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Proline Sulfonamide-Based Organocatalysis: Better Late than Never

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Abstract

The history of proline sulfonamides for use in catalyzing highly enantioselective and diastereoselective C-C bond forming reactions is described. Highlighted is the development of *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide ("Hua Cat") and *N*-(carboxy-*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide ("Hua Cat-II") by Yang and Carter. Specific reactions covered include the aldol reaction, Mannich reaction, formal aza-Diels-Alder reaction, tandem Michael/Mannich reaction and Yamada-Otani reaction. The ability of proline aryl sulfonamides to construct all-carbon quaternary stereocenters in high enantioselectivity and diastereoselectivity is a notable feature of the reported work. The practicality of this chemistry for large scale and industrial applications is also included. Finally, a discussion of the future directions of proline sulfonamide organocatalysis is provided.

Keywords

asymmetric catalysis; amino acids; enantioselectivity; sulfonamides; solvent effects; aldol reaction; multicomponent reaction; Michael addition; phase-transfer catalysis

1. Introduction

A great deal of interest has been focused in the past decade towards the use of enantiomerically enriched organic molecules as catalysts for facilitating enantioselective transformations – particularly carbon-carbon bond forming reactions. This interest was largely catalyzed by the seminal work of Listⁱ and MacMillanⁱⁱ in 2000. Numerous reviews have been written on the subject.ⁱⁱⁱ Interestingly, while the name "Organocatalysis" was coined by MacMillan in 2000,ⁱⁱ the general concept has been around for far longer. As early as 1954, Prelog reported the use of cinchona alkaloids for an asymmetric cyano-hydrin reaction.^{iv} A flurry of activity began in field starting in the late 1960's. Yamada and co-workers exploited the utility of stoichiometric proline-derived enamines for inducing asymmetry in a range of transformations.^v Hajos and Parrish's seminal work focused on a proline-catalyzed process for an intramolecular aldol reaction to construct bicyclic ring systems.^{vi} Wiechert, Eder and Sauer also reported the use of chiral amino acids as catalysts in a related process.^{vii} These important early discoveries laid the groundwork for the 21st century renaissance that this field has enjoyed – leading to the wealth of exciting chemistry being developed today. The utility of proline and proline derivatives for facilitating organocatalyzed reactions has proven particularly significant.

The proline-based organocatalysts can be broken down into seven general categories: proline and 4-trans-hydroxyproline derivatives **2**, proline esters **3**, prolinamines **4**,

prolinamides **5**, proline tetrazoles **6**, prolinols **7** and protected prolinols **8** (Scheme 1). For the purposes of this account, prolinamides can be broken down further into three sub-categories: simple amides **9** which do not contain significant additional functionality or stereochemistry, polystereogenic amides **10** and sulfonamides **11** (Figure 1).

Interestingly, proline sulfonamides represent one of the most recent additions to this large family of compounds (Figure 2). Since the discovery of 4-hydroxyproline by Fischer in 1902,^{viii} a wealth of proline derivatives have been synthesized. Based on SciFinder Scholar searches, prolinamide (**12**),^{ix} diphenyl prolinol (**13**)^x and proline methyl ester (**14**)^{ii,xi} were first reported prior to 1940. 4-Methoxyproline (**15**),^{viiiib} prolinol (**16**)^{xii} and prolinamine (**17**)^{xiii} were produced shortly thereafter. Proline tetrazole (**18**) was first synthesized in 1971 by Grzonka and coworkers.^{xiv} Prolinol methyl ether (**19**)^{xv,xxic} and its diphenyl derivative **20**^{xvi} were first reported in 1977 and 1988 respectively. Ether **20** was the important precursor for more recent diarylsilyloxy organocatalysts developed by Jørgensen and others.^{xvii} In contrast, the first proline sulfonamide was not reported until a tRNA synthetase inhibitor was studied by Easton and co-workers in 2003.^{xviii} Prior reports of proline sulfonamides were limited to three patent applications.^{xix} Interestingly, sulfonamides have been viewed as comparable to carboxylic acids in acidity.^{xx,xxi,xxii} Herein, we provide a detailed account of how the field of proline sulfonamide organocatalysis developed and in what directions it may be headed. Included within this Account is our own discoveries of *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide ("Hua Cat")^{xxiii} and *N*-(carboxy-*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide ("Hua Cat-II").

2. Proline Sulfonamides

2.1 Synthesis of First Proline Sulfonamides

Berkessel and co-workers reported the synthesis of the first proline aryl sulfonamides in 2004 (Scheme 2).^{xxiv} They reported the potential organocatalytic activity of three proline aryl sulfonamide catalysts (catalysts **21**, **25**, and **26**) with the reaction of acetone and *p*-nitrobenzaldehyde in a series of solvents and catalyst loadings.

In the following year, Ley and co-workers reported the synthesis of the parent members of the sulfonamide family - proline methyl sulfonamide **22** and proline phenyl sulfonamide **30** (Scheme 3).^{xx} These catalysts proved modestly effective at facilitating both aldol reactions and Mannich reactions – although the scope of substrates screened in this article was fairly narrow. In the same manuscript, Ley also reported their work with tetrazole **18** which Ley has continued to focus on after in subsequent manuscripts.^{xxv} In contrast, this article represents the sole published work from the Ley group on sulfonamide organocatalysis. Ley commented that the tetrazole **18** provided "significant advantages" over sulfonamide catalysts **22** or **30** through shorter reaction times and lower catalyst loading on otherwise identical transformations. Tetrazole **18** also provided unique reactivity that the sulfonamide catalysts were incapable of generating such as the Michael addition of cyclohexanone to α,β -unsaturated nitro compounds. Ley did note that sulfonamides **22** and **30** performed well in aldol reactions, as represented in Equation 3 (Scheme 3). Dichloromethane proved to be the optimum solvent in these transformations. It should be noted that the enantioselectivity in most cases was modest and the diastereoselectivity was general low. Finally, they observed that sulfonamides **22** and **30** had improved solubility properties to tetrazole **18** and proline.

In 2005, Adolfsson and Córdova reported the use of sulfonamides for the α -oxidation of ketones and enones using nitrosobenzene in up to 80% yield with excellent enantioselectivity (Scheme 4).^{xxvi} Ley's methyl sulfonamide catalyst **22** proved to be the most effective out of a range of catalysts screened in the process. Córdova also screened catalyst **22** for use in aza-Diels-Alder reactions, but found proline to be more effective.^{xxvii}

2.2 Early Proline Sulfonamide Organocatalysis

Several laboratories reported examples of using proline sulfonamides as organocatalysts in enantioselective aldol reactions. Zhao and Wang developed dendritic proline sulfonamide catalysts for use in aqueous aldol reactions.^{xxviii} Gouverneur and co-workers utilized phenyl sulfonamide catalyst **30** in an aldol reaction involving an α -OMOM protected ketone and benzaldehydes.^{xxix} Liu and co-workers showcased the ability of the same sulfonamide catalyst **30** to facilitate aldol reactions with trifluoromethyl ketone.^{xxx} Frongia explored the synthesis of phenylthio- and phenoxyaldol adducts using catalyst **30**.^{xxxi}

Kokotos and co-workers reported the first examples of 4-hydroxy proline derived sulfonamides (Scheme 5).^{xxxii} The authors commented that the benzyl ether protecting group on the 4-position imparted improved solubility properties as compared to proline itself.^{xxxiii,xxxiv} The scope of the reaction was limited to a single substrate and a polar solvent (DMF) was still utilized in the reaction. Interestingly, use of the standard sulfonamides **22** and **30** gave similar results (62–81% yield, 76–85% ee). Fu and co-workers later reported the use of 4-silyloxy proline sulfonamides in a related transformation.^{xxxv} Unfortunately, 4-*trans*-hydroxyproline is only commercially available in the (2*S*,4*R*) configuration shown below and is approximately ten times more expensive than proline itself.

We were particularly intrigued by Hayashi and coworkers' publication in late 2007 in which they detailed their elegant work utilizing 4-silyloxy proline as a viable organocatalyst.^{xxi} Within this full paper, a brief investigation into the use of long alkyl chains on an alkyl proline sulfonamide scaffold was included (Scheme 6). They screened two alkyl sulfonamides **40** and **41** and explored a single aldol reaction between benzaldehyde and cyclohexanone in aqueous media. Interestingly, a strong relationship between the length of the alkyl chain and the chemical yield of the aldol reaction was observed.

Nakamura, Toru and co-workers illustrated a nice example of proline sulfonamides' organocatalytic potential in their convolutamydine synthesis. A thiophene-containing proline sulfonamide was used as the key organocatalyst for facilitating an aldol reaction between acetone and dibromoisatin **43** (Scheme 7).^{xxxvi} They hypothesized a favorable hydrogen-bonding interaction between the thiophene and the sulfonamide as shown in transition state **45** to explain the improved stereoselectivity. Rasmini and coworkers demonstrated another interesting application of the proline sulfonamide through their use as polymeric aldolase mimics.^{xxxvii}

With the exception of Ley's early Mannich examples on five different substrates^{xx,xxxiiid} and Cordova's oxygenation work,^{xxvi} the majority of the chemistry reported using proline sulfonamide organocatalysis focused on the aldol reaction. In addition, there were several examples of transformations in which other catalysts such as the proline tetrazole **18**^{xx,xxxviii} or proline itself^{xxvii,xxxix,xl,xli} prove superior. It became clear to us that while preliminary work demonstrated the viability of proline sulfonamides as organocatalysts, the unique reactivity of these catalysts had not been fully realized. Furthermore, no chemistry had been developed with proline sulfonamides that alternative catalysts could not also facilitate effectively.

3. Hua Cat

3.1 Discovery of Hua Cat

The practical ease of these organocatalytic transformations (usually not requiring inert atmosphere or anhydrous conditions) coupled with the inexpensive source of chirality and lack of toxic reagents have attracted literally hundreds of research groups to the burgeoning

research area. Consequently, the highly competitive nature of the field has led to multiple cases of independently and concurrently discoveries of the same (or closely related) transformation. Furthermore, one possible viewpoint of the field could be that its pioneers have already made most of the key discoveries with organocatalyst-based scaffolds.

Our research group entered the field of organocatalysis with great trepidation to address a stereochemical challenge in our synthetic efforts towards the *lycopodium* alkaloids.^{xlii} In 2006, we were exploring an intramolecular Michael addition reaction of a ketosulfone onto a methyl enone moiety in compound **47**. This transformation was central to establishing the C_{7,8} stereochemical array of lycopodine. While we had initially expected that the existing organocatalysis literature would allow us to address this challenge in short order, we quickly realized that none of the known catalyst systems were effective at accomplishing this transformation. The challenge with this reaction was that we required non-polar solvents and low temperatures to achieve reasonable levels of enantiomeric excess. Unfortunately, most catalysts that proved effective at room temperature were simply not soluble in non-polar solvents at lower temperatures. In fact, the catalysts would often crystallize out of the reaction mixture upon cooling to below 0°C. To make matters worse, an unwanted background reaction became more prevalent at lower temperatures leading to the formation of a more complicated mixture. These two attributes led to the consistent observation that reduced temperatures led to worse levels of enantioselectivity!

One of the catalyst systems that we had initially screened was the proline sulfonamides — specifically catalysts **21**, **22** and **30**. We had not expected these catalysts to prove useful in this transformation as Ley reported little success using them in Michael addition reactions.^{xxa} Interestingly, these sulfonamides proved to be some of the most active catalysts we screened for this transformation. The similar reactivity between the phenyl and the *p*-tolyl sulfonamides **30** and **21** respectively presented us with an interesting question: if the *para*-substitution on the aromatic ring was not detrimental, could we attach a non-polar sidearm to further improve solubility? A scan of the literature revealed that either *para*-dodecylbenzenesulfonic acid chloride **51** was commercially available from Wako Chemicals as was the sodium sulfonate salt **50** from a vast array of manufactures. The sulfonate salt **50** can be readily converted to the sulfonyl chloride **51** by treatment with 3 equiv. of oxalyl chloride at room temperature for 13 h in quantitative yield. This scaffold is widely used to make detergents and is available inexpensively on metric ton scale. While the dodecyl chain on the aromatic ring existed as an isomeric mixture (e.g. 1-dodecyl, 2-dodecyl, etc.), we did not feel this would adversely impact the reaction. In fact, the mixture of dodecyl isomers might improve the solubility of any proline-derived sulfonamide catalyst. We quickly ascertained that the corresponding sulfonamide **52** could be prepared from sulfonyl chloride **51** by treatment with ammonium hydroxide in high yield. Subsequent coupling with Cbz-protected proline **53** followed by hydrogenation gave the target dodecylphenyl substituted sulfonamide **55**.^{xliib,xliii} This catalyst has been commercialized and will be available soon through Sigma-Aldrich and Synthetech, Inc.^{xxiii}

3.2 Intramolecular Michael Additions

With the catalyst **55** in hand, we investigated its performance in the intramolecular Michael addition. While this work was only published recently,^{xliib} it was the origin of our entry into the field of organocatalysis. To our delight, the catalyst **55** performed beautifully — generating the key cyclohexanone in high levels of enantioselectivity, diastereoselectivity and chemical yield. Due to the high solubility of **55**, we were able to successfully lower the reaction temperature and catalyst loading all the while increasing the reaction concentration. The optimized conditions employed 10 mol % of catalyst **55**. Ironically, this catalyst system, while useful, did not matriculate into the total synthesis of lycopodine,^{xlii} but the foundation for the sulfonamide-based organocatalysis had been established.

Given the success at this individual transformation, we quickly screened to see if these reaction conditions could function more broadly for a range of intramolecular Michael additions.^{xliib} We observed good levels of diastereoselectivity, enantioselectivity and chemical yields for these transformations. Both 5- and 6-membered cycloalkanones **57** (n = 1, 2) were accessible using this catalyst system.

3.3 Aldol Reactions

The success that we observed with the intramolecular Michael addition prompted us to investigate if catalyst **55** might prove more generally useful. Enantioselective aldol reactions have been often probed as a testing ground for new catalyst systems. While early examples of successful proline sulfonamide-based organocatalysis had been demonstrated by Berkessel, Ley and others, the scope of substrates explored was quite modest. Most examples had focused on acetone or cyclohexanone with *p*-nitrobenzaldehyde. Additionally, the level of diastereoselectivity and enantioselectivity varied from low (e.g. 2:1 dr) to encouraging. Finally, the solvent systems employed had continued to focus on more polar media – likely due to the modest solubility of the previous catalyst systems in non-polar solvents such as dichloromethane. For example, the solubility of **1**, **21**, **22**, and **30** in dichloromethane is all less than 5 mg/mL. In contrast, catalyst **55** displays excellent solubility in dichloromethane (300 mg/mL).^{xliib} We expected that improved levels of stereoselectivity might be accessible if these transformations were performed in less polar solvents.

Based on our successes in the intramolecular Michael additions, we felt non-polar solvents such as dichloroethane or dichloromethane would prove highly effective in these transformations. Our expectations were realized with excellent levels of diastereoselectivity and enantioselectivity as well as chemical yield in the aldol reaction on a wide range of substrates.^{xliii} While dichloroethane was the primary solvent reported in our original 2008 communication,^{xliia} we also have demonstrated that more industrially friendly solvents such as 2-methyl-tetrahydrofuran or neat reaction media are also effective in these transformation.^{xliib} The use of neat reaction conditions allowed us to dramatically drop the catalyst loading down to just 2 mol %. We even showed the practicality of this chemistry by conducting a 1 mole scale reaction in a single 500 mL round bottom flask. Based on this excellent reactivity, the fellow researchers in the group nicknamed the catalyst **55** “Hua Cat” (pronounce “Wha Cat”) after Dr. Hua Yang.

We also thought it was important to demonstrate whether our catalyst system was uniquely effective under these reaction conditions or if the yield and stereoselectivity was a general phenomenon for this transformation on the specified reaction conditions. Using our optimized conditions, we screened against the gamut of alternate sulfonamides **21–22** and **30** as well as proline (**1**) and its corresponding tetrazole **18**. In each case, Hua Cat **55** gave superior results as compared to the other catalysts.^{xliii} While all sulfonamides appeared to give improved levels of diastereoselectivity under the reaction conditions, the increased yields are likely due to the high solubility of **55**.

In 2009, Oregon State University hired a new computational organic chemist as a faculty member - Dr. “Paul” Ha-Yeon Cheong from Ken Houk’s group at UCLA. Through our collaboration with Professor Cheong’s research group, we have worked to garner a better understanding of this and related transformations. Consequently, we have recently developed an explanation for the improved level of diastereoselectivity observed with the proline sulfonamides (Figure 4).^{xliib} A non-classical hydrogen bond between the aldehyde C-H and the sulfonamide S-O appears to be key to the increased diastereoselectivity.

3.4 Mannich Reactions

As the Ley group had demonstrated early reactivity for proline sulfonamides in Mannich reactions,^{xx} extension of this catalyst system to a thorough probe of this transformation seemed to be the logical next step (Scheme 13). Once again, catalyst **55** showed good substrate scope and provided reasonable levels of enantioselectivity and diastereoselectivity.^{xliv} A total of sixteen examples were demonstrated with this transformation many of which provided access to α or β -amino acids. The stereoselectivities and chemical yields of these transformations were generally good to excellent. Industrially friendly solvents such as 2-methyl tetrahydrofuran or neat reaction conditions could be employed. A 100 mmol example of a Hua Cat-catalyzed Mannich reaction was also conducted to showcase the potential scalability of this process.

3.5 Aza Diels-Alder Reactions

With good successes in both the aldol and Mannich reactions, we began to look for chemistry that Hua Cat (**55**) could possibly address that has not proven particularly effective with other catalysts systems. One structural class that had caught our attention was the azabicyclo-[2.2.2]-octanes (or isoquinuclidines). These compounds have generated considerable synthetic attention due to their presence in numerous alkaloid natural products,^{xliv,xlvi} including the pharmaceutically relevant iboga alkaloids.^{xlvi} Prior asymmetric work in the field had primarily focused on using enantioenriched BINOL-derived, phosphoric Brønsted acids with modestly *endo*-selective products (typically 3–4:1 *endo:exo* selectivity) and reasonable enantioselectivities (typically 76–88% ee).^{xlvi,xlix,1,li} Pioneering work in the field by Rueping and Azap is shown in Scheme 14.^{xlviia}

Cordova and co-workers disclosed the only organocatalyzed examples with this reaction class in 2005 (Scheme 15).^{xxvii} Interestingly, they found in their reaction screening that proline (**1**) or tetrazole **18** worked better than the corresponding proline methyl sulfonamide **22**. The manuscript principally focused on variation of the enone motif (6 or 7-membered rings, γ,γ -dimethyl substituted cyclohexanones). While their reactions proceeded well under these parameters, the chemistry was limited to formaldehyde-derived imines. They reported a single exception using the highly activated α -imino glyoxylate **29**, which worked in only modest yield (25%), but with high *exo* selectivity. We hoped that our proline sulfonamide **55** might be able to expand the reaction scope - particularly on the imine substrate.

We were pleased to see that again Hua Cat (**55**) was able to deliver the required improvements to this transformation (Scheme 16).^{lii} Sixteen examples of a wide array of aromatic imines can be utilized. In side-by-side comparisons, our sulfonamide **55** provided higher levels of chemical yield and enantioselectivity when compared to proline (**1**). These reactions are performed in the absence of solvent – which demonstrates the scalability and practicality of this chemistry for industrial processes. Finally, a complete reversal in the *endo:exo* selectivity is observed as compared to the chiral phosphoric acids – catalyst **55** favored exclusively the *exo* product. The reason for this reversal in selectivity is presently unknown.

3.6 Quaternary Center Formation

During our exploration of the aza-Diels-Alder chemistry, we attempted to expand our imine substrate scope to include aliphatic imines. These substrates are particularly challenging due to their inherent ability to undergo imine/enamine tautomerization. Consequently, prior work in the field had largely avoided such substrates. Interestingly, use of catalyst **55** on these aliphatic imine structures revealed a divergent reaction pathway (Scheme 17).^{lii} For example, treatment of alkyl imines **77** under the standard conditions did not result in the formation of the corresponding azabicyclo-[2.2.2]-octane product. Instead, the all-carbon

bicyclo-[2.2.2]-octane variant **78** was produced.^{liii} This product likely arises through a slow tautomerization of the imine structure to an enamine, which undergoes conjugate addition to iminium-activated cyclohexenone. We demonstrated that a variety of symmetrical dialkyl imines **77** were tolerated in this transformation. Monoalkyl imines and unsymmetrical alkyl imines generated inferior chemical yields using these conditions. While we were unsure at the time as to an exact mechanistic picture for this transformation, reviewers of this manuscript pressed for inclusion of a possible explanation. Consequently, we included in the manuscript a possible mechanistic cartoon where we involve a long range, hydrogen-bonding interaction between the sulfonamide nitrogen and the enamine N-H derived from tautomerization of imine **77**.

3.7 Stereogenic, All-Carbon Quaternary Center Formation in Bicyclic Scaffolds

We were particularly excited by the discovery of the reaction to form bicycle **78**, which constructed two separate C-C bonds including an all-carbon quaternary center. While we only demonstrated a small subset of examples in Scheme 17, we quickly realized the potential in this transformation. If we could harness the quaternary center-forming capability of this chemistry for establishing *stereogenic, all-carbon quaternary centers*, this technology could have significant scientific impact. While the chemical yield is less than optimal, we were pleased to demonstrate a preliminary example for this transformation as shown in Scheme 18.^{lii} We consider the construction of stereogenic, all-carbon quaternary centers to be one of the true remaining challenges in asymmetric catalysis – particularly in cases where few (if any) electron-withdrawing groups are bonded directly to the circled carbon in **81**.^{liv,lv} Inspection of the product **81** shown in Scheme 18, illustrates that the potential is present for addressing many of these challenges.

One major hurdle that we needed to address urgently in this chemistry was increasing the equilibrium ratio of the enamine(s) derived from the imine (Scheme 19). We saw two immediate solutions to this issue. First, the nature of the substituent R bonded directly to nitrogen should have an impact on imine/enamine ratio. For example, switching from the resonance electron-donating *p*-methoxyphenyl (PMP) moiety to a non-conjugated protecting group (e.g. Bn) should lower the pKa of the α -hydrogen and increase the ratio of enamine/imine tautomerization. Second, the use of benzylic imines (e.g. **86**) should have a similar impact by providing additional stabilization to the enamines **85** and **87**.

Recently, we have begun to address these challenges – by providing access to benzylic, all-carbon quaternary centers in high enantio- and diastereoselectivity (Scheme 20).^{lvi} As we had hypothesized, key to this advance was the observation that 2-aryl substituted propanals **88** and benzyl amine (instead of *p*-methoxyphenylaniline) more readily generate the key enamine species. We demonstrated ten examples **89** – each containing four contiguous stereogenic centers in up to 98.3:1.7 er with excellent diastereoselectivity (>20:1 dr) and chemical yield (up to 76%). It is important to note that these multi-component reactions generate an equivalent of water through formation of the imine/enamine. Attempts to sequester this water through the use of molecular sieves led to inferior results. These scaffolds **89** should be applicable to a range of natural products such as kopsonoline (**90**).^{lvii}

3.8 Yamada-Otani Reaction

We next became interested in extending this chemistry to acyclic enone systems. Yamada and Otani laid the groundwork for this chemistry in the early days of organocatalysis (Scheme 21).^v Despite their encouraging early success, the Yamada-Otani reaction laid essentially dormant for over four decades. We suspect that the reactivity in these systems has proven significantly more challenging to modulate on substrates not containing two-resonance electron-withdrawing substituents. Additionally, controlling diastereoselectivity

in the key Michael addition step on acyclic enones possessing a β -non-hydrogen substituent adds an additional degree of complexity.

After some additional optimization, we were able to extend our technology to the Yamada-Otani reaction with acyclic enone substrates (Scheme 22).^{lviii} One important discovery was that a second-generation catalyst (Hua Cat-II) **98** provided improved levels of enantioselectivity. We attribute the difference in reactivity to the electron-withdrawing effect on the *p*-substituted ester on the aryl sulfonamide, which likely reduces the pKa of the sulfonamide N-H. We demonstrated twenty separate examples of this transformation with an average chemical yield of 60%. This methodology should be applicable to the synthesis of numerous steroidal natural products including viridin (**100**)^{lix} and hinokione (**101**).^{lx} During the peer review process of our work, Kotsuki and co-workers reported a greatly improved version of Yamada and Otani's reaction.^{lxi} Their elegant protocol involves a one-pot, two-step approach with a dual catalyst system of 30 mol % (*1R,2R*)-1,2-cyclohexanediamine and 30 mol % (*1R,2R*)-1,2-cyclohexanedicarboxylic acid and is effective on enone substrates which contain no substitution in the β -position. We view this work as a nice complement to our research as our sulfonamide catalysis shown in Scheme 22 works on enone substrates, which contain a β -non-hydrogen substituent on the enone.

4 Future Directions

We have only begun to tap the potential of proline sulfonamides (Figure 4). New catalyst structures should lead to unique reactivity and new transformations. Our recent work on the Yamada-Otani reaction with our second-generation catalyst **98** is a prime illustration of the potential we see for catalyst modification.^{lviii} We have also started to report additional examples of proline sulfonamide catalysts such as the deoxy catalyst **102** and the pyridyl catalyst **103**.^{xlviib}

Despite the wealth of research that has been conducted in the field of organocatalysis, it is our view that the synthetic community is only beginning to harness the full power of this technology. Proline sulfonamide organocatalysis may have emerged relatively late to the field, but the utility that our group and other laboratories have showcased bodes well for its future. The development of new reaction pathways (and catalysts) that push the boundaries of modern synthetic chemistry with increased structural complexity will likely continue for many years to come. Proline sulfonamide organocatalysis is well positioned to contribute to the future growth in this field.

5 Conclusion

A detailed account of the development of proline sulfonamide organocatalysis is provided. Pioneering work by Berkessel,^{xxiv} Ley^{xx} and Cordova^{xxvi} and leading examples from other research laboratories in the field are discussed. Our research program subsequently entered this field through the introduction of the *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (nicknamed "Hua Cat"). This catalyst **55** has proven useful at facilitating a range of organocatalytic transformations. Recent introduction of our second generation catalyst, *N*-(carboxy-*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (nicknamed "Hua Cat-II"), has helped to further advance the field of proline sulfonamide organocatalysis to include the construction of all-carbon quaternary centers in a high enantioselective and diastereoselective fashion.

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Figure 1.
Subclasses of Prolinamides.

Figure 2.
Timeline of Proline Derivatives.

Figure 4. Preferred *Anti-Re* Transition State Based on Computational Model of Aldol Reaction with Proline Sulfonamides.

Figure 4.
Future Generations of Proline Sulfonamide Organocatalysts.

Scheme 1.
Classes for Proline Derivatives.

Scheme 2.
Berkessel's Early Sulfonamide Aldol Examples (2004).

Scheme 3.
Ley's Early Sulfonamide Examples (2005).

Scheme 4.

Adolfsson and Córdova's α -Oxidation of Ketones and Enones (2005).

Scheme 5.
Kokotos's 4-Benzyoxyproline Sulfonamide-Catalyzed Aldol Reactions.

Scheme 6.
Hayashi's Alkyl Sulfonamide Catalyzed Aldol Reaction.

Scheme 7.
Nakamura and Toru's Thiophene-Derived Proline Sulfonamide Catalyst.

Scheme 8.
Intramolecular Michael Addition for Lycopodine Core.

Scheme 9.
Synthesis of Hua Cat.

Scheme 10.
Application of Hua Cat to Lycopodium Core.

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Scheme 12.
Aldol Reactions Catalyzed by Hua Cat.

Scheme 13.
Mannich Reactions Catalyzed by Hua Cat.

Scheme 14.
Rueping's Bronsted Acid-Catalyzed Formal Aza Diels Reaction.

Scheme 15.
Cordova's Proline Catalyzed Formal Aza-Diels Alder Reaction.

Scheme 16.
Aza Diels-Alder Reaction Catalyzed by Hua Cat.

Scheme 17.

Discovery of Quaternary Center Forming Reaction Cascade.

Scheme 18.

Preliminary Example of the Formation of an All-Carbon Stereogenic Center.

Scheme 19.
Equilibrium Between Enamines and Imine.

Scheme 20.
Enantioselective Synthesis of Stereogenic, All-Carbon Quaternary Center-Containing [2.2.2]
Bicycles Catalyzed by Hua Cat.

Scheme 21.
Yamada and Otani's Pioneering Work.

Scheme 22.
Enantioselective Synthesis of Stereogenic, All-Carbon Quaternary Center-Containing
Cyclohexenones Catalyzed by Hua Cat-II.