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A General Catalytic Asymmetric Prins Cyclization

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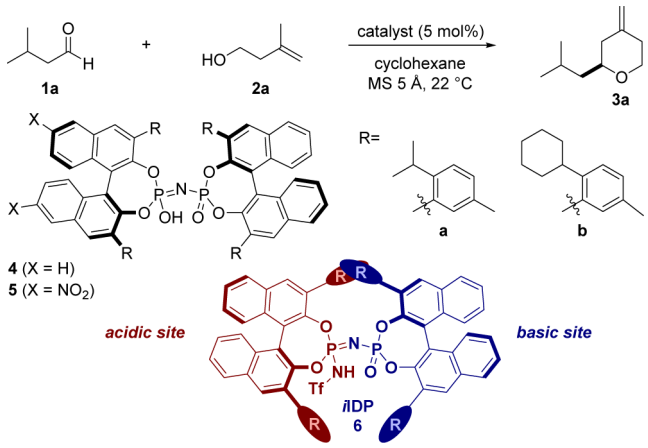
Supporting Information

ABSTRACT: A new class of highly acidic confined imino-imidodiphosphate (*i*IDP) Brønsted acids catalyze the asymmetric Prins cyclization of both aliphatic and aromatic aldehydes. Diverse functionalized 4-methylenetetrahydropyrans are obtained in good to excellent yields and with good to excellent regio- and enantioselectivities. Our *i*IDP catalysts provide an efficient and scalable enantioselective approach to various fragrances, including rose oxide and doremox.

Chiral functionalized tetrahydropyran (THP) rings are widely used as scaffolds in fragrances and pharmaceuticals and are frequent substructures of natural products.[1] Because of their prevalence, various methods have been developed to furnish THPs.[2] One particular efficient approach is the acid-catalyzed cyclocondensation of an aldehyde with a homoallylic alcohol, also known as Prins cyclization.[3] Catalytic enantioselective variants have been described but require activated substrates, such as salicylaldehydes,[4b] limiting the applicability of this elegant and atom-economical methodology.[4,5] Herein we disclose the design, synthesis, and application of confined imino-imidodiphosphates (*i*IDPs) as a new class of highly acidic Brønsted acid catalysts, enabling the first general asymmetric Prins cyclization of diverse aromatic and aliphatic aldehydes in good to excellent yields and enantioselectivities.

At the onset of our studies, we proposed that to successfully engage small aliphatic substrates such as aldehyde **1a** and homoallylic alcohol **2a** in an enantioselective Prins cyclization, a confined chiral catalyst microenvironment would be required. The implementation of this concept has previously rewarded us with extraordinary selectivities in asymmetric acetalization reactions and other small-molecule transformations.[4b,6] However, our previously developed confined imidodiphosphate (IDP) catalysts have proven to be insufficiently acidic to promote asymmetric Prins cyclizations of unactivated aldehydes. Indeed, IDPs **4a** and **4b** are barely able to catalyze this reaction (Table 1, entries 1 and 2). These limitations encouraged us to design more acidic confined Brønsted acids. Indeed, the introduction of electron-withdrawing nitro groups on the BINOL backbone in catalysts **5**[7] significantly enhanced the reactivity and gave product **3a** with promising enantioselectivity (entries 3 and 4). In this context, we hypothesized that an alternative approach toward acidifying our IDP catalysts may involve the replacement of an oxo group with a strong electron acceptor, such as the NSO_2CF_3 (NTf) group. This general strategy has previously been exploited by the Yamamoto group in the design of *N*-triflyl phosphoramides[8] and also in our recently developed highly acidic phosphoramidimidates.[9]

Table 1. Confined Acid Catalysts in the Prins Cyclization[a]



entry	catalyst	time (days)	conv. (**3a**) (%)	er[b]
1	**4a**	5	7	ND
2	**4b**	5	13	ND
3	**5a**	5	52	91:9
4	**5b**	2.5	83	87:13
5	**6a**	2.5	>99	95.5:4.5
6	**6b**	2.5	>99	94:6

[a]Unless otherwise indicated, all of the reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), catalyst (5 mol %), and 50 mg of 5 Å molecular sieves in 1.0 mL of solvent. [b]Determined by GC analysis.

Applications of such modified acids illustrate the potential of this approach to significantly broaden the scope of transformations susceptible to asymmetric Brønsted acid catalysis.[8−10] We envisioned that a confined imino-imidodiphosphate (*i*IDP) structure such **6** would not only be more acidic than the parent IDP catalyst but also allow individual modulation of the acidic and basic components of the inherently bifunctional catalyst. Furthermore, the additional stereocontrolling nitrogen substituent of the acidic fragment may enable task-specific modification of the catalyst's steric microenvironment (Table 1). Synthetic access to *i*IDP catalysts **6** was readily obtained from triflyl phosphoramidites and phosphorazidates on a multigram scale via Staudinger coupling (see the Supporting Information). Benevolently, catalyst **6a** indeed gave THP **3a** with an increased enantiomeric ratio of 95.5:4.5 at a significantly reduced reaction time (entry 5).

Various linear, α-, and β-branched aliphatic aldehydes were suitable substrates for catalyst **6a** (Table 2, entries 1−8), and

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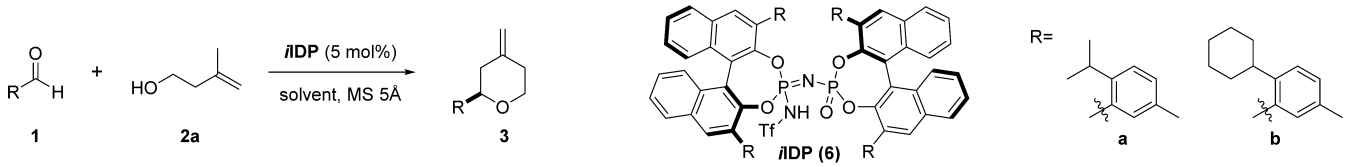
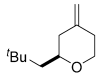
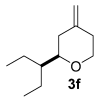
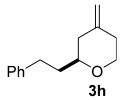
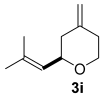
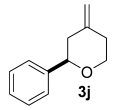
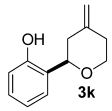
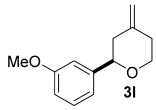
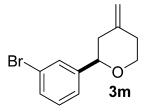
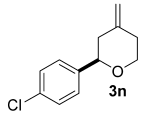
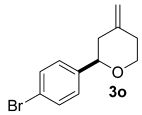
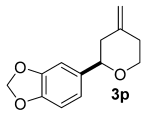
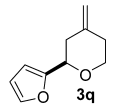
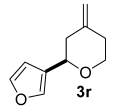
Table 2. Asymmetric Prins Cyclization of Aliphatic and Aromatic Aldehydes[a]



entry	product	T (°C)	time	Yield[b] (%)	er[c]	rr[d]
1	 3a	22	2.5 d	89	95.5:4.5	9:1
2	 3b	10	7 d	60	95:5	10:1
3	 3c	0	7 d	85	95:5	>20:1
4	 3d	22	7 d	60	98:2	>20:1
5	 3e	22	7 d	94	95:5	9:1
6	 3f	22	3 d	85	95:5	13:1
7	 3g	22	3 d	90	98:2	20:1
8	 3h	22	2 d	80	90:10	>20:1
9[e]	 3i	-30	7 d	87	95:5	11:1

entry	product	T (°C)	time	Yield[b] (%)	er[c]	rr[d]
10	 3j	10	2 d	69	96:4	>20:1
11	 3k	0	2 d	80	95.5:4.5	>20:1
12	 3l	0	2 d	65	95:5	12:1
13	 3m	10	5 d	73	95:5	15:1
14	 3n	10	2 d	81	96:4	>20:1
15[f]	 3o	10	2 d	86	96.5:3.5	>20:1
16	 3p	0	2 d	68	94:6	16:1
17	 3q	10	2 d	73	95:5	13:1
18	 3r	0	5 d	82	95:5	14:1

[a]Unless otherwise indicated, all of the reactions were carried out with **1** (0.12 mmol), **2a** (0.1 mmol), *i*IDP catalyst **6** (5 mol %), and 50 mg of 5 Å molecular sieves in 1.0 mL of solvent (0.1 M); cyclohexane was used as the solvent when $T \geq 10$ °C, whereas methylcyclohexane was used as the solvent when $T < 10$ °C; catalyst **6a** was used to give products **3a**–**h**, and catalyst **6b** was used to give **3i**–**r**. [b]Isolated yields of **3h** and **3j**–**3r** are given; yields of the volatile products **3a**–**g** and **3i** were determined by ^{1}H NMR analysis of the reaction mixtures using an internal standard. [c]Determined by GC analysis. For the er of minor isomers, see the Supporting Information. [d]The regiomeric ratio (rr) between exo- and endocyclic alkenes was determined by GC analysis. [e]10 mol % catalyst was used. [f]Absolute configuration of **3o** (see the Supporting Information).

excellent enantioselectivities and good yields were generally obtained under our optimized standard reaction conditions. Volatile alkenes **3** were obtained in good to excellent regiomeric ratios (rr; ratio of exo- to endocyclic isomers) of up to >20:1. 2-Phenylacetaldehyde (**1h**) was converted with reasonable enantioselectivivity (90:10 er) (entry 8). Contrarily, α,β-unsaturated aldehyde **1i** required higher catalyst loadings of *i*IDP **6b** and prolonged reaction times to realize high yield and enantioselectivity (entry 9). Aromatic aldehydes, such as benzaldehyde, were also selectively converted to the corresponding THPs, such as **3j**. Volatile ether **3j** was isolated in 69% yield with an excellent enantiomeric ratio of 96:4 (entry 10). Systematic substitution on the benzaldehyde core at the ortho, meta, and para positions with electron-donating and electron-withdrawing groups was tolerated by catalyst **6b** under the optimized reaction conditions. For instance, THPs **3k**–**p** were obtained in good yields (65–86%), high to excellent enantiomeric ratios (up to 96.5:3.5 er), and high to excellent regioselectivities (up to >20:1) (entries 11–16). Furthermore, heterocyclic aromatic aldehydes **1q** and **1r** successfully

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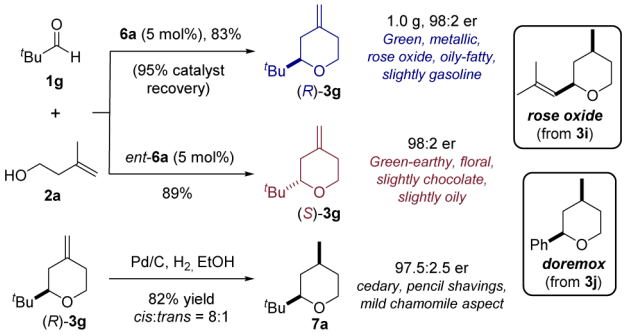
furnished the desired Prins cyclization products **3q** and **3r** (entries 17 and 18).[11]

With a robust and general methodology at hand, we investigated the potential utility of readily accessible THPs **3** (Scheme 1). As a result of the high substrate tolerance, a variety

Scheme 1. Access to Diverse Scents, Gram-Scale Experiment, Synthesis of Both Enantiomers, and Derivatization



of known and potentially novel fragrances could now be efficiently prepared. Indeed, the perfume ingredients rose oxide and doremox can be obtained via hydrogenation of Prins products **3i** and **3j**.[12] THP (*R*)-**3g** was synthesized on a gram scale, and catalyst **6a** was recovered in 95% yield. For cyclic ether **3g**, different scents of the corresponding enantiomers were revealed. (*S*)-**3g** can be recognized by its floral and slightly chocolate bouquet. Furthermore, (*S*)-**3g** smells 1 order of magnitude more intense than its corresponding (*R*)-enantiomer (see the Supporting Information). Hydrogenation of product **3g** to saturated derivative **7a** led to yet another smell, illustrating the fast and straightforward access to diverse scents using our methodology.

In summary, we have introduced a new class of confined highly acidic imino-imidodiphosphates (*i*IDPs), which enabled a highly general asymmetric Prins cyclization of aliphatic and aromatic aldehydes. Our methodology provides an efficient and scalable enantioselective strategy to synthesize diverse THPs, such as well-established and potentially new fragrances. Further applications of our new catalyst motif and variations will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07240.

Additional detailed synthetic protocols and analytical data for all compounds (PDF)
Crystallographic data for **3o** (CIF)

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Author Contributions

†L.L. and P.S.J.K. contributed equally.

Notes

The authors declare no competing financial interest.

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