Approaching Sub-ppm-Level Asymmetric Organocatalysis of a Highly Challenging and Scalable Carbon–Carbon Bond-Forming Reaction

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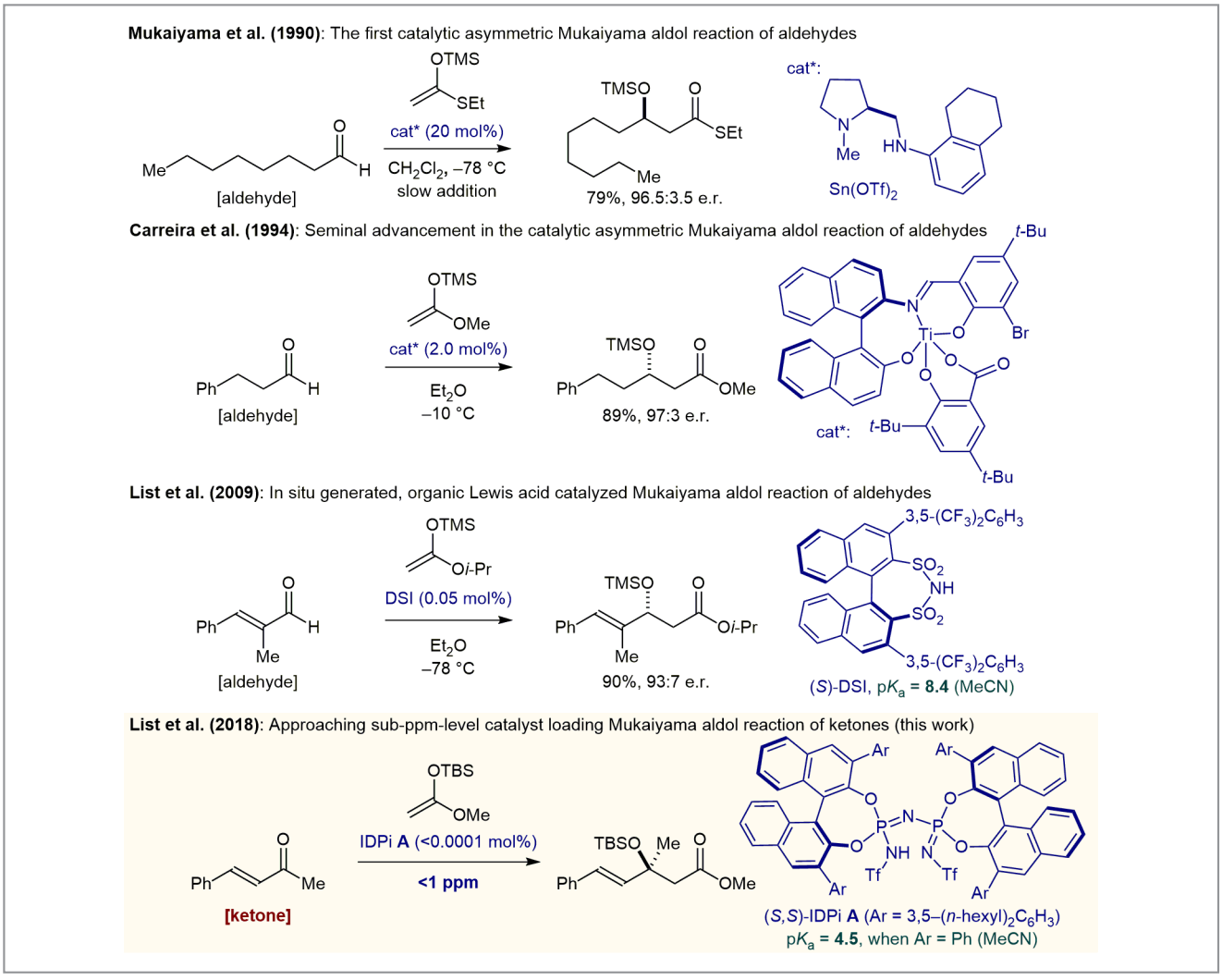
The Mukaiyama aldol reaction of silyl ketene acetals as preformed enolates with carbonyl compounds is a widely applied carbon–carbon bond-forming reaction. "Since Mukaiyama's initial report on the non-enantioselective aldol reaction of ketone-derived silyl enol ethers with aldehydes in 1973,[1] significant advances of this powerful synthetic tool have been made during the past 45 years," said Professor Ben List at the Max-Planck-Institut für Kohlenforschung (Germany), who explained that the first catalytic enantioselective version, using silyl ketene thioacetal in the presence of a chiral tin(IV)



Scheme 1 Representative examples of catalytic asymmetric Mukaiyama aldol reactions of silyl ketene (thio)acetals. cat* = chiral catalyst.

complex (20 mol%) was also reported by the same group (Scheme 1, first row).[2a] "A powerful catalytic system based on titanium(IV), a tridentate Schiff base ligand, and di-*tert*-butylsalicylic acid (2 mol%) was developed by Carreira and coworkers[2b] and proved to be highly active and enantioselective (Scheme 1, second row)," added Professor List. He also pointed out that despite numerous well-established methods using aldehydes,[2c] the utilization of ketones as acceptors to afford chiral tertiary β-hydroxy esters is still challenging in terms of substrate scope, enantioselectivity, and scalability (for known catalytic examples, see: Denmark et al.[3a] using 10 mol% of a chiral bis-*N*-oxide Lewis base; Shibasaki et al.[3b] using 4 mol% of a chiral copper(I) fluoride–phosphine complex and stoichiometric additives).

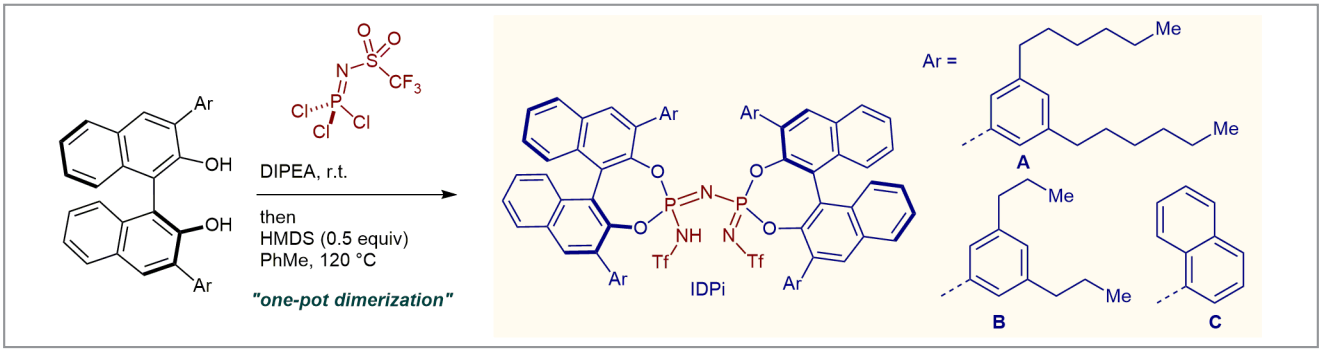
Recently, Professor List's group reported a new class of chiral organocatalysts, which enable the challenging enantioselective Mukaiyama aldol reaction of ketones in the presence of extremely low catalyst loading (Scheme 1, fourth row). In their article, the newly developed highly acidic (pK_a = 4.5 in acetonitrile) imidodiphosphorimidate (IDPi)[4] compounds were employed as potent catalysts for the Mukaiyama aldol reaction of commercially available silyl ketene acetals with ketones. "Previously developed chiral disulfonimides[5] (DSI, pK_a = 8.4 in acetonitrile), which proved to be efficient catalysts of the Mukaiyama aldol reaction of aldehydes, failed to achieve the desired transformation (Scheme 1, third row)," explained Professor List.

"The preparation of our IDPi catalysts is simple. A one-pot condensating dimerization of readily accessible 3,3′-disubstituted binols in the presence of [(trifluoromethyl)sulfonyl] phosphorimidoyl trichloride and hexamethyldisilazane provides the catalysts. In our laboratory, we have set up a convenient and routine synthesis protocol, which enables the facile preparation of structurally diverse IDPi catalysts," Professor List emphasized (Scheme 2).

The scope of the developed method is extensive, as presented in the original paper, and summarized by a few selected examples shown in Scheme 3a. "Besides (hetero)aryl-alkyl ketones, alkyl-alkyl ketones were also converted with good to excellent enantiomeric ratios (e.r.). An alkynyl ketone also gave an excellent e.r. Interestingly, benzylideneacetone-type α,β-unsaturated ketones were highly reactive and generally gave good 1,2- versus 1,4-regioselectivity (~10:1) and excellent enantioselectivity. In particular, loadings of 2.8–500 ppm (0.00028–0.05 mol%) with the IDPi catalysts **A**, **B** or **C** proved to be sufficient to provide the desired enantioenriched products, even on a preparative scale (grams to decagrams)," explained Professor List.

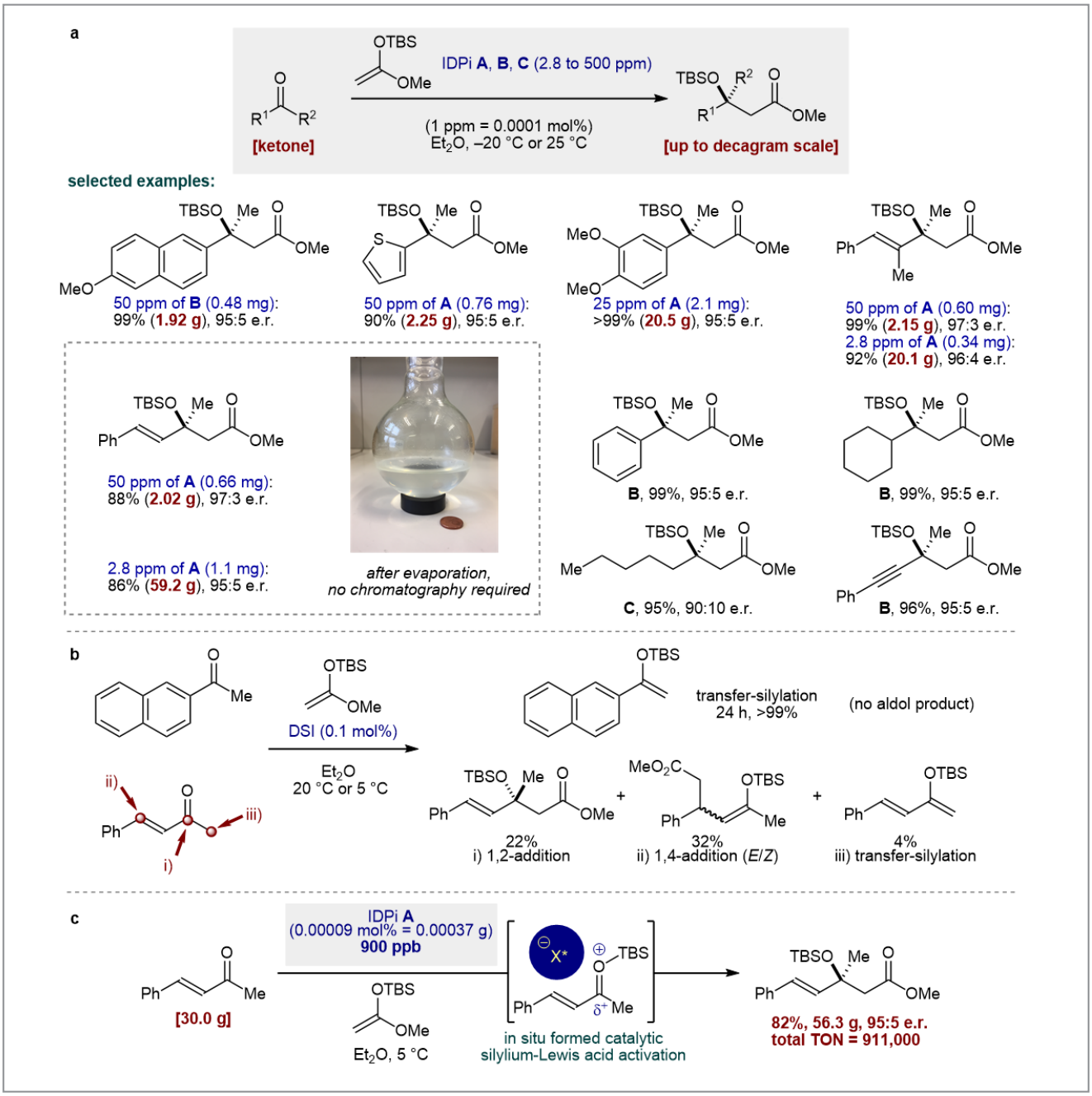
"Interestingly, in sharp contrast to the formidable catalytic activity of the IDPi catalysts, our DSIs unexpectedly led to a completely different outcome under identical reaction conditions," said Dr. Han Yong Bae. He continued: "In the case of using 2-acetonaphthone as the starting material, instead of the desired tertiary aldol product, quantitative silyldeprotonation of the ketone was observed (Scheme 3b, top). In the case of benzylideneacetone, both transfer-silylation and 1,2-/1,4-reactions competitively occurred (Scheme 3b, bottom)."

"The significance of this method was further demonstrated by conducting large-scale, extremely low catalyst loading experiments. We could readily reduce the catalyst loading to a ppm level, ultimately even approaching parts-per-billion (ppb) levels. This surprisingly high reactivity can probably be attributed to the extreme Lewis acidity of the in situ generated silylium ion Lewis pair, which is formed in a reaction of the IDPi catalyst with the silyl ketene acetal. While the reactions under these extreme conditions require purified reagents and rather long reaction times, to our knowledge, the catalyst loadings reported are unprecedented in asymmetric carbon–carbon bond-forming reactions," added Professor List.



Scheme 2 Preparation of representative chiral IDPi **A**, **B**, and **C** catalysts used in this study.

He concluded: "The developed method is operationally simple, scalable, and the obtained products are highly valuable and can be readily derivatized. Generally, only ppm level loadings of the catalyst, in one case even less than 1 ppm, is required. We think that our discovery represents a major milestone, not only in the field of organocatalysis but in chemical synthesis as a whole."



Scheme 3 IDPi-catalyzed Mukaiyama aldol reactions of ketones. a) Substrate scope. b) Results of using DSI as catalyst instead of IDPis. c) Experiment of approaching ppb-level (0.00009 mol%) catalyst loading.

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About the authors

Dr. H. Y. Bae

Han Yong Bae was born in Daegu, Republic of Korea (1983). He received his B.Sc. (2010) and Ph.D. (2015) degrees from Sungkyunkwan University (SKKU, Korea), conducting studies on biomimetic Brønsted base catalyzed asymmetric catalysis under the supervision of Professor Choong Eui Song. During his graduate studies, Han Yong developed a polyketide biosynthesis mimic, the first organocatalytic decarboxylative aldol reaction of malonic acid half-thioester with aldehyde in collaboration with Professor Benjamin List's laboratory. He then moved to Germany and is currently pursuing postdoctoral research with Professor List at the Max-Planck-Institut für Kohlenforschung. His research mainly focuses on the development of new methodologies for challenging organic Lewis acid catalyzed asymmetric reactions and, ultimately, finding useful applications of the developed methods. He has received prizes such as the Global Ph.D. Fellowship (2012, Ministry of Education of Korea), the DOW Chemical Scholarship (2015), the Chancellor's Award/Valedictorian (2015, SKKU), the Award for Best Ph.D. Thesis (2015, Korean Chemical Society), and a RESOLV Post-doctoral Fellowship (2016, German Research Foundation).

Professor B. List

Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (Germany) in 1993 and received his Ph.D. (1997) from the University of Frankfurt. After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute (USA), he became a Tenure Track Assistant Professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol-, Mannich-, Michael-, and α-Amination reactions. In 2003 he moved to the Max-Planck-Institut für Kohlenforschung (Germany), where he has been a director since 2005. From 2012 until 2014 he was the managing director of the institute. Since 2004 he also serves as an honorary professor at the University of Cologne (Germany). His research interests are new catalysis concepts and chemical synthesis in general. He has pioneered and contributed several concepts including aminocatalysis, enamine catalysis, and asymmetric counteranion-directed catalysis (ACDC). His accomplishments have been recognized by several awards including the Otto Bayer Prize (2012), the Mukaiyama Award (2013), the Cope-Scholar Award (2014), the Gottfried Wilhelm Leibniz Prize (2016), and admission as a member of the German National Academy of Sciences Leopoldina (2018).