

## Organocatalysis

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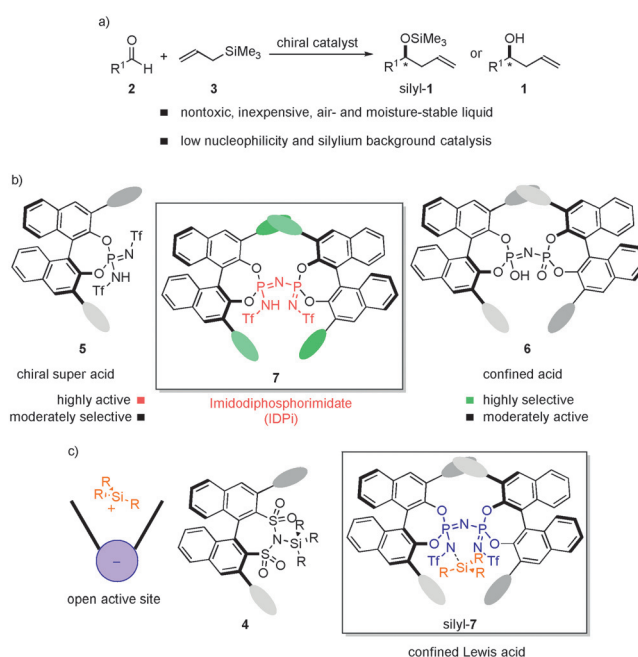
## Extremely Active Organocatalysts Enable a Highly Enantioselective Addition of Allyltrimethylsilane to Aldehydes

Philip S. J. Kaib, Lucas Schreyer, Sunggi Lee, Roberta Properzi, and Benjamin List\*

**Abstract:** The enantioselective allylation of aldehydes to form homoallylic alcohols is one of the most frequently used carbon–carbon bond-forming reaction in chemical synthesis and, for several decades, has been a testing ground for new asymmetric methodology. However, a general and highly enantioselective catalytic addition of the inexpensive, nontoxic, air- and moisture-stable allyltrimethylsilane to aldehydes, the Hosomi–Sakurai<sup>[1]</sup> reaction, has remained elusive.<sup>[2,3]</sup> Reported herein is the design and synthesis of a highly acidic imidodiphosphorimidate motif (IDPi), which enables this transformation, thus converting various aldehydes with aromatic and aliphatic groups at catalyst loadings ranging from 0.05 to 2.0 mol% with excellent enantioselectivities. Our rationally constructed catalysts feature a highly tunable active site, and selectively process small substrates, thus promising utility in various other challenging chemical reactions.

Enantiomerically pure homoallylic alcohols **1** are common synthetic intermediates, and are typically generated by allylmetal–aldehyde addition reactions.<sup>[3]</sup> In 1978, the first enantioselective allylation of aldehydes **2** was reported by Hoffmann et al., employing a camphor-derived allylboronic ester as the nucleophile.<sup>[4]</sup> A few years later, Brown et al. introduced *B*-allyldiisopinocampheylborane, which has been the most popular chiral allylating agent until today.<sup>[5]</sup> Such chiral reagents<sup>[6–8]</sup> have proven to be of considerable synthetic value, although the intrinsic need for wasteful stoichiometric, and usually non-recoverable amounts of enantiopure auxiliaries affect atom economy, cost, environmental impact, and the overall synthetic appeal of the methodology.<sup>[3]</sup> To this end, several effective catalytic variants with achiral allylboron reagents,<sup>[9,10]</sup> allylstannanes,<sup>[11–13]</sup> allyl halides,<sup>[14,15]</sup> and allyl acetates<sup>[16]</sup> have been developed. Nevertheless, the non-negligible high toxicity of stannanes and chromium complexes<sup>[14,15]</sup> significantly restricted the broad application of some of these methods. Alternatives, such as the multi-component catalyst systems employing iridium complexes,<sup>[16]</sup> require high temperature and a large excess of reagents. Comparatively, allylsilanes are considered nontoxic, air- and moisture-stable, often commercially available, and easily

prepared and handled.<sup>[3,17,18]</sup> Despite significant effort,<sup>[3]</sup> however, a general and broadly applicable allylation of aldehydes with allyltrimethylsilane (**3**) as a highly attractive allyl-transfer reagent has proven to be extremely challenging<sup>[2,3,19]</sup> (Figure 1a).



**Figure 1.** Catalyst design. a) Hosomi–Sakurai<sup>[1]</sup> reaction. b) Design of highly acidic and sterically constrained imidodiphosphorimidate (IDPi) Brønsted acids **7**. c) Design of a confined silylium Lewis acid organocatalyst. Tf = SO<sub>2</sub>CF<sub>3</sub>.

Previously developed variants exploiting cyclic alkoxy boranes (CAB)<sup>[20]</sup> or titanium-based<sup>[2,11,21]</sup> catalysts generate the corresponding homoallylic alcohols with moderate to good yields and enantioselectivities. These methods require exhaustive exclusion of air and moisture and are limited with regard to substrate diversity.<sup>[2,3]</sup> Most importantly, and enhanced by the low nucleophilicity of allyltrimethylsilane,<sup>[22]</sup> catalytic enantioselective Hosomi–Sakurai reactions struggle with highly efficient and competitive non-enantioselective background silylium catalysis.<sup>[23]</sup> This fast process, which is readily initiated by most chiral Lewis acids,<sup>[24]</sup> diminishes enantioselectivity and leads to the requirement of high catalyst loadings.<sup>[23,25]</sup> As a solution to this problem, we have recently expanded our asymmetric counteranion-directed catalysis (ACDC)<sup>[26]</sup> concept to silylium-based Lewis acid organocatalysis. Accordingly, in situ generated

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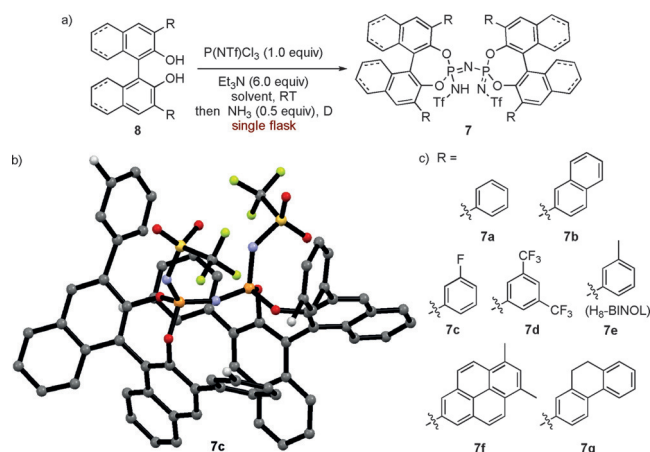
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of charge from The Cambridge Crystallographic Data Centre.

silylium ions, paired with an enantiopure counteranion, function as powerful and highly enantioselective Lewis acid catalysts (Figure 1c, left). This strategy has proven to be successful in a variety of Mukaiyama style silyl-transfer reactions<sup>[19]</sup> and also in non-silyl-transfer reactions, such as the Diels–Alder reaction of cinnamates.<sup>[24]</sup>

Attractive features of silylium-based Lewis acid organocatalysis include the in situ regeneration of the catalyst (“self-healing”) and relatively low catalyst loadings,<sup>[19,24]</sup> thus suggesting a practical synthetic method for the allylation of aldehydes with allyltrimethylsilane. However, because of the low nucleophilicity of this reagent (Mayr nucleophilicity:  $N = 1.6$ ),<sup>[22]</sup> its employment in asymmetric, catalytic addition reactions to aldehydes requires extremely reactive Lewis acids,<sup>[2]</sup> and previously reported catalysts, including our silylated disulfonimides (DSI) **4** and our chiral C–H acids,<sup>[19,24,27–29]</sup> were insufficiently active in this transformation (Figure 1a). In contrast, the recently reported highly acidic BINOL-derived phosphoramidimides **5**<sup>[30]</sup> (Figure 1b) efficiently promoted the Hosomi–Sakurai reaction, however, without relevant enantiodiscrimination. We also investigated our confined Brønsted acids, which have previously been shown to be highly effective in processing small substrates.<sup>[28]</sup> Unfortunately, the imidodiphosphates (IDP) **6**<sup>[28a]</sup> (Figure 1b), even those of increased acidity,<sup>[28b,c]</sup> failed in the catalysis of the Hosomi–Sakurai reaction. We hypothesized that the high acidity of **5** could be ideally combined with the superb selectivity of our IDP catalysts **6** in the newly designed imidodiphosphorimidates (IDPi) **7**. In this context, a highly efficient trimethylsilylium ion Lewis acid, paired with a confined imidodiphosphorimidate anion (silyl-**7**), could even enable the processing of highly challenging small aliphatic substrates at high rates and low catalyst loadings (Figure 1c). Additionally, this design would overcome current substrate limitations present in “open-active-site” catalysts, such as **4**.

To access the novel structural motif of **7** (Figure 1b), the 3,3'-substituted BINOL derivatives **8** (Scheme 1) were initially dimerized with commercially available bis(dichlorophosphino)methylamine [(PCl<sub>2</sub>)<sub>2</sub>NMe], followed by a Staudinger oxidation with triflyl azide (TfN<sub>3</sub>) to generate the N-methylated IDPi core. Subsequent demethylation with tetrabutylammonium iodide [N(*n*Bu)<sub>4</sub>I] afforded the desired catalyst upon acidification. Initial studies with IDPi **7a** quickly revealed the new motif to be highly reactive and enantioselective in the Hosomi–Sakurai reaction.

These early findings prompted us to develop a straightforward, single-flask protocol for catalyst synthesis (Scheme 1a). Here, the crucial element was to access triflylphosphorimidoyl trichloride [P(NTf)<sub>3</sub>Cl<sub>3</sub>] in analytically pure form. All described methods to generate P(NTf)<sub>3</sub>Cl<sub>3</sub> required either explosive and/or toxic chemicals and gave impure material.<sup>[31,32]</sup> We therefore developed a new solid-state Kirsanov reaction<sup>[31]</sup> to afford analytically pure P(NTf)<sub>3</sub>Cl<sub>3</sub> after a single fractional distillation. Remarkably, treating P(NTf)<sub>3</sub>Cl<sub>3</sub> with BINOLs **8** and ammonia directly furnished the desired catalyst **7** (Scheme 1a). Structural crystallographic analyses of the imidodiphosphorimidates **7** reveal a confined active site within a sterically highly demanding chiral environment (Scheme 1b). The P–N–P bond angles for electron-rich,



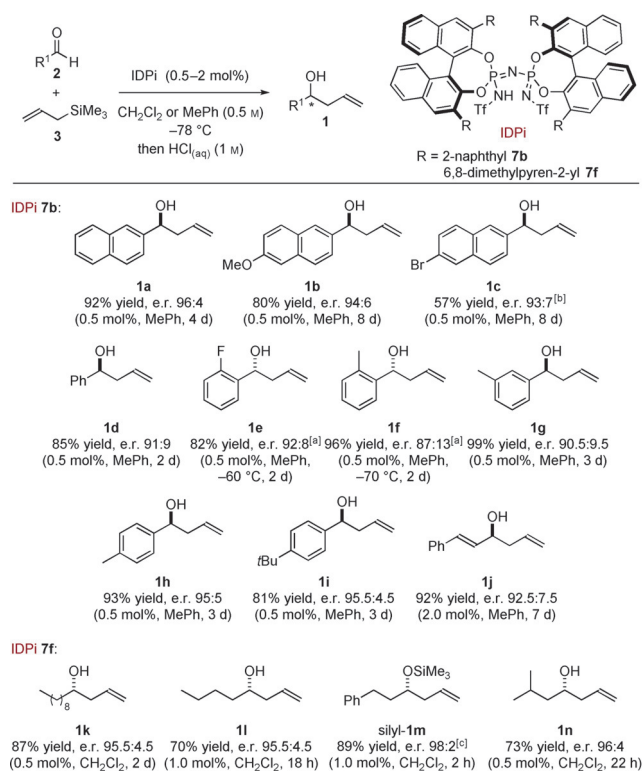
**Scheme 1.** Synthetic access to new chiral Brønsted acid catalysts.

a) Single-flask synthesis of the imidodiphosphorimidates **7**. b) Crystal structure color coding: dark gray carbon, purple nitrogen, red oxygen, green or silver fluorine, yellow sulfur, orange phosphorus. c) Selected examples of the developed catalyst library.

electron-neutral, and electron-deficient IDPis (**7c–e**) predominantly range from 160–163° (Scheme 1b and the Supporting Information). This structural observation suggests the acidic proton to be located on a triflyl-bound nitrogen atom rather than the bridging nitrogen atom, which is also inaccessible to substrates because of the installed 3,3'-substituents on the BINOL backbone.

Our effort in catalyst design was quickly rewarded with a highly enantioselective organocatalytic addition of allyltrimethylsilane to aromatic aldehydes (Scheme 2). IDPi catalysts **7** proved to be general, and diverse homoallylic alcohols were obtained in good yields and high enantioselectivities. Aromatic aldehydes were converted at –78°C with 0.5 mol % of IDPi **7b** bearing 2-naphthyl substituents in the 3,3'-positions of the BINOL backbones. The aromatic alcohols **1a–d** and **1g–j** were obtained in good yields and enantioselectivities. Systematic substitution on the benzaldehyde core revealed high tolerance toward *meta* and *para* substitution on the electrophile, as well as negligible electronic effects on naphthaldehyde derivatives. In contrast, *ortho* substitution, with concomitant increased steric hindrance, caused significant repulsion in the catalyst–substrate adduct. In this context, catalyst **7g** was found to furnish the *ortho*-substituted aromatic alcohols **1e** and **1f** at elevated temperatures with good enantioselectivities. The formation of product **1j** from an  $\alpha,\beta$ -unsaturated aldehyde required a higher catalyst loading and prolonged reaction time.

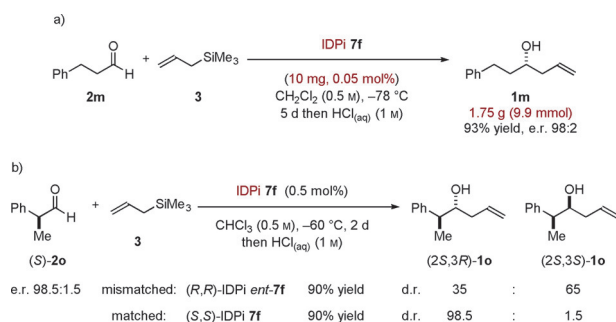
An extensive catalyst optimization and development was needed for aliphatic aldehydes (Scheme 2). The electronic properties of the installed 3,3'-substituents showed a significant effect on chemoselectivity. Remarkably, both electron-deficient and electron-rich substituents performed at far more elevated reaction temperatures compared to electronically unmodified polyaromatic groups. Catalysts possessing strong electron-withdrawing substituents, such as IDPi **7d**, were barely active in the Hosomi–Sakurai reaction and were prone to trimerize the aliphatic aldehydes. In contrast, electron-



**Scheme 2.** Scope with respect to aliphatic and aromatic aldehydes **2**. Reactions were conducted on 0.3–1.0 mmol scales. Catalyst loadings are given in mole percent (mol%). All yields are those of isolated products, and the enantiomeric ratios (e.r.) were determined by high-performance liquid chromatography (HPLC) or gas chromatography (GC) analysis with chiral stationary phases. Absolute configurations were assigned according to referenced literature or by crystallographic analysis. [a] IDPi **7g**, R = 9,10-dihydrophenanthryl, was used. [b] 95 % yield based on recovered starting material (low solubility of the starting material). [c] Desilylation with HCl to determine enantiomeric ratio.

donating groups, as depicted for catalyst **7e**, induced silyl-group-transfer reactions to generate the corresponding enol silanes. Gratifyingly, electronically neutral polyaromatic 3,3'-substituents, such as the 6,8-dimethylpyren-2-yl substituted catalyst **7f**, afforded the desired homoallylic alcohols **1** in good to excellent yields and enantioselectivities. Contrarily to aromatic aldehydes, even lower temperatures (–90 °C) and catalyst loadings (0.05 mol%) could be employed with aliphatic aldehydes, such as 3-phenylpropanal (**2m**). Increased catalyst loadings (1 mol%) furnished the trimethylsilyl protected alcohol **1m** (89 % yield) in less than two hours at –78 °C (Scheme 2), thus rendering a highly atom-economic and practical allylation method. Linear, β- and γ-branched aldehydes (**2**) were also suitable substrates for **7f**, furnishing alcohols **1k–n** (Scheme 2). On preparative scale, 1.4 grams of **2m** were converted by **7f** (10 mg, 0.05 mol%) at –78 °C within 5 days, furnishing homoallylic alcohol **1m** in 93 % yield and with an enantiomeric ratio of 98:2 (Scheme 3a).

We also explored an enantiopure α-branched aldehyde, (*S*)-2-phenylpropanal [(*S*)-**2o**; Scheme 3b]. In the mismatched case (*R,R*)-IDPi *ent*-**7f** afforded homoallylic alco-



**Scheme 3.** Synthetic applications. a) Large-scale Hosomi–Sakurai reaction. b) Diastereoselective Hosomi–Sakurai reaction. Reactions were conducted on 0.3 to 10.6 mmol scales and catalyst loadings are given in mole percent (mol%). All yields are those of the isolated products and enantiomeric (e.r.) and diastereomeric ratios (d.r.) were determined by high-performance liquid chromatography (HPLC) analysis with chiral stationary phases. Absolute configurations were assigned according to referenced literature and prepared authentic samples.

hols **1o** with a diastereomeric ratio of 65:35. In contrast, the matched catalyst, (*S,S*)-IDPi **7f** afforded **1o** with a d.r. value of 98.5:1.5. In both cases, the configuration of the pre-existing stereogenic center was preserved. Our results show that confined organocatalysts with extreme acidity and steric demand can overcome current synthetic limitations and solve a long standing problem in chemical synthesis. Our designed high-performance organocatalysts enable the first general and enantioselective catalytic addition of allyltrimethylsilane to aldehydes.

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