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A Highly Enantioselective Catalytic Intramolecular Stetter Reaction

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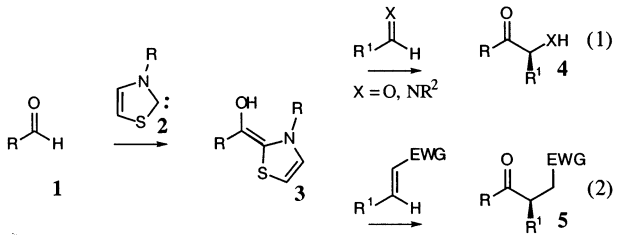
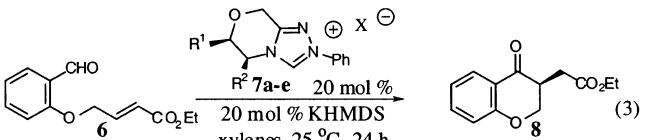
Umpolung reactivity of functional groups is a potentially powerful method for reversing the normal mode of a reaction and can provide access to new bond disconnections.[1] One such reaction family is exemplified by the benzoin reaction, a nucleophile-catalyzed aldehyde addition into an aldehyde or imine with concomitant formation of a stereocenter, eq 1.[2] Thiazolium salts, in the presence of base, are among several types of nucleophiles that have been illustrated to promote this reaction.[3] A number of workers have attempted to render this process asymmetric with chiral thiazolium and triazolium salts.[4] The Stetter reaction is an extension of this transformation and provides access to 1,4-dicarbonyl systems.[5] Should the Michael acceptor involve a prochiral alkene, this reaction would generate a new stereocenter, eq 2. Despite the potential of this reaction,[6] a single example of an asymmetric variant has appeared.[7] Herein we report the development of a family of chiral catalysts leading to a highly enantioselective intramolecular[8] Stetter reaction.



Chiral triazolium salts such as **7a**−**d** are conveniently prepared in 30−50% overall yield from amino acids in a modification of the literature procedure.[9] These salts are air- and water-stable crystalline solids with melting points around 200 °C. Treatment of the salt with a base results in removal of the acidic triazolyl proton and generation of the carbene intermediate.[10] A survey of common bases identified KHMDS as providing an optimal balance between yield and selectivity in this reaction.[11] A subsequent solvent screen revealed that low-polarity solvents led to consistently higher ee's, with xylenes providing the best results.[12]

Under optimized conditions, the reactivity of a series of structurally similar carbenes was studied, eq 3. *tert*-Leucine derived catalyst **7b** proved to be inactive in the intramolecular Stetter reaction, which we ascribe to steric congestion. The benzyl catalyst was found to be superior to both valine- and phenylglycine-derived catalysts. Last, a catalyst derived from the Merck aminoindanol showed optimal selectivities, with slightly reduced yields.

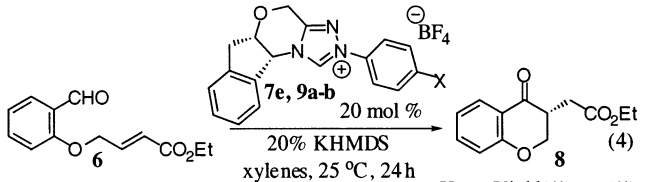
In an effort to improve yields and maintain high selectivities, the electronic nature of the phenyl ring on the triazole nitrogen was varied. We reasoned that upon addition of the carbene to the aldehyde and formation of the Breslow intermediate **3**,[3b] a more electron-rich complex should be more nucleophilic, which would



	R^1/R^2	X	Yield (%)	ee (%)
a	H/Bn	BF_4	85	90
b	H/*t*-Bu	BF_4	0	-
c	H/*i*-Pr	Cl	27	79
d	H/Ph*	Cl	48	80
e	Indanyl*	BF_4	58	95

*enantiomeric catalyst was used

facilitate addition into the electron-deficient alkene. In the event, substitution at the para position of the aromatic ring plays an important role in the reactivity of the catalyst, eq 4. 4-Methoxyphenyl catalyst **9b** was shown to provide product **8** in significantly higher yield than the parent phenyl **7e** and *p*-chloro **9a** catalysts with excellent enantioselectivity.



	X	Yield (%)	ee (%)
7e	H	58	95
9a	Cl	60	91
9b	OMe	94	94

An examination of the scope of this reaction showed that aminoindanol-derived catalyst **9b** and phenylalanine-derived catalyst **24** were optimal for providing high yields and enantioselectivities in the intramolecular Stetter reaction, Table 1. Salicylaldehyde-derived substrates **6**, **10**, **11**, and **12** demonstrate that substitution on the phenyl ring is tolerated and leads to subtle differences in reactivity and selectivity. The best results were obtained on substrates lacking steric bulk near the reactive site, particularly **6** and **10**, entries 1 and 2. Substrates **11** and **12** show that substitution of hydrogen at the 3 position of the aromatic ring by a larger group results in decreased selectivity, entries 3 and 4.

A series of similar substrates lacking the phenol ether linkage was prepared and subjected to the reaction, entries 5−8, Table 1. The presence of sulfur in place of oxygen in the tether provides high selectivity albeit slightly lower yields (entry 5). The reaction is tolerant of nitrogen in the tether, providing the product ketones in moderate yield with good enantiomeric excess, entries 6 and 7. Finally, although catalyst **9b** furnishes low yields in the reaction of **16**, the use of phenylalanine-derived catalyst **24** provides carbocycle **23** in 90% yield and 92% ee, entry 9.

It has been established that nucleophilic carbenes are strong bases,[13] and we were initially concerned that the newly formed

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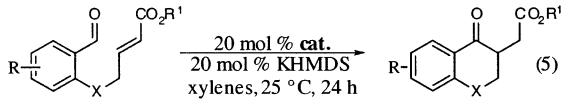
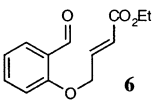
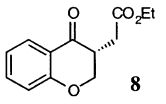
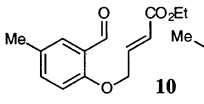
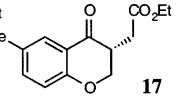
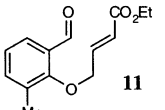
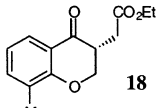
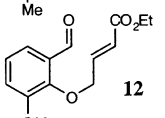
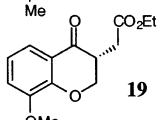
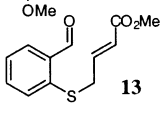
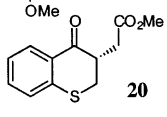
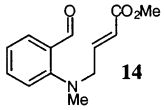
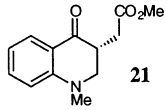
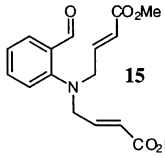
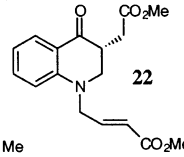
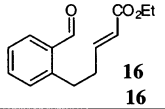
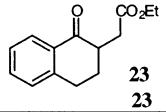
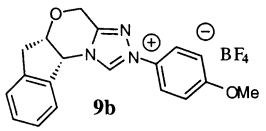
Table 1. Scope of the Enantioselective Intramolecular Stetter Reaction

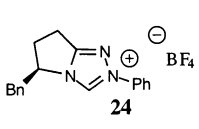


Entry[a]	Substrate	Product	cat.	Yield (%)	ee (%)[c]
1	 **6**	 **8**	**9b**	94	94
2	 **10**	 **17**	**9b**	80[b]	97
3	 **11**	 **18**	**9b**	90	84
4	 **12**	 **19**	**9b**	95[b]	87
5	 **13**	 **20**	**9b**	63	96
6	 **14**	 **21**	**9b**	64	82
7	 **15**	 **22**	**9b**	72	84
8	 **16**	 **23**	**9b**	35	94[d]
9	**16**	**23**	**24**	90	92[e]

[a] All reactions conducted in the presence of 20 mol% catalyst and 20 mol% KHMDS (0.5 M in toluene) in xylene for 24 h at 25 °C, unless otherwise stated. [b] Reaction conducted with 10 mol% catalyst and 10 mol% KHMDS. [c] Determined by chiral HPLC or GC. [d] (*S*) enantiomer. [e] (*R*) enantiomer.



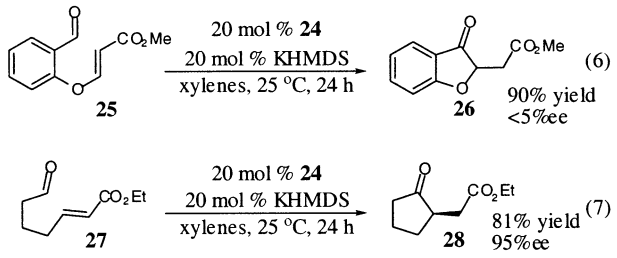
9b



24

stereocenter would not survive these reaction conditions. However, the use of our optimized conditions seems to avoid this pitfall. One exception was noted when substrate **25** was subjected to these reaction conditions, eq 6 in Scheme 1. In the presence of catalyst **24**, product **26** was isolated in 90% yield as a racemate. However, an examination of enantioselectivity as a function of conversion (chiral HPLC) revealed that **26** was formed with 80% enantiomeric excess at 10% conversion, with rapid erosion as the reaction progressed.[14] Since the benzofuran methine proton has a pK_a of ~13,[15] we turned our attention to a substrate that would afford a less acidic product.[16] In the event, the aliphatic aldehyde **27**

Scheme 1



underwent the Stetter reaction to form cyclopentanone **28** in excellent yield and enantiomeric excess, eq 7 in Scheme 1.

In conclusion, we have developed an enantioselective intramolecular Stetter reaction. A variety of substrates undergo this reaction in good yield with high asymmetric induction in the presence of chiral carbene catalysts. Studies aimed at improving the efficiency of the catalysts and determining the mechanism of this reaction are currently underway.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In the reaction of **6** with 20 mol % catalyst **7a** and 20 mol % base in THF at room temperature for 24 h, the following results were obtained: Et_3N (64% yield, 72% ee), NaOMe (27% yield, 87% ee), BuLi (33% yield, 72% ee), KHMDS (50% yield, 82% ee).
(12) In a related system, the following enantioselectivities were observed by solvent: DMF: 64%, CH_2Cl_2: 72%, Et_2O: 65%, pentane: 85%, hexanes: 90%, xylenes: 91%. Xylenes was consistently better than hexanes.
(13) (a) 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene, pK_a = 24 (DMSO): Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267. (b) 1,3-di-*tert*-butylimidazol-2-ylidene, pK_a = 22.7 (DMSO): Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757.
(14) Enantioselectivity was found to have eroded to 50% at 30% conversion and <5% at 75% conversion.
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(16) Epimerization may also be rationalized by a phenoxide elimination/conjugate addition sequence.

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