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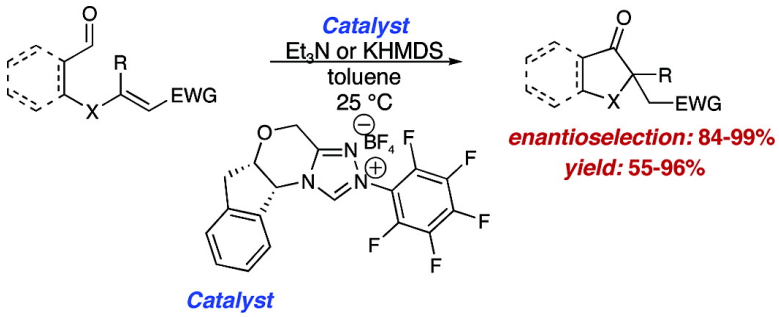

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Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction

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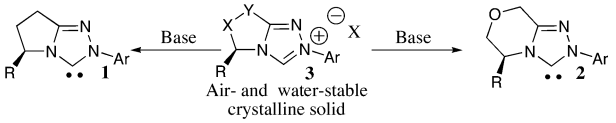
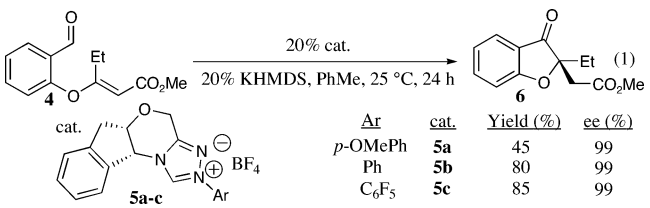
The asymmetric formation of quaternary stereocenters remains a formidable challenge in organic synthesis.[1] While the use of Meyers' chiral bicyclic lactam auxiliaries[2] continues to be the benchmark for versatility and predictability in this challenging bond construction, a number of elegant methods for catalytic formation of quaternary stereocenters have recently been reported. Included in this company are the intramolecular Heck reaction,[3] rearrangement of enol carbonates,[4] transition metal-mediated π-allyl chemistry,[5] copper-catalyzed S_N2' displacement of allylic leaving groups[6] and conjugate additions of β-keto esters to acrylates,[1b] phase-transfer alkylation of 1-indanones,[7] and arylation of ketone enolates,[8] among others. Each of these approaches, however, is necessarily limited to specific substrates and many substitution patterns are unattainable by these or even stoichiometric methods. We report herein that the catalytic asymmetric intramolecular Stetter reaction is capable of forming tertiary ether, thioether, and quaternary stereocenters with excellent enantioselectivity.

Research in these laboratories has been directed toward exploiting the reactivity of carbenes of type **1** and **2**, easily formed in situ from highly stable and readily prepared triazolium salt precursors **3**, Scheme 1. We have previously reported that these carbenes are effective at catalyzing the intramolecular Stetter reaction[9] with good levels of enantiocontrol.[10] Our successes with this reaction prompted us to investigate the more challenging construction of quaternary stereocenters.

Scheme 1



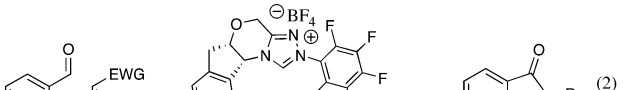
Trost and co-workers had illustrated that the Stetter reaction is capable of cyclizing an aldehyde onto a β,β-disubstituted Michael acceptor during the synthesis of hirsutic acid;[11] however, three equivalents of achiral thiazolium salt were required to effect the reaction. The apparent inefficiency of this catalyst was a significant cause for concern, and although they are somewhat electronically dissimilar, it was not obvious that our triazolium catalysts would lend themselves to an efficient catalytic process. Nevertheless, we initiated our investigation into rendering this reaction enantioselective by examining vinylogous carbonate **4** as a test substrate with a series of aminoindanol-derived catalysts. Gratifyingly, tertiary ether **6** was formed in excellent enantioselectivity in all cases, eq 1.



(1)

Ar	cat.	Yield (%)	ee (%)
p-OMePh	**5a**	45	99
Ph	**5b**	80	99
C_6F_5	**5c**	85	99

Table 1. Aromatic Substrates



(2)

Entry	Substrate	Product[a]	Yield (%)	ee (%)[b]
1	X = H **4**	X = H **6**	96	97
2	Br **7**	Br **8**	92	89
3[c]	**9**	**10**	95	92
4	**11**	**12**	95	99
5[d]	**13**	**14**	55	99

[a] Absolute configuration assigned by analogy to **10**. [b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. [c] Absolute configuration established by single-crystal X-ray analysis. [d] Catalyst added in two portions.

Anisyl-substituted catalyst **5a**, which has been shown to be highly effective in the intramolecular Stetter reaction, provided a disappointing 45% yield, albeit with 99% ee. Interestingly, parent phenyl-substituted catalyst **5b**, while typically underperforming **5a** in terms of conversion,[10a] gave the product benzofuranone in 80% yield. This result suggests the presence of subtle mechanistic differences between this system and β-monosubstituted substrates. Further screening identified pentafluorophenyl catalyst **5c** as the most effective under these conditions. Subsequent optimization indicated that triethylamine[12] was optimal for providing a balance of the highest reactivity and selectivity.[13,14]

With the optimized conditions in hand, a series of aromatic aldehyde substrates was prepared to test the scope of this transformation, Table 1. Reaction of aldehydes **4** and **7** at room temperature for 24 h provided benzofuranones **6** and **8** in high yield and enantiomeric excess, entries 1 and 2. Thioether **9** similarly undergoes cyclization in good yield and selectivity to form benzothiophenone **10**, entry 3. Exposure of ethyl ester **11** to the reaction conditions led to the formation of indanone **12** in 95% yield and remarkable selectivity, entry 4. The corresponding six-membered ring may also be formed with concomitant generation of a quaternary stereocenter, although a lower yield accompanies this reaction. Nevertheless, chromanone **14** can be isolated in

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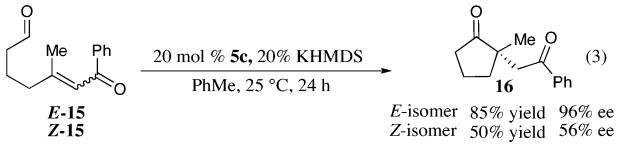
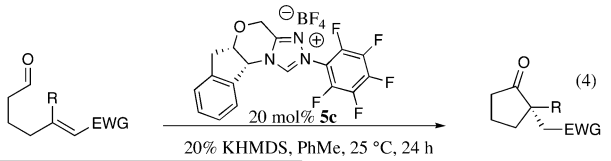
moderate yield and excellent enantioselectivity, entry 5.



We have previously shown that aliphatic aldehydes are also competent substrates in the asymmetric intramolecular Stetter reaction.[10] These systems allowed us to readily compare the effect of alkene geometry. Exposure of α,β-unsaturated phenyl ketone ***E*-15** to the reaction conditions provided an 85% yield of cyclopentanone **16** bearing the quaternary stereocenter with 96% ee.[15] The corresponding isomer ***Z*-15** was examined under identical reaction conditions and found to proceed more sluggishly to give a lower yield and ee. This spurred us to focus on substrates possessing a trans relationship between the pendant aldehyde and activating group for the rest of this study.

Table 2. Aliphatic Substrates

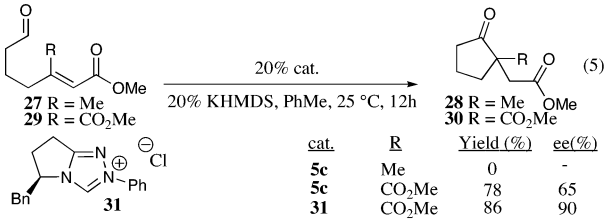


Entry	Substrate		Product[a]		Yield (%)	ee (%)[b]
1	Ar = 4-Py	**17**	Ar = 4-Py	**18**	85	96
2	*p*-NO_2Ph	**19**	*p*-NO_2Ph	**20**	90	84
3	R = Me	**21**	R = Me[c]	**22**	81	95
4	$(CH_2)_2$Ph	**23**	$(CH_2)_2$Ph	**24**	63	99
5	*n*-Bu Ph	**25**	*n*-Bu	**26**	71	98

[a] Absolute configuration assigned by analogy to **22**. [b] Enantiomeric excess determined by GC or HPLC analysis on a chiral stationary phase; see Supporting Information for details. [c] Absolute configuration established by comparison of optical rotation to known compound, see Supporting Information for details.

The reaction of a variety of aliphatic substrates was subsequently investigated, Table 2. Other aromatic ketones react in similar fashion to give high yields of the product cyclopentanones **18** and **20**, entries 1 and 2. An excellent ee is obtained in the cyclization of 4-pyridyl ketone **17**, while a slight decrease in selectivity accompanies the reaction of *p*-nitrophenyl ketone **19**. Furthermore, aliphatic ketones **21** and **23** react under these conditions to give products **22**[16] and **24**, entries 3 and 4, in excellent selectivity and good yield. Moderate changes in sterics are also tolerated in the reaction as *n*-butyl substituted **25** cyclizes with a 71% yield and 98% ee, entry 5.

Attempts to perform the Stetter reaction on the less activated alkene in methyl ester **27** failed, and starting material was recovered nearly quantitatively, eq 5. However, a second activating group on the olefin allows for cyclization of bis-methyl ester **29** in 78% yield, although with an enantioselectivity of only 65%. Fortunately, steric and electronic properties of these easily tunable carbene catalysts can be exploited, as catalyst **31** allows for cyclization to proceed in 90% ee and good yield.



cat.	R	Yield (%)	ee(%)
5c	Me	0	-
5c	CO_2Me	78	65
31	CO_2Me	86	90

In conclusion, we have demonstrated the feasibility of enantioselective formation of quaternary stereocenters via a catalytic asymmetric Stetter reaction. This process delivers the product 1,4-dicarbonyl compounds bearing a quaternary stereocenter in high yield and selectivity under exceedingly mild conditions. We have also described a new electron-deficient catalyst with improved performance in these reactions, illustrating that subtle electronic requirements are present in this and related transformations. Efforts aimed at elucidating the factors responsible for this effect and expanding the reactivity of these carbenes are ongoing.

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Supporting Information Available: Experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389−401. (b) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688−1690. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367.
(2) (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843−9873. (b) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569.
(3) Shibasaki, M.; Vogl, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 475−487.
(4) (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368−13369.
(5) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760.
(6) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460.
(7) Battacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476−477.
(8) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919.
(9) The Stetter Reaction: (a) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, pp 407−496. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890−2896. Intramolecular Stetter: (c) Ciganek, E. *Synthesis* **1995**, 1311−1314. Enantioselective Intramolecular Stetter: (d) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902. (e) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, published online March 25, http://dx.doi.org/10.1021/ar030050j.
(10) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (b) Kerr, M. S.; Rovis, T. *Synlett* **2003** 1934−1936.
(11) Trost, B. M.; Shuey, C. D.; Dinnino, F.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284−1285.
(12) This product is prone to racemization, presumably through a phenoxide elimination/conjugate addition sequence. Stirring a toluene solution of **6** of 98% ee for 24 h with DBU results in quantitative recovery of **6** of 66% ee.
(13) Catalyst screening was also performed under these conditions. Triazolium chloride **31** provided product **6** in quantitative yield, although with a modest 86% ee. Catalyst **5b** gave only trace amounts of product.
(14) Other solvents typically provide poorer selectivity but can allow for much lower catalyst loading. For example, reaction of **4** with 1% triazolium salt **5c** with 10 equiv Et_3N in *i*-PrOH for one week provides a 78% yield of **6** with 83% ee. Toluene provides consistently high yields and enantioselectivity.
(15) Triethylamine provided the product in 90% yield and 88% ee.
(16) The apparent reversal in stereoinduction between the aliphatic and aromatic series is presently under investigation.

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