ORGANIC LETTERS

2012
Vol. 14, No. 12
2972–2975

Enantioselective Diels–Alder Reaction of α-(Acylthio)acroleins: A New Entry to Sulfur-Containing Chiral Quaternary Carbons

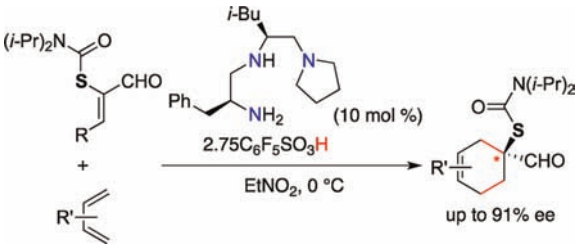
Akira Sakakura,[†] Hiroki Yamada,[‡] and Kazuaki Ishihara*[,‡,§]

EcoTopia Science Institute, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan, and JST, CREST, Furo-cho, Chikusa, Nagoya 464-8603, Japan

ishihara@cc.nagoya-u.ac.jp

Received April 10, 2012

ABSTRACT



A catalytic and enantioselective Diels–Alder reaction of α-(carbamoylthio)acroleins induced by an organoammonium salt of chiral triamine is described. α-(Carbamoylthio)acroleins are designed and synthesized as new sulfur-containing dienophiles for the first time. The Diels–Alder reaction affords chiral tertiary thiol precursors with up to 91% ee.

The Diels–Alder reaction is one of the most powerful carbon–carbon bond-forming reactions and is widely used for the synthesis of various bioactive natural compounds.[1] We previously reported the catalytic enantioselective Diels–Alder reaction and [2 + 2] cycloaddition reaction of α-(acyloxy)acroleins and α-(phthalimido)acroleins induced by organoammonium salts of chiral triamine **1** with $C_6F_5SO_3H$ or Tf_2NH (Scheme 1).[2] α-(Acyloxy)acroleins and α-(phthalimido)acroleins are useful dienophiles for the synthesis of chiral α-quaternary α-hydroxy or α-amino acid equivalents. In this context, α-(acylthio)acroleins would also be useful dienophiles for the construction of sulfur-containing quaternary carbons. The corresponding adducts are potential chiral intermediates for the synthesis of sulfur-containing bioactive natural products.[3] For example, the Diels–Alder adduct of an α-(acylthio)acrolein

[†] EcoTopia Science Institute.
[‡] Graduate School of Engineering.
[§] CREST.

(1) (a) Ishihara, K.; Sakakura, A. In *Stereoselective Synthesis*; Evans, P. A., Ed.; Georg Thieme Verlag KG: Stuttgart, 2011; Vol. 3, pp 67–123. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (d) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 315–399.

(2) (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504; correction **2005**, *127*, 13079. (b) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229. (c) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457. (d) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930. (e) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893. (f) Sakakura, A.; Ishihara, K. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 313.

(3) For representative examples of bioactive compounds bearing sulfur-containing quaternary carbons, see: (a) Hofmeister, H.; Hoyer, G.-A.; Cleve, G.; Laurent, H.; Wiechert, R. *Chem. Ber.* **1976**, *109*, 185. (b) Costa, M. d. C.; Teixeira, S. G.; Rodrigues, C. B.; Ryberg Figueiredo, P.; Marcelo Curto, M. J. *Tetrahedron* **2005**, *61*, 4403. (c) Asthana, R. K.; Srivastava, A.; Singh, A. P.; Deepali; Singh, S. P.; Nath, G.; Srivastava, R.; Srivastave, B. S. *J. Appl. Phycol.* **2006**, *18*, 33. (d) Sawant, S.; Youssef, D.; Mayer, A.; Sylvester, P.; Wali, V.; Arant, M.; El Sayed, K. A. *Chem. Pharm. Bull.* **2006**, *54*, 1119. (e) Dormann, K. L.; Brückner, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1160.

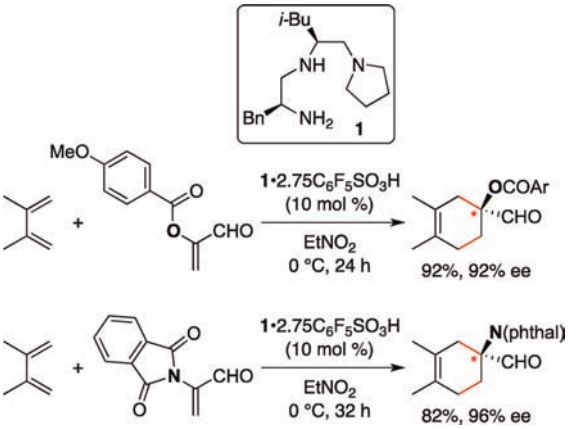
(4) Pattenden, G.; Shuker, A. J. *Tetrahedron Lett.* **1991**, *32*, 6625.

(5) (a) Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939. (b) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 5689. (c) Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041. (d) Lu, H.; Zhang, F.; Meng, X.; Duan, S.; Xiao, W. *Org. Lett.* **2009**, *11*, 3946. (e) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.

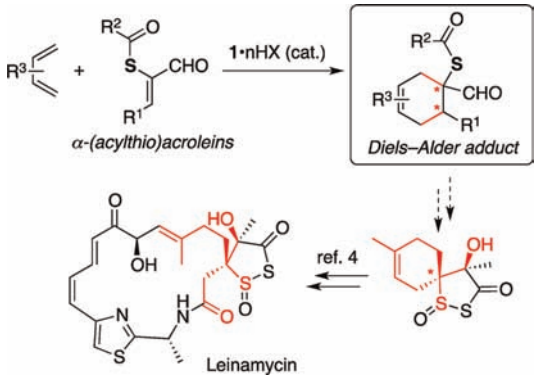
10.1021/ol300921f
Published on Web 05/25/2012

with isoprene would be readily converted to a key synthetic intermediate of leinamycin[4] (Scheme 2). Although some methods for the synthesis of sulfur-containing quaternary stereogenic centers have been reported,[5] most of these methods produce chiral thioethers and only a few can give tertiary thiols.[5b,e] We report here the catalytic and enantioselective Diels–Alder reaction of α-(acylthio)acroleins to give optically active tertiary thiol precursors.

Scheme 1. Enantioselective Diels–Alder Reaction of α-(Acyloxy)acroleins and α-(Phthalimido)acroleins[2]

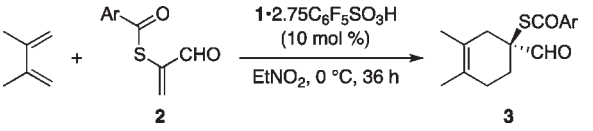


Scheme 2. Diels–Alder Reaction of α-(Acylthio)acroleins for the Synthesis of Sulfur-Containing Quaternary Carbons



On the basis of our previous results, benzoyl groups were considered to be promising candidates as protecting groups for the α-mercapto group. We first synthesized β-unsubstituted α-(benzoylthio)acroleins **2** based on the acylation[6] of 2-(diethoxymethyl)thiirane.[7,8] The Diels–Alder reaction of **2a**–**d** with 2,3-dimethylbutadiene (4 equiv) was conducted in the presence of **1**·2.75$C_6F_5SO_3H$ (10 mol %) in $EtNO_2$ at 0 °C (Table 1). As a result, the enantioselectivities of the corresponding adducts **3** highly depended on the benzoyl groups. The introduction of an electron-donating dialkylamino group at the 4-position increased the enantioselectivity, and dienophile **2d** bearing a pyrrolidinyl group gave the highest enantioselectivity (entry 4). However, the enantioselectivity of **2d** (72% ee) was still lower than those of α-(4-methoxybenzoyloxy)acrolein (92% yield, 92% ee)[2a] and α-(phthalimido)acrolein (82% yield, 96% ee)[2e] in the **1**·2.75$C_6F_5SO_3H$-catalyzed Diels–Alder reaction of 2,3-dimethylbutadiene. It is conceivable that the formation of stronger hydrogen bonding between the acyl group and an ammonium proton of the catalyst might stabilize the conformation of the transition state to increase the enantioselectivity (Figure 1). The lower basicity of thioesters compared to esters and imides resulted in the lower enantioselectivity of α-(benzoylthio)acroleins **2a**–**d** than α-(4-methoxybenzoyloxy)acrolein and α-(phthalimido)-acrolein. In addition, although the α-benzoylacroleins **2c** and **2d** gave good enantioselectivities, the yields of the corresponding adducts **3c** and **3d** were low (entries 3 and 4). The low yields were mainly attributed to the low solubilities of **2c** and **2d** in $EtNO_2$. Therefore, both the solubility and the basicity of the acyl group of **2** had to be improved to achieve high yield and enantioselectivity.

Table 1. Enantioselective Diels–Alder Reaction of α-(Benzoylthio)acroleins **2**[a]



entry	**2** [Ar]	**3**, yield (%)	ee[b] (%)
1	**2a** [Ph]	**3a**, 58	43
2	**2b** [4-(MeO)C_6H_4]	**3b**, 53	44
3	**2c** [4-(Me_2N)C_6H_4]	**3c**, 28	68
4	**2d** [4-[$(CH_2)_4N$]C_6H_4]	**3d**, 30	72

[a] Reaction of **2** (0.1 mmol) with 2,3-dimethylbutadiene (4 equiv) was conducted in the presence of **1**·2.75$C_6F_5SO_3H$ (10 mol %) in $EtNO_2$ at 0 °C for 36 h. [b] Determined by HPLC analysis.

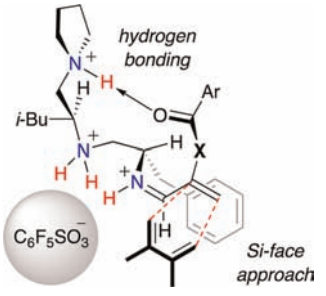
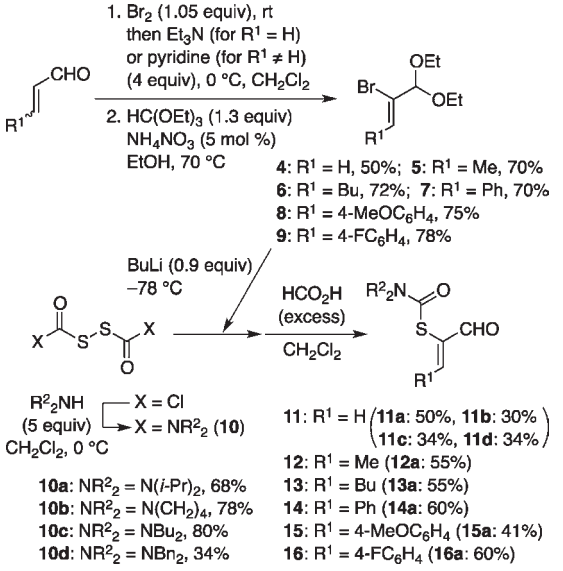


Figure 1. Proposed transition-state assembly.

(6) (a) Sander, M. *Chem. Rev.* **1966**, *66*, 297. (b) Silvestri, M. G.; Wong, C.-H. *J. Org. Chem.* **2001**, *66*, 910.
(7) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.
(8) See the Supporting Information for details.
(9) Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 4750.

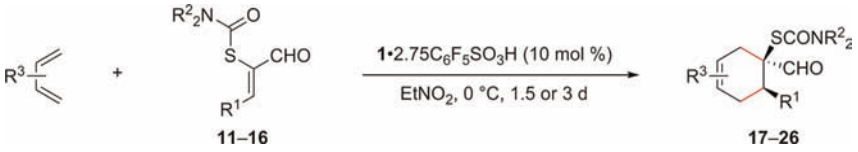
Thus, we next designed α-(carbamoylthio)acroleins **11a–d** (R^1 = H, Scheme 3) as new α-sulfur-substituted acroleins to overcome the above problems. The carbamoyl groups were expected to have a stronger electron-donating ability than the benzoyl groups. However, it would be very difficult to promote the carbamoylation of 2-(diethoxymethyl)thiirane with dialkylcarbamoyl chlorides, since the dialkylcarbamoyl chlorides were much less electrophilic than the carboxylic chlorides. Thus, we developed a new synthetic route for **11** based on the umpolung strategy: C–S bond formation between a "carbamoylthio cation R_2NCOS^+" and a "vinyl anion RCH=C^-CHO" (Scheme 3). According to this strategy, bis(carbamoyl)disulfides **10**, synthetic equivalents of a carbamoylthio cation, were prepared from bis(chlorocarbonyl)disulfide[9] and secondary amines. Lithiation[10] of α-bromoacrolein diethylacetals **4**[11] generated the corresponding vinyl anion. The reaction of the vinyl anion with **10** followed by acid hydrolysis of the acetal moiety gave **11a–d** in yields of 30–50%.

Scheme 3. Synthesis of α-(Carbamoylthio)acroleins **11–16**



As expected, α-(carbamoylthio)acroleins **11a–d** were readily soluble in $EtNO_2$ under the reaction conditions, and showed high reactivities and enantioselectivity in the **1**·2.75$C_6F_5SO_3H$-catalyzed Diels–Alder reaction with 2,3-dimethylbutadiene (entries 1–4, Table 2). Although **11b** bearing a pyrrolidinecarbonylthio group gave the highest enantioselectivity (76% ee), the yield of the corresponding adduct **17b** was low (20%) because **11b** was labile under the reaction conditions (entry 2). Dienophile **11a** bearing an *N,N*-diisopropylaminocarbonylthio group was

Table 2. Enantioselective Diels–Alder Reaction of α-(Carbamoylthio)acroleins **11–16**[a]



entry	diene	dienophile			adduct	17–27, yield (%)	*exo*/*endo*[b]	ee (%)[c]
		R^1	R^2					
1		**11a**	H	$N(i\text{-}Pr)_2$	SCONR$^2_2$, CHO	**17a**, 65	—	74
2		**11b**	H	$N(CH_2)_4$		**17b**, 20	—	76
3		**11c**	H	NBu_2		**17c**, 67	—	67
4		**11d**	H	NBn_2		**17d**, 48	—	48
5		**11a**	H	$N(i\text{-}Pr)_2$	SCON(*i*-Pr)$_2$, CHO	**18**, 68	—	81
6		**11a**	H	$N(i\text{-}Pr)_2$	SCON(*i*-Pr)$_2$, CHO	**19**, 67	—	73
7		**11a**	H	$N(i\text{-}Pr)_2$	SCON(*i*-Pr)$_2$, CHO	**20**, 74	—	67
8		**11a**	H	$N(i\text{-}Pr)_2$	CHO, SCON(*i*-Pr)$_2$	**21**, 79	56:44	0
9		**12a**	Me	$N(i\text{-}Pr)_2$	CHO, R^1, (*i*-Pr)$_2$COS	**22**, 88	87:13	88
10		**13a**	Bu	$N(i\text{-}Pr)_2$		**23**, 83	91:9	84
11		**14a**	Ph	$N(i\text{-}Pr)_2$		**24**, 68	75:25	91
12		**15a**	4-$(MeO)C_6H_4$	$N(i\text{-}Pr)_2$		**25**, 42	78:22	90
13		**16a**	4-FC_6H_4	$N(i\text{-}Pr)_2$		**26**, 67	75:25	90

[a] Reactions of **11–16** (0.1 mmol) with a diene (4 equiv) were conducted in the presence of **1**·2.75$C_6F_5SO_3H$ (10 mol %) in $EtNO_2$ at 0 °C for 1.5 days (for **11**) or 3 days (for **12–16**). [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis.

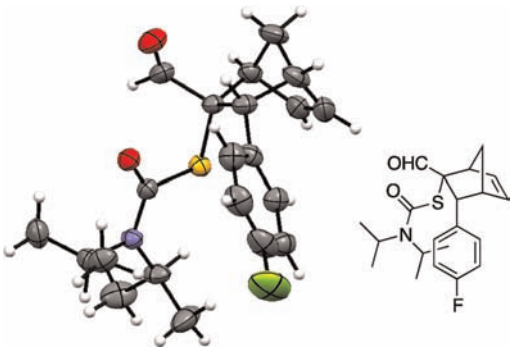


Figure 2. X-ray single-crystal structure of *exo*-**26** with thermal ellipsoids drawn at a 50% probability level. C = black, H = white, N = blue, O = red, S = yellow, F = green.

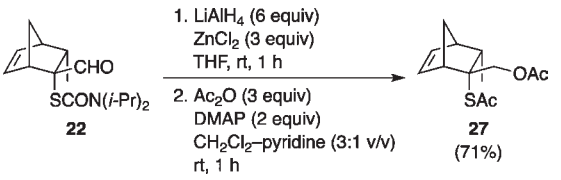
stable and gave the adduct **17a** in 65% yield with 74% ee (entry 1). With the optimized dienophile **11a** in hand, we next examined the enantioselective Diels–Alder reaction with representative dienes (entries 5–8). 2-Alkyl-substituted dienes such as isoprene, myrcene, and (*E*)-β-farnesene smoothly reacted with **11a** to give the corresponding 4-alkyl-substituted adducts **18**–**20** with >99% regioselectivity and 67–81% ee. In contrast, the reaction of **11a** with cyclopentadiene gave the corresponding adduct **21** in racemic form (entry 8).

According to the synthetic method for **11** desribed in Scheme 3, β-substituted α-(carbamoylthio)acroleins **12a**–**16a** ($R^1 \neq H$) were synthesized in 41–60% yields. In this reaction sequence, the bromination of β-substituted acroleins followed by acetalization selectively afforded *cis*-β-substituted α-bromoacrolein diethylacetals **5**–**9** despite the fact that the starting β-substituted acroleins were isomeric mixtures.[12]

The Diels–Alder reactions of β-substituted α-(carbamoylthio)acroleins **12a**–**16a** with cyclopentadiene were also catalyzed by **1**·$C_6F_5SO_3H$ (10 mol %) and gave the corresponding adducts **22**–**26** with high enantioselectivities (entries 9–13). In particular, β-aryl-substituted dienophiles **14a**–**16a** showed more than 90% ee (entries 11–13). The absolute configuration of the major diastereomer of the adduct **26** was determined to be (2*R*,3*R*) by X-ray crystallographic analysis (Figure 2).[8] The stereochemical outcome of *exo*-**26** was consistent with those of the Diels–Alder adducts of α-(acyloxy)acroleins and α-phthalimidoacroleins.[2]

The carbamoyl group in the Diels–Alder adducts could be removed by reductive cleavage. For example, the treatment of **22** with $LiAlH_4$ (6 equiv) and $ZnCl_2$ (3 equiv)[13] followed by acetylation of the resultant hydroxyl group and mercapto group gave **27** in 71% yield (Scheme 4).

Scheme 4. Derivatization of **22**



In conclusion, we have developed an organocatalytic and enantioselective Diels–Alder reaction of α-(carbamoylthio)acroleins to provide chiral tertiary thiol precursors for the first time. β-Unsubstituted or β-substituted α-(carbamoylthio)acroleins **11**–**16** were designed and synthesized as new sulfur-containing dienophiles.

Acknowledgment. Financial support for this project was provided by JSPS.KAKENHI (20245022 and 23350039). H.Y. thanks "the Nagoya University IGER Program in Green Natural Sciences for Leading Graduate Schools from MEXT" for a research fellowship.

Supporting Information Available. Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521.

(11) Barlow, A. j.; Compton, B. J.; Weavers, R. T. *J. Org. Chem.* **2005**, *70*, 2470.

(12) (a) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088. (b) Gilly, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631.

(13) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217.

The authors declare no competing financial interest.