VOLUME 73, NUMBER 6 JOC Featured Article MARCH 21, 2008

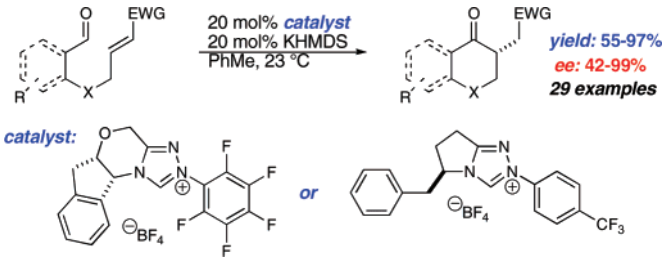
Scope of the Asymmetric Intramolecular Stetter Reaction Catalyzed by Chiral Nucleophilic Triazolinylidene Carbenes

Javier Read de Alaniz, Mark S. Kerr, Jennifer L. Moore, and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

rovis@lamar.colostate.edu

Received November 3, 2007



A highly enantioselective intramolecular Stetter reaction of aromatic and aliphatic aldehydes tethered to different Michael acceptors has been developed. Two triazolium scaffolds have been identified that catalyze the intramolecular Stetter reaction with good reactivity and enantioselectivity. The substrate scope has been examined and found to be broad; both electron-rich and -poor aromatic aldehydes undergo cyclization in high yield and enantioselectivity. The tether can include oxygen, sulfur, nitrogen, and carbon linkers with no detrimental effects. In addition, the incorporation of various tethered Michael acceptors includes amides, esters, thioesters, ketones, aldehydes, and nitriles. The catalyst loading may be reduced to 3 mol % without significantly affecting the reactivity or selectivity of the reaction.

Introduction

The inversion of the normal mode of reactivity of aldehydes catalyzed by cyanide or heteroazolium salt derived carbenes has emerged as a synthetically useful way of constructing carbon−carbon bonds.[1] Two catalytic reaction processes that employ umpolung reactivity of aldehydes are the benzoin and Stetter reactions. The key element of the benzoin and Stetter reactions is the polarity reversal of the carbonyl initiated by nucleophilic attack of the catalyst to an aldehyde generating an acyl anion equivalent that can facilitate the formation of a carbon−carbon bond. The benzoin reaction results from the addition of the acyl-anion equivalent to another aldehyde molecule resulting in the formation of α-keto-alcohols. Due to problems with chemoselectivity, this reaction is often limited to homocoupling of aldehydes.[2]

The synthetic utility of the acyl-anion equivalent has been extended to the formation of 1,4-dicarbonyl compounds employing Michael acceptors as the electrophilic partner, a transformation known as the Stetter reaction.[3] The most commonly used (pre)catalysts for the achiral Stetter reaction are alkali metal cyanide or thiazolium salts in the presence of base. The achiral reaction proceeds well with a wide range of substrates. Michael acceptors that contain β-substituents often result in diminished reactivity and are typically restricted to

(1) For reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328. (c) Pohl, M.; Lingen, B.; Muller, M. *Chem. Eur. J.* **2002**, *8*, 5288−5295. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655. (e) Rovis, T. *Chem. Lett.* **2008**, 2−7.

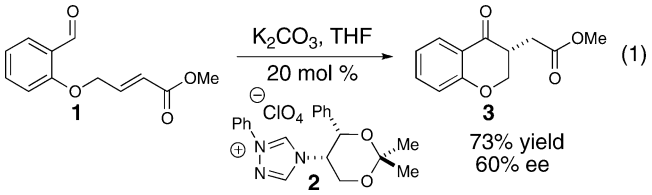
(2) For recent examples of an asymmetric benzoin reaction, see: (a) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891−1893. (b) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743−1745. An intramolecular crossed-benzoin reaction has been demonstrated; see: (c) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463−1467. (d) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492−3494. For an elegant solution to the intermolecular cross-benzoin chemoselectivity problem, see: (e) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.

(3) (a) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407−496. (b) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632−2634. (c) Webber, P.; Krische, M. J. *Chemtracts: Org. Chem.* **2007**, *19*, 262.

10.1021/jo702313f CCC: $40.75
Published on Web 02/27/2008

chalcones or other highly activated alkenes. The asymmetric Stetter reaction has been limited to only two examples prior to 2002.[4]

Enders and co-workers were the first to report an asymmetric intramolecular Stetter reaction in 1996.[4b] Utilizing chiral triazolium salt **2** as a pre-catalyst, the products are obtained in moderate yield and enantioselectivity, eq 1. Despite the moderate selectivity, the implementation of a chiral triazolinylidene carbene in the asymmetric Stetter reaction laid the foundation for future work.



(1)

Subsequent to our first communication in this area,[5] Bach[6] and Miller[7] have independently described the use of chiral thiazolium salts as pre-catalysts for the asymmetric intramolecular Stetter reaction. The salicylaldehyde-derived substrate **1** initially reported by Ciganek[8] for the intramolecular Stetter reaction has become the standard test substrate to compare the efficiency of different catalyst architectures. Bach and co-workers have employed a novel axially chiral *N*-arylthiazolium salt to obtain Stetter products in moderate enantioselectivity. Miller found that thiazolium salts embedded in a peptide backbone could impart modest enantioselectivity on the intramolecular Stetter reaction. Very recently, Tomioka has reported a C_2-symmetric imidazolinylidine catalyst for the Stetter reaction, active and modestly enantioselective even at 110 °C.[9] In a related process, Johnson and co-workers have developed an asymmetric metallophosphite-catalyzed intermolecular Stetter-like reaction employing acyl silanes.[10] Acyl silanes are effective aldehyde surrogates capable of forming an acyl anion equivalent after a [1,2] Brook rearrangement.[11] Taking advantage of this concept, Johnson was able to fashion the catalytic enantioselective synthesis of 1,4-dicarbonyls in 89−97% ee and good chemical yields for α,β-unsaturated amides. Scheidt and co-workers have recently reported the application of silyl-protected thiazolium carbinols as stoichiometric carbonyl anions for the intermolecular acylation of nitroalkenes.[12] The newly formed stereocenters can be controlled by the stoichiometric addition of a chiral thiourea with the desired product formed in 74% ee.

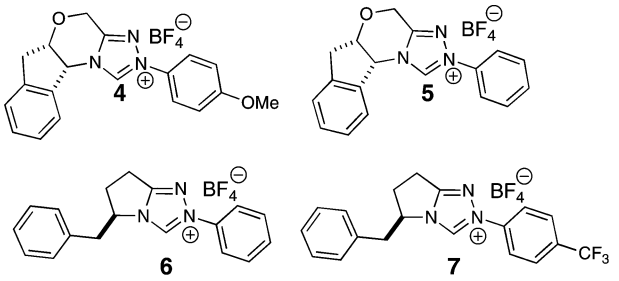


FIGURE 1. Chiral triazolium salts.

We have recently developed a family of chiral triazolium salts that incorporate readily available chiral primary amines into a rigid framework (Figure 1).[13] Upon deprotonation, these triazolium salts form carbenes which catalyze the asymmetric intramolecular Stetter reaction. In the early stage of this research, we hypothesized that an enantioselective intramolecular Stetter reaction could be developed by tuning the electronic and steric environment of the triazolium catalyst. In our initial report, we illustrated the reduction of this concept to practice utilizing 10−20 mol % of the aminoindanol-derived catalyst **4**.[14] In this paper, we report a full investigation of the scope and limitations of the intramolecular Stetter reaction with aromatic and aliphatic aldehydes tethered to a variety of α,β-unsaturated Michael acceptors. We also disclose the results using phenylalanine-derived catalyst **6** and illustrate the similarities and differences between the two chiral bicyclic catalysts in the asymmetric intramolecular Stetter reaction. Furthermore, we demonstrate that the catalyst loading can be reduced to 3 mol % without significantly affecting the efficiency or selectivity of the reaction.

Results and Discussion

In our initial communication,[5] we reported that the asymmetric intramolecular Stetter reaction may be catalyzed by 20 mol % of triazolium salts **4** and **6** utilizing 20 mol % KHMDS as base in xylenes. Catalysts **4**−**7** each provide the Stetter adducts with good selectivity. In particular, aminoindanol-derived catalyst **4** and phenylalanine-derived catalyst **6** provide complementary reactivity and selectivity in a number of instances. This fortuitous relationship enabled the development of the scope of the intramolecular Stetter reaction utilizing both triazolium catalysts. We initially disclosed the results of the asymmetric intramolecular Stetter reaction utilizing triazolium salt **4**, as it provides slightly higher enantioselectivity than the corresponding triazolium salt **6**. It is important to note, however, that both triazolium salts perform the asymmetric Stetter reaction with high enantioselectivity and excellent reactivity. In general, the aminoindanol chiral scaffold affords the desired product in modestly higher enantioselectivity, entries 1−13 (Table 1). Conversely, the all-carbon phenylalanine-derived scaffold generally affords higher yields (compare entries 7 vs 8, 9 vs 11).

(4) (a) Enders, D.; Breuer, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Ed.; Springer: New York, 1999; Vol. 3, pp 1093−1102. (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902.

(5) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299.

(6) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025−2035.

(7) Mennen, S. M.; Blank, J. T.; Tran-Dubè, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195−197.

(8) Ciganek, E. *Synthesis* **1995**, 1311−1314.

(9) Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, *47*, 5843−5846.

(10) (a) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2377−2379. (b) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751−2756.

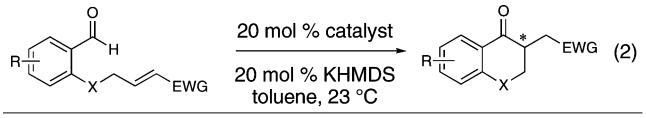
(11) For related examples of acyl silanes in the Stetter reaction, see: (a) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315. (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465−2468.

(12) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932−4933.

(13) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725−5728.

(14) (a) Reference 5. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877. (c) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284−6289. (d) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368−6378. (e) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552−2553. (f) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *49*, 11477−11482. (g) Liu, Q.; Rovis, T. *Org. Proc. Res. Dev.* **2007**, *11*, 598−604.

TABLE 1. Comparison of Different Catalysts on Selectivity and Reactivity



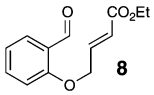
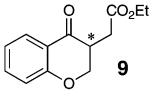
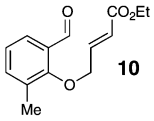
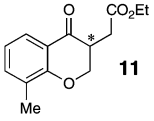
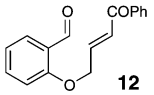
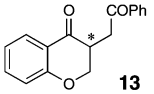
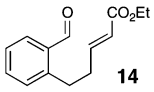
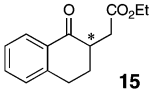
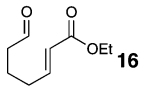
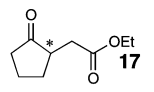
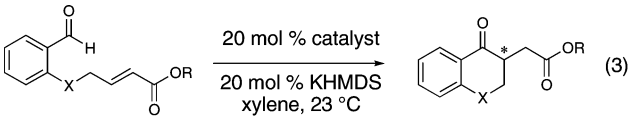
Entry	Substrate	Product	Catalyst	Yield (%)	ee (%)
1	 **8**	 **9**	**4**	94	94 (R)
2			**5**	80	90 (R)
3			**6**	94	90 (S)
4			**7**	95	92 (S)
5	 **10**	 **11**	**4**	90	84 (R)
6			**6**	94	80 (S)
7	 **12**	 **13**	**4**	50	81 (R)
8			**6**	85	68 (S)
9	 **14**	 **15**	**4**	35	94 (S)
10			**5**	50	94 (S)
11			**6**	90	92 (R)
12	 **16**	 **17**	**4**	80	81 (R)
13			**6**	81	95 (S)

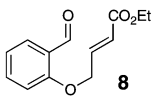
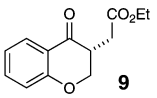
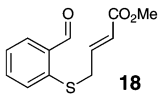
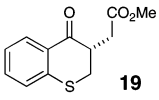
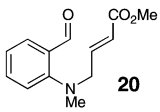
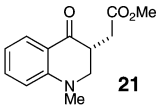
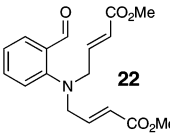
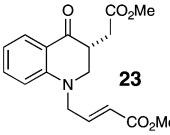
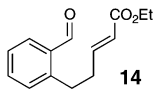
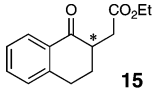
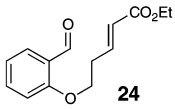
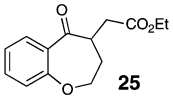
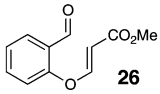
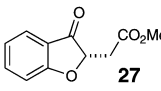
Table 1 highlights the complementarity between the different catalyst scaffolds.

Effects of the Tether on the Intramolecular Stetter Reaction. The length and nature of the tethered Michael acceptor was examined, and their effects on enantioselectivity and reactivity were determined (Table 2). The reaction affords high yields and enantioselectivities for products containing oxygen, sulfur, and nitrogen tethers (entries 1−4). Removal of the heteroatom in the linker results in only 35% yield utilizing catalyst **4** (entry 6). Use of the more reactive catalyst **6** with this substrate affords the desired product in 92% ee and 90% yield (entry 8). Increasing the tether length by one methylene unit results in complete suppression of the reaction and recovery of unreacted starting material (entry 9). Benzofuranone formation occurs in good yield using substrate **26** but the product is formed as a racemate (entry 10). Investigation of the enantioselectivity as a function of conversion reveals that **27** forms in 80% enantiomeric excess at 10% conversion, with rapid erosion to 50% ee at 30% conversion. Erosion could arise via one of two possible scenarios. The benzofuran methine proton has a pK_a of ~13[15] and may epimerize under the basic reaction conditions. Alternatively, removal of the acidic proton α to the ester in the product could result in a phenoxide elimination; subsequent cyclization should result in racemic product.[16]

Electronic Effect of the Aromatic Backbone of the Aldehyde. Electron-donating and electron-withdrawing substituents were placed around the aromatic backbone of the aldehyde in an effort to understand their effects on reactivity and selectivity (Table 3). Within this series, substitution of hydrogen at the 3 position of the aromatic ring results in decreased selectivity (entries 2−3). High enantiomeric excesses are obtained with substrates bearing substitution at the 4- and 5-position of the aromatic ring (entries 7−18). Substrates bearing electron-donating groups (EDG) on the ring afford higher enantioselectivities utilizing catalyst **6** relative to those with electron-withdrawing groups (EWG) in the same position on the aromatic ring. We observe that electron-withdrawing substituents lead to partial product racemization under the reaction conditions;[17] similar results were also noted by Miller and co-workers.[7] Selectivities may be increased by the use of the less basic catalyst **7**, entries 6, 10, and 13.[18] Increasing the electron-donating ability at the 4-position from methoxy to diethylamino results in an increase of an undesired aldol-elimination side reaction from trace amounts to 30%, respectively, generating the seven-membered elimination products (entry 19 illustrates an example of the elimination product obtained). Subjection of **40** to the reaction conditions in the presence of KHMDS but in

TABLE 2. Effect of the Tether on the Intramolecular Stetter Reaction



Entry	Substrate	Product	Catalyst	Yield (%)	ee (%)
1	 **8**	 **9**	**4**	94	94
2	 **18**	 **19**	**4**	63	96
3			**6**	84	90
4	 **20**	 **21**	**4**	64	82
5	 **22**	 **23**	**4**	72	84
6	 **14**	 **15**	**4**	35	94[a]
7			**5**	50	94[a]
8			**6**	90	92[b]
9	 **24**	 **25**	**4**	0[d]	NA
10	 **26**	 **27**	**4**	90	<5[c]

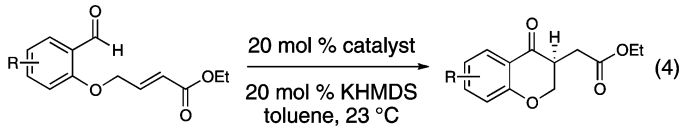
[a] *S*-Enantiomer. [b] *R*-Enantiomer. [c] Prone to racemization; see text. [d] Catalysts **5** and **6** similarly provide no product.

(15) Capon, B.; Kwok, F.-C. *J. Am. Chem. Soc.* **1989**, *111*, 5346−5356.

(16) We have shown that benzofuranones lacking the methine proton may be formed in extremely high enantiomeric excesses (99% ee); this product epimerizes slowly upon prolonged exposure to DBU suggesting that phenoxide elimination/conjugate addition is a viable pathway for racemization; see ref14b,f.

(17) Optically enriched product **35** was resubjected to an intramolecular Stetter reaction with 20 mol % triazolium salt **6**, 20 mol % KHMDS for 24 h and was reisolated as the racemate.

TABLE 3. Electronic Effects of the Aromatic Aldehyde on the Intramolecular Stetter Reaction



Entry	Substrate	Product	Catalyst	Yield (%)	ee (%)
1	**8**	**9**	**4**	94	94
2	**10**	**11**	**4**	90	84[a]
3			**6**	94	80[b]
4	**28**	**29**	**4**	95	87[a]
5			**6**	95	80[b]
6			**7**	86	95[b]
7	**30**	**31**	**4**	80	97[a]
8			**6**	94	90[b]
9	**32**	**33**	**6**	94	90
10			**7**	84	93
11	**34**	**35**	**4**	68	57[a]
12			**6**	95	89
13			**7**	94	92
14	**36**	**37**	**6**	94	88
15			**7**	94	91
16	**38**	**39**	**6**	45	90
17			**7**	94	91
18	**40**	**41**	**7**	55	95
19	**40**	**42**	**6**	30	--
20	**43**	**44**	**6**	80	64

[a] *R*-Enantiomer. [b] *S*-Enantiomer.

the absence of catalyst also affords the elimination product, suggesting a base-induced aldol-type mechanism. However, a Baylis−Hillman reaction catalyzed by the nucleophilic carbene cannot be discounted. Application of catalyst **7** completely suppresses the formation of the undesired side reaction and affords the desired products in higher yield with good enantioselectivity (entry 18).

Variations in the Michael Acceptor. The effects of the Michael acceptor on the intramolecular Stetter reaction using catalyst **5** have been reported.[19] However, catalyst **5** is unable to cyclize α,*β*-unsaturated aldehydes, amides, or *Z*-enoates. In addition, the steric effects of the Michael acceptor on the intramolecular Stetter reaction were not investigated. With access to a larger family of chiral catalysts, we have re-examined the effects of the Michael acceptor on reactivity and selectivity (Table 4). The reaction is remarkably tolerant of a variety of Michael acceptors, with the successful cyclization of α,*β*-unsaturated aldehyde, amide, nitrile, esters, thioesters, and ketones utilizing catalyst **45**. Increasing the steric bulk of the α,*β*-unsaturated esters from methyl to *tert*-butyl results in a slight increase in selectivity (entries 1−3), an observation also made by Tomioka.[9] Cyclization of the (*Z*)-α,*β*-unsaturated methyl ester **50** can now be achieved albeit with low enantioselectivity (entry 4). As anticipated, the cyclization of α,*β*-unsaturated ketones affords the desired product in excellent overall yield; however, a decrease in selectivity is evident when moving from the α,*β*-unsaturated ethyl ketone **52** to the phenyl ketone **12** (entries 5−6). The α,*β*-unsaturated thioester **54** and amide **56** are well tolerated in the intramolecular Stetter reaction (entries 7 and 8). The incorporation of the thioester[20] and the Weinreb amide[21] offers an excellent handle for further manipulations. α,*β*-Unsaturated nitrile **58** was subjected to the reaction as an inseparable 1:1 mixture of *E*/*Z* olefin isomers and was found to afford the desired product in good yield and 80% enantioselectivity. The enantioselectivity of the product is similar to the reaction commencing from isomerically pure (*E*)-α,*β*-unsaturated nitrile **60** (entry 10). This unexpected result clearly illustrates that the *Z* olefin isomer is tolerated but the result-

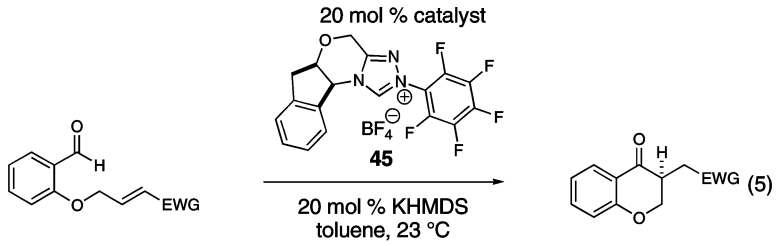
(18) Reactions that contain an EWG on the aromatic backbone typically proceed to completion in 15−60 min. If the reaction is allowed to stir for 24 h, the product is isolated with enantiomeric excess between 67−80%. In addition, we briefly examined if erosion occurs during purification by column chromatography. Optically enriched **35** was dissolved in toluene and stirred with silica gel and the enantioselectivity decreased from 90% to 66% ee. Erosion of enantioselectivity could be avoided by treating the silica gel with 15% acetic acid prior to column chromatography.

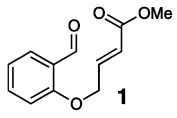
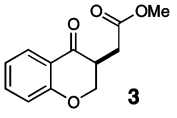
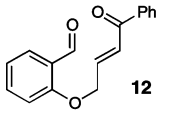
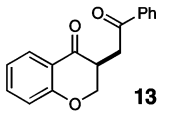
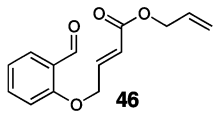
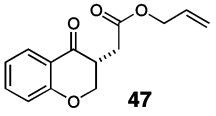
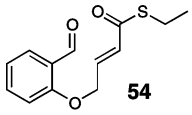
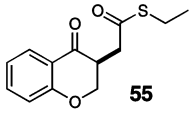
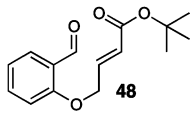
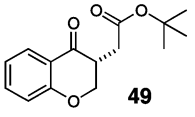
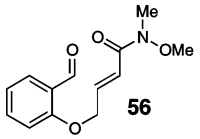
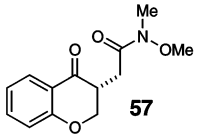
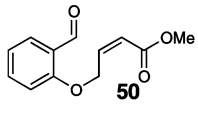
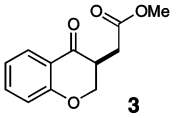
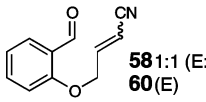
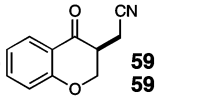
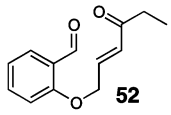
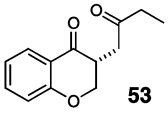
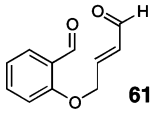
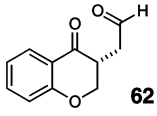
(19) Kerr, M. S.; Rovis, T. *Syntlett* **2003**, 1934−1936.

(20) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189−3192.

(21) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

TABLE 4. Effect of the Michael Acceptor on the Intramolecular Stetter Reaction



Entry	Substrate	Product	Yield (%)	ee (%)	Entry	Substrate	Product	Yield (%)	ee (%)
1	 **1**	 **3**	94	95	6	 **12**	 **13**	94	78
2[b]	 **46**	 **47**	94	93	7	 **54**	 **55**	85	70
3[b]	 **48**	 **49**	94	97	8[b]	 **56**	 **57**	94	92
4	 **50**	 **3**	80	22	9 10[a]	 **58** 1:1 (E:Z) **60** (E)	 **59** **59**	88 80	80 78
5[b]	 **52**	 **53**	94	92	11[b]	 **61**	 **62**	50	30

[a] 20 mol % of catalyst **5** was used. [b] Opposite antipode of the chiral triazolium salt **45** was used.

ing enantioselectivity depends on the nature and size of the Michael acceptor (vide infra). The α,β-unsaturated aldehyde affords the desired product in 50% isolated yield, but only 30% ee.

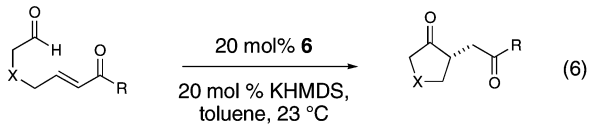
Expanding the Scope To Include Aliphatic Aldehydes. After successfully performing a highly enantioselective intramolecular Stetter reaction on a broad range of aromatic aldehydes, we turned our attention to the potentially more difficult aliphatic aldehydes. Aliphatic aldehydes may bear acidic hydrogens α to the carbonyl and we were initially concerned that this could pose a problem. To our gratification, a number of aliphatic aldehydes bearing acidic hydrogens participate in the intramolecular Stetter reaction (Table 5). Cyclopentanones **17** and **64** are each generated in excellent yield and selectivity (entries 1 and 2). Nitrogen is tolerated in the tether, affording the desired product in excellent enantiomeric excess. This reaction thus offers a new approach toward optically enriched pyrolidinones such as **66** (entry 3). The intramolecular Stetter reaction providing cyclohexanone products was more challenging, presumably due to increased degrees of freedom, and employment of α,β-unsaturated ethyl esters results in only recovered starting material (entry 4). However, increasing the electrophilic nature of the Michael acceptor results in successful cyclization of cyclohexanones **70** and **72** in good yields and modest to good enantioselectivities (entries 5 and 6).

Practical Considerations. Throughout the course of our investigations, we have noted that both water and air have detrimental effects on the outcome of the intramolecular Stetter reaction. The requirements for excessive care in the setup or execution of this reaction would clearly constitute an impediment to its application in other laboratories, and we therefore spent some effort rendering the process more user-friendly. To that end, we conducted the optimized Stetter reaction open to the atmosphere, entry 2 in Table 6. Enantioselectivities are not affected, but chemical yield is significantly lower, a situation we ascribe to premature catalyst decomposition.[22,23] We further note that utilizing ACS grade toluene as the solvent, drawn directly from the bottle without any purification, results in decreased reaction efficiency and formation of an undesired aldol product **73** in 30% yield.

(22) One can ascribe the cause of this decomposition to both water and molecular oxygen. However, we hypothesize that in this particular experiment, oxygen is the real culprit, partly due to Colorado's arid climate and therefore a lower concentration of moisture, and partly to our subsequent observations involving the beneficial effects of argon bubbling through the solution.

(23) Decomposition products derived from the triazolinylidene carbene have so far resisted efforts directed towards their isolation and conclusive identification. Addition of water to the free carbene in an NMR tube generates a spectrum consistent with an aminal, the product of net water addition to the carbene carbon.

TABLE 5. Aliphatic Aldehydes in the Intramolecular Stetter Reaction



(6)

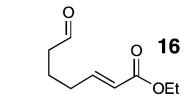
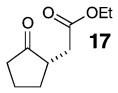
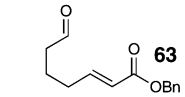
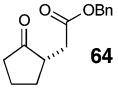
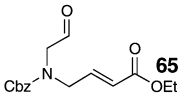
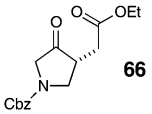
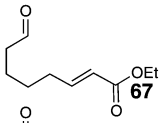
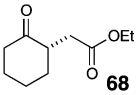
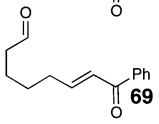
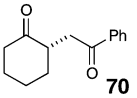
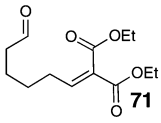
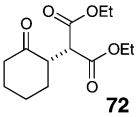
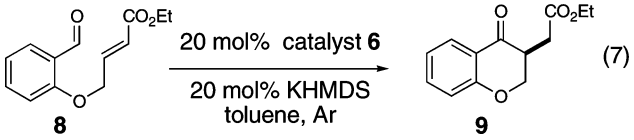
Entry	Substrate	Product	Yield (%)	ee (%)
1	 **16**	 **17**	81	95
2	 **63**	 **64**	85	90
3	 **65**	 **66**	80	99
4	 **67**	 **68**	0	NA
5	 **69**	 **70**	60	42
6	 **71**	 **72**	97	82

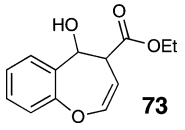
TABLE 6. Effect of Water and Oxygen on the Stetter Reaction



(7)

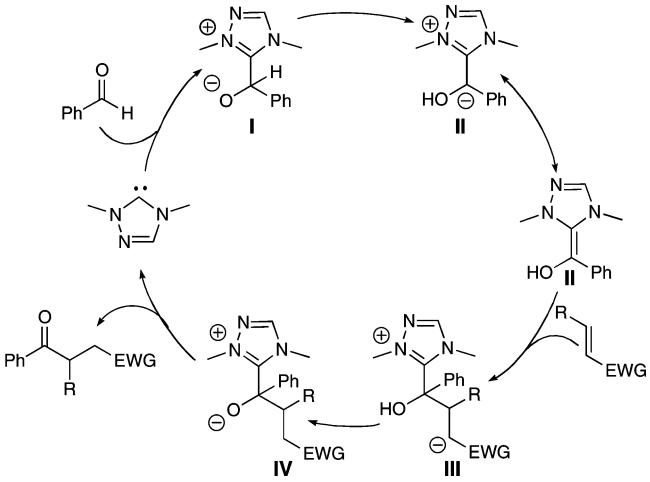
entry	change from above conditions	yield (%)	ee (%)
1	none	94	90
2	open to air	42	90
3	PhMe from bottle (ACS grade)	70[a]	82
4	PhMe saturated with H_2O	0	NA
5	PhMe (ACS) + MS 4 Å	90	85
6	PhMe (ACS) + Na_2SO_4	80	82
7	PhMe (ACS) + $MgSO_4$	90	87

[a] Compound **73** isolated in 30% yield.

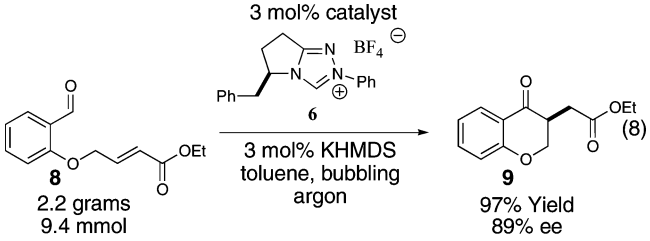


We speculated that trace water in commercial toluene may have been the cause of this reactivity difference. Indeed, the use of water-saturated toluene as solvent results in no reaction, entry 4 in Table 6. A number of common water scavengers were surveyed in an attempt to provide a practical solution. The addition of molecular sieves, sodium sulfate (Na_2SO_4), or magnesium sulfate ($MgSO_4$) results in a decrease in reaction time, increased yields and suppression of the undesired side reaction, but provides the product in slightly reduced enantioselectivity (Table 6, entries 5−7). Despite the slight decrease in enantioselectivity, the utility of ACS grade toluene in the presence of $MgSO_4$ makes this process synthetically attractive, especially when anhydrous toluene is not readily available.

SCHEME 1. Proposed Catalytic Cycle



Since a slight erosion of enantioselectivity is observed in the presence of water scavengers, large-scale reactions with decreased catalyst loading are routinely conducted with anhydrous toluene. To exclude adventitious amounts of oxygen, argon is bubbled through the solution of toluene before and during the course of the reaction. Using this protocol, subjection of 2.2 g (9.4 mmol) of **8** to a solution of 3 mol % triazolium salt **6** and corresponding amounts of base in anhydrous toluene under argon results in 97% isolated yield of the desired product in 89% ee (eq 8).[24]



(8)

Discussion

The Stetter reaction is likely intimately related to the much better studied benzoin reaction and a proposed mechanism is illustrated in Scheme 1.[25] According to the proposed mechanism, intermediate **I** results from nucleophilic attack of the carbene into the aldehyde. Subsequent proton transfer affords the acyl anion equivalent **II**, whose resonance structure is the enolamine,

(24) Enders has illustrated that triazolinylidene carbenes react with molecular oxygen, forming cyclic ureas; see: (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Liebigs Ann. Chem.* **1996**, 2019−2028. (b) Enders, D.; Breuer, K.; Teles, J. H.; Gielen, H. *J. Prakt. Chem.* **1997**, *339*, 397−399.

(25) Mechanism of the thiamine-catalyzed benzoin condensation reaction: (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702. (c) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131. Mechanism of the cyanide-catalyzed reaction: (d) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995−1005. (e) do Amaral, L.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1972**, *94*, 7579−7580. For the mechanism of the cyanide-catalyzed crossed silyl benzoin reactions, see: (f) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833−1840.

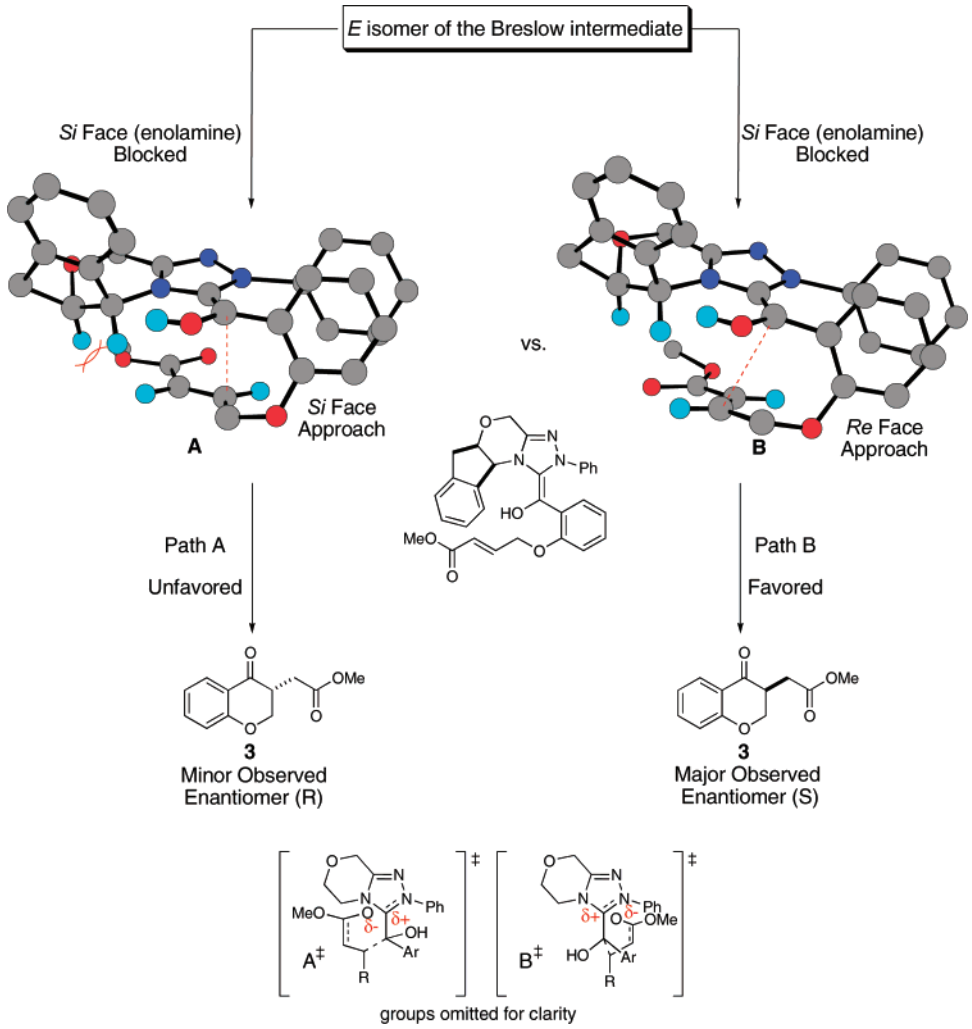


FIGURE 2. Proposed stereochemical model.

commonly referred to as the Breslow intermediate. Carbon−carbon bond formation results from nucleophilic attack of the Breslow intermediate **II** into a Michael acceptor, generating enolate **III**. A stereochemical model to rationalize observed stereochemistry will focus on this step. Enolate protonation followed by release of the catalyst generates the 1,4-dicarbonyl and closes the catalytic cycle.

The absolute configurations of products **3** and **17** formed with catalyst **6** were determined to be *S* by comparison of the measured optical rotation value with the corresponding literature data.[26] The absolute configurations of **49** and **55** were assigned by chemical correlation, with the rest assigned by analogy; aliphatic substrate **72**[27] was assigned by chemical correlation with the rest assigned by analogy to **17**.[28] In a computational study modeling the transition state for the benzoin reaction with a related triazolinylidene carbene, Dudding and Houk note that the *E* isomer of the Breslow intermediate is more stable.[29,30] Our working model to explain the stereochemical outcome of the reaction, illustrated in Figure 2,[31] thus assumes that carbon−carbon bond formation takes place from the *E* isomer of the Breslow intermediate. The chiral residue sterically shields the *si* face of the Breslow intermediate thus gearing the Michael acceptor toward the enolamine's *re* face. The enantiodiscriminating step would then result from attack on either the *re* or *si* face of the tethered Michael acceptor. Attack on the *re* face of the Michael acceptor results in the observed stereochemistry as depicted by path B. Subtle differences between models **A** and **B** are apparent. The use of the nonpolar solvent toluene may promote a requirement for minimal charge separation in the transition state, placing the carbonyl oxygen in close proximity to the triazolium carbene carbon atom, models $A^{‡}$ and $B^{‡}$. We speculate that a steric clash between the ester substituent and the underside of the morpholine ring may destabilize model **A** in relation to **B**.

(26) (a) See ref 4b. (b) Wang, S.; Chen, G.; Kayser, M. M.; Iwaki, H.; Lau, P. C. K.; Hasegawa, Y. *Can. J. Chem.* **2002**, *80*, 613−621.

(27) Ebinger, A.; Heinz, T.; Umbricht, G.; Pfaltz, A. *Tetrahedron* **1998**, *54*, 10469−10480.

(28) Our original assignment for the absolute stereochemistry of **17** was based on the assumption that the aliphatic series was analogous to the aromatic series (see ref 14a). This has since proved incorrect. The correct absolute chemistry is assigned by comparison to ref 26b.

(29) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770−5775.

(30) The proposed transition state is further supported by a recent example by Enders and co-workers utilizing chiral triazolium salts in an asymmetric intramolecular crossed-benzoin reaction. See ref 2c.

(31) This model is an MM2 minimization (Chem 3D) of the catalyst framework and substrate, followed by simple manipulation of the substituents within that software, and is meant to serve as a mnemonic rather than a transition state approximation. We are currently engaged in a collaboration to provide theoretical and computational support for this model.

This model provides a suitable rationale for several of our experimental observations. A larger ester on the Michael acceptor provides a slight increase in selectivity (95% ee for methyl ester, 97% ee for *tert*-butyl ester, entries 1 and 3, Table 4), due to a more deleterious steric interaction in model **A**. The *Z*-enoate substrate, on the other hand, provides much lower selectivity (entry 4, Table 4). Exchange of the α-proton and ester carbonyl in model **B** results in a significant steric interaction with the phenyl substituent on the triazole ring, thus significantly disfavoring this orientation. Last, our observation that enenitriles provide lower selectivities, apparently independent of olefin geometry may also be rationalized (entries 9 and 10, Table 4). The considerably smaller size of the cyano group reduces steric interactions in both models **A** and **B**; it is also apparent that its smaller size may be accommodated in the *Z*-isomer as well.

Conclusion

The scope of a highly enantioselective intramolecular Stetter reaction has been described. The reaction proceeds at room temperature with a variety of substrates providing 1,4-dicarbonyl compounds in good chemical yield and the catalyst loading can be decreased to 3 mol % without loss of reactivity or enantioselectivity. The substrate scope has been extended to include aliphatic aldehydes as well as electron rich and poor aromatic aldehydes. In addition, the incorporation of various tethered Michael acceptors has been improved and now includes amides, esters, thioesters, ketones, aldehydes, and nitriles. Importantly, we have identified triazolium pre-catalysts bearing electron-deficient aryl groups that consistently provide better yields and selectivities for this transformation.

Experimental Section

General Procedure for the Asymmetric Intramolecular Stetter Reaction. A flame dried round-bottom flask was charged with triazolium salt (0.2 equiv) and toluene (5 mL). To this solution was added KHMDS (0.5 M in toluene prepared prior to use from 0.05 g of KHMDS in 0.5 mL of toluene) (0.2 equiv) via syringe, and the solution was stirred at ambient temperature for 5 min. A solution of the substrate (1 eq, 0.12 mmol) in toluene (2 mL) was added. The resulting solution was allowed to stir at ambient temperature and monitored by TLC. The reaction mixture was placed directly onto a silica gel column. The desired product was purified by flash column chromatography, eluted with a suitable solution of hexane and ethyl acetate (typically 4:1). Evaporation of solvent afforded analytically pure product.

(*2S*)- 3-(2-Oxo-2-phenylethyl)chroman-4-one (13). According to the general procedure, 14.0 mg (0.030 mmol) of **45**, 60.0 μL (0.030 mmol) of KHMDS, and 40.0 mg (0.150 mmol) of **12** were reacted for 24 h. Workup afforded 37.2 mg (94%) of the desired product as a colorless oil: R_f (1:1 hexane to ethyl acetate) = 0.7; $[\alpha]^{23}_D = -36.2$ ($CHCl_3$); HPLC analysis − Chiralcel OD-H column (90:10 hexanes to isopropanol, 1.0 mL/min). Major enantiomer: 10.9 min, minor enantiomer: 13.9 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.97 (2H, m), 7.88 (1H, m), 7.56 (1H, m), 7.49−7.44 (3H, m), 7.01 (1H, m), 6.97 (1H, m), 4.62 (1H, dd, *J*= 5.3, 11.1 Hz), 4.29 (1H, dd, *J*=11.3, 11.5 Hz), 3.69 (1H, dd, *J*= 3.8, 18.1 Hz), 3.58 (1H, dddd, *J*= 3.8, 5.3, 8.5, 11.9 Hz), 3.00 (1H, d, *J*= 8.3, 17.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 193.6, 162.0, 136.6, 136.2, 133.6, 128.9, 128.3, 127.6, 121.6, 120.8, 118.0, 70.6, 42.0, 34.5; IR (NaCl, CH_2Cl_2) 1680, 1607, 1483 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}O_3$ $(M + H)^+$ 267.1016, found 267.1028.

(2*R*)-3-Ethoxycarbonylmethyl-4-oxopyrrolidine-1-carboxylic Acid Benzyl Ester (66). According to the general procedure, 12.0 mg (0.032 mmol) of **6** and 65.0 μL (0.032 mmol) of KHMDS and 50.0 mg (0.164 mmol) of **65** were reacted for 24 h. Workup afforded 40.0 mg (80%) of the desired product as a colorless oil: R_f (1:1 hexane to ethyl acetate) = 0.5; $[\alpha]^{23}_D = +23.1$ ($CHCl_3$); GC analysis (B-DM column 80 °C for 120 min then ramp to 120 °C over 10 min). Minor enantiomer: 144.0 min, major enantiomer: 148.7 min; ^{1}H NMR (300 MHz, $C_6D_5CD_3$ (80 °C)) δ 7.24−7.10 (5H, m), 5.09 (2H, s), 3.92−3.80 (4H, m), 3.58 (1H, dd, *J* = 18.9, 18.9 Hz), 3.42 (1H, dd, *J* = 18.8, 18.8 Hz), 2.98 (1H, dd, *J* = 10.5, 9 Hz), 2.34−2.13 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 171.1, 169.0, 136.5, 128.8, 128.4, 128.3, 67.5, 61.4, 52.7, 48.3, 44.0, 33.0, 14.3; IR (NaCl, CH_2Cl_2) 1760, 1709, 1418 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{20}NO_5$ $(M + H)^+$ 306.1336, found 306.1333.

Acknowledgment. We thank the National Institute of General Medical Sciences (GM72586) and the National Institutes of Health (minority supplement to J.R.) for support. J.R. thanks the National Institutes of Health (Ruth L. Kirschstein Minority Pre-doctoral fellowship) and Colorado PEAKS AGEP (graduate fellowship). M.S.K. thanks Boehringer-Ingelheim for a graduate fellowship. J.L.M. thanks the National Institutes of Health (Ruth L. Kirschstein Minority Pre-doctoral fellowship). T.R. gratefully acknowledges Merck Research Laboratories, GlaxoSmithKline, Amgen, Johnson & Johnson, Eli Lilly, and Boehringer-Ingelheim for support. T.R. thanks the Monfort Family Foundation for a Monfort Professorship. T.R. is a fellow of the Alfred P. Sloan Foundation. We thank Michael C. Hillier and Donald Gauthier (Merck) for a generous gift of aminoindanol.

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

JO702313F