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Catalytic Asymmetric Vinylogous Prins Cyclization: A Highly Diastereo- and Enantioselective Entry to Tetrahydrofurans

Youwei Xie, Gui-Juan Cheng, Sunggi Lee, Philip S. J. Kaib, Walter Thiel, and Benjamin List*

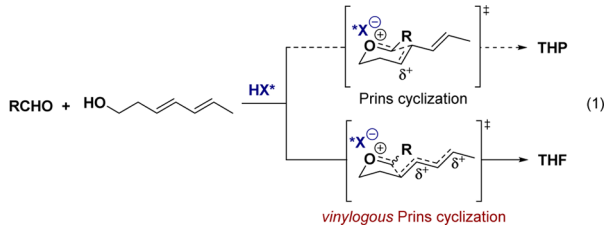
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

Supporting Information

ABSTRACT: We describe the design and development of the first catalytic asymmetric vinylogous Prins cyclization. This reaction constitutes an efficient approach for highly diastereo- and enantioselective synthesis of tetrahydrofurans (THFs) and is catalyzed by a confined chiral imidodiphosphoric acid (IDP). Aromatic and heteroaromatic aldehydes react with various 3,5-dien-1-ols to afford 2,3-disubstituted THFs in excellent selectivity (d.r. > 20:1, e.r. up to 99:1). Aliphatic aldehydes react with similarly excellent results when a highly acidic imidodiphosphorimidate (IDPi) catalyst is used. With a racemic dienyl alcohol, the reaction proceeds via a kinetic resolution. DFT calculations suggest an explanation for unusually high stereoselectivity.

Initially reported by Hanschke in 1955,[1] the Prins cyclization has evolved into an important approach to biologically relevant tetrahydropyrans (THPs).[2−6] Catalytic asymmetric variants of this transformation have emerged only recently,[7] including an organocatalytic approach by our group.[7a,b] Despite the maturity of the Prins cyclization, it almost invariably leads to THPs rather than to the equally important and biologically active tetrahydrofurans (THFs).[8] We show that by using a confined chiral imidodiphosphoric acid catalyst a previously unknown vinylogous Prins cyclization can be realized that leads to THFs in excellent regio-, diastereo-, and enantioselectivity.

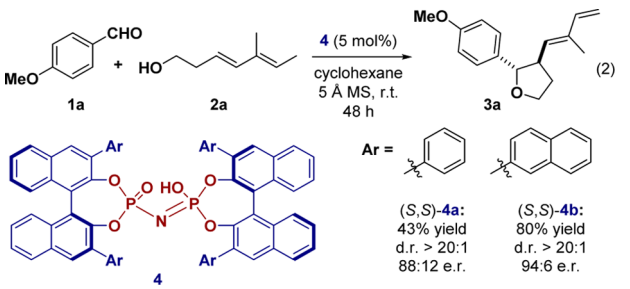
In the Prins cyclization, acid-catalyzed condensation of an aldehyde with a homoallylic alcohol leads to the formation of an oxocarbenium ion, undergoing a 6-endo-trig cyclization to deliver THP product selectively.[2−5] We hypothesized that with a dienyl homoallylic alcohol a vinylogous Prins cyclization to the corresponding THF product via 5-endo-trig pathway should be preferred as it would proceed via an allylic cation:



(1)

A challenge in developing such a THF synthesis is to achieve high stereoselectivity: Unlike 6-membered cyclic TS of the normal Prins cyclization, adopting a well-defined chair conformation to deliver THP products with high diastereoselectivity,[3e] 5-membered TS of THF formation can exist in two diastereomeric forms of similar energy.[8a,9] We speculated that the confined chiral pocket provided by our recently developed imidodiphosphates could further enhance the energetic difference of the two diastereomeric TSs and lead to highly enantioenriched THF products.[10]

We started by reacting anisaldehyde (**1a**) with dienyl alcohol **2a** in the presence of various chiral Brønsted acids (eq 2), including phosphoric acids,[11] disulfonimides,[12] and imidodiphosphates:[10]



Most imidodiphosphoric acids tested showed significantly improved diastereoselectivity (>20:1) compared to those of achiral Brønsted acids (4−5:1) and to chiral phosphoric acids and disulfonimides (3−6:1), although yields and enantioselectivity varied dramatically (a full list of catalysts and reaction conditions investigated is in Table S3). Extensive experimentation with chiral Brønsted acids revealed two lead catalysts, (*S*,*S*)-**4a** and (*S*,*S*)-**4b**, which both catalyze the reaction in toluene with promising enantioselectivity (e.r. 85:15). Further optimization of the reaction conditions with these two catalysts showed that when used at room temperature in cyclohexane in the presence of 5 Å molecular sieves as dehydrant, catalyst (*S*,*S*)-**4b** catalyzed the reaction with good diastereo- and enantioselectivity; corresponding 2,3-*trans* THF product **3a** was obtained as sole product in 80% isolated yield with e.r. of 94:6.

These reaction conditions were then used to explore the scope of the catalytic asymmetric vinylogous Prins cyclization (Table 1). Various commercially available aldehydes bearing different substituents were submitted to the reaction conditions using **4b**. Electron-rich (**1a**), -neutral (**1b**), and -deficient (**1c**) aldehydes were all suitable substrates; corresponding THF products were obtained in good yields and excellent diastereo- and enantioselectivity. Other common substituents, e.g., alkynyl (**3d**), vinyl (**3e**), and alkyl (**3f**), were also tolerated. Disubstituted **3g** was also obtained in good yield and excellent selectivity. Tested heteroaromatic aldehydes showed even better reactivity

Received: August 31, 2016

DOI: 10.1021/jacs.6b09129
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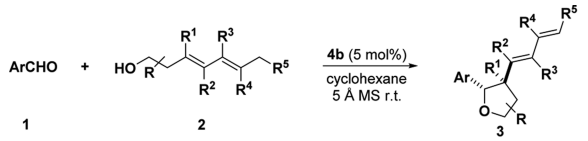
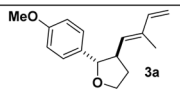
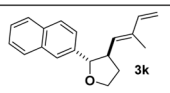
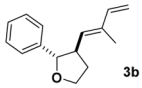
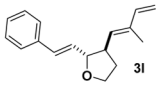
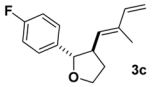
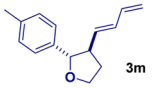
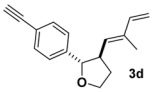
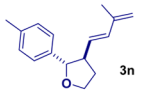
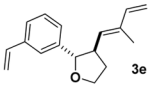
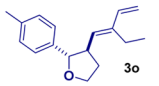
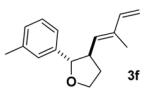
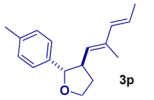
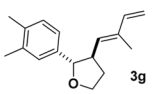
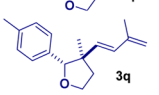
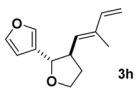
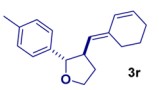
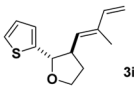
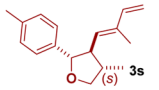
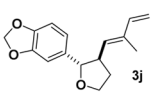
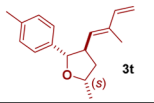
Table 1. Scope of the Asymmetric Vinylogous Prins Cyclization[a]



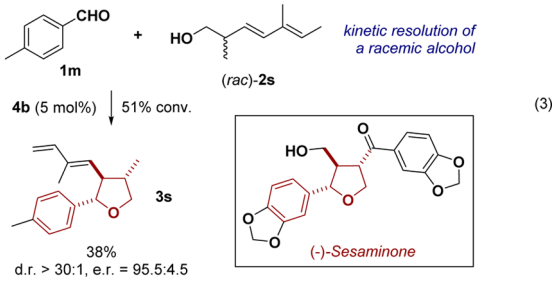
(d.r. >20:1 for all products shown)

Entry	Product	Time	Yield(%)[b]	e.r.	Entry	Product	Time	Yield(%)[b]	e.r.
1		2 d	80	94:6	11		2 d	73	97.5:2.5
2		4 d	78	97:3	12		2 d	77	95:5
3		3 d	80	98:2	13		3 d	71	95:5
4		6 d	84	96:4	14		3 d	82	96:4
5		7 d	80	98:2	15		6 d	75	96.5:3.5
6		5 d	75	97:3	16		4 d	74	97:3
7		3 d	81	96:4	17		36 h	82	92:8
8		2 d	70	99:1	18		2 d	92	97:3
9		2 d	80	97:3	19[c]		3 d	74	>99:1
10		2 d	81	96:4	20[c]		3 d	60	>99:1

[a]Reaction conditions: r.t. in cyclohexane (0.1 M), **4b** (5 mol %), 1.05 equiv of **1**, 1.0 equiv of **2**, and 5 Å molecular sieves (0.3 g mmol^{-1}) for the specified period of time. [b]Isolated yields are reported. [c]Only one disastereomer was obtained. Starting dienyl alcohol was enantiomerically pure; absolute configuration of the stereogenic center is indicated in corresponding product. No THP formation was detected. For more examples, see the SI.

compared to that of common aromatic aldehydes and gave corresponding products **3h** and **3i** with slightly improved e.r. Piperonal (**1j**) and 2-naphthaldehyde (**1k**) were also viable substrates. Aliphatic α,β-unsaturated aldehydes could not be used in this transformation due to an oxa-Michael side reation, but cinnamaldehyde reacted smoothly to give **3l** in good yield and selectivity. The absolute configuration of **3b** was determined by derivatization to a known compound; those of the others were assigned by analogy (Supporting Information (SI))

We also explored some dienyl alcohols with varied substitution patterns (Table 1, entries 13−18). Alkyl substituents at different positions of diene moieties were all well-tolerated (**3m**−**3r**). Of note is **3q**, in which a quaternary center has been formed with excellent diastereoselectivity but slightly diminished enantioselectivity. The double bond of the diene can also be part of a ring to deliver corresponding product **3r** in excellent yield and selectivity. 2,3,4- or 2,3,5-Trisubstituted THFs can be accessed when enantiomerically enriched chiral dienyl alcohols are used (Table 1, entries 19 and 20). A "match"/"mismatch" effect was observed for these substrates depending on the absolute configuration of the chiral dienyl alcohol. In the match case, **3s** and **3t** were formed in excellent diastereoselectivity; in the mismatch case, the reaction was much slower and an inseparable mixture of diastereomers was obtained (SI). This observation encouraged us to explore the possibility of a kinetic resolution:



(3)

Indeed, (*rac*)-**2s** reacted selectively with **1m** to give **3s** in excellent selectivity in the presence of **4b**. This methodology bears some promise for the syntheses of biologically active

DOI: 10.1021/jacs.6b09129
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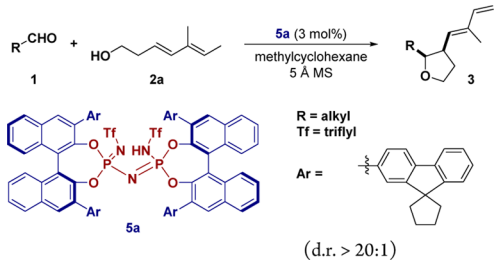
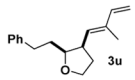
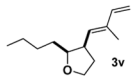
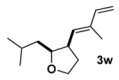
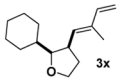
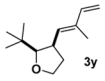
natural products and therapeutic agents that contain highly substituted THFs. For example, the stereochemical arrangement around the THF ring in **3s** matches that of the lignan natural products Sesaminone and Tanegool.[15,16]

Simple aliphatic aldehydes could not be used in this transformation when **4b** was used due to exclusive formation of acetals, which do not react further, even at elevated temperature. To solve this problem, catalysts with enhanced acidity were evaluated, including nitrated imidodiphosphates (*n*IDP),[13] iminoimidodiphosphates (*i*IDP),[7b] and imidodiphosphorimidates (IDPi).[14] To our delight, by using extremely reactive IDPi catalysts recently introduced by our group, aliphatic aldehydes became viable substrates. With optimized **5a**, linear (**1u**−**1v**), *β*-branched (**1w**), and *α*-branched (**1x**−**1y**) aldehydes all reacted smoothly to give corresponding *cis*-products in good yields and good to excellent diastereo- and enantioselectivity (Table 2; see the SI for catalyst and reaction condition optimization).

Table 2. Vinylogous Prins Cyclization of Aliphatic Aldehydes



(d.r. > 20:1)

Entry	Product	Time	Yield(%)	e.r.
1[a]		2 d	82[c]	94.5:5.5
2[a]		2 d	86[d]	96:4
3[a]		3 d	79[d,e]	96.5:3.5
4[b]		1 d	88[c]	97.5:2.5
5[b]		1 d	85[d]	98:2

[a]Reactions were performed at −20 °C in methylcyclohexane (0.1 M) with catalyst **5a** (3 mol %), 1.05 equiv of **1**, 1.0 equiv of **2**, and 5 Å molecular sieves (0.3 g mmol^{-1}) for the specified period of time. [b]Reaction was performed at 0 °C. [c]Isolated yield. [d]NMR yield with an internal standard. No tetrahydropyran formation was detected. [e]d.r. = 10:1.

DFT calculations were performed to elucidate the origin of diastereoselectivity of chiral imidodiphosphoric acid catalyzed Prins cyclization reaction.[17,18] The calculated potential energy profile (Figure S1) suggests that C−C bond formation is the stereoselectivity-determining step. TS_{trans} is more stable than TS_{cis} by 4.0 kcal/mol when using (*S*,*S*)-**4a** as catalyst, in agreement with high diastereoselectivity observed experimentally. Figure 1 shows 3D structures of the most stable conformations of TS_{trans} and TS_{cis}, respectively. Several non-

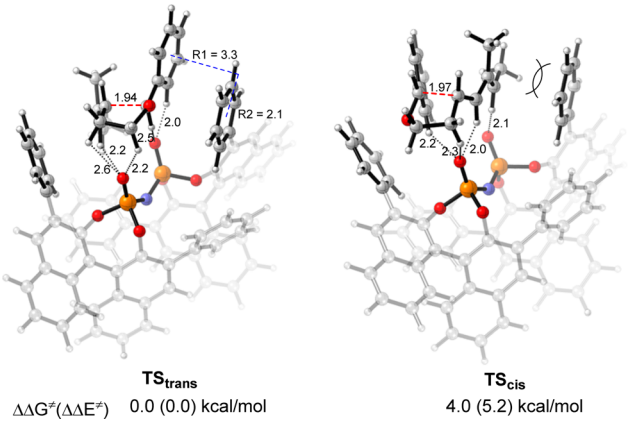


Figure 1. 3D structures and relative activation free energies (relative activation energies) of TS_{trans} and TS_{cis} for the reaction catalyzed by chiral confined acid (*S*, *S*)-**4a**. Distances are given in Å.

classical C−H···O H-bonds between substrate and catalyst direct the substrate into the confined pocket of (*S*,*S*)-**4a**.[8k,19] The C−H···O H-bond between the C−H bond of the oxocarbenium moiety and catalyst which stabilizes TS_{trans} does not exist in TS_{cis} because that C−H bond is oriented away from catalyst due to the bulky methyl group of the substrate. Further stabilization of TS_{trans} originates from *π*−*π* stacking interactions between the phenyl group of the substrate and the phenyl ring of the catalyst which are well-oriented to achieve a parallel-displaced geometry at a distance of 3.3 Å and with a displacement of 2.1 Å.[8k,20] The interaction energy between substrate and catalyst decreases by 5.0 kcal/mol when replacing the phenyl ring of the catalyst by H, suggesting *π*−*π* stacking interaction (Table S1). In TS_{cis}, the two phenyl groups are not parallel to each other; the terminal methyl group of substrate suffers steric repulsion with catalyst. Therefore, C−H···O H-bonding, *π*−*π* stacking, and steric interactions between substrate and imidodiphosphoric acid assist in the discrimination of the two TSs, leading to very high diastereoselectivity.

We have developed an organocatalytic asymmetric vinylogous Prins cyclization for the synthesis of 2,3-disubstituted THFs. Various aldehydes and dienyl alcohols react to give products with excellent diastereo- and enantioselectivities. 2,3,4- and 2,3,5-Trisubstituted THFs are also available from chiral dienyl alcohols. We have also introduced confined **4b** and **5a** as powerful catalysts. These catalysts not only control reactivity and enantioselectivity but also help enlarge the energetic difference between two diastereomeric TSs in THF formation, leading to very high diastereoselectivity. Further exploration of this methodology, particularly toward applying it in the total synthesis of biologically and pharmaceutically relevant molecules, is currently in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09129.

Screening data; synthetic procedures; spectra and HPLC traces; computational methods and results (PDF)

DOI: 10.1021/jacs.6b09129
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Author

*list@kofo.mpg.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT") is gratefully acknowledged. Y.X. thanks the Alexander von Humboldt Foundation for a postdoctoral fellowship. We also thank our technicians and the members of our NMR, MS, GC, and HPLC departments for their excellent service.

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DOI: 10.1021/jacs.6b09129
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX