Cluster Preface: Challenges of Proline-Based Aminocatalysis

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Abstract: During the last eleven years, aminocatalysis, the catalysis of carbonyl transformations via iminium ion and enamine intermediates has become a highly successful and general approach to asymmetric synthesis. There are now several dozens of different reaction types with hundreds of variants that are mediated by primary and secondary amine catalysts, of which proline continues to be a privileged motif. This Cluster highlights recent attempts towards solving some of the remaining challenges in the area.

Key words: proline, aminocatalysis, enamine catalysis, iminium ion catalysis

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I vividly remember the day in 1999 when I set up an experiment that today likely bores to tears each and every chemist around the globe: the proline-catalyzed aldol reaction of acetone with *p*-nitro benzaldehyde. Not particularly much was expected from this experiment and I reasoned that somebody must have tried this before. Neither would I have predicted the highly successful outcome of this reaction,[1] nor what would happen in subsequent years, which brought literally hundreds of papers suggesting to have taken inspiration from my initial observation.[2] Key to the phenomenal growth of our finding into an entire field was not so much the discovery of the proline-catalyzed intermolecular aldol reaction via an enamine intermediate or the subsequent amino acid derivative catalyzed Diels–Alder reactions via an iminium ion,[3] but rather the realization that *enamine catalysis and iminium ion catalysis are truly generic carbonyl activation modes*.[4] Once this had been fully appreciated, the 'aminocatalysis explosion' took off.

Some highlights of this development include the proline-catalyzed Mannich reaction, the aldehyde cross-aldolization, enamine catalytic α-alkylations and α-functionalizations, various Michael additions, SOMO catalysis, ACDC, and of course the many wonderful organocascade processes that make combined use of enamine and iminium ion catalysis (for a small collection of proline-based catalytic transformations, see Scheme 1).[4] In addition to the many new reactions that continue to be explored and advanced, several new proline-based catalysts have also been designed and discovered of which the prolinol silyl ethers are probably the most versatile. But other successful motifs have also been described, including highly active and enantioselective proline amides, some remarkable fully synthetic motifs, and cinchona-derived primary amines with complementary reactivity.

So what are the challenges of proline-based aminocatalysis? I think we now largely appreciate the scope of the catalysis principle, and to some extend the requirements for designing effective catalysts. I doubt though that there will be many more fundamentally new reactions discovered soon, although I still see substantial room for important research in the area. There are three main interrelated topics that will likely be addressed: (1) mechanistic understanding, (2) substrate scope enlargement of the various reactions, and (3) advanced catalysts. While proline-based enamine catalysis has delivered truly marvelous reactions, consider for example the scope and enantioselectivity of the proline-catalyzed Mannich reaction, certain issues remain to be solved. It may not sound so important, but a *general* aldehyde cross-aldol reaction that furnishes *syn* instead of the common *anti* products would be considered a true breakthrough by many in the field. Similarly, direct aldehyde α-alkylations are still narrow in scope and yet could be extremely useful. These are just two high-profile challenges, but there are many other problems that remain to be solved. One issue concerns the development of advanced catalysts. Activity and selectivity need to be constantly refined and improved, and catalyst recyclability will become a more important issue. It is clear that such advancements are likely only to be achievable through further mechanistic understanding and it is therefore gratifying to see that mechanistic studies are currently a hot topic in organocatalysis as a whole.

This Cluster, edited by Hisashi Yamamoto and myself, presents some recent work by leading experts in the field of proline-based aminocatalysis that addresses some of the above issues. Isn't it amazing how much high quality research this field continues to deliver? I am very grateful

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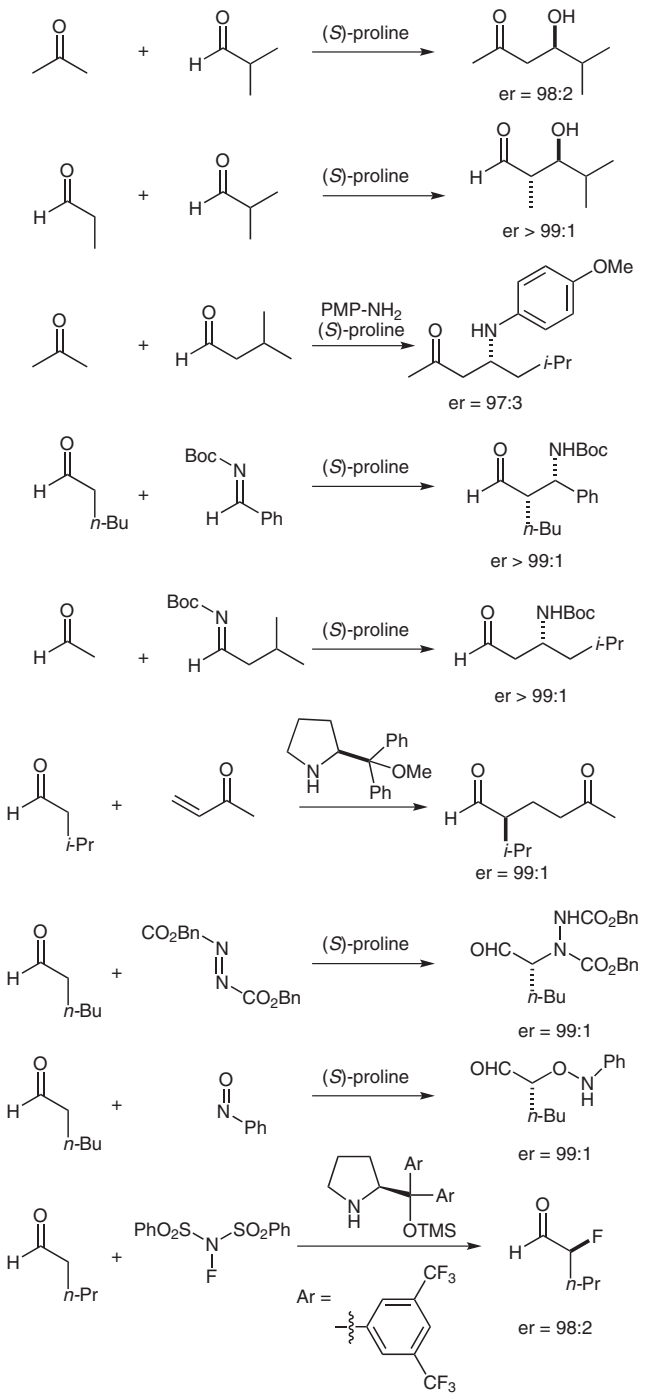

Scheme 1 A small and incomplete selection of highly enantioselective proline (derivative) catalyzed reactions.[2,4,5]

to all authors for their wonderful contributions and can't wait to see the advancements of the next decade….

References and Notes

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