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Catalytic Asymmetric [4+2]-Cycloaddition of Dienes with Aldehydes

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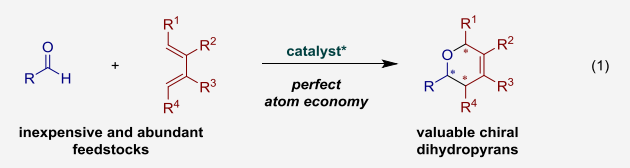
ABSTRACT: Despite its significant potential, a general catalytic asymmetric [4+2]-cycloaddition of simple and electronically unbiased dienes with any type of aldehyde has long been unknown. Previously developed methodologies invariably require activated, electronically engineered substrates. We now provide a general solution to this problem. We show that highly acidic and confined imidodiphosphorimidates (IDPis) are extremely effective Brønsted acid catalysts of the hetero-Diels–Alder reaction of a wide variety of aldehydes and dienes to give enantiomerically enriched dihydropyrans. Excellent stereoselectivity is generally observed and a variety of scents and natural products can be easily accessed.

The hetero-Diels–Alder reaction (HDA) between dienes and aldehydes is a fundamental reaction in chemical synthesis and arguably the most efficient and atom economical approach for the construction of dihydropyrans, an extremely frequent substructure of carbohydrates, pharmaceuticals, agrochemicals, and fragrances[1]. Catalytic and enantioselective variations have been investigated during the last 30 years, but current methodologies are limited to electronically biased substrates and therefore lack generality[2]. Electron-deficient dienophiles, such as glyoxylates and/or electron-rich dienes, such as Danishefsky-, Brassard-, or Rawal-type dienes are typically required to achieve both high reactivity and stereoselectivity[3−6]. In contrast, simple and unactivated dienes and aldehydes are inexpensive and abundant chemical feedstocks. For example, isoprene, a common diene, is produced by many plants and humans, and makes up around one-third of all hydrocarbons emitted into the atmosphere. Likewise, aldehydes are prepared industrially on a several million-ton scale each year. Yet, while a catalytic asymmetric [4+2]-cycloaddition reaction between these abundant substrate classes is clearly desirable and would deliver highly valuable enantiomerically enriched dihydropyran products (Eq. 1), such a process has remained an unmet challenge in chemical synthesis. We reasoned that this is due to the inability of current catalysts to simultaneously reduce the large energy difference between the involved frontier orbitals[7,8] of unactivated dienes and aldehydes, and at the same time avoid various potential side reactions.



Encouraged by our recent success in asymmetric Brønsted acid-catalyzed reactions involving aldehydes and olefins[3b,9,10], we recognized the potential of Brønsted acids in the asymmetric catalysis of the diene/aldehyde [4+2]-cycloaddition reaction. We reasoned that strong Brønsted acids would be required to significantly lower the LUMO of the aldehyde (dienophile) and thereby narrow the energy gap between the involved frontier orbitals. We further hypothesized that a highly confined chiral microenvironment of the catalyst would be essential to enable efficient stereocontrol with small and unfunctionalized substrates, and to preclude side reactions such as a Prins, carbonyl–ene, aldol, and/or cationic oligomerization reaction[11−14].

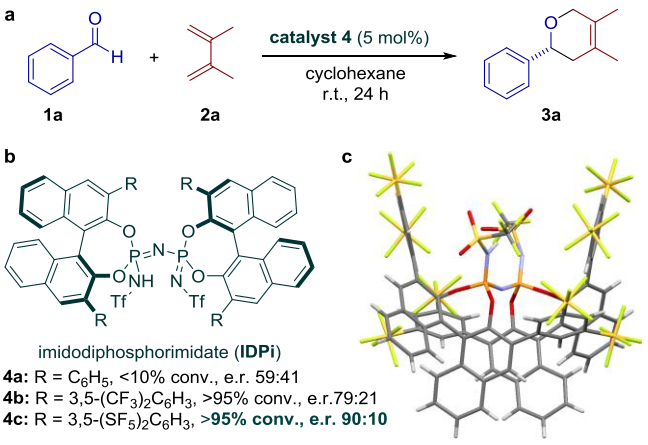
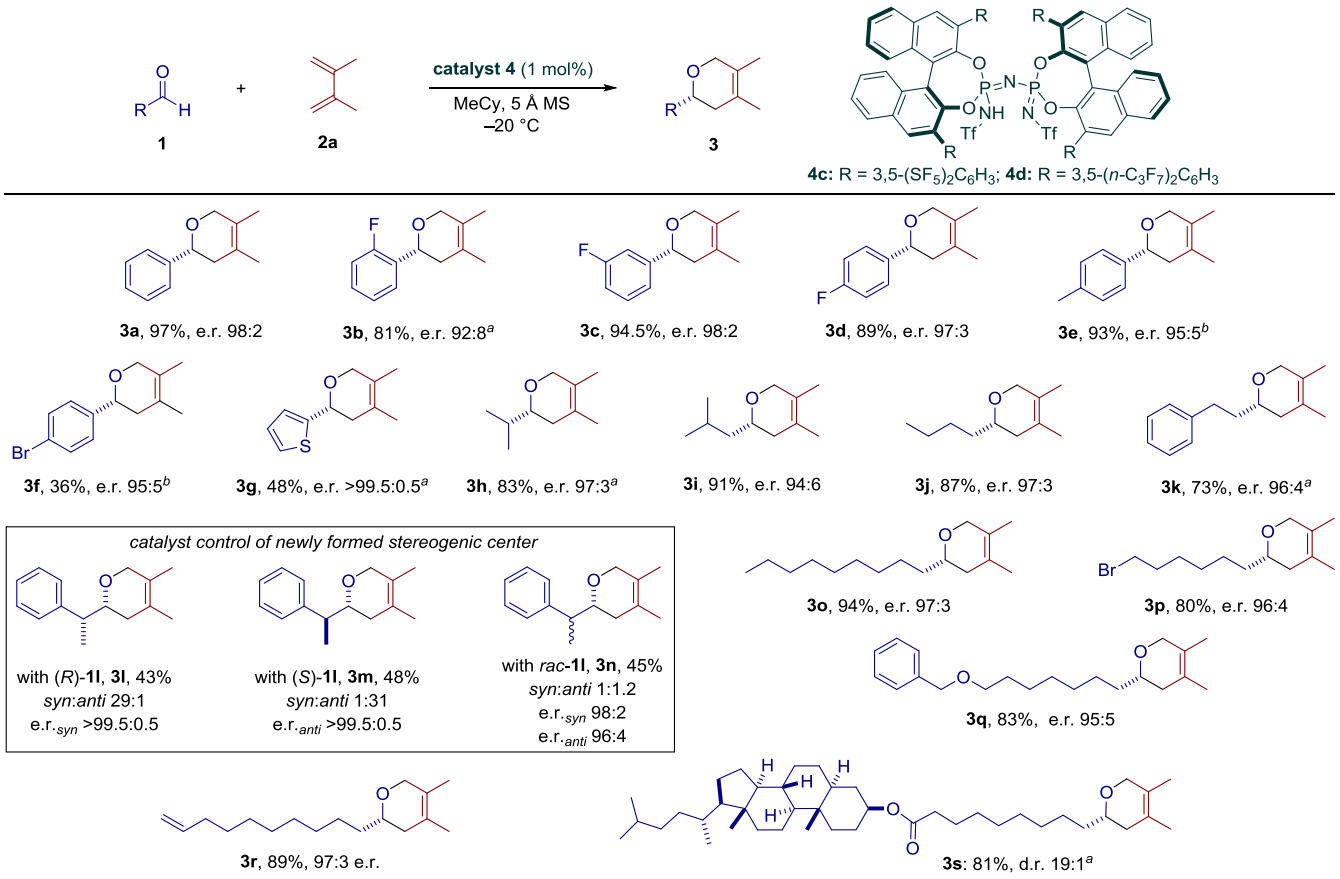


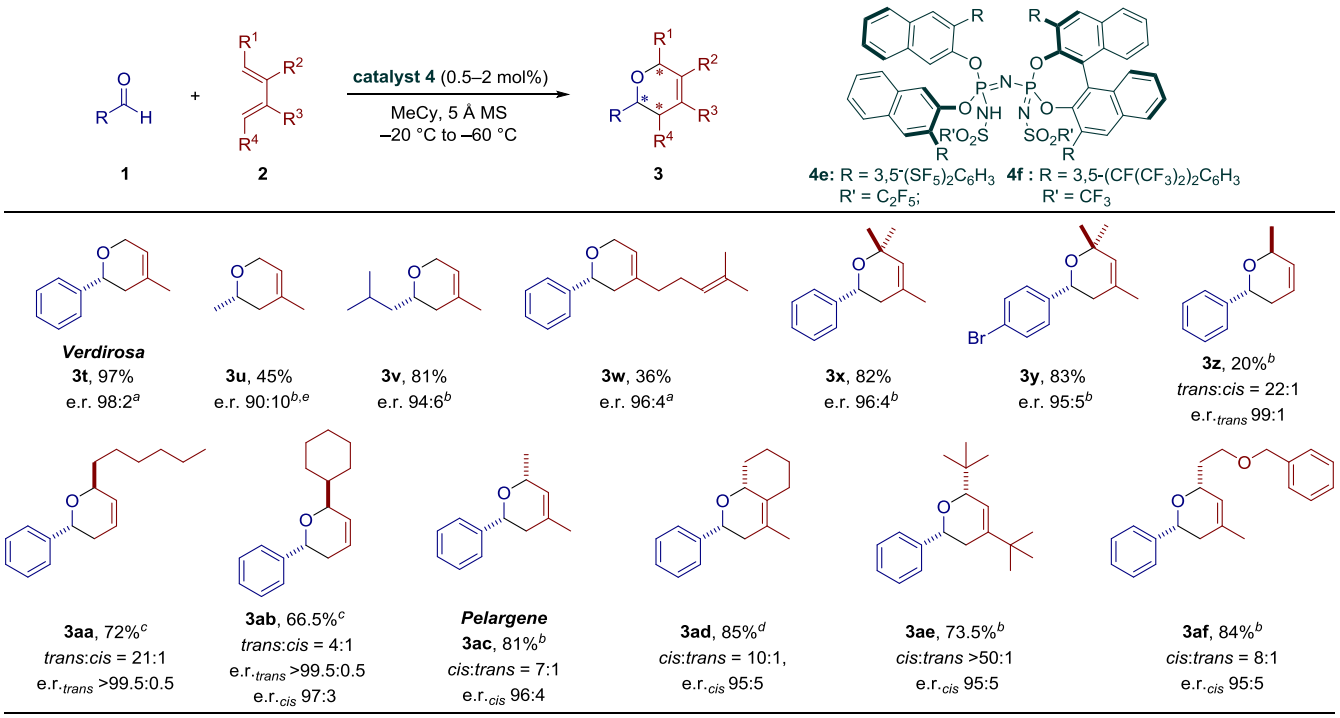
Figure 1. Catalyst Evaluation. a, Model [4+2]-cycloaddition of benzaldehyde (**1a**) with diene **2a**. b, Catalyst screening. c, X-ray crystal structure of **4c**.

At the outset, the asymmetric HDA reaction between benzaldehyde (**1a**) and 2,3-dimethyl-1,3-butadiene (**2a**) was investigated (Fig. 1). A variety of previously reported strong chiral Brønsted acids were explored. Phosphoric acids[15], disulfonimides[16], and imidodiphosphates[17] all proved insufficiently active and essentially no desired cycloadduct **3a** was detected (Supplementary Table S1). Product **3a** was formed using an *N*-triflylphosphoramide catalyst[18], albeit with poor conversion (11% conv., 64:36 e.r., see Supplementary Table S1). Inspired by the compact active sites of enzymes, we previously designed and synthesized highly confined BINOL-derived Brønsted acid imidodiphosphates (IDPs). Recently, the strategic replacement of oxo-groups within the active site of IDP catalysts with strongly electron withdrawing NSO_2CF_3 (*N*Tf) groups has been successfully implemented, leading to extremely confined *and* acidic imidodiphosphorimidate (IDPi) catalysts **4**[19]. We envisioned that this newly developed catalyst class would offer a promising platform for the desired [4+2]-cycloaddition. Indeed, cycloadduct **3a** was obtained using reported IDPi catalysts **4a** and **4b** (<10% conv., 59:41 e.r. with IDPi **4a**; >95% conv., 79:21 e.r. with IDPi **4b**). Rational tuning of the 3,3'-substituents of the BINOL backbone of **4** significantly boosted both reactivity and enantioselectivity (Supplementary Table S2). Remarkably, IDPi **4c** cleanly furnished product **3a** with a promising 90:10 e.r. (Fig. 1). Gratifyingly, excellent yield and enantioselectivity (97%, 98:2 e.r.) were achieved with this catalyst by lowering the reaction temperature to –20 °C and the catalyst loading could be reduced to 1 mol% (Scheme 1, **3a**). Toward a general and highly enantioselective [4+2]-cycloaddition between all types of simple dienes and aldehydes, we developed and screened a series of IDPi catalysts (Scheme 1 and 2, **4c**–**4f**).

Using the optimized reaction conditions, we first explored the scope of aldehydes in the asymmetric cycloaddition with 2,3-dimethyl-1,3-butadiene (**2a**). Various aromatic aldehydes were tolerated, regardless of their electronic properties, affording the corresponding cycloadducts in high enantioselectivities and moderate to good yields (**3a**–**3g**). The absolute configuration of product **3f** was determined to be (*R*) by single-crystal X-ray analysis, corresponding to a *re*-aldehyde-enantiofacial selectivity of the catalyst. Rewardingly, simple and unactivated aliphatic aldehydes also proved to be effective substrates in the reactions with catalyst **4d**, affording products **3h**–**3o** with high stereoselectivities and yields. The superb catalyst control in the establishment of the newly created stereogenic center was revealed with chiral aldehyde **1l**. Enantiopure aldehyde (*R*)-**1l** afforded *syn*-diastereomer **3l** (29:1 d.r., >99.5:0.5 e.r.$_{syn}$), while its enantiomer (*S*)-**1l** was converted into the corresponding *anti*-diastereomer **3m** (31:1 d.r., >99.5:0.5 e.r.$_{anti}$). Accordingly, both in the match and mismatch case, exceptionally high *re*-diastereofacial differentiation was enforced by the catalyst, overriding the preference of the substrate. As a consequence, racemic aldehyde *rac*-**1l** afforded **3n** as a mixture of both *syn*- and *anti*-diastereomers, each with high enantioselectivity.



Scheme 1. Aldehyde Scope. Reactions of aromatic aldehydes were performed using catalyst **4c**. Reactions of aliphatic aldehydes were performed using catalyst **4d**. [a]Reaction performed at –10 °C. [b]Reaction performed at –60 °C. Yields refer to isolated material. d.r., diastereomeric ratio; e.r., enantiomeric ratio; MeCy, methylcyclohexane. For more details, see the supplementary material.



Scheme 2. Diene Scope. [a]Catalyst **4c** used. [b]Catalyst **4d** used. [c]Catalyst **4e** used. [d]Catalyst **4f** used. [e]50 mol% acetic acid added. For more details, see the supplementary material.

The yields of the reactions with this particular aldehyde were diminished due to a side product resulting from the trimerization of aldehyde **1l**. Furthermore, aldehydes functionalized with halide, ester, and olefin groups (**1p**–**1r**), and a large, dihydrocholesterol-derivatized aldehyde (**1s**), were well-tolerated under the reaction conditions.

Having established a remarkably general scope of tolerable aldehydes in this cycloaddition reaction, we next investigated the diene scope (Scheme 2). Natural dienes such as isoprene and beta-myrcene proved to be suitable substrates, generating the desired products with generally high enantioselectivities (**3t**–**3w**). A diverse set of simple and unactivated dienes were explored, and the corresponding products were all obtained in good to excellent yields with high stereoselectivities (**3x**–**3ae**). Moreover, a functionalized diene was also compatible under the optimized reaction conditions (**3af**). The low yields of **3w** and **3z** were due to Prins and oligomerization side reactions[13a,14]. We have also explored several other types of dienes but found them to be less reactive.[20] The absolute and relative configurations of products **3z** and **3ac** were found to be *trans*-(2*R*,6*S*) and *cis*-(2*R*,6*R*), respectively, as determined by comparison to reported optical rotation values[21]. Different from **3z**, the thermodynamically favored *cis*-diastereoisomer **3ac** was obtained when using the more nucleophilic diene **2h**. We currently speculate that the differing diastereoselectivities result from different reaction mechanisms (possibly concerted vs. stepwise; vide infra). Our methodology provided an efficient and enantioselective approach to commercialized fragrances *Verdirosa* (**3t**) and *Pelargene* (**3ac**).

Several preparative scale experiments were performed (Fig. 2). For example, product **3a** was obtained on a gram scale with excellent yield and enantioselectivity using only 0.2 mol% of catalyst **4c** and 1.2 equivalent of diene **2a**. Meanwhile, catalyst **4c** could be easily recovered in 97% yield, via flash chromatography followed by acidification. Similarly, a [4+2]-cycloaddition between aliphatic aldehyde **1o** and diene **2a**, afforded 0.95 g of product **3o**.

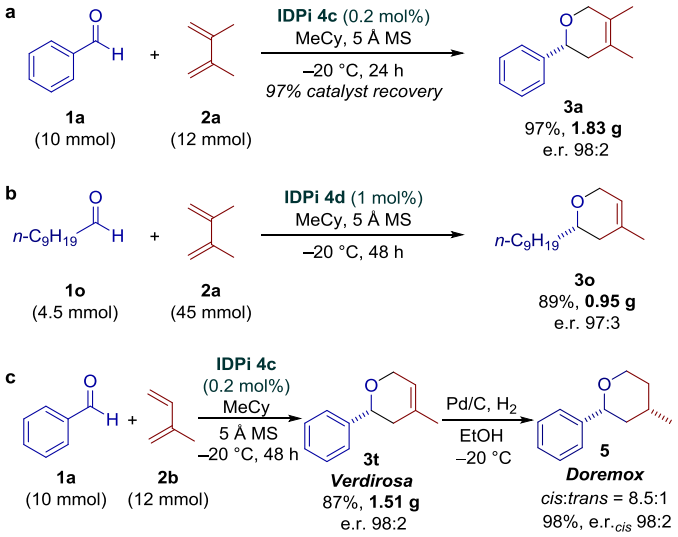


Figure 2. Scale-Up Reactions and Derivatization.

We also scaled up the reaction of isoprene (**2b**) with benzaldehyde (**1a**) to provide *Verdirosa* (**3t**) on a gram scale with high enantiopurity. Subsequently, the new rose oxide replacement compound *Doremox* (**5**) was readily obtained from *Verdirosa* via diastereoselective hydrogenation (Fig. 2c).

We initially envisioned two mechanistic scenarios for the described Brønsted acid-catalyzed [4+2]-cycloaddition reaction: either a concerted, pericyclic reaction or a stepwise, carbocationic pathway (Fig. 3a). In either case, the protonation of aldehyde **1a** will result in the lowering of its LUMO[9], promoting an electronically-matched interaction with the

HOMO of the diene. Subsequently, a concerted [4+2]-cycloaddition could furnish the corresponding *hetero*-Diels–Alder adduct **3a** after deprotonation. Alternatively, a stepwise pathway proceeding via an allylic cation that undergoes a cyclization, can be envisioned. Toward elucidating the reaction mechanism, an intramolecular ^{13}C kinetic isotope effect (KIE, $k^{12}C/k^{13}C$) experiment of the reaction leading to product **3a** was conducted at the natural isotopic abundance, under the reaction conditions (Fig. 3b)[22–24]. The relative ^{13}C compositions of **3a** at C3 and C4 were respectively assigned to be 1.000 in this intramolecular KIE measurement. The ^{13}C KIE at C2 of 0.998(3)–0.999(4) indicated that the NMR measurements were accurately performed, since a negligible ^{13}C KIE at C2 would be expected for either of the envisioned mechanisms. We observed a substantial ^{13}C KIE at C1 of 1.022(3)–1.025(4), which suggested that the reaction proceeds via a stepwise mechanism. The observed KIE is also consistent with a concerted, though highly asynchronous pathway and additional mechanistic studies, including DFT calculations, are needed and currently ongoing in our laboratory.

The reported general and highly enantioselective catalytic [4+2]-cycloaddition of unactivated dienes with aldehydes was enabled by the development of highly acidic *and* confined chiral Brønsted acids. Our methodology provides an efficient and enantioselective access to functionalized dihydropyrans and potentially has an impact on the synthesis of fragrances, natural products, and pharmaceuticals.

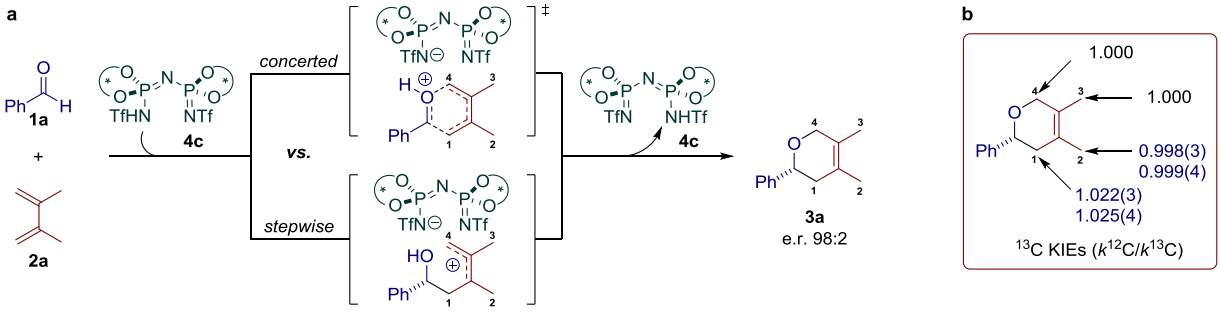


Figure 3. Mechanistic Studies. a, Plausible reaction pathways. b, Intramolecular ^{13}C KIEs at 15 ± 0.6% and 16 ± 0.8% completion of **2a** (relative to starting diene **2a**). For more details, see the supplementary material.

ASSOCIATED CONTENT

Supporting Information

Additional detailed synthetic protocols and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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