

Acetaldehyde Silyl Enol Ethers in Enantioselective Mukaiyama Aldol Reactions – Enzyme-Like Catalysis in Action

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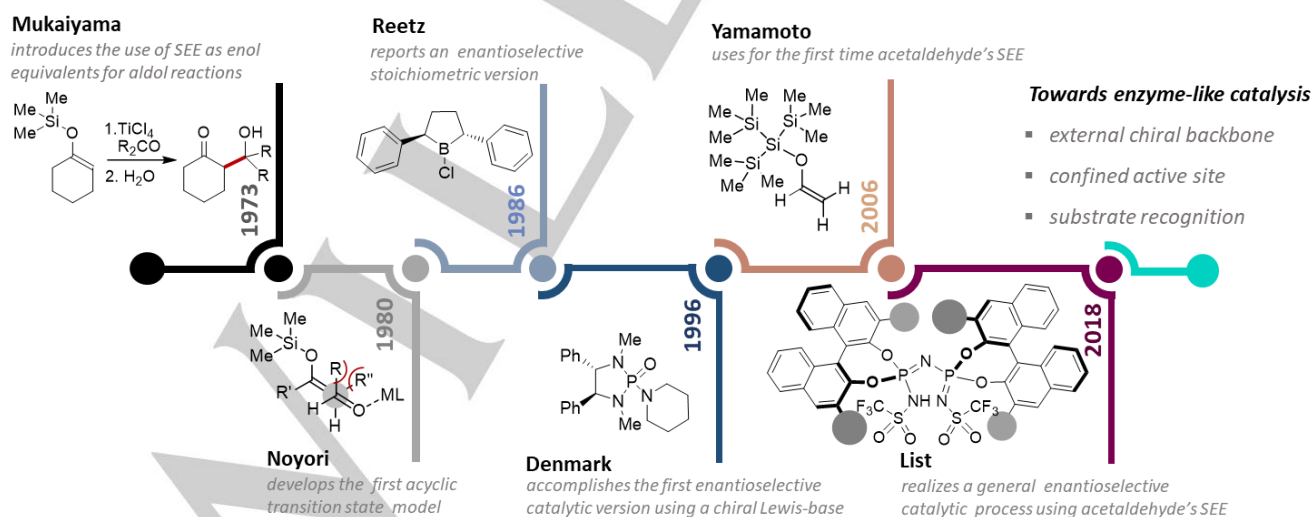
To the memory of Prof. T. Mukaiyama (1927-2018) for his invaluable contribution to organic chemistry

Since its discovery in 1973, the Mukaiyama aldol reaction (MAR) - featuring the use of storable, and easy-to-use silyl enol ethers (SEEs) – has been responsible for the tremendous progress in synthetic organic chemistry, becoming one of the most powerful techniques for the straightforward construction of C-C bonds.^[1] Supported by the development of a robust transition state model by Noyori in 1980,^[2] enantioselective and catalytic asymmetric versions rapidly appeared, as partially depicted in the timeline of Figure 1.^[1,3] The first enantioselective version of the MAR was reported by Reetz and co-workers employing a stoichiometric amount of a chiral boron-based Lewis acid.^[4] Ten years later, Denmark et al. outlined a general and efficient approach using chiral Lewis base organocatalysts.^[5] Over the years, the MAR experienced additional advances, including the development of cascade reactions,^[6] vinylogous variants,^[7] and on-water protocols.^[8]

Despite these advances, one fundamental piece of the puzzle was still missing: the efficient and truly general use of the smallest enolizable aldehyde, acetaldehyde. The use of this substrate was frustrated by seemingly unescapable issues, in particular, the inability of the small acetaldehyde SEE to discriminate between the starting aldehyde acceptor and the product aldehyde, thus leading to extensive polymerization. The first encouraging results, that attempted to address this issue, were obtained by Yamamoto and co-workers in 2006,^[9] who were first to recognize that an extremely bulky tris(trimethylsilyl) SEE (“super-silyl”) of

acetaldehyde could be employed to develop a successful catalytic (although racemic) MAR. Only recently, List and co-workers reported the very first example of a catalytic enantioselective MAR efficiently employing acetaldehyde SEE.^[10]

Over the past decade, the List group has been pioneers in the field of asymmetric counteranion-directed catalysis (ACDC), and most of the key C-C bond-forming reactions were revisited in an efficient and stereoselective manner by exploiting this concept.^[11,12] In particular, the use of “super-acidic” Brønsted acid precatalysts – evolving from phosphoric acids, disulfonic acids, disulfonimides, imidodiphosphates, to the recent imidodiphosphorimidates (IDPi) – in couple with achiral silylating species has provided, after hydrogen-silicon exchange, the in situ formation of highly Lewis acidic silylium-ACDC organocatalysts (*vide infra*). These active species display unique catalytic properties for a wide range of chemical transformations.^[13] The catalytic system presents two main features: (i) the active catalyst ion pair consists of the substrate-activating cationic and achiral silylium component and the hydrolytically stable and highly confined enantiopure counteranion; and (ii) extremely low pre-catalyst loading is sufficient to obtain high-performance/high turnover/highly selective catalysis. Given these general features, List and collaborators now had the tools to address the specific and delicate acetaldehyde-SEE issue. Careful adjustment of the imidodiphosphorimidate backbone and the overall catalytic system resulted in the realization of highly effective *enzyme-like* catalysis.



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Figure 1. Historical timeline of the Mukaiyama aldol reaction – selected advances for MARs involving acetaldehyde SEE (MAR = Mukaiyama aldol reaction; SEE = silyl enol ether).

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In order to provide unprecedented and optimal results, several aspects of the catalytic system proved crucial, including the fine tuning of the *IDPi catalyst backbone*, the *size of the donor*, and the *solvent*. As for the fine tuning of the *IDPi catalyst backbone*: substitution at the binaphtholic positions with either dimethylhydropyrenyl- or 3,5-dialkylphenyl moieties (grey circles in Figure 2a) gave the best results in terms of both reaction efficiency and enantioselectivity. The confined, bulky core-shell of these adapted IDPis were found to be very important in the chemoselective discrimination between the small starting aldehyde **2** and the more hindered aldehyde product **3** (Figure 2). In fact, when less selective triflimide was used as a catalyst (Figure 2c, left), extensive polymerization was observed. Concerning the *size of the donor* through the prudent choice of the SEE silyl group, TES- or TBS-enol ethers were found to give the best results and avoid product decomposition. When the less bulky TMS-enolate was used, inferior results were obtained (Figure 2c, right). Regarding *the solvent*, halogenated solvents performed better, providing the highest isolated yields. The solvent can arguably impact on the catalyst conformation, altering the distance between the counterions,^[11] while altering the open cavity size within the IDPi.

From the experimental observations, a definite picture arises, graphically summarized in Figure 2a, where the IDPi catalyst acts in a manner that presents some of the features proper of enzymatic catalysis, perfectly allocating the two desired reagents,

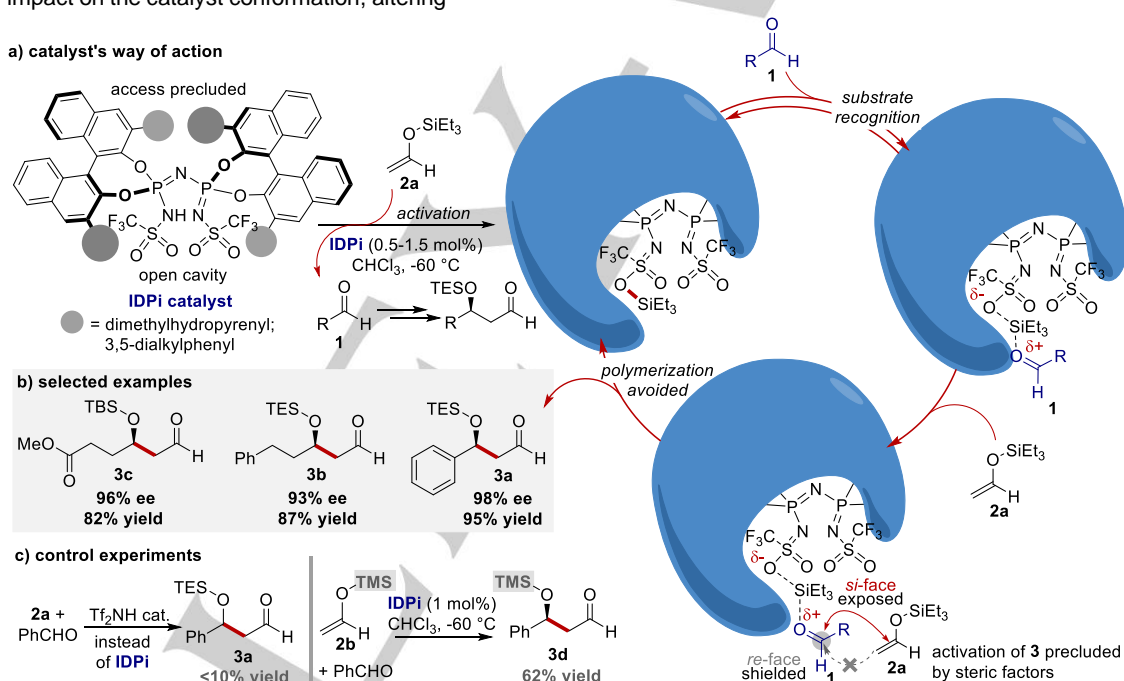


Figure 2. a) The IDPi catalyst developed by List and co-workers in action and similarities with an enzyme's active site. b) Selected examples of products **3** obtained from acetaldehyde SEE **2** and different aromatic and aliphatic aldehydes **1**. c) Control experiments pointing to a selective substrate recognition by the IDPi catalyst.

We herein highlighted how a carefully designed organic molecule solved an intricate synthetic problem. Thanks to the presence of a confined active site and to an effective substrate recognition, resembling enzymatic activity,^[14] the chemistry firstly introduced by Mukaiyama can now be applied to smaller and useful SEEs in an enantioselective catalytic fashion. Remarkably, the IDPi catalysis can serve as a general tool for diverse synthetic transformations. The fine tuning of IDPi allows the specific issue to be solved, in a similar manner to the evolutionary adaptation of the active site of an enzyme to provide solutions for specific

aldehyde **1** and SEE **2a**, into the *active site*. Mechanistic investigations ruled out the hypothesis of any non-linear effects,^[10] hence indicating that a single IDPi molecule is responsible for the activation of aldehyde **1**. Looking at the reaction mechanism (Figure 2, on the right), based on previous reaction progress kinetic analysis and NMR-based spectroscopic studies, the authors propose that, after the precatalyst deprotonation/silylation by a sacrificial amount of SEE **2a**, aldehyde **1** enters the accessible catalyst cavity, while being activated by the silyl group. The SEE **2** is now able to attack the exposed *si*-face of **1** to generate the chiral β -silyloxy aldehyde **3**. Interestingly, by accurately tuning the substitution pattern at the binaphtholic backbone, both aliphatic and aromatic aldehydes can productively participate in the enantioselective MAR (Figure 2b). Remarkably, due to steric impediments, aldehyde product **3** cannot enter the catalyst *active site*. Like an enzyme, the IDPi catalyst is capable of discriminating among the different aldehydes **2** or **3** present in solution, thus avoiding any polymerization end-reaction.

biological transformations.^[15] *The versatility of a synthetic molecule with the effective substrate recognition of an enzyme.*

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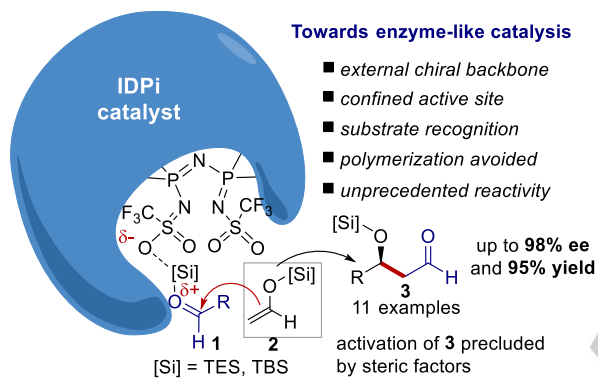
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