At the outset, about a dozen of the most plausible combinations were evaluated,[41] from which a selection of the lowest in energy was made for further refinement (Figure 6). Of the various H-bonds identified, the intramolecular OH···O=C interaction in **1** and the intermolecular H-bond between the ketone carbonyl group of **1** and external acid are of special importance regarding enone activation. Additional stabilization as well as geometry constraints may be due to interactions between the hydroxy group in **1** and the external acid.

From the calculated energies, the first, expected observation is that the external acid reduces the energy of the transition states by formation of H-bonds between the acid and **1**. Furthermore, these interactions are stronger in the transition states than in the starting enone/acid complexes, and therefore reaction acceleration is predicted to occur. Thus, the uncatalyzed reaction shows a free Gibbs activation energy of 30.1 kcal/mol ($\mathbf{TS_{A1}}$), which is reduced in the presence of TFA to 26.1 kcal/mol ($\mathbf{TS_{B1}}$). The more acidic triflic acid exerts a more pronounced barrier reduction (23.9 kcal/mol, $\mathbf{TS_{C1}}$), which accounts for the 6 kcal/mol lower barrier compared with that of the uncatalyzed reaction, that is, more than 10^4-fold enhancement of reaction speed, in fair agreement with the catalytic effect experimentally observed with 10 mol % triflic acid.

On the other hand, the calculated TS geometries allow for a rational explanation of the facial selectivity observed experimentally in the laboratory. In particular, the methyl group at C1 of the camphor-structure strongly shields the *re* face of enone making the *si*-face approaching of cyclopentadiene more feasible. For example, in the uncatalyzed reaction, the large energy difference between the *re* ($\mathbf{TS_{A1}}$) and *si* ($\mathbf{TS_{A3}}$) approaches ($\Delta\Delta G^{\ddagger}$ = +4.4 kcal/mol) is in good agreement with the ratio of diastereomers experimentally observed (>98:2). This facial selectivity is essentially not affected by incorporating one molecule of TFA or TfOH, and for these latter cases transition states involving the less favorable *re* face attack (structures not shown in Figure 6) lie about 3 kcal/mol higher in energy.

More in-depth examination of the geometries and bond distances in the most salient TSs for the TfOH- and TFA-assisted Diels−Alder reactions is worthy of comment. Considering first the TFA-assisted reaction, for the *endo*/*re* approach two lowest-energy transition states ($\mathbf{TS_{B1}}$ and $\mathbf{TS_{B2}}$) were located after extensive structural search. In $\mathbf{TS_{B1}}$, the ketone-carbonyl is doubly H-bonded to the intramolecular hydroxy group, on the one hand (r = 1.9 Å), and the OH group of TFA, on the other hand (r = 1.6 Å). In $\mathbf{TS_{B2}}$ comparatively less stabilization ($\Delta\Delta G^{\ddagger}$ = +1.4 kcal/mol) is observed, and it corresponds to a cyclic arrangement of the H-bonding complex between the hydroxy-ketone and the carboxylic acid. A similar trend is observed for the two main transition states identified in the *exo* approach ($\mathbf{TS_{B3}}$ vs. $\mathbf{TS_{B4}}$). Slight differences are observed with respect to the calculated transition states for the TfOH-assisted reactions. In general, the higher acidity and conformational ambiguity of TfOH, which bears two S=O groups that become diastereotopic within the complex, induce a larger number of possible transition states. The lowest in energy (activation barrier 23.9 kcal/mol) is $\mathbf{TS_{C1}}$ wherein the ketone is fully protonated by the strong acid. In contrast to the TFA-assisted reaction, in the TfOH-assisted reaction TS structure showing the ketone carbonyl doubly H-bonded ($\mathbf{TS_{C2}}$) is the second most stable (activation barrier 24.9 kcal/mol) with H···O distances of 1.4 and 2.0 Å for the inter- and intramolecular H-bonds, respectively. Similar comments apply to the *exo* structures $\mathbf{TS_{C3}}$ and $\mathbf{TS_{C4}}$.

Interestingly, the *endo*/*exo* selectivity increases as the pK_a of the acid decreases. Thus the *endo*/*exo* ratio ranges from

(37) In the discussion that follows, the reactivity concerning the enone moiety is considered only in its *s-cis* conformation. TS involving the *s-trans*-enone lie much higher in energy (>3 kcal/mol) in all cases and will not be discussed here.

(38) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974–12980.

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision E.01*; Gaussian, Inc.: Wallingford CT, 2004.

(40) For details on computational methods, see Supporting Information.

(41) For the full collection of H-bonded structures considered for first evaluation, see Supporting Information.

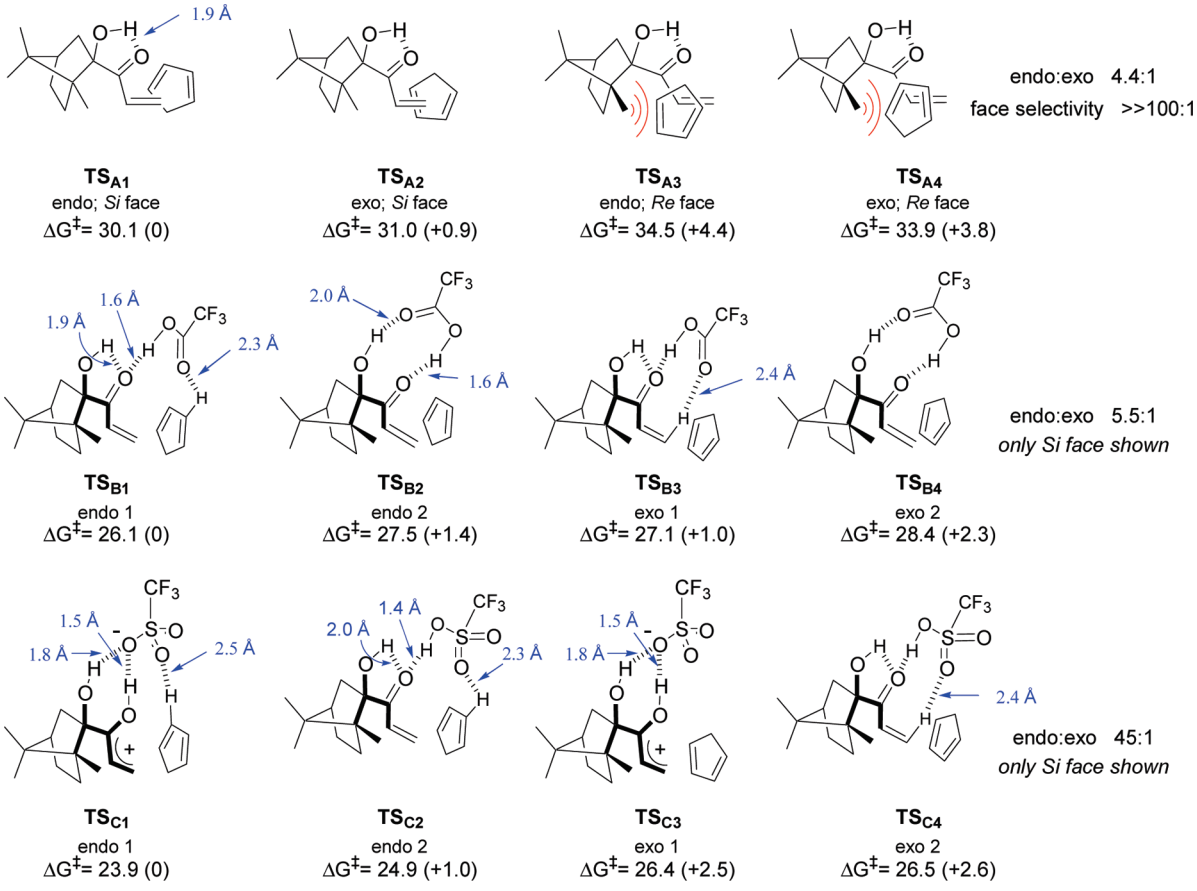


FIGURE 6. Computational data for the Diels−Alder reaction of enone **1** with cyclopentadiene: (**TS$_A$**) uncatalyzed reaction; (**TS$_B$**) trifluoroacetic acid assisted reaction; (**TS$_C$**) triflic acid assisted reaction. Activation free energies in kcal/mol.

4.4:1 for the uncatalyzed reaction to 5.5:1 for the TFA-assisted reaction and to 45:1 for the TfOH-assisted reaction, a correlation that has also been observed experimentally (Table 3). In this regard, three of the four *endo* transition states for the catalyzed reaction (**TS$_{C1}$**, **TS$_{C2}$**, **TS$_{B1}$**) present an additional H-bond interaction between the S=O or C=O lone pairs of the Brønsted acid and a hydrogen atom at the sp^2 hybridized carbon of the diene. This secondary H-bond interaction,[42] which to the best of our knowledge has been previously unnoticed for Diels−Alder reactions, although weak, may contribute in creating an efficient H-bond network during the TS with consequences in both the reactivity and *endo*/*exo* selectivity of the reaction.[43,44]

Conclusions

α′-Hydroxy enones are efficient and versatile dienophiles for asymmetric catalytic Diels−Alder reactions and constitute competitive bidentate templates based on the following features: (1) Both chiral and achiral versions of α′-hydroxy enones are readily available from (1*R*)-(+)-camphor and acetone, respectively, two commodity chemicals available in bulk. (2) Catalytic activation (LUMO lowering) of α′-hydroxy enones against [4 + 2] cycloadditions with dienes can be achieved by either Lewis acids, particularly Cu(OTf)$_2$, or Brønsted acids, particularly triflic acid. (3) The resulting catalytically formed 1,4-metal or 1,4-proton coordination complexes are tight enough to allow for an efficient chirality transfer in either of the two feasible alternatives: substrate-controlled Diels−Alder reactions (chiral α′-hydroxy enones derived from camphor) or catalyst-controlled Diels−Alder reactions (simple achiral α′-hydroxy enones in combination with Evans chiral bisoxazoline-Cu catalysts). (4) The aforementioned transient complexes exhibit remarkable reactivity and stereoselectivity even against poorly reactive diene/dienophile counterparts, which perform badly with most previous Diels−Alder protocols. (5) Removal of the auxiliary from the Diels−Alder adducts to afford the corresponding carboxylic acids, ketones, and aldehydes, proceeds smoothly, with camphor or acetone as the only organic side product that can be easily recovered and recycled. As illustrated, these methods based on α′-hydroxy enones are extremely attractive for the asymmetric synthesis of complex molecules such as natural products. We hope this robust Brønsted acid catalyzed Diels−Alder technology will continue to provide a convenient platform for the access of building blocks that remain elusive or difficult targets for

(42) For relevant information on the CH···O hydrogen bond, see: (a) Desiraju, G. R. *Chem. Comm.* **2005**, 2995–3001. For the importance of dual activation of substrate acceptors and donors in asymmetric synthesis, see: (b) Ma, J.-A.; Cahard, D. *Angew. Chem.* **2004**, *116*, 4666–4683. (c) *Angew. Chem., Int. Ed.* **2004**, *43*, 4566−4583.

(43) The possibility of such H-bonding network between the acid catalyst and both the diene and the dienophile being also established in other systems, especially those involving enones, should not be discarded. See Supporting Information.

(44) One referee suggested that the observed selectivity trend could be rationalized on the basis of sterics alone, considering the triflate, the one that imparts the best selectivity, is the largest counterion.

other methodologies. Finally, a rationale of both substrate activation and efficient chirality transfer can be drawn for these Brønsted acid promoted Diels−Alder reactions in which multiple H-bonding is crucial. The way specific H-bonds contribute to keep in close contact both diene and dienophile reactants as well as the Brønsted acid promoter in our models may also serve to help better understand the role played by such weak interactions in a more general context within catalysis.

Experimental Section

General Procedure A: Uncatalyzed Diels−Alder Reactions of 1. To a solution of the α′-hydroxy enone **1** (0.208 g, 1 mmol) in CH_2Cl_2 (4 mL) was added dropwise the corresponding diene (5 mmol), and the mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel column chromatography using ethyl acetate/hexane 1:60 as eluant.

General Procedure B: $Cu(OTf)_2$-Catalyzed Diels−Alder Reactions of 1. To a solution of the α′-hydroxy enone **1** (0.208 g, 1 mmol) in CH_2Cl_2 (4 mL) cooled to 0 °C under nitrogen atmosphere, the corresponding diene (5 mmol) and $Cu(OTf)_2$ (36 mg, 0.1 mmol) were added, and the mixture was stirred at the same temperature until TLC analysis indicated that the reaction was complete. Then CH_2Cl_2 (10 mL) and water (10 mL) were added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product was effected by flash silica gel column chromatography using ethyl acetate/hexane 1:60 as eluant.

General Procedure C: Brønsted Acid Catalyzed Diels−Alder Reactions. To a solution of triflic acid in CH_2Cl_2 (0.125 M, 0.4 mL, 0.05 mmol for enones **1**, **12a**, and **12g**; 0.125 M, 2 mL, 0.25 mmol, for enones **12b** and **12c**; 0.125 M, 1.2 mL, 0.15 mmol, for enones **12d**, **12e**, and **12f**) cooled to −78 °C under a nitrogen atmosphere were added the corresponding α′-hydroxy enone **1** or **12** (0.5 mmol) and diene (2.5 mmol). The mixture was stirred at −78 °C for the specified time (from 1 to 72 h) and then was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product was effected by flash silica gel column chromatography using ethyl acetate/hexane 1:60 as the eluant.

(1*R*)-2-*endo*-[(1*R*,2*S*,3*S*,4*S*)-3-Cyclohexylbicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (21). The title compound was prepared according to General Procedure C from enone **12b** (0.145 g, 0.5 mmol) and cyclopentadiene (0.20 mL, 2.5 mmol) in 18 h: 0.112 g (63%); oil; $[\alpha]^{25}_D$ +48.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3484 (OH), 1689 (CO); ^1H NMR ($CDCl_3$) δ 6.28 (dd, 1H, J_1 = 3.3 Hz, J_2 = 5.5 Hz), 5.69 (dd, 1H, J_1 = 2.2 Hz, J_2 = 5.5 Hz), 3.21 (m, 2H), 2.80 (m, 1H), 2.39 (d, 1H, *J* = 9.5 Hz) 2.30 (s, 1H), 2.07−0.81 (m, 20H), 1.08 (s, 3H), 1.01 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.7, 138.9, 131.9, 86.4, 52.7, 52.1, 49.8, 48.5, 47.6, 47.1, 44.7, 41.6, 41.3, 32.9, 32.1, 29.8, 26.6, 26.5, 26.4, 20.7, 20.3, 10.6. Anal. Calcd for $C_{24}H_{36}O_2$ (356.60) C, 80.83; H, 10.20. Found: C, 80.80; H, 10.23.

(1*R*)-2-*endo*-[(1*R*,2*S*,3*S*,4*S*)-3-Cyclohexylbicyclo[2.2.1]oct-5-en-2-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (22). The title compound was prepared according to General Procedure C from enone **12b** (0.145 g, 0.5 mmol) and 1,3-cyclohexadiene (0.20 mL, 2.5 mmol) in 60 h: 0.124 g (67%); oil; $[\alpha]^{25}_D$ −29.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3534 (OH), 1693 (CO); ^1H NMR ($CDCl_3$) δ 6.40 (t, 1H, *J* = 6.9 Hz), 5.86 (t, 1H, *J* = 7.0 Hz), 2.96 (m, 1H), 2.75 (dd, 1H, J_1 = 1.83 Hz, J_2 = 5.5 Hz), 2.65 (m, 1H) 2.32 (s, 1H), 2.07−0.81 (m, 23H), 1.09 (s, 3H), 1.04 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.3, 137.3, 129.6, 86.0, 53.2, 52.7, 49.8, 44.8, 42.4, 42.0, 40.9, 32.9, 32.6, 31.3, 30.5, 29.8, 27.0, 26.5, 26.3, 25.9, 20.7, 20.4, 19.0, 10.9. Anal. Calcd for $C_{25}H_{38}O_2$ (370.57) C, 81.03; H, 10.34. Found: C, 81.06; H, 10.32.

(1*R*)-2-*endo*-[(1*S*,6*R*)-6-Cyclohexyl-4-methylcyclohex-3-en-1-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (23). The title compound was prepared according to General Procedure C from enone **12b** (0.145 g, 0.5 mmol) and isoprene (0.25 mL, 2.5 mmol) in 55 h: 0.103 g (57%); white solid; mp 90−92 °C; $[\alpha]^{25}_D$ +51.0 (*c* 0.5, CH_2Cl_2); IR (neat, cm^{-1}) 3529 (OH), 1690 (CO); ^1H NMR ($CDCl_3$) δ 5.29 (m, 1H), 3.19 (m, 1H), 2.29 (d, 1H, *J* = 12.8 Hz), 2.21 (s, 1H), 2.16−0.94 (m, 22H), 1.65 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.0, 133.6, 118.3, 88.2, 52.5, 50.7, 44.9, 43.9, 41.7, 39.9, 32.6, 30.2, 29.9, 29.7, 28.1, 27.1, 26.8, 26.7, 26.6, 23.5, 20.9, 20.5, 10.9. Anal. Calcd for $C_{24}H_{38}O_2$ (358.62) C, 80.37; H, 10.70. Found: C, 80.41; H, 10.77.

(1*R*)-2-*endo*-[(1*S*,6*R*)-6-Cyclohexyl-3,4-dimethylcyclohex-3-en-1-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (24). The title compound was prepared according to General Procedure C from enone **12b** (0.145 g, 0.5 mmol) and 2,3-dimethyl-1,3-butadiene (0.29 mL, 2.5 mmol) in 72 h: 0.112 g (60%); white solid; mp 60−62 °C; $[\alpha]^{25}_D$ +51 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3547 (OH), 1691 (CO); ^1H NMR ($CDCl_3$) δ 3.23 (m, 1H), 2.30 (d, 1H, *J* = 12.4 Hz), 2.23 (s, 1H), 2.06−0.88 (m, 22H), 1.62 (s, 3H), 1.58 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.0, 125.2, 123.0, 88.1, 52.5, 50.6, 45.2, 44.9, 42.0, 41.7, 39.9, 36.6, 32.7, 31.4., 29.8, 28.0, 27.2, 26.9, 26.8, 26.7, 20.9, 20.5, 19.0, 18.6, 10.9. Anal. Calcd for $C_{25}H_{40}O_2$ (372.65) C, 80.57; H, 10.84. Found: C, 80.52; H, 10.87.

(1*R*)-2-*endo*-[(1*R*,2*S*,3*S*,4*S*)-3-*tert*-Butylbicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (25). The title compound was prepared according to General Procedure C from enone **12c** (0.132 g, 0.5 mmol) and cyclopentadiene (0.20 mL, 2.5 mmol) in 18 h: 0.088 g (53%); solid; mp 110−113 °C. $[\alpha]^{25}_D$ +91.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3507 (OH), 1686 (CO); ^1H NMR ($CDCl_3$) δ 6.36 (dd, 1H, J_1 = 3.3 Hz, J_2 = 5.5 Hz), 5.69 (dd, 1H, J_1 = 2.6 Hz, J_2 = 5.1 Hz), 3.30 (m, 1H), 3.22 (m, 1H), 2.70 (m, 1H), 2.32 (d, 1H, *J* = 13.5 Hz), 2.19 (s, 1H), 2.06−0.82 (m, 9H), 1.10 (s, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.3, 140.2, 131.8, 86.9, 52.9, 52.5, 50.0, 48.7, 47.9, 47.0, 44.8, 44.5, 42.2, 32.3, 29.8, 29.1, 26.9, 20.8, 20.5, 10.9. Anal. Calcd for $C_{22}H_{34}O_2$ (330.56) C, 79.93; H, 10.39. Found: C, 79.95; H, 10.43.

(1*R*)-2-*endo*-[(1*S*,6*S*)-3,4-Dimethyl-6-*tert*-butylcyclohex-3-en-1-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (26). The title compound was prepared according to General Procedure C from enone **12c** (0.132 g, 0.5 mmol) and 2,3-dimethyl-1,3-butadiene (0.29 mL, 2.5 mmol) in 72 h: 0.091 g (53%); colorless oil; $[\alpha]^{25}_D$ +30 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3546 (OH), 1691 (CO); ^1H NMR ($CDCl_3$) δ 3.25 (m, 1H), 2.47 (s, 1H), 2.19 (d, 1H, *J* = 13.5 Hz), 2.07−0.90 (m, 11H), 1.57 (s, 3H), 1.50 (s, 3H), 1.05 (s, 3H), 0.88 (s, 3H), 0.81 (s, 9H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 215.7, 124.7, 120.4, 87.1, 51.8, 49.6, 43.9, 42.4, 41.2, 40.6, 33.2, 32.0, 30.2, 29.2, 27.8, 25.6, 19.8, 19.5, 18.0, 17.7, 9.7. Anal. Calcd for $C_{23}H_{38}O_2$ (346.61) C, 79.69; H, 11.07. Found: C, 79.74; H, 11.03.

(1*R*)-2-*endo*-[(1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.2]oct-5-en-2-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (28). The title compound was prepared according to General Procedure C from enone **12d** (0.14 g, 0.5 mmol) and 1,3-cyclohexadiene (0.20 mL, 2.5 mmol) in 16 h at −50 °C. Purification was effected by flash chromatography using a 1:50 ethyl acetate/hexane

mixture: 0.169 g (93%); oil; $[\alpha]^{25}_D$ +73.3 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3510 (OH), 1689 (CO); ^1H NMR ($CDCl_3$) δ 7.44−7.27 (m, 5H) 6.70 (t, 1H, J = 7.3 Hz), 6.14 (t, 1H, J = 7.0 Hz), 3.59 (d, 1H, J = 6.6 Hz), 3.32 (d, 1H, J = 4.8 Hz), 3.03 (s, 1H), 2.96 (d, 1H, J = 4.8 Hz) 2.57 (d, 1H, J = 3.7 Hz), 2.32 (d, 1H, J = 13.9 Hz), 2.19−0.43 (m, 10H), 1.16 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 215.8, 142.1, 136.4, 129.9, 128.2, 127.9, 126.3, 85.9, 53.4, 49.9, 46.5, 45.0, 40.4, 37.8, 33.1, 29.3, 27.1, 26.5, 20.6, 20.0, 17.9, 9.8. Anal. Calcd for $C_{25}H_{32}O_2$ (364.57) C, 82.36; H, 8.86. Found: C, 82.41; H, 8.83.

Diels−Alder Reaction with Enol Phosphate 33. Synthesis of (1*R*)-2-*endo*-[(1*R*)-4-Diethylphosphoryloxycyclohex-3-en-1-ylcarbonyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (34). To a solution of **1** (0.104 g, 0.5 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C under a nitrogen atmosphere were added dienyl phosphate **33** (0.515 g, 2.5 mmol) and copper triflate (0.054 g, 0.15 mmol). The mixture was stirred at 0 °C for 72 h and then was quenched with water (5 mL). The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product **34** was effected by flash silica gel column chromatography using a 1:4 ethyl acetate/hexane mixture as the eluant: 0.185 g (89%); yellow oil; $[\alpha]^{25}_D$ −11 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3377 (OH), 1701 (CO), 1255, 1135 (phosphate); ^1H NMR ($CDCl_3$) δ 5.42 (m, 1H), 4.08 (m, 4H), 3.04 (m, 1H), 2.27 (s, 1H), 2.18 (m, 1H), 2.11−1.10 (m, 12H), 1.29 (m, 6H), 1.06 (s, 3H), 0.91 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 216.2, 146.8 (d), 108.9 (d), 88,1, 64.1 (d), 52.2, 50.4, 44.9, 41.6, 41.0, 30.3, 27.2, 26.7 (d), 26.3, 20.7, 20.4, 16.1, 16.0, 10.8. Anal. Calcd for $C_{21}H_{35}O_6P$ (414.47) C, 60.85; H, 8.51. Found: C, 60.79; H, 8.47.

Oxidative Removal of the Auxiliary from Adducts. Synthesis of (1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde (58). To a stirred solution of the adduct **28** (0,366 g, 1 mmol) in dry THF (5 mL) at 0 °C under nitrogen atmosphere was added dropwise $LiAlH_4$ (1 M in THF, 3 mL, 3 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with 1 N HCl (2 mL) and was diluted with Et_2O. The organic extract was washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product obtained was sufficiently pure to use in the next step without further purification. To a solution of the crude oil in acetonitrile (12 mL) at 0 °C was added dropwise a solution of ceric ammonium nitrate (CAN) (1.64 g, 3 mmol) in water (6 mL) and the mixture was stirred at 0 °C for 15 min. Then, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated. Purification of the crude product was effected by flash silica gel column chromatography using a 1:30 ethyl acetate/hexane mixture as the eluant: 0.166 g (78%); white solid; mp 66−68 °C; $[\alpha]^{25}_D$ +82 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 1722 (CO); ^1H NMR ($CDCl_3$) δ 9.51 (s, 1H), 7.40−7.20 (m, 5H), 6.54 (t, 1H, J = 8.1 Hz), 6.21 (t, 1H, J = 6.6 Hz), 3.23 (d, 1H, J = 6.2 Hz), 3.11 (m, 1H), 2.85 (d, 1H, J = 6.2 Hz), 2.64 (m, 1H), 1.76−1.04 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 202.5, 141.9, 137.0, 130.9, 128.4, 127.9, 126.3, 55.9, 43.2, 36.6, 31.3, 25.6, 18.8. Anal. Calcd for $C_{15}H_{16}O$ (212.31) C, 84.85; H, 7.61. Found: C, 84.81; H, 7.66.

Synthesis of (−)-Nicolaioidesin C. TfOH-Catalyzed Diels−Alder Reaction with Myrcene. Synthesis of 62. To a solution of α′-hydroxy ketone **12d** (0,28 g, 1 mmol) in CH_2Cl_2 (4 mL) cooled to −78 °C under a nitrogen atmosphere were added dropwise myrcene (0.85 mL, 5 mmol) and triflic acid (0.01 mL, 0.1 mmol). The mixture was stirred at −78 °C for 20 h and then was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product was effected by flash silica gel column chromatography using hexane as the eluant: 0.36 g (85%); colorless oil; $[\alpha]^{25}_D$ +9 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3559 (OH), 1700 (CO), 1453; ^1H NMR ($CDCl_3$) δ 7.32−7.21 (m, 5H), 5.50 (m, 1H), 5.14 (t, 1H, J = 6.6 Hz), 3.54 (m, 1H), 3.05 (dt, 1H, J_1 = 11.4 Hz, J_2 = 5.1 Hz), 2.60−0.60 (m, 14H), 1.94 (d, 1H, J = 13.2 Hz), 1.71 (s, 3H), 1.63 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.76 (s, 3H), 0.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 216.5, 143.7, 136.9, 131.5, 128.4, 128.3, 126.9, 124.0, 118.9, 87.8, 51.9, 51.0, 48.0, 44.8, 44.2, 41.8, 37.3, 34.6, 30.4, 30.2, 26.4, 26.0, 25.7, 20.9, 20.6, 17.8, 11.2. Anal. Calcd for $C_{29}H_{40}O_2$ (420.63) C, 82.80; H, 9.60. Found: C, 82.85; H, 9.63.

Synthesis of Aldehyde 63. To a stirred solution of the aduct **62** (0,42 g, 1 mmol) in dry THF (5 mL) at 0 °C under nitrogen atmosphere was added dropwise $LiAlH_4$ (1 M in THF, 3 mL, 3 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with 1 N HCl (2 mL), diluted with Et_2O, and filtered through Celite. The organic extract was washed with water (2 × 10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product obtained was sufficiently pure to use in the next step without further purification. $Pb(AcO)_4$ (0.88 g, 2 mmol) was added in portions to a solution of the crude oil in benzene (4 mL) at 5 °C. After stirring for 50 min, an aqueous saturated solution of $NaHCO_3$ (4 mL) was slowly added. The resulting mixture was filtered through a Celite pad eluting with CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and dried with $MgSO_4$. The solvent was evaporated and the resulting crude product was purified by column chromatography (eluent EtOAc/Hex 1:50) providing the corresponding aldehyde as a colorless oil: 0.23 g, (84%); $[\alpha]^{25}_D$ +22 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 1726 (CO), 1453; ^1H NMR ($CDCl_3$) δ 9.49 (d, 1H, J = 2.9 Hz), 7.38−7.23 (m, 5H), 5.52 (m, 1H), 5.11 (t, 1H, J = 6.6 Hz), 3.13 (m, 1H), 2.77 (m, 1H), 2.50−2.06 (m, 8H), 1.71 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.2, 143.5, 137.6, 131.6, 128.7, 127.3, 126.6, 124.0, 118.2, 51.3, 41.2, 37.3, 36.0, 26.3, 25.7, 24.9, 17.7. Anal. Calcd for $C_{19}H_{24}O$ (268.43) C, 85.01; H, 9.03. Found: C, 85.07; H, 9.06.

2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene. A solution of 2-bromo-5-methoxyresorcinol[45] (0.22 g, 1 mmol) in dry DMF (2.4 mL) was added slowly to a stirred suspension of NaH (0.18 g, 7 mmol) in dry DMF (2.4 mL) at 0 °C. After stirring 20 min at 0 °C, chloromethyl methyl ether (0.31 mL, 4 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h, diluted with Et_2O, and washed with H_2O (3 × 15 mL), a saturated solution of $NaHCO_3$ (15 mL), and brine (15 mL). The organic phase was dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica (EtOAc/hexane, 1:15) to give the desired compound (0.26 g, 86%) as a white solid: mp 39−41 °C; IR (neat, cm^{-1}) 1586; ^1H NMR ($CDCl_3$) δ 6.45 (s, 2H), 5.21 (s, 4H), 3.75 (s, 3H), 3.50 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.9, 155.0, 96.1, 94.9, 94.5, 56.2, 55.3. Anal. Calcd for $C_{11}H_{15}BrO_5$ (307.14) C, 43.02; H, 4.92. Found: C, 43.05; H, 4.93.

Nucleophilic Alkylation of Aldehyde 63. Synthesis of Carbinol 64. *n*-BuLi (2.5 M in hexanes, 0.38 mL, 0.95 mmol) was added to a solution of 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)-benzene (0.30 g, 1 mmol) in THF (20 mL) cooled to −78 °C under a nitrogen atmosphere. After stirring for 30 min at the same temperature, aldehyde **63** (0.30 g, 1.1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was allowed to stir for 2 h at room temperature and then was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), the combined

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organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by flash silica gel column chromatography using a 1:10 mixture of EtOAc/hexane as the eluant: 0.41 g (82%); IR (neat, cm^{-1}) 3568 (OH), 1609, 1592; ^1H NMR ($CDCl_3$) δ (major diastereomer) 7.33−7.18 (m, 5H), 6.41 (s, 2H), 5.49 (m, 1H), 5.15 (m, 1H), 5.15 (s, 4H), 4.91 (m, 1H), 4.05 (m, 1H), 3.78 (s, 3H), 3.46 (s, 6 H), 2.94 (m, 1H), 2.38−1.61 (m, 8H), 1.70 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 159.6, 156.1, 146.0, 136.8, 131.3, 128.0, 127.4, 125.8, 124.2, 120.1, 112.5, 94.7, 94.6, 68.8, 56.3, 55.4, 44.9, 42.3, 37.5, 36.4, 26.5, 25.8, 24.0, 17.8. Anal. Calcd for $C_{30}H_{40}O_6$ (496.63) C, 72.55; H, 8.12. Found: C, 72.57; H, 8.11.

Oxidation of 64 and Final Deprotection. To a solution of alcohol **64** (0.50 g, 1 mmol) in dry CH_2Cl_2 (6 mL) was added Dess-Martin periodinane (0.85 g, 2 mmol) in two equal batches in a 5 min interval at room temperature. Water (20 μL, 1.10 mmol) was dissolved in 20 mL of CH_2Cl_2 by drawing the solvent mixture into, and expelling it from, a disposable pipet several times. Thus prepared wet CH_2Cl_2 was added slowly via dropping funnel to a vigorously stirring solution of alcohol **64** and Dess-Martin periodinane in CH_2Cl_2. The clear solution grew cloudy toward the end of wet CH_2Cl_2 addition, which required 30 min. After 90 min the reaction was quenched by adding a $Na_2S_2O_3$ doped saturated $NaHCO_3$ solution (15 mL) and stirring until both layers appeared clear. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were combined, washed with saturated NaCl (35 mL), dried with $MgSO_4$, and filtered, and the solvent was removed in vacuo. Purification of the crude product was effected by flash silica gel column chromatography using a 10:1 mixture hexane/EtOAc as the eluant: 0.46 g (94%); colorless oil; $[\alpha]^{25}_D$ −32.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 1700 (CO), 1605; ^1H NMR ($CDCl_3$) δ 7.30−7.11 (m, 5H), 6.30 (s, 2H,), 5.47 (m, 1H), 5.11 (m, 1H), 4.95 (d, 2H, J = 2.6 Hz), 4.93 (d, 2H, J = 2.6 Hz), 4.90 (m, 1H), 3.75 (s, 3H), 3.48 (m, 1H), 3.38 (s, 6 H), 3.33 (m, 1H), 2.36−1.87 (m, 8H), 1.68 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.9, 161.9, 155.9, 145.4, 137.1, 131.4, 128.1, 128.0, 127.8, 125.7, 124.1, 119.1, 115.2, 94.6, 94.5, 56.1, 55.4, 52.7, 42.1, 37.3, 37.2, 28.4, 26.4, 25.7, 17.8. To a stirred solution of the above ketone (0.49 g, 1 mmol) in a mixture of CH_2Cl_2 (11 mL)/MeOH (11 mL) was added *p*-toluenesulfonic acid monohydrate (0.096 g, 0.5 mmol). The reaction was refluxed at 40 °C for 3.5 h. Then, water (15 mL) was added, and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated. Purification of the crude product was effected by flash silica gel column chromatography using a 10:1 mixture hexane/EtOAc as the eluant: 0.35 g (86%); yellow solid; mp 104−108 °C; $[\alpha]^{25}_D$ −49.1 (*c* 1.0, MeOH); IR (neat, cm^{-1}) 3291 (OH), 1626 (CO), 1583; ^1H NMR ($CDCl_3$) δ 7.28−7.08 (m, 5H), 5.89 (s, 2H), 5.54 (d, 1H, J = 4.4 Hz), 5.14 (t, 1H, J = 6.6 Hz), 4.54 (m, 1H), 3.73 (s, 3H), 3.36 (m, 1H), 2.66−2.00 (m, 8H), 1.71 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.9, 165.4, 163.1, 145.4, 137.4, 131.5, 128.3, 127.2, 125.9, 124.1, 119.2, 105.4, 94.3, 55.4, 50.0, 42.8, 38.3, 37.3, 30.7, 26.4, 25.7, 17.8. Anal. Calcd for $C_{26}H_{31}O_4$ (406.56) C, 76.80; H, 7.45. Found: C, 76.66; H, 7.71. MS (ESI, m/z) 405.0 ($M - H^+$).

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Supporting Information Available: Preparation of starting enones; experimental procedures and characterization data of all remaining new compounds, including NMR spectra; details of the kinetic measurements; Cartesian coordinates of all computed stationary points and relative and absolute activation energies for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.