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Scalable and Highly Diastereo- and Enantioselective Catalytic Diels−Alder Reaction of α,β-Unsaturated Methyl Esters

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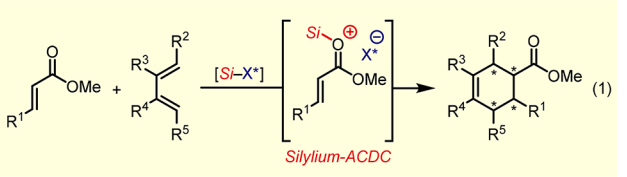
Supporting Information

ABSTRACT: Despite tremendous advances in enantioselective catalysis of the Diels−Alder reaction, the use of simple α,β-unsaturated esters, one of the most abundant and useful class of dienophiles, is still severely limited in scope due to their low reactivity. We report here a catalytic asymmetric Diels−Alder methodology for a large variety of α,β-unsaturated methyl esters and different dienes based on extremely reactive silylium imidodiphosphorimidate (IDPi) Lewis acids. Mechanistic insights from accurate domain-based local pair natural orbital coupled-cluster (DLPNO-CCSD(T)) calculations rationalize the catalyst control and stereochemical outcome.

The discovery of the Diels−Alder reaction by Kurt Alder and Otto Diels is regarded as one of the transforming events in organic chemistry.[1] The power and efficiency to rapidly build up complexity by forming up to four stereocenters at once was quickly realized and led to many important and elegant applications in the chemical synthesis of complex natural products,[2] agrochemicals, pharmaceuticals and fragrances.[3] In the historical development of stereoselective synthesis, the Diels−Alder reaction has served as one of the most prominent platforms and α,β-unsaturated carboxylic acid derivatives have been a widely applied class of dienophiles. In fact, a very early approach to asymmetric synthesis was the Lewis acid-mediated Diels−Alder reaction of enantiopure acrylates with cyclopentadiene.[4] Within the area of asymmetric Lewis acid catalysis, chiral complexes based on aluminum, titanium, copper, boron and others have emerged,[5] which enabled high enantioselectivities with α,β-unsaturated *N*-acyl oxazolidinones, aldehydes, ketones, and trifluoroethyl esters as dienophiles. Also some simple, unactivated α,β-unsaturated esters, such as methyl or ethyl acrylate and crotonate, in combination with cyclopentadiene can engage in highly enantioselective Diels−Alder reactions catalyzed either by chiral alkyldichloroboranes introduced by Hawkins[6] or Corey's cationic oxazaborolidines (CBS),[5c,7] which undoubtedly represent the most versatile family of chiral Lewis acids to date. In addition, various organocatalytic approaches have been described for α,β-unsaturated aldehydes and ketones via asymmetric iminium ion or Brønsted acid catalysis.[8,9] Despite these examples, the application of simple α,β-unsaturated esters as a highly abundant and fundamental class of dienophiles is still severely limited in scope due to their particularly low reactivity.[10]



In our efforts to overcome existing challenges in asymmetric Lewis acid catalysis, we have recently proposed a new strategy to catalyze the Diels−Alder reaction of α,β-unsaturated esters with an achiral, cationic silylium ion and an enantiopure counteranion (eq 1).[11] This asymmetric counteranion-directed silylium Lewis acid catalysis (silylium-ACDC)[12] differs conceptually from conventional enantioselective Lewis acid catalysis, which typically utilizes metal(loid) complexes with chiral ligands or substituents.[13] Rendering such complexes cationic and combining them with weakly coordinating, achiral counteranions is often a powerful measure to increase their activity. In contrast, the inversion of the chiral entities within the ion pair, as provided with silylium-ACDC, allows for the unique feature in silylium catalysis of possessing a repair pathway upon hydrolytic deactivation.[11,14] The source of chirality is hydrolytically stable, converts back to the Brønsted acidic state, and can be reactivated in the presence of a suitable silylating reagent. Providing a slight excess of the silylating reagent compared to the chiral Brønsted acid then allows for very low catalyst loadings of the chiral Brønsted acid

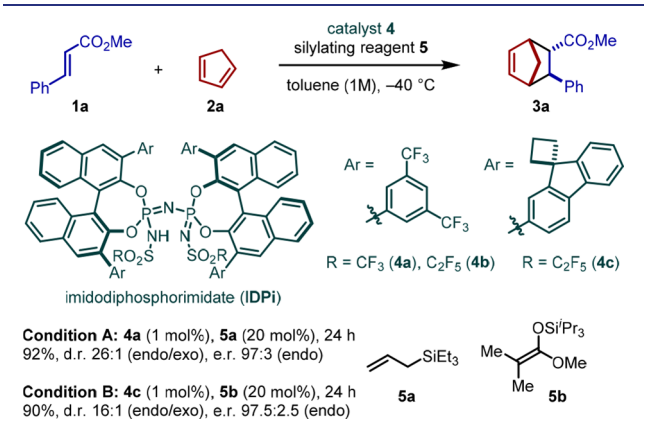


Figure 1. Reaction development and catalyst systems.

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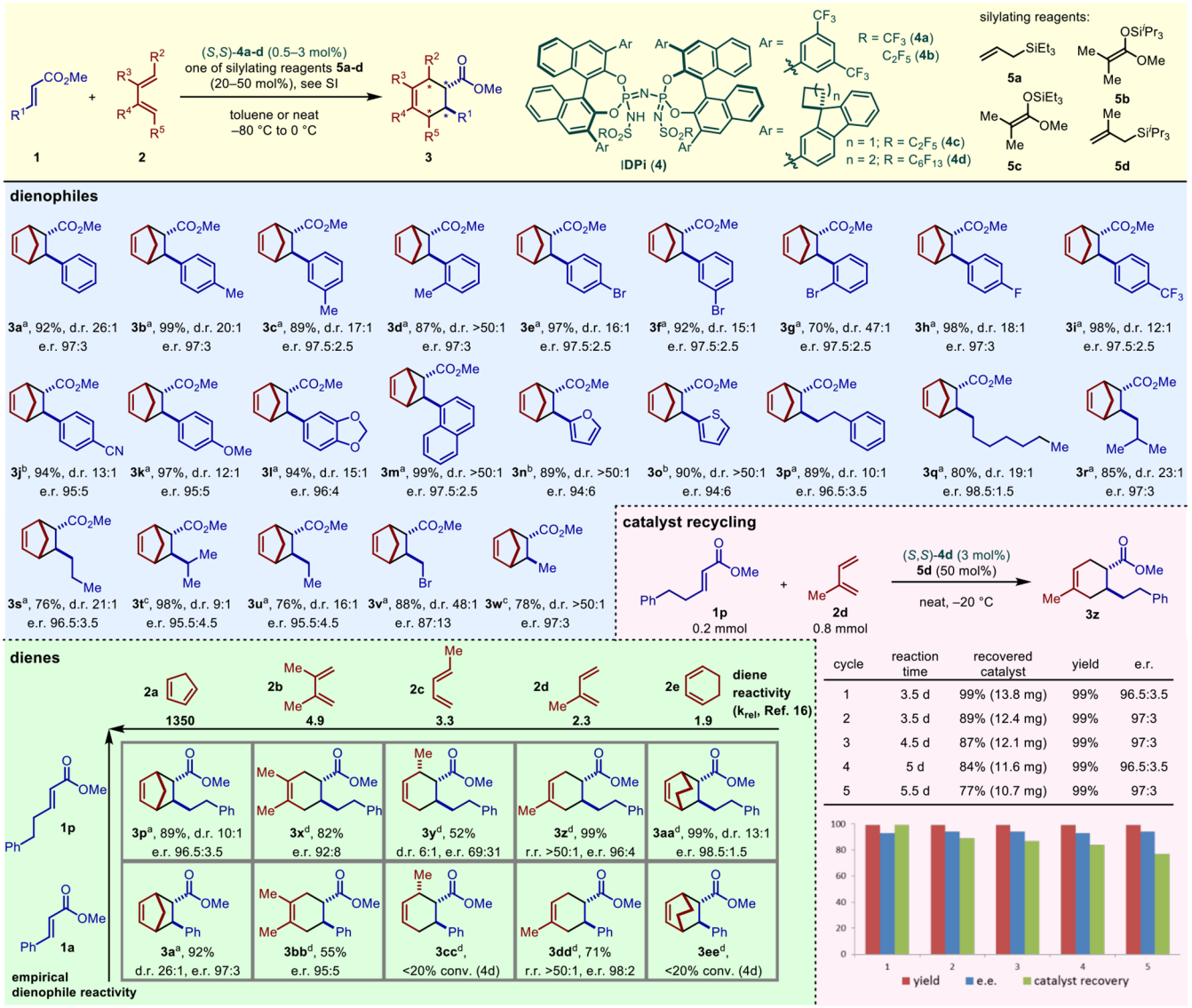

Figure 2. Substrate/diene scope and catalyst recycling. Reactions of α,β-unsaturated methyl esters with dienes: [a]with catalyst **4a**; [b]with catalyst **4b**; [c]with catalyst **4c**; [d]with catalyst **4d** (3 mol %).

precatalyst. In addition, the logic of designing more stabilized and weaker coordinating enantiopure anions also applies here and leads to higher activity of the corresponding cationic silylium species.

After demonstrating this concept for the catalytic asymmetric Diels–Alder reactions of 9-fluorenylmethyl cinnamate esters with a chiral C–H acid as the Lewis acid precursor,[11] we were recently able to utilize simple α,β-unsaturated methyl esters in enantioselective Mukaiyama–Michael reactions with silyl ketene acetals (SKA) and highly acidic and confined imidodiphosphorimidate (IDPi) catalysts.[15] We now report the development of a catalytic asymmetric Diels–Alder methodology for a large variety of α,β-unsaturated methyl esters and different dienes, including normally unreactive substrate combinations.

We chose the Diels–Alder reaction between only weakly reactive methyl *trans*-cinnamate (**1a**) and cyclopentadiene (**2a**) as our model reaction (Figure 1) and conducted an extensive catalyst evaluation. We found that our IDPi acids provided both sufficient activity and promising enantioselectivities compared to other chiral acids tested (for more details, see the Supporting Information). Gratifyingly, we could identify two distinct families of IDPi catalysts, which after optimization gave very high enantio- and diastereoselectivities. Catalysts **4a** and **4b** possess 3,5-(trifluoromethyl)phenyl substituents, while IDPi **4c** features cyclobutyl-derivatized 3-fluorenyl substituents on the BINOL backbone. In general, inner core modification toward longer perfluoroalkyl groups (e.g., R = C_2F_5)[15e–h] increased catalytic activity, while the impact on enantioselectivity varied. The type of silylating reagent (**5**) suitable to activate the IDPi Brønsted acid precatalysts to the silylium-Lewis acids depends on catalyst acidity and activation temperature. We investigated silyl ketene acetals (SKA), methallylsilanes, and allylsilanes as activators and found that their silylating power decreased in this order. Though the type of reagent had no effect on enantioselectivity, the impact of the silyl group on both reaction rate and stereoselectivity was quite significant. Independent reaction optimization with both privileged catalysts revealed triethyl allylsilane **5a** as the optimal activator of catalyst **4a** (condition A), while catalyst **4c** performed best with triisopropylsilyl (TIPS) SKA **5b** (condition B). Both catalyst systems gave

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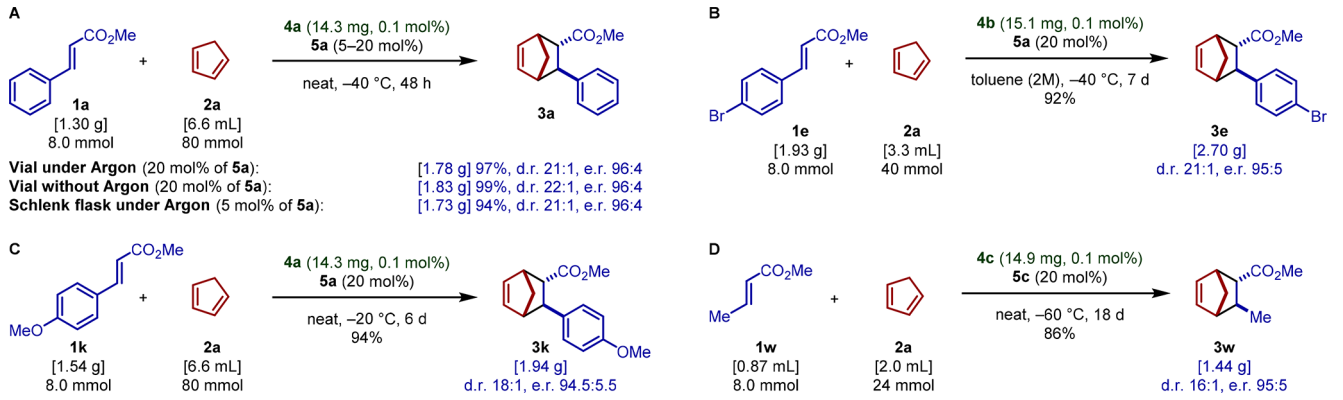

Figure 3. Scale-up experiments and reduced catalyst loadings.

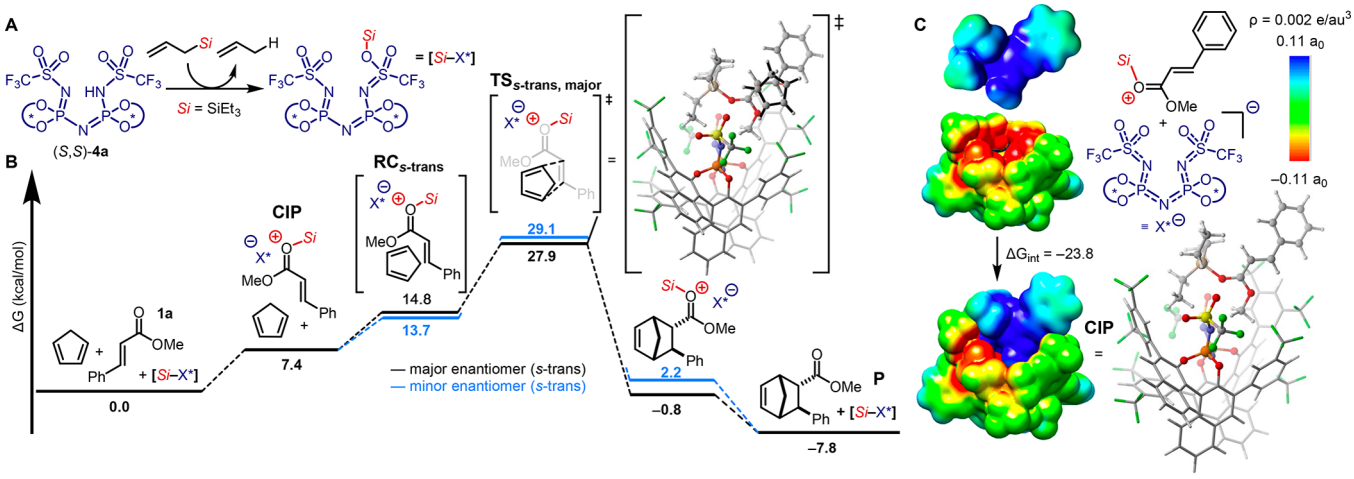

Figure 4. Computational Studies. (A) Catalyst activation. (B) Diels–Alder reaction profiles. (C) Interaction within the chiral ion pair (CIP); Geometry optimizations with PBE-D3(BJ)/def2-SVP; single-point energies with DLPNO-CCSD(T)/def2-TZVP+C-PCM(toluene).

equally high yields and enantioselectivities (e.r. ≥ 97:3) in our model reaction using only 1 mol % of IDPi and a substoichiometric amount of silylating reagent at −40 °C.

With this flexibility and optional fine-tuning in hand, we proceeded to explore the scope of α,β-unsaturated esters as dienophiles with cyclopentadiene (**2a**) (Figure 2). As condition A provided higher reactivity and increased diastereoselectivity, we tested a variety of methyl- and bromo-substituted cinnamates with catalyst **4a** and found that these arene-substitutions were well tolerated, and the desired products (**3b–g**) were obtained in high yields and excellent enantio- and diastereoselectivities. Similar results were achieved for *para*-fluoro- or trifluoromethyl-substituted products **3h** and **3i** under the same conditions. For stronger electron-deficient substrates such as cinnamate **1j** and 3-heteroaryl-substituted acrylates **1n** and **1o**, we used catalyst **4b** to efficiently catalyze the reaction. When electron-rich substrates were tested to afford products **3k** and **3i**, increased catalyst loading (3 mol % of **4a**) and temperature (−20 °C) provided sufficient reactivity to obtain high yields and stereocontrol. As 3-alkyl acrylates were empirically found to be more reactive than 3-aryl acrylates,[5c] both available catalyst systems were explored at decreased temperatures (−80 °C) and gave product **3p** in comparably excellent yields and enantioselectivities. With catalyst **4a**, various alkyl-substituted products (**3q–s**, **3u–v**) were isolated with consistently very high levels of stereocontrol, while the enantioselectivities slightly decreased with shorter chain lengths. With γ-branched methyl 4-methylpent-2-enoate (**1t**) and methyl crotonate (**1w**); however, switching to catalyst **4c** in combination with the triethylsilyl (TES) group under neat conditions was necessary to obtain excellent results for products **3t** and **3w**.

In light of the extremely high activity of our silylium-Lewis acids, we proceeded to explore other representative dienes, such as 2,3-dimethylbutadiene **2b** (k_{rel} = 4.9), *trans*-pentadiene **2c** (k_{rel} = 3.3), isoprene **2d** (k_{rel} = 2.3) and cyclohexadiene **2e** (k_{rel} = 1.9), which are orders of magnitude less reactive than cyclopentadiene **2a** (k_{rel} = 1350), in reference to butadiene (k_{rel} = 1).[16] We found that IDPi's of the 3-fluorenyl substitution family were generally superior over 3,5-(trifluoromethyl)-phenyl derivatives **4a** and **4b** in enantiodiscrimination, whereas significantly higher activities could be achieved by attaching a longer, linear perfluoroalkyl chain (R = C_6F_{13}) to the inner core sulfonyl groups. This led to the identification of cyclopentyl-derivative **4d** as the optimal catalyst in combination with TIPS methallylsilane **5d** as the activator. Diels–Alder reactions of representative dienophiles **1a** and **1p** covering a range of reactivity and both 2,3-dimethylbutadiene and isoprene proceeded with a very high degree of stereocontrol in good yields under neat conditions. A higher catalyst loading of 3 mol % was used in these cases. However, catalyst recyclability over five cycles gave consistently high yields and enantioselectivities, while only small losses of the catalyst were observed, presumably due to chromatographic reisolation.

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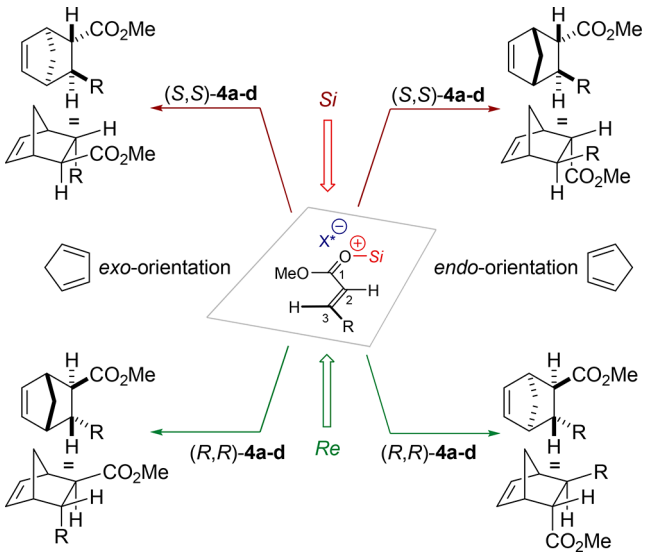

Figure 5. Stereochemical mnemonic.

Highly challenging reactant combinations involving *trans*-pentadiene and cyclohexadiene gave significantly lower conversions and only low enantioselectivity for product **3y**. With methyl cinnamate, both dienes gave no isolatable amounts of the products even after prolonged reaction time. In contrast, the expected order of diene reactivity was observed in nonenantioselective Diels–Alder reactions with TMS-NTf_2 as the catalyst, confirming the strong influence of the confined IDPi environment in these cases. We also found that increasing the reaction temperature to above 0 °C proved to be deleterious for the reaction rate and a significant amount of catalyst methylation was observed, presumably due to a collapse of the chiral ion pair consisting of the silylated methyl ester substrate and its counteranion.

To highlight the synthetic potential of our methodology for scale-up applications, we lowered the catalyst loading further to only 0.1 mol % and conducted several gram-scale reactions under neat conditions to furnish products **3a**,**k**,**e**,**w** in nearly quantitative yields and very high enantioselectivities (Figure 3). Importantly, only small amounts of easily filterable cyclopentadiene polymerization products were formed. As our silylium-Lewis acid approach conveniently includes self-drying conditions,[11,15g] we could also run these reactions without an inert gas atmosphere and observed essentially identical results. On the other hand, strictly anhydrous conditions allowed us to reduce the amount of silylating reagent to 5 mol %.

In order to obtain deeper insight into the reaction mechanism and the catalyst's mode of action, we investigated the reaction profile for methyl cinnamate, cyclopentadiene and (*S*,*S*)-**4a** at the DLPNO-CCSD(T)/def2-TZVP + C-PCM-(toluene) // PBE-D3 (BJ)/def2-SVP level of theory.[17] Silylation of the IDPi acid with allylsilane **5a** to give the active catalyst occurs instantaneously at r.t. as observed by NMR and propene formation was detected (Figure 4A).

Subsequently, the silyl group is transferred onto the carbonyl group of the substrate to form a chiral ion pair (CIP, Figure 4B) in an endothermal process (ΔG = 7.4 kcal/mol) with the *s*-trans conformation as the most stable intermediate. Interaction of cyclopentadiene with the CIP gives a reactant complex ($RC_{s\text{-trans}}$) as a subsequent intermediate toward the Diels–Alder transition states. The competing transition states for each of the endoenantiomers ($TS_{s\text{-trans}}$; marked in black and blue) are predicted to give an e.r. of 93:7 ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol), which is in good agreement with the experimental data (e.r. 97:3, $\Delta\Delta G^{\ddagger}$ = 1.6 kcal/mol). The most stable TS features two stabilizing nonclassical C–H···O hydrogen bonds (between an oxygen atom of the SO_2CF_3 group of the catalyst and the C–H groups of the cyclopentadiene) that are missing in the other TS structures. Subsequently, desilylation and release of the product is thermodynamically favored rendering the silylated IDPi as the resting state within the catalytic cycle. We further investigated the CIP in greater detail to understand the origin of enantioselectivity (Figure 4C). The electrostatic potential maps revealed that the most favorable interaction mode (ΔG = −23.8 kcal/mol) for this structure orients the phenyl ring of **1a** far from the counteranion, consistent with the high enantioselectivities observed for various substitutions at the 3-position. In addition, the methyl group of the substrate is pointing inside the chiral pocket of the IDPi moiety, overall resulting in a striking geometrical match of the ion pair. In this context, we also tested ethyl and benzyl *trans*-cinnamate as substrates, but not only detected sluggishly reactivity with **4a** but also significantly diminished enantioselectivities (e.r. 75:25 with ethyl cinnamate; e.r. 57.5:42.5 with benzyl cinnamate), which can be rationalized by an improper fit with such bulkier groups. Upon rationalizing catalyst-substrate interactions and enantioinduction, we derived a stereochemical mnemonic based on steric shielding of the enantiotopic faces by the IDPi anion (Figure 5).

In summary, we report the development of a catalytic asymmetric Diels–Alder methodology for a large variety of poorly reactive α,β-unsaturated methyl esters and different dienes to give the cycloaddition products in excellent yields, enantio- and diastereoselectivities. Many of the products have previously been inaccessible with known chiral Lewis acids, while the corresponding Diels–Alder reactions can now be accomplished with very low catalyst loadings of only 0.1–3 mol %. Future work will focus on overcoming remaining challenges in catalytic asymmetric Diels–Alder reactions and on synthetic applications toward important target structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b07092.

Additional detailed information on reaction development, synthetic protocols, analytical data for all compounds, and the computational strategy (PDF)

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Notes

The authors declare the following competing financial interest(s): Patent WO2017037141 (A1) has been filed by the MPI für Kohlenforschung covering the IDPi catalyst class and their applications in asymmetric synthesis.

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