Confined acids catalyze asymmetric single aldolizations of acetaldehyde enolates

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Abstract: Reactions that form a product with the same reactive functionality as one of the starting compounds frequently end in oligomerization. As a salient example, selective aldol coupling of the smallest, though arguably most useful, enolizable aldehyde, acetaldehyde, with just one partner substrate has proven to be extremely challenging. Herein, we report a highly enantioselective Mukaiyama aldol reaction with the simple triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBS) enolates of acetaldehyde and various aliphatic and aromatic acceptor aldehydes. The reaction is catalyzed by recently developed, strongly acidic imidodiphosphorimidates (IDPi), which, like enzymes, display a confined active site but, like small molecule catalysts, have a broad substrate scope. The process is scalable, fast, efficient (0.5 to 1.5 mole % catalyst loading), and greatly simplifies access to highly valuable silylated acetaldehyde aldols.

One Sentence Summary: Confined acids enable highly enantioselective single aldol additions of acetaldehyde enolsilanes without competing oligomerization.

Main Text: The aldol addition is one of the most fundamental carbon-carbon bond forming reactions in chemical synthesis (*1*). The resulting β-hydroxy carbonyl compounds are versatile building blocks to numerous synthetic targets, in particular oligoketides (*2, 3*), with antibiotic, antiproliferating, antifungal and cholesterol-lowering properties (*4*). A fundamental challenge is the synthesis of β-hydroxy aldehydes, which can be envisioned either in a direct cross-aldol reaction between two aldehydes, or in an indirect aldol reaction, in which the donor aldehyde is employed as its corresponding enolmetalloid (*5*). Both approaches frequently suffer from oligomerization or polymerization that results from the preservation of the reacting functional group in the product (Fig. 1A) (*6*). Traditional approaches have circumvented this problem by installing less reactive surrogates for the critical aldehyde moiety, e.g. olefins (*7*) or esters (*8*), and therefore requiring additional transformations to access the desired aldehyde species. In recent years, researchers have turned their attention to the development of enantioselective aldol reactions to afford the targeted β-hydroxy aldehydes in a single transformation. The first report came from Denmark and Ghosh in 2001 and comprised an indirect, chiral Lewis base-catalyzed aldol reaction of aldehyde-derived trichlorosilyl enolates with aldehydes (*9*). Subsequent reports were based on chiral amines as Lewis basic catalysts for the direct cross-aldol reaction between non-equivalent aldehydes (*1, 6, 10-12*). In spite of all previous efforts, the smallest enolizable donor aldehyde, acetaldehyde, has remained a challenge in this transformation. The few reports in which this particular donor aldehyde is employed have encountered severe limitations in the scope of substrates to non-enolizable, typically electron-poor acceptor aldehydes (*1, 13, 14*). Another drawback is the intrinsic lability (*15*) of the products obtained by these methods, which frequently require protection via *O*-silylation of the β-hydroxy group after direct cross-aldol reactions (*16*), or in situ derivatization of the valuable aldehyde moiety by acetal formation (*14*) or reduction (*1, 13*). In contrast, the single addition products of the Mukaiyama aldol reaction are significantly more stable, and can be readily isolated by conventional purification methods when silyl groups larger than trimethylsilyl are employed. However, simple (e.g. triethyl-) silyl enolates of acetaldehyde mostly afford oligomers when the powerful small molecule triflimide ($HNTf_2$) is employed as catalyst in this transformation (Fig. 1B). In 2006, Boxer and Yamamoto successfully realized a non-enantioselective variant, in which high selectivities toward single and double additions were controlled by the exceptionally bulky tris(trimethylsilyl)silyl group (Fig. 1C) (*3*). Yet, an enantioselective version has remained elusive. In light of the challenging transformations enabled by our recently developed, highly acidic and confined imidodiphosphorimidate (IDPi) catalysts (*17-22*) we envisioned an enantioselective Mukaiyama aldol reaction with simple enolsilanes of acetaldehyde. This transformation would potentially benefit from the confined space of the binding site in IDPi catalysts thereby effecting selective single additions of enolsilane due to steric differentiation between the substrate and product aldehydes (Fig. 1D).

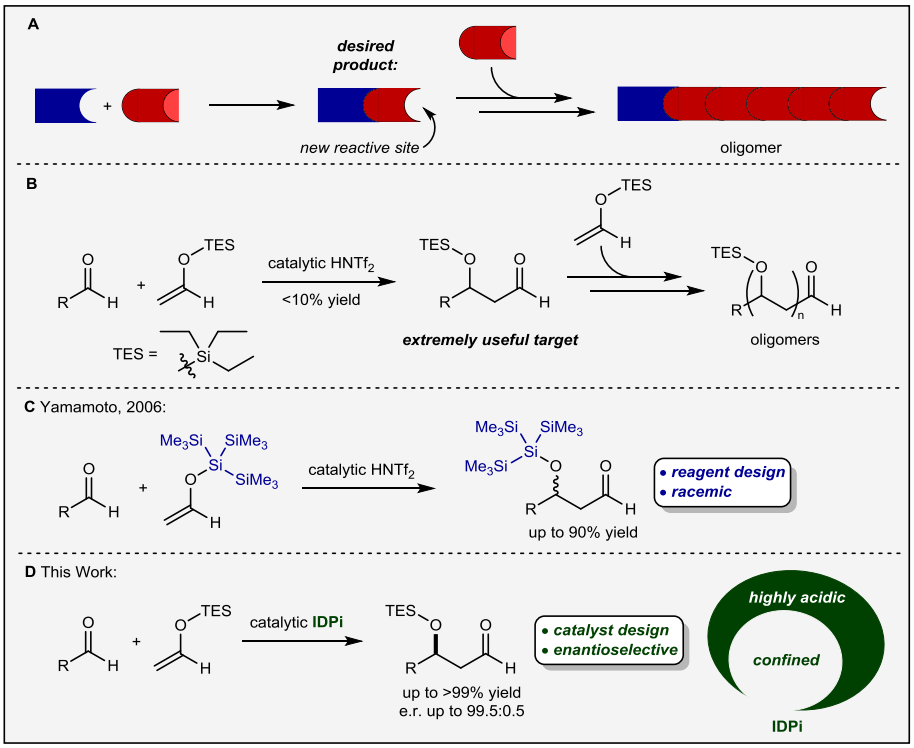

Fig. 1. Indirect aldol reactions with enolsilanes of aldehydes. (**A**) The principal selectivity problem. (**B**) A Mukaiyama aldol reaction with the simple TES enolate of acetaldehyde: no control over multiple additions with triflimide ($HNTf_2$) as catalyst. (**C**) A reagent-controlled, non-enantioselective Mukaiyama aldol reaction with the tris(trimethylsilyl)silyl enolate of acetaldehyde (*3*), (**D**) This work: a catalyst-controlled, highly enantioselective Mukaiyama aldol reaction with simple enolsilanes of acetaldehyde.

Although several different classes of previously developed chiral acids failed in this endeavor, due to lack of any catalytic activity (e.g. chiral phosphoric acids and imidodiphosphates (*23*)) or unselective multiple additions (disulfonimides (*24*)), we were intrigued to observe that phenyl-substituted IDPi **4a** cleanly converted 3-phenylpropanal (**1a**) and enolsilane **2a** to afford aldol **3a** in 79% yield and a promising enantiomeric ratio (e.r.) of 66:34 (Fig. 2).

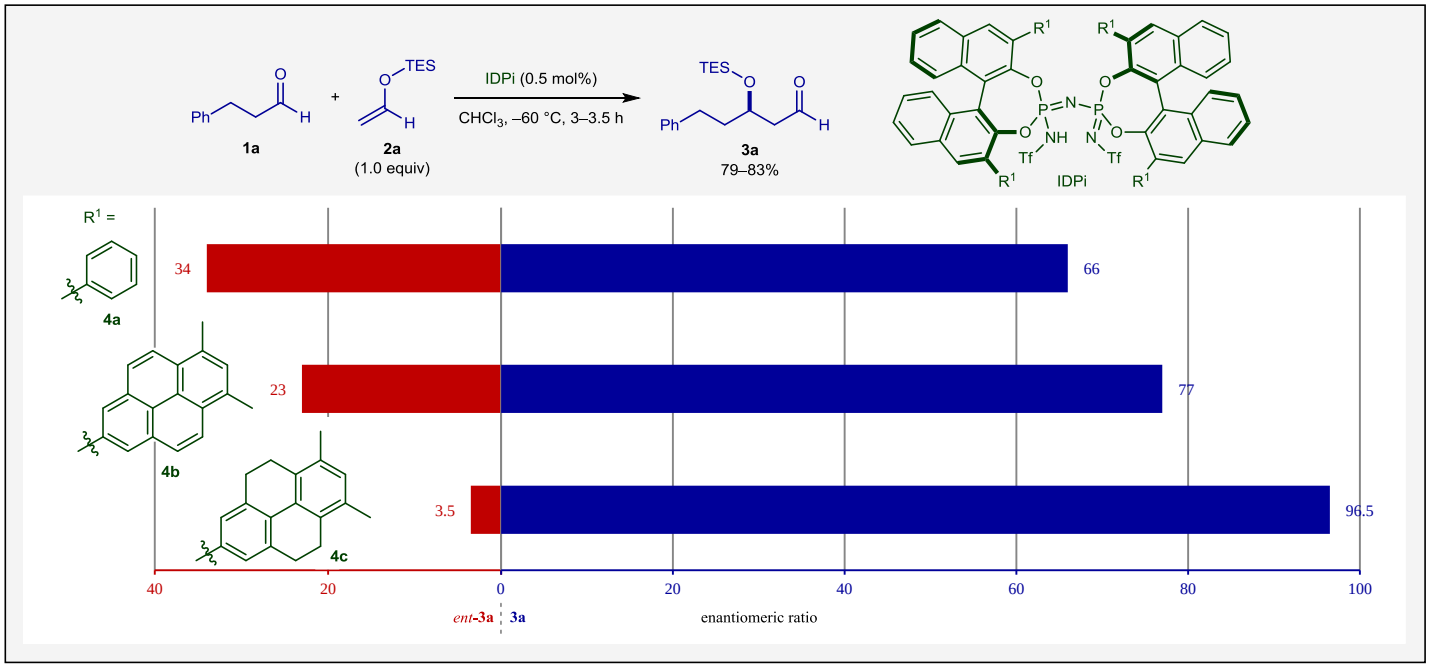

Fig. 2. Catalyst optimization. All yields were determined by ^{1}H NMR spectroscopy, with Ph_3CH as internal standard. For the determination of the e.r., aldol **3a** was reduced and desilylated to the corresponding 1,3-diol **S1a** with $NaBH_4$ and TBAF, respectively (for details, see supplementary materials). E.r. were determined by high-performance liquid chromatography (HPLC) with a chiral stationary phase. The absolute configuration was determined by comparison of the optical rotation of the corresponding 1,3-diol **S1a** with a value reported in the literature. Tf = trifluoromethanesulfonyl.

Inspired by this initial result, we aimed to enhance the enantioselectivity through fine-tuning of our IDPi's substituents R^1. Whereas our previously developed dimethylpyrenyl-substituted IDPi **4b** – the most powerful catalyst in the allylation of aliphatic aldehydes (*17*) – performed with only moderate enantioselectivity, we were pleased to find that its partially saturated analog **4c** gave access to the desired aldol of 3-phenylpropanal (**3a**) in excellent yield and enantioselectivity (83%, e.r. = 96.5:3.5).

Other aliphatic aldehydes such as pivalaldehyde (**1b**) and benzyloxyacetaldehyde (**1c**) were transformed into aldols **3b** and **3c** in similarly high yields and enantioselectivities using TBS enolate **2b**, yet in the case of aldol **3c** with an unexpected inversion of the facial selectivity of the nucleophilic addition (Fig. 3A).

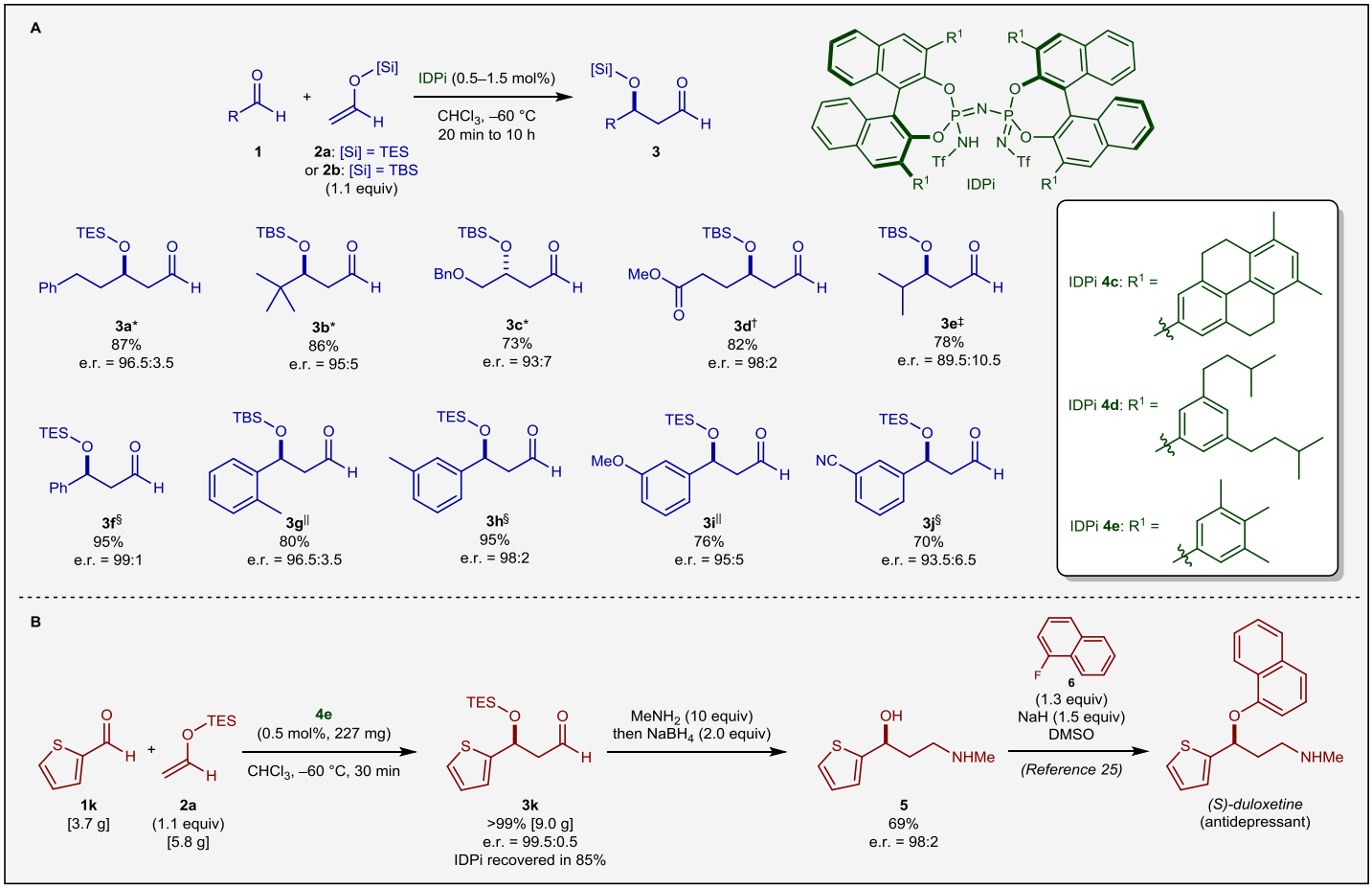

Fig. 3. IDPi catalyzed Mukaiyama aldol reaction with enolsilanes of acetaldehyde. (**A**) Substrate scope. Reactions were performed with 0.5 mmol of aldehydes **1**. * Using IDPi **4c**. † Using IDPi **4d** and 1.4 equivalents of enolsilane **2b**. ‡ Using IDPi **4d** and 1.2 equivalents of enolsilane **2b**. § Using IDPi **4e**. || Reactions were performed in $CHCl_3$/*n*-hexane (5:4) at -78 °C using IDPi **4e**. (**B**) Scaled-up aldol reaction and application to the formal synthesis of *(S)-duloxetine*. All yields are those of isolated materials. For the determination of the e.r., aldols **3** were reduced and desilylated to the corresponding 1,3-diols **S1** with $NaBH_4$ and TBAF, respectively (the 1,3-diols derived from aldols **3b** and **3e** were further derivatized to acetonides **S2b** and **S2e**, respectively; for details, see supplementary materials). E.r. were determined either by HPLC or gas chromatography (GC) with chiral stationary phases. Absolute configurations were determined by comparison of optical rotations of the aldol products and/or the corresponding 1,3-diols **S1** with values reported in the literature. The absolute configuration of aldol **3c** was additionally determined by HPLC analysis of the corresponding 1,3-diol **S1c** derived from commercial, enantiomerically enriched (*R*)-1,2,4-butantriol (**S1n**; for details, see supplementary materials).

For the aldol reactions of methyl 4-oxobutanoate (**1d**) and isobutyraldehyde (**1e**), the best performances were obtained when employing 3,5-dialkylphenyl substituted IDPi **4d**, which afforded aldol **3d** in high yield and an excellent e.r. of 98:2, and aldol **3e** in 78% yield and an e.r. of 89.5:10.5.

We subsequently turned our attention to aromatic acceptor aldehydes, for which a systematic methylation of the core phenyl substituents R^1 in IDPi **4a** revealed trimethylphenyl analog **4e** to be the optimal catalyst, affording benzaldehyde-derived aldol **3f** in 95% yield and a remarkable e.r. of 99:1 (for details, see supplementary materials). Tolualdehyde-derived aldols **3g** and **3h** were obtained in high yields and enantioselectivities (Fig. 3A). *meta*-Anisaldehyde (**1i**) and *meta*-cyanobenzaldehyde (**1j**) also were well tolerated substrates, rendering the corresponding aldols **3i** and **3j** in good yields and enantioselectivities.

To illustrate the utility of the obtained aldol products, we envisioned accessing the antidepressant *(S)-duloxetine* in a concise synthesis from aldol **3k** via reductive amination and the reported nucleophilic aromatic substitution with 1-fluoronaphthalene (**6**; Fig. 3B) (*25*). A gram scale aldol synthesis was therefore performed, in which 0.5 mol% (227 mg) of IDPi **4e** furnished 9.0 g (>99% yield) of thiophene-2-carbaldehyde derived aldol **3k**, and a superb e.r. of 99.5:0.5. The subsequent reductive amination employing methylamine and sodium borohydride, and a concomitant desilylation under the reaction conditions afforded the desired, known (*25*) amino alcohol **5**, which can be converted into *(S)-duloxetine* in a single step.

The rationale for the differentiation between substrate and product aldehyde by the developed catalyst system is a pivotal question. The unique properties of our IDPi catalysts in this regard are best illustrated by a direct comparison with triflimide as catalyst. Namely, while IDPi **4e** afforded aldol **3f** in 88% yield, under otherwise identical conditions, the yield with triflimide was below 10% due to oligomerization (Fig. 4A).

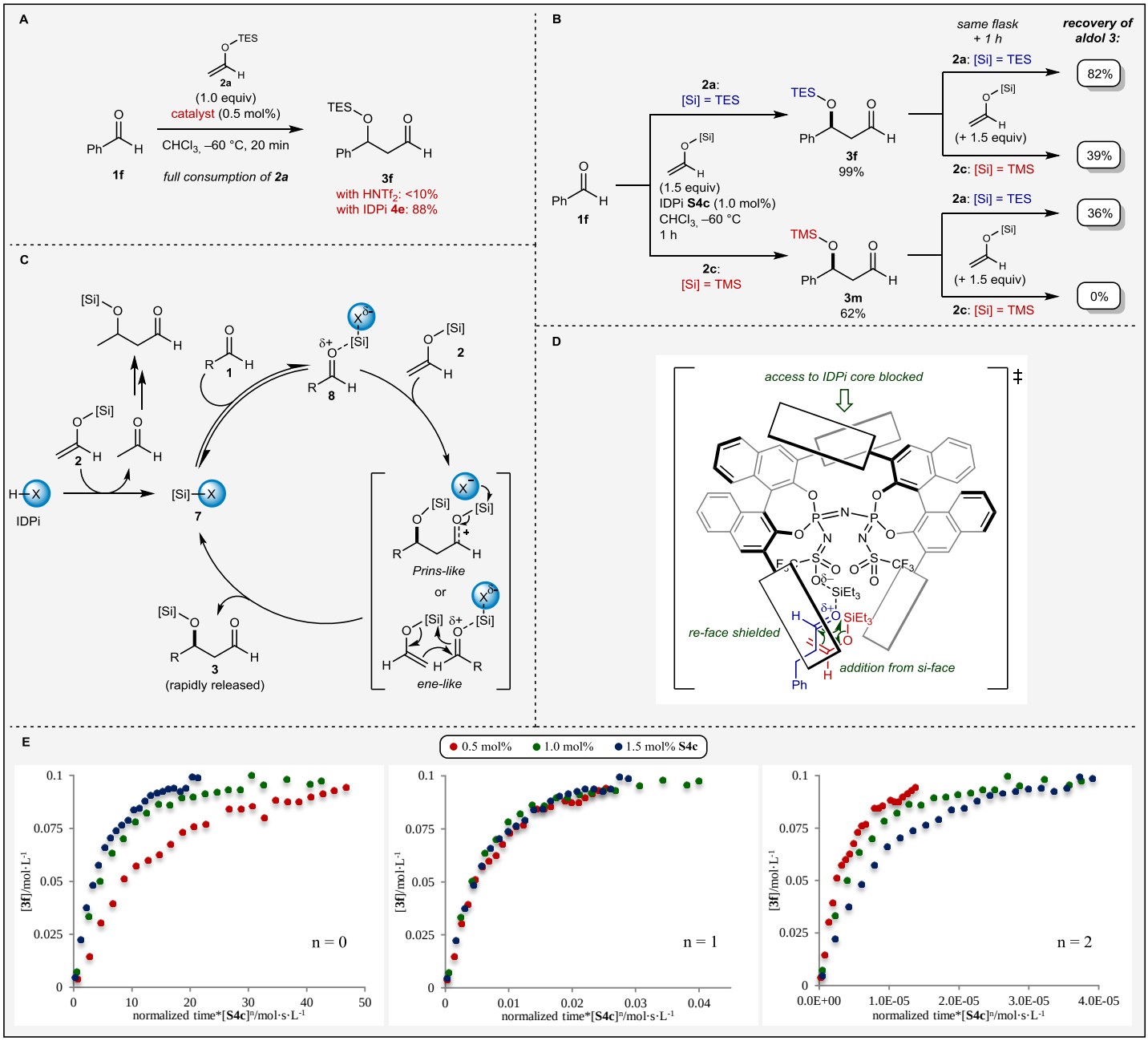

Fig. 4. Mechanistic investigations. (**A**, **B**) Influence of the catalyst and the silyl group, respectively, on the selectivity toward single addition of enolsilane **2**. IDPi **S4c**: see Fig. S1. (**C**) Proposed catalytic cycle, based on reaction progress kinetic analysis and NMR spectroscopic studies. (**D**) Proposed transition state for the aldol reaction of 3-phenylpropanal (**1a**) and enolsilane **2a** to afford (*R*)-configured aldol **3a**, following the ene-like mechanism. (**E**) The method of Burés revealed a first-order dependence on the catalyst concentration. In this method, the substrate (or product) concentration is plotted against a normalized time scale, t•[cat]^n, where "t" is the normalized time (for details, see supplementary materials), and [cat] is the (total) catalyst concentration. The exponent "n" equals the order of the catalyst where the plots of several reactions with different catalyst concentrations overlap, which in this case is n = 1. Yields were either determined by ^{1}H NMR spectroscopy, with Ph_3CH as internal standard, or GC, using *n*-octane as internal standard.

In addition to the catalyst, the solvent and the silyl group had significant effects on the reaction profile. Typically, the highest yields of aldols **3** were obtained when the reaction was conducted in chloroform (*26*). The steric bulk of the silyl group greatly affected the extent to which aldols **3** were consumed in the course of the reaction (Fig. 4B). Under otherwise identical conditions, using 1.5 equivalents of the TES (**2a**) and TMS (**2c**) enolates of acetaldehyde, the aldol products of benzaldehyde (**3f**, **3m**) were formed in 99 and 62% yield, respectively. Upon addition of a further 1.5 equivalents of either nucleophile, both aldols **3** were consumed in varying amounts depending on the silyl group combinations, lowering the yields of aldol **3f** to 82% (TES/TES) and 39% (TES/TMS) and that of **3m** to 36% (TMS/TES). When TMS enolate **2c** was employed at both stages, aldol **3m** was fully consumed (for details, see supplementary materials). These results suggest that the discrimination between substrate and product aldehyde are of steric nature, with the sterically demanding β-silyloxy groups in the aldol products, as well as the size of the nucleophile, as contributing factors. Based on reaction progress kinetic analysis (*27*) and NMR spectroscopic studies (*28*), we propose the reaction to commence with in situ silylation of the IDPi by enolsilane **2** (Fig. 4C). Aldehyde **1** then reversibly coordinates to the silylated catalyst **7**, giving rise to intermediate **8**, in which the formyl group of the substrate is sufficiently activated for the irreversible addition of enolsilane **2**. As the incorporation of the silyl group of nucleophile **2** into the aldol product **3** is preferred to the incorporation of the silyl group of a differently pre-silylated catalyst **7**, we propose two competing mechanisms for the carbon-carbon bond forming step. One involves a Prins-like intermediate as part of a

stepwise process, in which the silyl group of the catalyst results in aldol **3**, whereas the other entails a concerted ene-like transition state, in which the silyl group of nucleophile **2** results in the aldol product. In either case, aldol **3** is rapidly released from the catalyst, re-establishing the silylated species **7**. Based on X-ray crystallographic data of related catalysts (*17*), we propose that the stereoselectivity of the C-C bond-forming step primarily arises from the shielding of the *re*-face of the catalyst-bound substrate by one of the 3,3'-substituents on the BINOL backbones. This allows the addition of the enolsilane (following either mechanism) only from the *si*-face, as illustrated for the aldol reaction of 3-phenylpropanal (**1a**) with enolsilane **2a** (Fig. 4D). We currently aim to confirm this model with high level computational methods. First-order dependence on the catalyst concentration confirmed the involvement of a single catalyst molecule in the rate determining step of the reaction, as identified by the graphical method of Burés (Fig. 4E) (*29*).
We believe that our method strongly simplifies the enantioselective access to a class of broadly applicable compounds, of which the synthesis to this point typically involved sequences of several distinct steps (*30*).

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Author contributions: B.L. and L.S. jointly conceived and directed the project. S.L. first identified the reactivity discussed in this publication. L.S., with the assistance of P.S.J.K. and R.P. developed the optimized catalysts. L.S. and V.N.W. conducted screenings of catalysts, substrates and reaction conditions. P.S.J.K., R.P. and S.L. prepared the racemates. C.O. conducted the mechanistic studies. L.S. and B.L. prepared the manuscript.

Competing interests: B.L., P.S.J.K., L.S., R.P. and S.L. are inventors on patent WO2017037141 (A1) filed by the MPI für Kohlenforschung covering the IDPi catalyst class and its applications in asymmetric synthesis. **Data and materials availability:** All data are available in the main text or the supplementary materials.

Supplementary Materials:

Materials and Methods

Supplementary Text

Figs. S1 to S40

Tables S1 to S32

References (*31-69*)