Highlight Review

Development of Chiral Bicyclic Triazolium Salt Organic Catalysts: The Importance of the *N*-Aryl Substituent

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Abstract

The development of a family of chiral bicyclic triazolium salts is described. Treatment of these salts with base provides a nucleophilic carbene which may be used as an organic catalyst for asymmetric acyl anion chemistry including the benzoin and Stetter reactions, and some recently developed redox chemistry. Throughout the development of these reactions, the nature of the *N*-aryl substituent on the triazole ring has proven to have a profound effect on both reactivity and selectivity. These observations have also paralleled those made by others using our family of catalysts.

♦ Introduction

The development of novel methods for stereoselective bond formation is of paramount importance in organic synthesis. Reactions that take advantage of reversed reactivity are of particular interest since they lead to non-classical bond disconnections. This reversed mode of reactivity has been termed umpolung.[1] Although a variety of umpolung approaches have been reported, we have been interested in the conversion of aldehydes into acyl anion equivalents using catalytic amounts of triazolium salts in the presence of base. Typified by the benzoin reaction catalyzed by cyanide, this reactivity dates back to 1832 in a landmark paper by Wöhler and Liebig,[2] a scant four years after Wöhler's synthesis of urea[3] dispelled the myth that organic chemicals only came from living organisms.

Lapworth first proposed the correct mechanism for the benzoin reaction in 1903.[4] In 1943, Ukai et al. showed that thiazolium salts, in the presence of base, also catalyze the benzoin reaction,[5] reminiscent of the action of thiamine pyrophosphate in biological systems. Breslow's elucidation of the mechanism, which confirmed that the base serves to deprotonate the 2-position of thiazolium salt thereby generating the ylidic/carbenic active catalyst, was published in 1958.[6] Initial work by Sheehan et al. using chiral thiazolium salts as precatalysts generated benzoin in low yield and poor enantiomeric excess (ee) but served to validate the concept that an enantioenriched catalyst relayed stereochemical information to the product.[7] Sheehan's work was rich in foresight, but the efficiency of these catalysts (59% yield, 4% ee) left much to be desired.

♦ Catalyst Design

In 2000, we initiated a program aimed at the development of chiral, nucleophilic carbenes for use in organic synthesis. Our design benefited extensively from the knowledge acquired over the 35 years since Sheehan's original paper. A bicyclic restriction with the placement of the stereocenter proximal to the azolium seemed to be most promising. That said, thiazolium salts were problematic in spite of their demonstrated success in catalyzing the benzoin[8] and their presence in thiamine pyrophosphate. This deficiency was due to their lack of a substituent in three of the four quadrants surrounding the reactive carbene center, Figure 1. This problem was endemic in asymmetric thiazolium-catalyzed benzoin reactions, which, despite extensive efforts from various individuals, uniformly provide low ee's of product.[9] We turned our attention to triazolium salts, previously disclosed by Enders, Teles, et al.[10] to be active in the benzoin reaction.[8] These would allow us to tune the electronic and steric nature of the group on nitrogen in order to optimize both reactivity and selectivity.

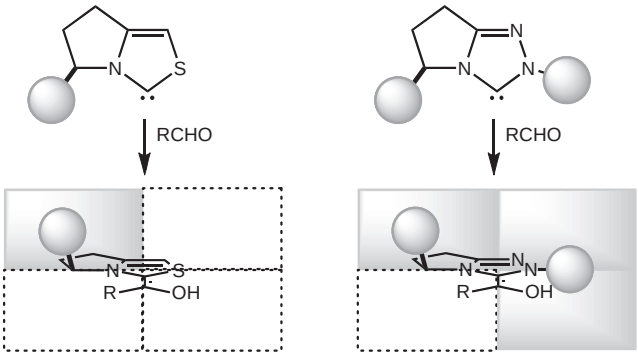

Figure 1. Rationale for triazolium catalysts.

This analysis led us to design two complementary families of catalysts: the morpholine-fused triazolium salts **1** and the pyrrolidine-fused triazolium salts **2**. Both catalysts are modular, bearing a hydrazine, a formate moiety and a lactam, the latter ultimately derived from amino acids and amino alcohols. The chirality and the nature of its substituents are derived from the chiral pool, taking advantage of the ready availability of many different R groups and the comparable cost of both enantiomers. The assembly of these catalysts is both rapid and scaleable.[11,12]

The hydrazine portion allows us to install a variety of aryl groups on the nitrogen in order to investigate the steric and electronic impact of variation at this position. Indeed, the proximity

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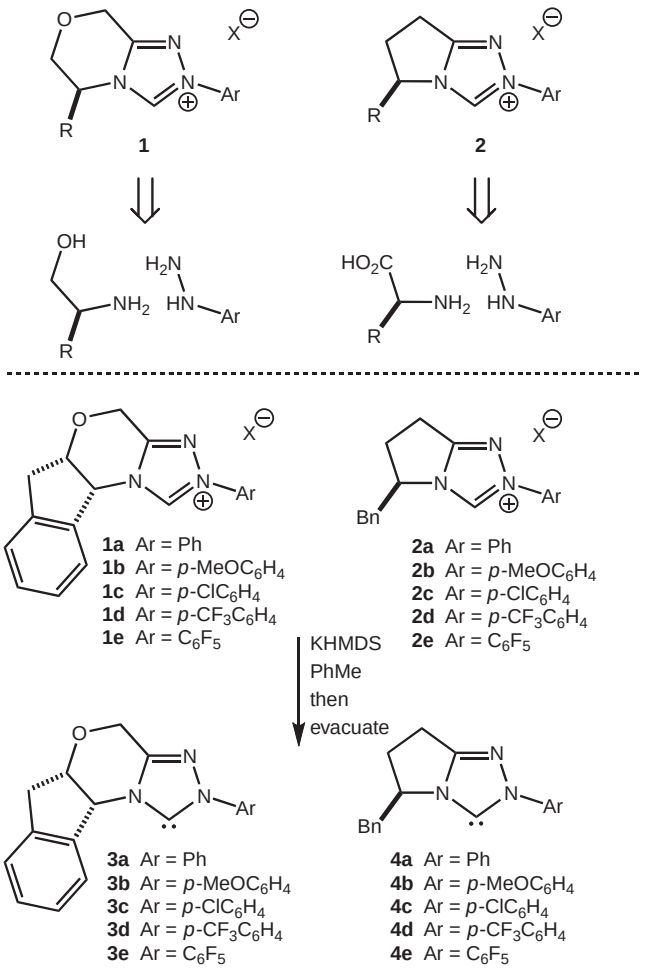


Scheme 1. Chiral triazolium catalysts.

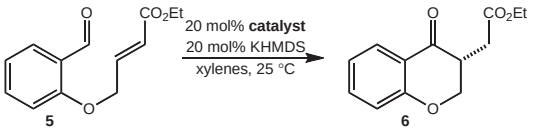
of this group to the reacting carbene center would likely affect reactivity by altering the energies of diastereomeric transition states. More subtle is the consideration of electronics at the carbene carbon. Though the electron-releasing or electron-withdrawing nature of the aryl substituent will play a role in the overall stability of the carbene, it was also foreseen that electronics would play a role in modulating the inherent basicity of these organocatalysts. Nucleophilic carbenes are known to be basic, with di-*tert*-butylimidazolylidine having a pK_a of 23 in DMSO.[13] We felt that electronic tuning of the aromatic ring on the azolium would modulate basicity without disrupting the beneficial effects imparted by the sterics of the system. The hope was to generate enantioenriched products bearing alpha-chiral, alpha-acidic carbonyls, avoiding subsequent epimerization. This analysis, along with some serendipitous discoveries, led us to a family of catalysts outlined in Scheme 1. The two parallel families of aminoindanol-derived morpholinyl catalysts **1** and the pyrrolidine-derived catalysts **2** behave analogously, with the former providing greater selectivities while the latter is more reactive. We have also developed a protocol which generates the carbene in the absence of conjugate acid by evacuating the flask after addition of KHMDS (to remove the volative HMDS conjugate acid). These latter catalysts, **3** and **4**, behave differently in some cases and merit independent consideration.

♦ *Asymmetric Stetter Reaction*

With a rapid and modular synthesis of these azolium salts in hand, we turned our attention to using them as precatalysts in a number of asymmetric transformations. Although we initially targeted a variety of acyl-anion-mediated reactions, our attention immediately focused on the Stetter reaction, the addition of an aldehyde into a Michael acceptor.[14] Extensive work by Stetter revealed that aromatic and aliphatic aldehydes can participate in a conjugate addition to Michael acceptors. The range of Michael acceptors was somewhat worrisome, with unsubstituted systems dominating (acrylates and vinyl ketones). Beyond this, chalcones and related systems were also shown to participate, but these substrates did little to allay our fears since the products would be alpha-aryl ketones, susceptible to epimerization in the presence of weak bases. Of course, some of these issues could be alleviated if the catalysts proved to be weakly basic.

With these caveats in mind, we began our investigations by applying our catalysts to the same substrates used by Enders in his seminal asymmetric Stetter study.[15,16] These salicylaldehyde-derived tethered systems were previously shown by Ciganek to undergo the intramolecular Stetter reaction in good yield.[17] The caveats listed above were largely avoided with the added limitation of an intramolecular reaction.

Our optimization studies revealed strong bases such as KHMDS along with low polarity solvents such as xylenes or toluene to be optimal in inducing high enantioselectivities. Within these parameters, precatalyst **1a** bearing the aminoindanol sidechain proved best in terms of selectivities, but only afforded modest yields (eq 1). Following the rationale described above, we adjusted the nucleophilicity of the carbene and the resultant nucleophilic alkene, also known as the Breslow intermediate, by installing an electron-releasing para-methoxy group on the azolium aryl ring, which had the desired effect, maintaining enantioselectivity while significantly raising conversion and overall efficiency. Interestingly, the slightly more electron-deficient *para*-chloro catalyst **1c** yielded results identical to the parent phenyl precatalyst **1a**. Parallel optimization with the pyrrolidine-fused salts **2** revealed that **2a** was also an efficient precatalyst.[18]



(1)

catalyst	
1a·BF$_4$	58%, 95% ee
1b·BF$_4$	94%, 94% ee
1c·BF$_4$	60%, 91% ee
2a·BF$_4$	94%, 90% ee
2d·BF$_4$	95%, 92% ee

These two catalysts **1b** and **2a** proved general and allowed us to facilitate the transformation of a variety of substituted salicylaldehyde-derived Stetter substrates **7** and **8** as well as aliphatic aldehydes **9** (Scheme 2). That said, we also identified some problems with these salts. A number of substrates gave inexplicably lower ee's: for example, *meta*-methoxy- and *meta*-halo-salicylaldehydes, all of which are sigma-withdrawing groups. The use of more electron-deficient catalysts allowed us to improve enantioselectivities in a range of substrates **10**–**14** (Scheme 2). Intriguingly, although ee's were the greatest

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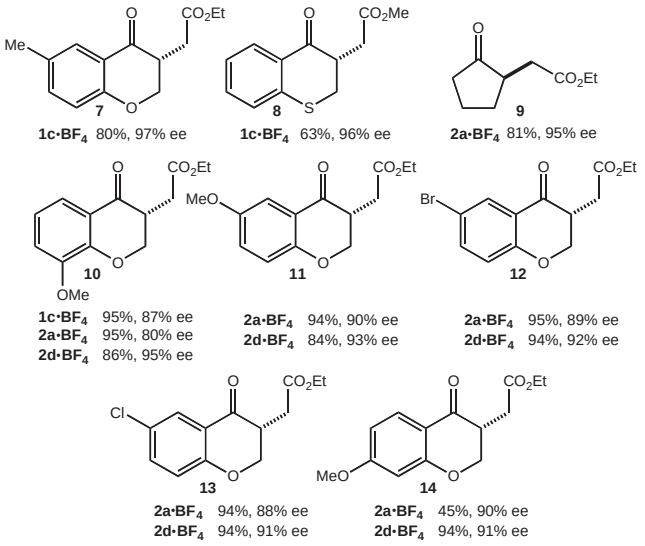
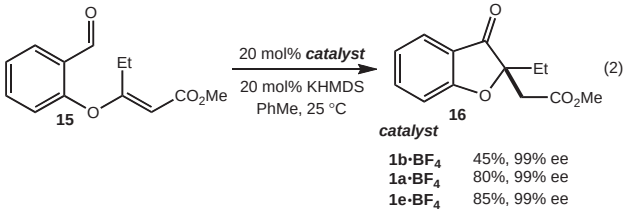


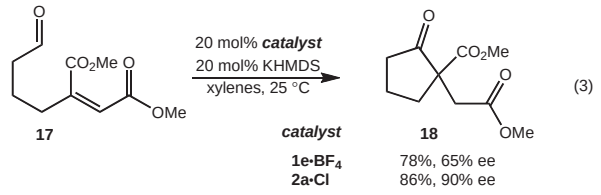
Scheme 2. Asymmetric intramolecular Stetter.

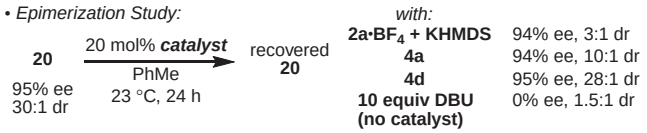
benefactor, conversion and yield are also subject to improvement **14**.[18]

The advent of more electron-deficient catalysts and their unexpected impact on the Stetter reaction allowed us to tackle more difficult problems, such as cyclization onto trisubstituted alkene acceptors. Vinylogous carbonate **15**, bearing a β,β-disubstituted Michael acceptor, was examined in the Stetter reaction. The use of the *p*-anisyl precatalyst **1b** provides the adduct in exquisitely high ee's but modest yield, eq 2, likely a reflection of the difficulty of the cyclization. A marked improvement in efficiency was observed using the very electron-deficient pentafluorophenyl-containing catalyst **1e**.[19]



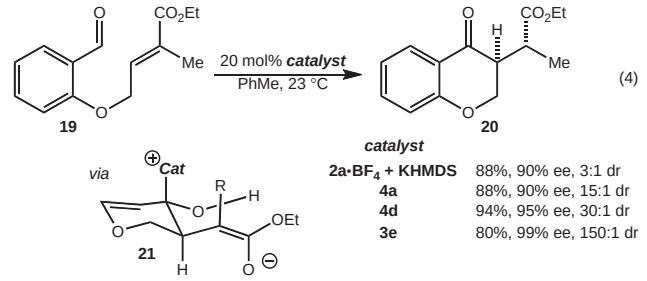
In the context of this study, we also identified a potential problem that suggested the electron-deficient catalyst **1e** may not be a global panacea. Cyclization of aliphatic aldehyde **17** onto the maleate acceptor results in disappointingly low ee's in spite of the tolerance of this catalyst to groups ranging in size from methyl to phenyl. Gratifyingly, the use of the pyrrolidine catalyst **2a** provides high ee's in this case, eq 3. Although the reasons are not clear, the use of catalyst **1e** has repeatedly provided low ee's when cyclizing onto very electron-deficient alkenes (vide infra).



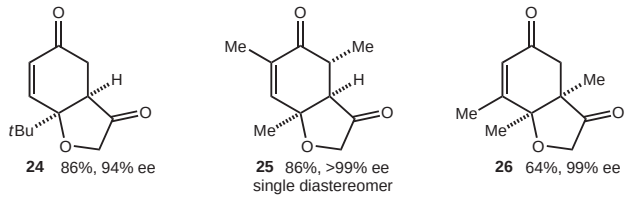


Scheme 3. Diastereoselective Stetter.

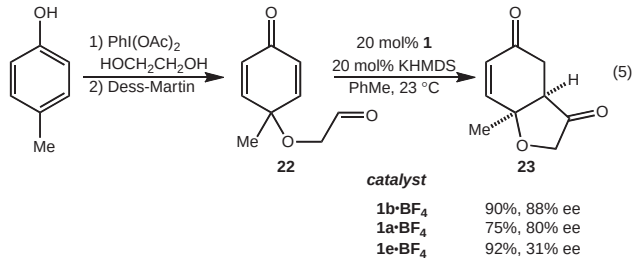
Installation of a third substituent on the Michael acceptor alpha to the electron-withdrawing groups provides an opportunity to develop a diastereoselective asymmetric Stetter reaction. Indeed, our family of catalysts competently mediate this transformation by virtue of a highly diastereoselective intramolecular proton transfer to set the second stereocenter. Catalyst structure once again affects the selectivities of this reaction. Enantioselectivities of the major diastereomer are almost uniformly high, but the diastereoselectivities vary as a function of electron-deficient nature of the aromatic ring. One hypothesis for this effect is that more basic catalysts cause partial epimerization in the process, thus reducing the high kinetic selectivities. Indeed, a series of control experiments revealed that partial epimerization occurs with all catalysts except the most electron-deficient ones such as **4d**, Scheme 3. Interestingly, the morpholine-backbone catalyst **3e** provides higher diastereoselectivities but slightly lower conversions. Gratifyingly, this procedure has proven to be very general.[20]



In an effort to expand the scope of this transformation, we sought to identify new structural and substrate motifs that would be amenable to catalysis. Oxidation of para-substituted phenols with hypervalent iodine reagents in the presence of nucleophiles is known to generate dienones.[21] The use of glycol as nucleophile provides, upon oxidation, a Stetter substrate. We have found that our suite of catalysts mediates this transformation readily.[22] Interestingly, and contrary to almost all of our previous work, the most electron-deficient precatalyst **1e** affords the lowest selectivities, while the most electron-releasing precatalyst **1b** is optimal. Control experiments revealed that the reaction is irreversible under all conditions surveyed. The cause of this extreme variation in enantioselectivity is not yet known. The approach, however, is remarkably general. Various substitutions are tolerated including the use of trisubstituted acceptors, Scheme 4, forming three contiguous stereocenters (**25**) as well as contiguous tetrasubstituted carbon stereocenters (**26**) in excellent efficiency.



Scheme 4. Dienone desymmetrization.

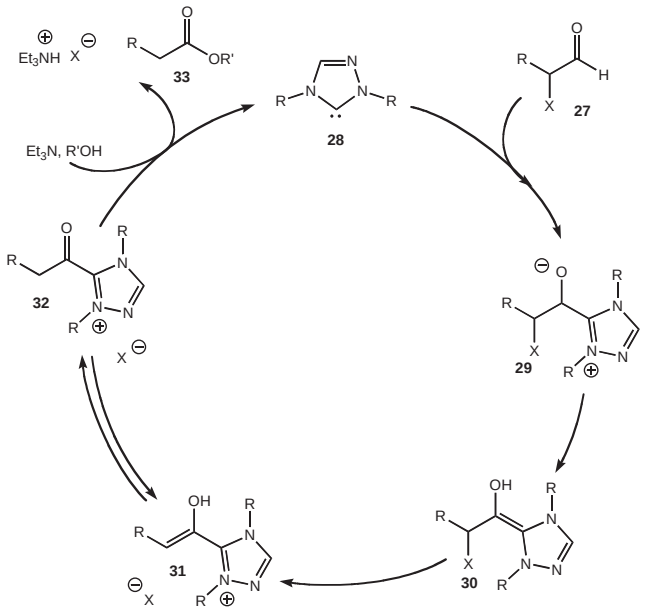


(5)

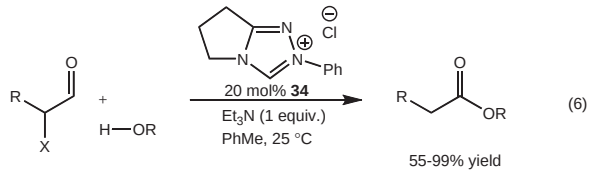
♦ Redox Catalysis

A parallel effort in our lab has centered on the identification of new reactivity associated with our carbene catalysts. Generation of the Breslow intermediate **30** in the presence of an α-reducible functionality should provide an enol-azolium **31** in situ which, upon tautomerization, should provide an acylazolium **32**, which has been demonstrated to undergo acyl-transfer chemistry in the presence of nucleophiles, Scheme 5.

In the event, the use of haloaldehydes as electrophiles and a variety of triazolium salts as precatalysts, in the presence of base, led to a redox esterification with primary and secondary alcohols as well as phenols, eq 6. The use of a chiral catalyst allows us to desymmetrize meso-diols in good ee.[23] It is notable that conceptually identical reactivity was concurrently demonstrated by Bode and coworkers.[24]

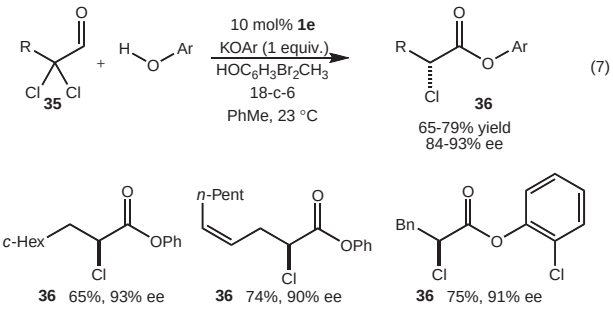


Scheme 5. Proposed redox catalytic cycle.



(6)

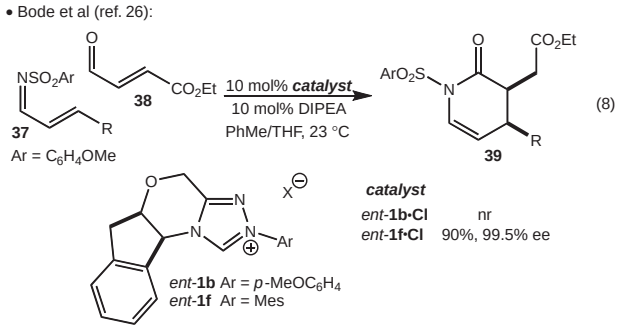
We were particularly intrigued with the idea of intercepting the enol-azolium intermediate **31** in an asymmetric enol(ate) functionalization using our suite of chiral catalysts. In an initial report we have demonstrated that 2,2-dichloroaldehydes undergo an asymmetric protonation/esterification reaction to generate enantioenriched α-halo aryl esters in good yield and selectivity, eq 7. Catalyst **1e** is almost uniquely effective in this chemistry, tolerating an excess of acidic phenols while still maintaining excellent reactivity.[25]



(7)

♦ Contributions from Other Labs

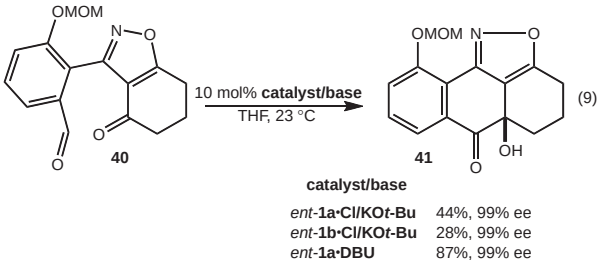
This family of chiral triazolium salts has also been exploited by other workers across the world. Bode has developed a hetero-Diels–Alder reaction between a reducible aldehyde and an α,β-unsaturated imine catalyzed by these chiral triazolium salts. The use of catalyst **1c**·Cl affords no product under these conditions, while the mesityl catalyst **1f**·Cl provides the cycloadduct in excellent yield and selectivity.[26]



(8)

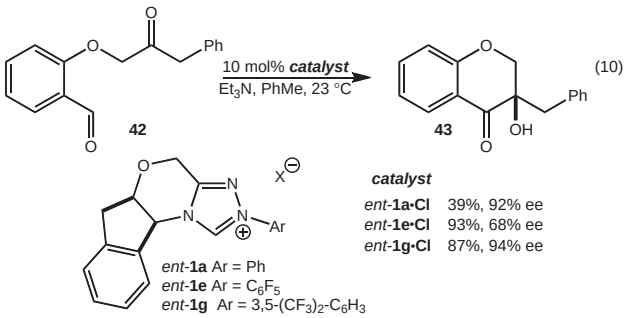
Suzuki has illustrated that this family of catalysts is extremely effective at inducing the asymmetric intramolecular cross-benzoin reaction between aldehydes and ketones, a transformation of potentially significant synthetic utility. Catalysts **1a** and **1b** each provide very high enantioselectivities but the former affords higher conversions and was chosen for further development.[27,28]

• Suzuki et al (ref. 27):



Recently, Suzuki has applied this reaction to the synthesis of (+)-sappanone B. Use of precatalyst **1a**•Cl and Et_3N in toluene provided the desired benzoin in excellent ee but low yield, complicated with significant amounts of aldol adducts, likely arising from base-induced enolization of the ketone. To overcome this effect, Suzuki tuned the electronics of the catalyst; precatalyst **1e** affords no aldol byproducts but provides low ee's. Further optimization revealed that precatalyst **1g**•Cl has the optimal mix of low basicity and high selectivity, eq 10.[29]

• Suzuki et al (ref. 29):



♦ *Conclusion and Outlook*

The development of chiral, nucleophilic carbenes for use in organic synthesis has benefited from the expected impact of the fused ring and nature of the side chain chirality. What was not expected is the significant impact of the *N*-aryl substituent, both in terms of sterics and electronics. Some of these effects are easy to rationalize; a more electron-releasing substituent is more likely to cause epimerization of the newly formed stereocenters, a situation demonstrated by ourselves and Suzuki. Other effects are far more subtle, such as the lower enantioselectivity caused by a more electron-deficient catalyst in cyclizations onto dienones. Ongoing experimental and theoretical efforts are focused on some of these issues.

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References and Notes

1 a) D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534. c) J. S. Johnson, *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. d) M. Pohl, B. Lingen, M. Müller, *Chem.—Eur. J.* **2002**, *8*, 5288. e) V. Nair, S. Bindu, V. Sreekumar, *Angew. Chem., Int. Ed.* **2004**, *43*, 5130. f) K. Zeitler, *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. g) M. Christmann, *Angew. Chem., Int. Ed.* **2005**, *44*, 2632.
2 F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249.
3 F. Wöhler, *Ann. Chem. Phys.* **1828**, *37*, 330.
4 A. J. Lapworth, *J. Chem. Soc., Trans.* **1903**, *83*, 995.
5 T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Sci. Jpn.* **1943**, *63*, 296.
6 R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.
7 a) J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666. b) J. C. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196.
8 a) D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217. b) J. H. Teles, J.-P. Meldes, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61.
9 a) W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478. b) J. Martí, J. Castells, F. López-Calahorra, *Tetrahedron Lett.* **1994**, *35*, 699. c) K. Yamashita, S.-I. Sasaki, T. Osaki, M. Nango, K. Tsuda, *Tetrahedron Lett.* **1995**, *36*, 4817. d) R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611. e) A. U. Gerhard, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3615. f) C. A. Dvorak, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 2925.
10 a) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021. b) D. Enders, K. Breuer, J. H. Teles, K. Ebel, *J. Prakt. Chem.* **1997**, *339*, 397. c) D. Enders, K. Breuer, U. Kallfass, T. Balensiefer, *Synthesis* **2003**, 1292. Leeper has also described a chiral bicyclic triazolium salt for use in the benzoin reaction: R. L. Knight, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891.
11 M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725.
12 Chiral triazolium salt **1e** is commercially available from Sigma Aldrich (Cat. No. 674788; CAS # 872143-57-2).
13 a) Y.-J. Kim, A. Streitweiser, *J. Am. Chem. Soc.* **2002**, *124*, 5757. b) R. W. Alder, P. R. Allen, S. J. Williams, *J. Chem. Soc., Chem. Commun.* **1995**, 1267. c) T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas, K. Toth, *J. Am. Chem. Soc.* **2004**, *126*, 4366.
14 a) H. Stetter, H. Kuhlmann, *Org. React.* **1991**, *40*, 407. b) J. Read de Alaniz, T. Rovis, manuscript submitted.
15 D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899.
16 Subsequent to our own work, several other groups have also described catalytic asymmetric Stetter reactions; see: a) J. Pesch, K. Harms, T. Bach, *Eur. J. Org. Chem.* **2004**, 2025. b) S. M. Mennen, J. T. Blank, M. B. Tran, J. E. Imbriglio, S. J. Miller, *Chem. Commun.* **2005**, 195. c) Y. Matsumoto, K. Tomioka, *Tetrahedron Lett.* **2006**, *47*, 5843. d) For a parallel study involving the asymmetric intermolecular addition of acylsilanes to enamides mediated by metallophosphite catalysts, see: M. R. Nahm, J. R. Potnick, P. S. White, J. S. Johnson, *J. Am. Chem. Soc.* **2006**, *128*, 2751.
17 E. Ciganek, *Synthesis* **1995**, 1311.
18 a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298. b) J. Read de Alaniz, M. S. Kerr, T. Rovis, manuscript submitted.

19 M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876.
20 J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284.
21 a) A. Pelter, S. M. A. Elgendy, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891. b) R. M. Moriarty, O. Prakash, *Org. React.* **2001**, *57*, 327. c) M. Trân-Huu-Dâu, R. Wartchow, E. Winterfeldt, Y. Wong, *Chemistry* **2001**, *7*, 2349. d) S. Canesi, D. Bouchu, M. A. Ciufolini, *Org. Lett.* **2005**, *7*, 175.
22 a) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552. b) Q. Liu, T. Rovis, *Org. Process Res. Dev.* **2007**, *11*, 598.
23 N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518.
24 K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126.
25 N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406.
26 M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.
27 H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem., Int. Ed.* **2006**, *45*, 3492.
28 Enders et al. have published a similar study using a slightly modified triazolium salt precatalyst; see: D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem., Int. Ed.* **2006**, *45*, 1463; For an asymmetric intermolecular benzoin, see: D. Enders, U. Kallfass, *Angew. Chem., Int. Ed.* **2002**, *41*, 1743.
29 H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713.