ORGANIC LETTERS

2011
Vol. 13, No. 7
1662–1665

N-(Heteroarenesulfonyl)prolinamides-Catalyzed Aldol Reaction between Acetone and Aryl Trihalomethyl Ketones

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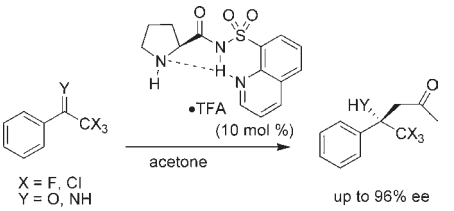
Received January 17, 2011

ABSTRACT



Enantiomerically enriched trihalomethyl-substituted alcohols having a quaternary chiral carbon center can be prepared by the catalytic enantioselective cross-aldol reaction of acetone with trihalomethyl ketones by using *N*-(8-quinolinesulfonyl)prolinamide as an organocatalyst. The MO calculations elucidate that the hydrogen bonding between the sulfonimide proton and the 8-quinolyl nitrogen atom plays an important role in exerting the enantioselectivity of the reaction.

Since the enantioselective aldol reaction with organocatalysts is recognized as one of the most powerful carbon−carbon bond-forming reactions,[1] the organocatalytic asymmetric aldol reaction to ketones as electrophiles has thus been investigated,[2] as it provides efficient access to chiral tertiary alcohols. However, it is still a challenging research field due to the poor reactivity of ketones as electrophiles and the difficulty of the differentiation of the reactive carbonyl face. Therefore, expanding the scope of the organocatalytic aldol reaction with ketones is highly desirable. Although chiral tertiary trihalomethyl carbinols are versatile building blocks in organic synthesis,[3] there have been only three examples of the cross-aldol reaction with ketones having trihalomethyl groups. Ya−Wen and co-workers have reported the L-proline-catalyzed enantioselective aldol reaction of acetone with 2,2,2-trifluoro-1-arylethanones as trihalomethyl ketones to give products with moderate enantioselectivity (up to 64% ee).[4] More recently, highly enantioselective organocatalytic aldol reactions between α,β-unsaturated trifluoromethyl ketones and ketones have been reported.[5] On the other hand, there are no reports on the reaction of trichloromethyl ketones probably due to their low reactivities and difficulties in obtaining high enantioselectivity. Although pioneering studies have been performed, the development of highly enantioselective catalyst systems with wide substrate tolerance is still a challenging research. Recently, we reported that *N*-(2-thiophenesulfonyl)prolinamide acted as a highly efficient organocatalyst for the reaction of acetone or

(1) For reviews, see: (a) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: New York, 2005. (b) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660.

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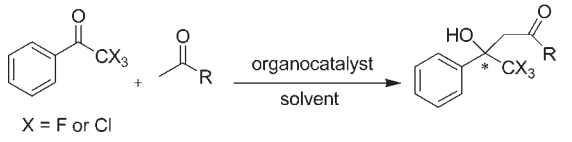
(5) (a) Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343. (b) Zhang, D.; Yuan, C. *Tetrahedron* **2008**, *64*, 2480.

10.1021/ol2001039
Published on Web 03/02/2011

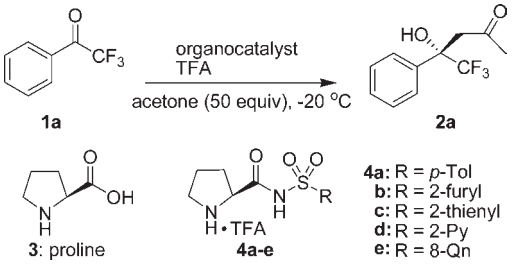
aldehydes with isatin derivatives.[6,7] We herein report the efficient synthesis of chiral tertiary alcohols or amines having a trihalomethyl group by the enantioselective reaction of trihalomethyl ketones or imines with acetone using *N*-(heteroarenesulfonyl)prolinamides (Scheme 1).

Scheme 1. Construction of a Quaternary Chiral Carbon Center by Asymmetric Aldol Reaction to Trihalomethyl Ketones



The fluoroalkyl group is one of the most attractive functional groups in organic chemistry because fluoroalkyl-containing molecules often play an important role in material, agricultural, and medicinal chemistry.[8] Especially, the synthesis of chiral trifluoromethylated compounds having a quaternary chiral center is highly desirable.[9] Therefore, we first examined the reaction of 2,2,2-trifluoro-1-phenylethanone **1a** with acetone in the presence of 10 mol % of various chiral organocatalysts **3**,**4**. The results are shown in Table 1. L-Proline **3** was an active catalyst, but exhibited poor asymmetric inducibility (entry 1). Enantioselectivity was improved in the reaction performed at a lower temperature, although the reactivity was lower (entry 2). The reaction using the TFA salt of *N*-(*p*-toluenesulfonyl)prolinamide (**4a**) proceeded to give product **2a** with moderate enantioselectivity (entry 3).[10] To improve enantioselectivity, we optimized the arenesulfonyl group of chiral organocatalysts (entries 4−7). Finally, the chiral organocatalyst *N*-(8-quinolinesulfonyl)prolinamide (**4e**) proved to be the catalyst of choice, and under the same reaction condition, afforded **2a** in 92% yield with 89% ee (entry 7). Importantly, by lowering the catalyst loading to 5, 2, and 1 mol % (entries 8−10), which represents the lowest catalyst loading employed in the asymmetric aldol reaction to ketones, there was no significant loss of enantioselectivity and yield.

Table 1. Enantioselective Addition of Acetone to 2,2,2-Trifluoro-1-phenylethanone **1a** in the Presence of Various Organocatalysts **3**,**4**

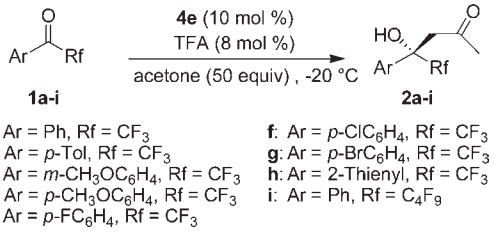


entry	catalyst (mol %)	TFA (mol %)	time (h)	yield (%)[a]	ee (%)[b]
1[c]	**3** (10)		12	97	27
2	**3** (10)		36	89	45
3	**4a** (10)	8	48	83	60
4	**4b** (10)	8	48	88	75
5	**4c** (10)	8	48	85	67
6	**4d** (10)	8	48	91	83
7	**4e** (10)	8	48	92	89
8	**4e** (5)	4	48	86	87
9	**4e** (2)	1.6	72	88	86
10	**4e** (1)	0.8	120	81	84

[a] Yield of isolated **2a** after purification on silica gel. [b] Ee was determined by HPLC analysis. [c] The reaction was carried out at room temperature.

With these optimized conditions, the reaction of a series of fluoroalkyl ketones and acetone using organocatalyst **4e** was examined (Table 2). The reaction of various aryl trifluoromethyl ketones **1a**−**h** gave products **2a**−**h** in high yield with high enantioselectivity (entries 1−7). The

Table 2. Enantioselective Addition of Acetone to Various Fluoroalkyl Ketones **1a**−**i**



entry	ketone **1**	product **2**	time (h)	yeld (%)[a]	ee (%)[b]
1	**1a**	**2a**	48	92	89
2	**1b**	**2b**	48	61	86
3	**1c**	**2c**	48	91	86
4	**1d**	**2d**	48	76	90
5	**1e**	**2e**	48	87	88
6	**1f**	**2f**	48	88	84
7	**1g**	**2g**	48	95	85
8	**1h**	**2h**	48	81	77
9	**1i**	**2i**	48	91	92

[a] Yields of isolated **2** after purification on silica gel. [b] Ee was determined by HPLC analysis.

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(7) Recently, Carter, Cheong, and co-workers have reported *N*-(2-pyridinesulfonyl)prolinamide as a organocatalyst, see: Yang, H.; Mahapatra, S.; Cheong, P. H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 7279.

(8) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) *Organofluorine Compounds in Medicinal and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. N., Eds.; Elsevier: Amsterdam, The Netherlands, 1993. (c) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000.

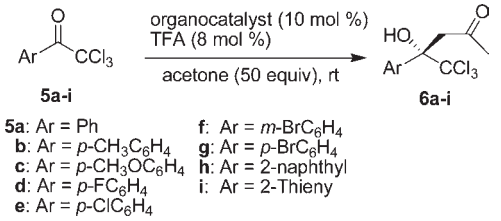
(9) Recently, our group has reported the enantioselective nucleophilic addition to trifluoromethyl ketones using organocatalysts, see: (a) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (b) Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1443.

(10) The addition of a substoichiometric amount of TFA is important, because TFA activates the background reaction of **1a** with acetone.

heteroatom containing arylaldehyde **1h** also resulted in a good enantioselectivity (entry 8). The reaction with fluoroalkyl ketone **1i** also gave product **2i** in high yield with high enantioselectivity (entry 9).

On the other hand, trichloromethyl-containing compounds have also been found to be useful in medicinal chemistry.[11] Furthermore, these compounds are important synthetic intermediates; they can be converted to α-amino acids, α-hydroxy acids, oxiranes, and α-fluoro acids.[3] Therefore, we next examined the reaction of trichloromethyl ketones **5a**−**i** with acetone using various organocatalysts **3**,**4** (Table 3). Moderate enantioselectivity

Table 3. Enantioselective Addition of Acetone to 1-Aryl-2,2,2-trichloroethanone **5a**−**i**

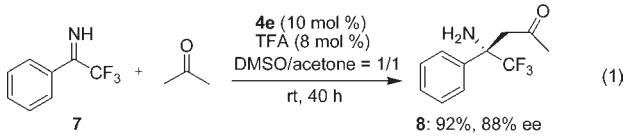


entry	5	catalyst	time (h)	yield (%)[a]	ee (%)[b]
1	**5a**	**3**	66	45	66
2	**5a**	**4c**	48	16	89
3	**5a**	**4d**	66	51	85
4	**5a**	**4e**	48	54	93
5	**5a**	**4e**	144	70	93
6	**5b**	**4e**	144	50	96
7	**5c**	**4e**	144	33	95
8	**5d**	**4e**	48	74	94
9	**5e**	**4e**	48	86	93
10	**5f**	**4e**	48	87	91
11	**5g**	**4e**	48	94	92
12	**5h**	**4e**	48	83	96
13	**5i**	**4e**	48	46	90

[a] Yield of isolated **2a** after purification on silica gel. [b] Ee was determined by HPLC analysis.

was obtained in the reaction with L-proline **3** (entry 1). The reaction with organocatalysts having heteroarenesulfonyl groups showed moderate yield and high enantioselectivity as well as the reaction of 1-aryl-2,2,2-trifluoroethanone (entries 2−4). We found that *N*-(8-quinolinesulfonyl)prolinamide (**4e**) is an efficient organocatalyst in the reaction of **5a** with acetone (entry 4). The yield of product **6a** can be improved with a longer reaction time (entry 5). The reaction of various trichloromethyl ketones **5b**−**i** gave products **6b**−**i** in good yield with high enantioselectivity (entries 6−12), although the reaction with trichloromethyl ketones **5b**,**c** having an electron-donating substitution attached to the para-position of the benzene ring decreased the reaction rate and yield (entries 6 and 7). The absolute configuration of product **6h** was determined by X-ray crystallography (see the Supporting Information), and the stereochemistry of other products was tentatively assumed by analogy. These results are the first example of a highly enantioselective aldol reaction of trichloromethyl ketones using organocatalysts.

To expand the scope of the catalyst system, we examined the enantioselective Mannich-type reaction of a ketimine with acetone. Although there are only a few reports for the enantioselective Mannich-type reaction with ketimines,[12] the reaction of 2,2,2-trifluoro-1-phenylethanimine **7** with acetone was catalyzed by 5 mol % of organocatalysts **4e** to give product **8** in high yield with high enantioselectivity (eq 1). The stereochemical outcome of the reaction is in agreement with the reaction of trichloromethyl ketone **5h**.



The enantioselective reaction of trihalomethyl ketones or a ketimine with acetone using organocatalyst **4e** having a heteroarenesulfonyl group gave products in good yield with good enantioselectivity, although the reaction using organocatalyst **4a** did not afford a good result (Table 1, entry 3 vs 7). Therefore, the heteroarenesulfonyl group plays an important role in exerting enantioselectivity of the reaction. To clarify the structure of the related compounds derived from **4e**, we studied the MO calculation of catalyst **4e** and enamine intermediate **9** prepared from **4e** with acetone by Gaussian 09[13] B3LYP/6-311+G** after conformational analyses. The most stable structures for **4e** are depicted in Figure 1. Two nitrogens for quinoline (N1) and

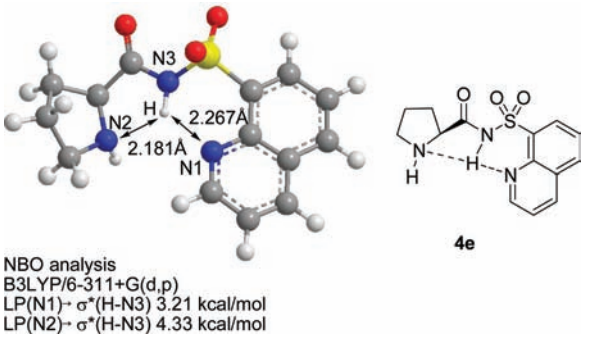


Figure 1. Optimized structure for catalyst **4e**.

pyrrolidine (N2) arranged to the hydrogen on sulfonimide. In the optimized structure, the distance between the sulfonimide hydrogen and nitrogens (N1, N2) is 2.267 Å and 2.181 Å, respectively. Furthermore, the NBO analysis[14] for

(11) (a) Prakash, G. K. S.; Hu, J. In *Science of Synthesis*; Thieme: Stuttgart, Germany, 2005; Vol. 22, p 617. (b) Darko, L. L. *J. Med. Chem.* **1971**, *14*, 527.

(12) (a) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (b) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. *Tetrahedron: Asymmetry* **2008**, *19*, 761. (c) Jiang, B.; Dong, J. J.; Si, Y. G.; Zhao, X. L.; Huang, Z. G.; Xua, M. *Adv. Synth. Catal.* **2008**, *350*, 1360. (d) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637.

4e estimated that the energy of interaction between lone pairs (LP) of both nitrogens and σ^* orbital for the N_{imide}−H bond was 3.21 and 4.33 kcal/mol, respectively. These results imply that the hydrogen on sulfonimide in **4e** makes hydrogen bonding to both nitrogens in quinoline and pyrrolidine.

The optimized structure for enamine intermediate **9** also shows hydrogen bonding between the nitrogen in quinoline and the hydrogen on sulfonimide, although the nitrogen in the pyrrolidine ring is separated from the sulfonimide hydrogen because of the formation of enamine (Figure 2). The NBO analysis for enamine **9** also shows the interaction between the lone pair of quinoline nitrogen and the σ^* orbital for the N_{imide}−H bond. The stabilizing energy for their hydrogen bonding was estimated to be 8.45 kcal/mol.

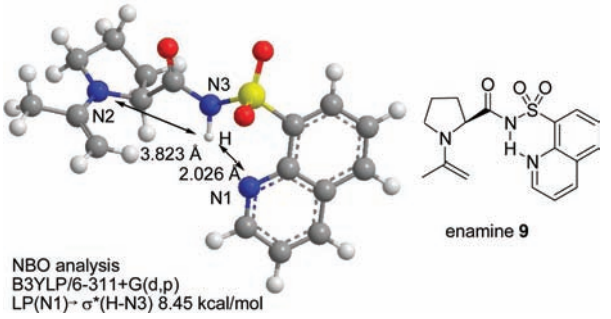


Figure 2. Optimized structure for enamine intermediate **9**.

From the above considerations, the assumed transition states for the enantioselective aldol reaction of trifluoromethyl ketones with acetone are shown in Figure 3. The hydrogen bonding between the sulfonimide proton and the 8-quinolyl nitrogen atom in the organocatalysts **4e** would play an important role in transition states. There are two plausible transition states **TS-*S*** and **TS-*R***. The reaction with **4e** proceeds more preferably through **TS-*S*** giving (*S*)-**2a**, because **TS-*R***, which gives (*R*)-**2a**, is destabilized by steric repulsion between the bulky trifluoromethyl groups and methyl or the 8-quinolyl groups in enamine **9**.[15]

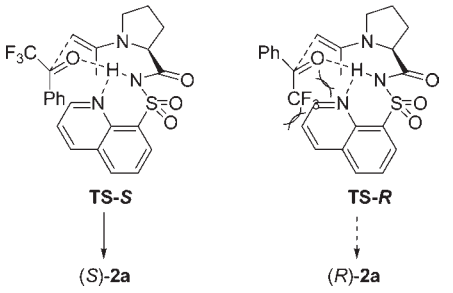


Figure 3. Assumed transition state for the cross-aldol reaction of **1a** with acetone, using **4e**.

In conclusion, we have developed a highly enantioselective construction of a quaternary carbon center by the reaction of trihalometyl ketones and a ketimine with acetone (up to 96% ee). We have identified 8-quinoline-sulfonylated catalyst **4e** to be a privileged organocatalyst for the reaction with various trihalometyl ketones and ketimine. Further studies are in progress to study the potential of these catalytic systems in other processes.

Acknowledgment. This work was supported by the Tatematsu Foundation. We are grateful to Zeon Co. for a gift of CPME.

Supporting Information Available. Representative experimantal procedures, HPLC analyses, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc., Wallingford, CT, 2009.

(14) *NBO* Version 3.1; Glendening, E. D., Reed, A. E., Carpenter, J. E., Weinhold, F. See also: (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(15) It is reasonable that the phenyl group is effectively a smaller group than the trifluoromethyl group. The order of relative sizes for trihalomethyl and phenyl group are $CCl_3 > CF_3 >$ Ph as indicated by the following reports, see: (a) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835. (b) Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (d) Tur, F.; Mansilla, J.; Lillo, V. J.; Saá, J. M. *Synthesis* **2010**, 1909. This assumption is in good agreement with the better enantioselectivity obtained from the reaction with trichloromethyl ketones **5** than that with trifluoromethyl ketones **1**.