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Confined Acid-Catalyzed Asymmetric Carbonyl−Ene Cyclization

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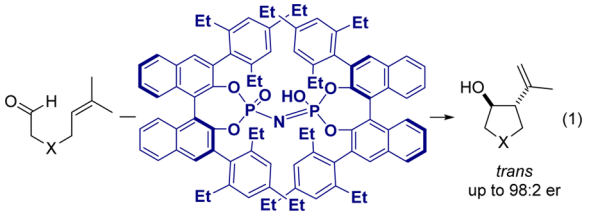
Supporting Information

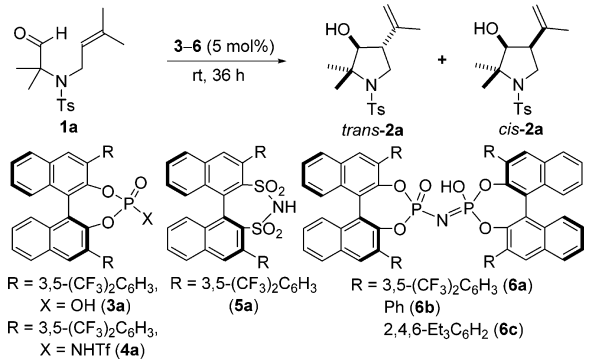
ABSTRACT: A highly enantioselective Brønsted acid catalyzed intramolecular carbonyl−ene reaction of olefinic aldehydes has been developed. Using a confined imidodiphosphate catalyst, the reaction delivers diverse *trans*-3,4-disubstituted carbo- and heterocyclic five-membered rings in high yields and with good to excellent diastereo- and enantioselectivities. ESI-MS, NMR, and DFT mechanistic studies reveal that the reaction proceeds via a stepwise pathway involving a novel covalent intermediate.

The carbonyl−ene reaction is arguably the most direct and atom economic carbon−carbon bond forming approach to homoallylic alcohols.[1] While intermolecular versions are challenging, and for example, the allylation of aldehydes with propene is still unknown, intramolecular carbonyl−ene cyclizations are frequently used, including in natural product synthesis and in an industrial route to menthol.[2] Catalytic enantioselective carbonyl−ene reactions are relatively rare, and intermolecular versions are limited to activated substrates.[3] Recently, Jacobsen et al. reported a general, enantioselective, and *cis*-diastereoselective carbonyl−ene cyclization that is catalyzed by a chiral dimeric chromium complex.[2d] We now show that a confined imidodiphosphate catalyst, which has previously found utility in asymmetric acetalizations and sulfoxidations,[4] catalyzes the carbonyl−ene cyclization with high enantioselectivity and *trans*-diastereoselectivity (eq 1). Mechanistic studies reveal the formation of an unusual covalent intermediate.



We initially investigated the acid catalyzed cyclization of olefinic aldehyde **1a**. On the basis of their proven efficacy in handling simple aliphatic aldehydes,[4b,c] we were particularly hopeful that our recently introduced confined chiral C_2-symmetric imidodiphosphates[5] could transform this substrate with good stereoselectivity and activity. Indeed, in contrast to the previously developed phosphoric acid **3a**,[6] *N*-triflylphosphoramide **4a**,[6b−d,7] and disulfonimide **5a**,[8] which all proved to be active though with only poor enantioselectivity, imidodiphosphate **6a** converted aldehyde **1a** to homoallylic alcohol **2a** efficiently and with improved stereoselectivity (Table 1, entries 1−4). Interestingly, while the phenyl-substituted variant **6b** proved to be only moderately active and stereoselective, confined catalyst **6c** was much more active and gave excellent enantioselectivity (Table 1, entries 5−6).

Table 1. Catalyst Screening[a]



entry	catalyst	solvent	conv (%)	*trans*/*cis*[b]	er$_{trans}$[b]
1	**3a**	CH_2Cl_2	>95	16:1	58:42
2	**4a**	CH_2Cl_2	>95	12:1	64:36
3	**5a**	CH_2Cl_2	>95	24:1	58.5:41.5
4	**6a**	CH_2Cl_2	>95	18:1	75.5:24.5
5	**6b**	CH_2Cl_2	56	19:1	53.5:46.5
6	**6c**	CH_2Cl_2	>95	43:1	97.5:2.5
7	**6c**	c-C_6H_{12}	>95	50:1	97.5:2.5

[a]Unless otherwise indicated, all reactions were carried out with **1a** (0.1 mmol) and catalyst (5 mol %) in 1.0 mL of solvent at room temperature for 36 h. Ts = *p*-toluenesulfonyl. [b]Determined by HPLC analysis on chiral stationary phase.

With optimized reaction conditions in hand, the scope of the reaction was next explored (Table 2). Different α,α-disubstituted α-amino olefinic aldehydes afforded functionalized pyrrolidines in generally high yields with excellent diastereoselectivities and good to excellent enantioselectivities (entries 1−4); only product **2d** was obtained with a more moderate diastereomeric ratio. Cyclic olefins were also successfully used (entries 5−6). The reaction of substrate **1f** proceeded smoothly to alcohol **2f** with >20:1 dr and 95.5:4.5 er, while the enantiomeric ratio (92:8 er) of **2e** was slightly lower. Alkenyl aldehydes without Thorpe−Ingold-type substitution[9] have previously been entirely unknown in asymmetric intramolecular carbonyl−ene reactions. To our delight, products **2g** and **2h** could both be obtained with good diastereoselectivities, excellent enantioselectivities, and in good yields by using slightly higher catalyst loadings and reaction

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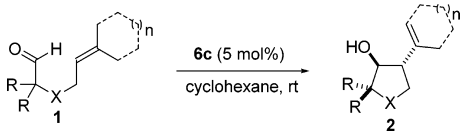
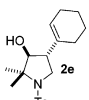
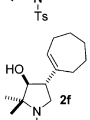
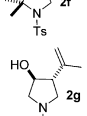
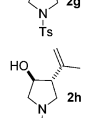
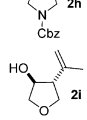
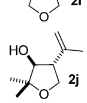
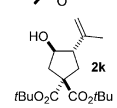
Table 2. Scope of the Asymmetric Carbonyl–Ene Cyclization[a]



entry	product	time	yield(%)	*trans*:*cis*[b]	er *trans*[c]
1	 **2a**	36 h	97	>20:1	97.5:2.5
2	 **2b**	4 d	81	>20:1	97:3
3	 **2c**	36 h	83	>20:1	95.5:4.5
4[d]	 **2d**	5 d	77	4:1	95:5
5	 **2e**	48 h	80	>20:1	92:8
6	 **2f**	48 h	96	>20:1	95.5:4.5
7[e,f]	 **2g**	5 d	85	10:1	98:2
8[e,f]	 **2h**	11 d	73	8:1	98:2
9[h]	 **2i**	4 d[g] 4 d[i]	78 60	>20:1 >20:1	97:3 97.5:2.5
10	 **2j**	4 d	90	>20:1	98:2
11[e,f]	 **2k**	5 d	81	>20:1	98:2

[a]Substrate **1** (0.1 mmol), catalyst **6c** (5 mol %) in cyclohexane (1 mL) at rt. Ts = *p*-toluenesulfonyl, Cbz = carboxybenzyl, *t*Bu = *tert*-butyl. [b]Determined by ^{1}H NMR. [c]Determined by HPLC or GC analysis. [d]Reaction at 10 °C. [e]**6c** (7.5 mol %). [f]Reaction at rt, then at 50 °C. [g]Neat conditions. [h]NMR yield using an internal standard. [i]**6c** (10 mol %).

temperatures, and by extending the reaction time (Table 2, entries 7–8). Moreover, 3,4-disubstituted tetrahydrofurans could be obtained in moderate to good yields and high enantiopurity (entries 9–10). It is noteworthy that the reaction rate of the conversion of non-Thorpe–Ingold-substrate **1i** increases under neat conditions. A carbocyclic five-membered ring was also obtained smoothly when using substrate **1k** (Table 2, entry 11). The absolute configuration of **2a** was determined to be 3*S*,4*R* by single-crystal X-ray analysis. It is worth mentioning that its *cis*-3*R*,4*R* diastereomer can be obtained using Jacobsen's complementary Cr-dimer catalyst.[2d]

To elucidate the mechanism of our reaction, we studied the cyclization of olefinic aldehyde **1a** with catalysts **6b** or **6c** as model reactions. Initially, we used Electrospray Ionization Mass Spectrometry (ESI-MS) (see Supporting Information (SI)), and selected spectra and HRMS data are shown in Figure 1a and 1b.

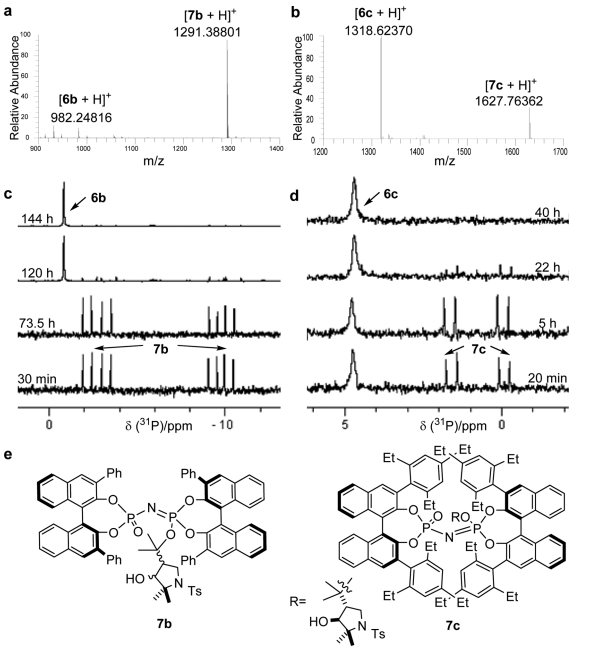


Figure 1. ESI-MS study of the reaction of **1a**: (a) using catalyst **6b**; (b) using catalyst **6c**. ^{31}P NMR spectra of reaction mixtures taken at different times: (c) using catalyst **6b**; (d) using catalyst **6c**; (e) covalent catalyst–substrate intermediates.

Remarkably, new peaks at *m*/*z* 1291 and 1627, matching the masses of catalyst–substrate adducts, appeared within minutes. Careful NMR studies revealed the formation of covalent adducts **7** as possible intermediates (for details, see SI). Selected ^{31}P NMR spectra are shown in Figure 1c and 1d. In accordance with the ESI-MS studies, compounds **7** are rapidly formed as soon as substrate **1a** and catalysts **6** are dissolved in CD_2Cl_2. Interestingly, when **6b** was used as the catalyst, eight peaks were detected in the ^{31}P NMR spectrum of **7b** (Figure 1c). These peaks reflect two different diastereomeric intermediates containing two chemically inequivalent phosphorus atoms that are coupling with each other, in line with the observed poor enantioselectivity and high *trans*-diastereoselectivity of **2a** (53.5:46.5 er and >20:1 dr). Moreover, during the entire reaction, free catalyst **6b** remained below the detection limit in both the ^{1}H and ^{31}P NMR spectra of the reaction mixture (see SI). These results suggest that the reaction indeed proceeds via covalent intermediate **7b** and that the release of catalyst **6b** from adduct **7b** could be the rate-determining step. Similarly, **7c** could be observed in the ^{31}P NMR spectrum when catalyst **6c** was used (10 mol %) (Figure 1d). The observed AB spin system of two chemically inequivalent ^{31}P nuclei of one single diastereomer is consistent with the high enantioselectivity and *trans*-diastereoselectivity observed with this catalyst (97.5:2.5 er and >20:1 dr). We suspected that, like adduct **7b**, compound **7c** also acts as an intermediate and that the elimination of catalyst **6c** from intermediate **7c** is the rate-determining step, even though free catalyst **6c** is observed throughout the reaction (Figure 1d). Accordingly, the use of a sufficiently small loading of **6c** should

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fully convert **6c** into adduct **7c** at the beginning of the cyclization of **1a**, such that the concentration of the intermediate **7c** would remain unchanged subsequently (quasi-steady-state kinetics).[10]

Consequently, we carried out another NMR kinetic study of the reaction of **1a** using only 1 mol % of catalyst **6c** at 294.2 K (Figure 2). Indeed, according to the ^{1}H and ^{31}P NMR spectra of

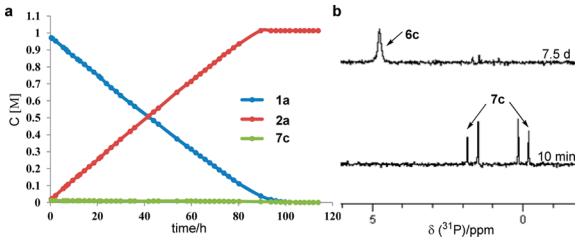

Figure 2. (a) ^{1}H NMR kinetics of the conversion of **1a** to **2a**; (b) ^{31}P NMR spectra of reaction mixtures taken at different times.

the reaction mixture, catalyst **6c** remained below the detection limit at the beginning of the reaction, while the concentration of compound **7c** stayed essentially constant. The continual transformation of compound **7c** accomplished the regeneration of catalyst **6c** and afforded product **2a** with a rate constant k = 3.01×10^{-4} s^{-1} (see Figure 2 and SI). An excellent 97:3 er and 30:1 dr of product **2a** were observed when **1a** was fully consumed. These results clearly demonstrate the unique role of compound **7c** acting as a reaction intermediate. Apparently, the elimination of **6c** from **7c** is the rate-determining step of the cyclization of **1a**. The activation enthalpy $\Delta H^{\ddagger}$ (18.47 ± 0.73 kcal/mol at 298.15 K) and activation free energy $\Delta G^{\ddagger}$ (22.08 ± 1.46 kcal/mol at 298.15 K) of the elimination step were determined by measuring the rate constant as a function of temperature on the basis of the Eyring equation (see SI).[11]

For a more detailed mechanistic understanding, density functional theory (DFT) was employed to study the carbonyl−ene cyclization, using substrate **1a** and catalyst **6c** as models. Geometry optimizations and intrinsic reaction coordinate (IRC) calculations were performed at the TPSS-D3/def2-SVP level, and single-point calculations at the gas-phase optimized geometries were carried out at the B3LYP-D3/def2-TZVP level with inclusion of continuum solvation (see SI for details). The calculated free energy (enthalpy) profile and the corresponding IRC path are presented in Figure 3. Initially, catalyst **6c** forms a hydrogen bond with the aldehyde group in **1a** (complex **Com**). Proton transfer through transition state **TS1** triggers ring formation in **1a** (new C1−C2 bond, with subsequent formation of the exocyclic O2−C3 bond) and yields the intermediate **7c**. The O2−C3 bond in **7c** (1.52 Å) is longer than usual and thus expected to be weak. In the computed catalytic cycle, the next step via **TS2** involves O2−C3 bond breaking and H-transfer from the C4−H2 bond of an exocyclic methyl group (originating from the substrate) to the O3 atom of the catalyst, accompanied by a H-bond rearrangement. In **TS2**, the migrating hydrogen atom in the C4···H2···O3 is halfway in between C4 and O3, while the C3−O2 bond is already dissociated (2.69 Å), and the substrate hydroxyl group is engaged in a strong O1−H1···O2 hydrogen bond (1.68 Å) with the O2 atom of the catalyst. The buildup of negative charge in the catalyst moiety (charges: −0.41e in **7c** and −0.67e in **TS2**; see SI) favors the dissociation of the C4−H2 bond and the H2 transfer to the catalyst. From the resulting product complex **8**, the catalytic cycle is completed by an endothermic elimination which

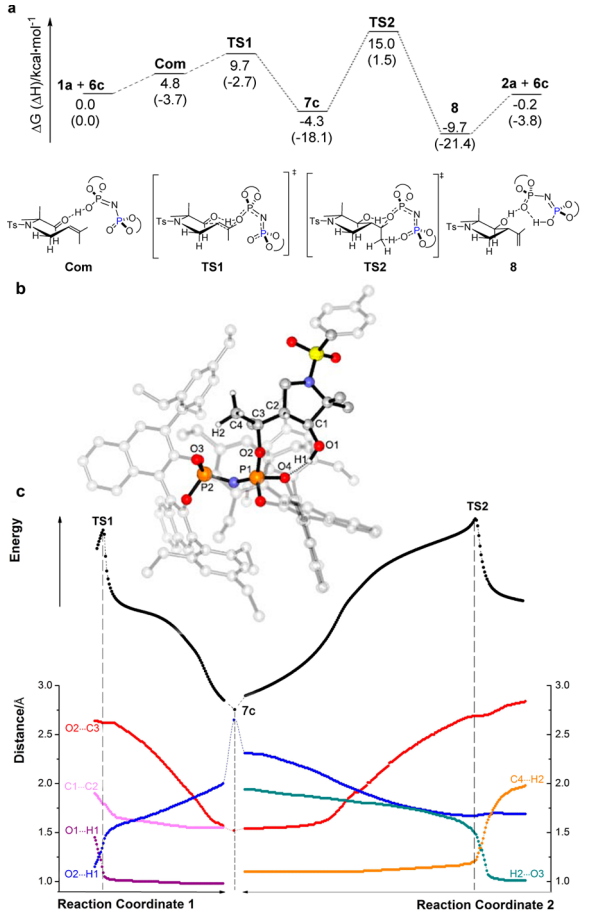

Figure 3. (a) Computed free energy (enthalpy) profile for the carbonyl−ene cyclization of **1a** and **6c** in CH_2Cl_2 solution. (b) Optimized structure of intermediate **7c** with the relevant atom labels. (c) Energy and selected distances along the IRC paths.

liberates cyclic product **2a** and regenerates catalyst **6c**. The computed IRC path in Figure 3c indicates that both reaction steps are concerted but highly asynchronous, presumably because of the conflicting geometric requirements of the competing bonding interactions along the reaction pathway (see SI).

According to the calculated energy profile (Figure 3a) the second step is rate-limiting. This is consistent with our NMR kinetic findings. The computed barriers $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ for the second step are 19.6 and 19.3 kcal/mol, respectively. Both are reasonably close to the experimentally derived values of 18.47 and 22.08 kcal/mol (see above). Our experimental and theoretical findings thus lead us to conclude that the confined imidodiphosphate-catalyzed asymmetric carbonyl−ene cyclization proceeds through a stepwise mechanism via a novel covalent intermediate.

In summary, we report the first organocatalytic asymmetric intramolecular carbonyl−ene reaction of olefinic aldehydes. Diverse *trans*-configured pyrrolidines, tetrahydrofurans, and cyclopentanes are accessible in good yields, with good to excellent diastereo- and enantioselectivities. ESI-MS, NMR, and DFT studies reveal that the reaction proceeds through a stepwise mechanism via a novel covalent intermediate. Further exploration of the application and extension of this methodology are currently in progress in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09484.

Computational methods and detailed computational results (PDF)

Crystallographic data for **2a** (CIF)

Additional screening tables; detailed synthetic procedures; spectra and HPLC traces for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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