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Kinetic Resolution of Racemic 2,3-Allenoates by Organocatalytic Asymmetric 1,3-Dipolar Cycloaddition

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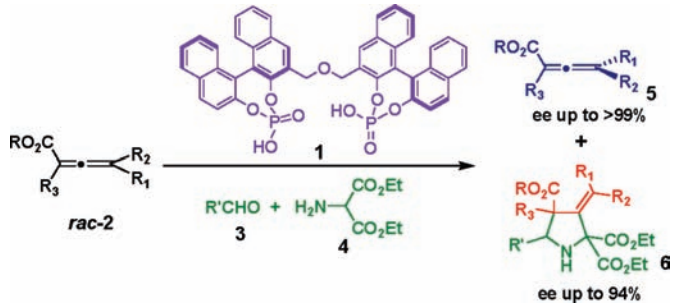
ABSTRACT



The kinetic resolution of racemic 2,3-allenoates was realized via 1,3-dipolar cycloaddition by using a bisphosphoric acid catalyst, affording the optically active 2,3-allenoates and 3-methylenepyrrolidine derivatives in high yields and enantioselectivities.

Axially chiral allenes are versatile core structures widely present in numerous natural and biologically active molecules[1] and serve as key intermediates in many asymmetric organic syntheses.[2] The synthesis of enantiomerically enriched allenes has relied on the transfer of chirality from a stereogenic center to the allene axis, optical resolution of racemic allenes, and recently, catalytic enantioselective synthesis of chiral allenes.[3] 2,3-Allenoates are an important class of functionalized allenes that serve as highly versatile synthetic intermediates.[2e,h] The cyclization of 2,3-allenoates furnishes functionalized chiral lactones such as butenolides and β-halobutenolides,[4] which are applicable to the preparation of a variety of natural products.[5] Thus, the synthesis of axially chiral 2,3-allenoates has drawn increased interest.[6] In this field, the dynamic kinetic protonation of racemic allenylsamarium species,[6a] the iron porphyrin-catalyzed

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(3) For reviews, see: (a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933. (b) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259, and references cited therein.

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(5) For a review, see: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (b) Knight, D. W. *Contemp. Org. Synth.* **1994**, 287.

(6) For selected excellent examples of synthesis of optically active 2,3-allenoates, see: (a) Mikami, K.; Yoshida, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 858. (b) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494. (c) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212. For enzymatic kinetic resolution of 2,3-allenoates, see: (d) Carballeira, J. D.; Krumlinde, P.; Bocola, M.; Vogel, A.; Reetz, M. T.; Bäckvall, J.-E. *Chem. Commun.* **2007**, 1913.

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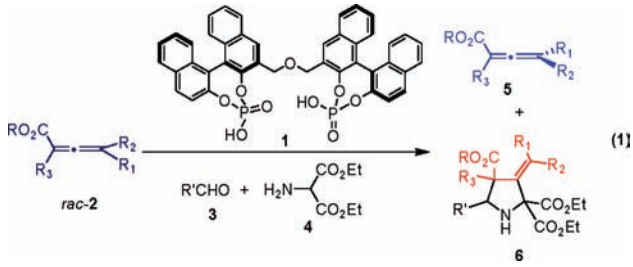
olefination of ketenes,[6b] and the chiral guanidine-catalyzed isomerization of 3-alkynoates exemplify elegant transformations with these reagents.[6c] However, few reports have described the catalytic asymmetric synthesis of chiral α-substituted 2,3-allenoic esters.[3b,6d]

Very recently, we established a series of chiral Brønsted acid-catalyzed 1,3-dipolar cycloaddition reactions of azomethine ylides.[7] In particular, the protocol is applicable to 2,3-allenoates, yielding 3-methylenepyrrolidine derivatives with high enantiopurity.[7d] Interestingly, when 2 equiv of racemic 4-ethyl buta-2,3-dienoates were reacted with the azomethine ylide derived from 4-bromobenzaldehyde, a moderate enantiomeric excess was observed for the recovered 4-ethyl buta-2,3-dienoates. In view of the widespread applications of enantiomerically enriched 2,3-allenoates, we were greatly interested in the kinetic resolution[8] of racemic 2,3-allenoates. Although there have been examples describing the preparation of allenes in optically pure form through kinetic resolution,[3b] organocatalytic kinetic variants have not been available. Herein, we will report an alternative to the known methods to access highly optically active α-substituted 2,3-allenoic esters by kinetic resolution of racemic 2,3-allenoates **2** via a chiral Brønsted acid-catalyzed asymmetric 1,3-dipolar cycloaddition reaction (eq 1).

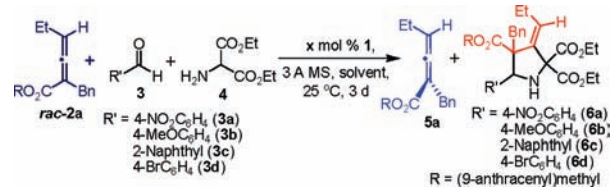


To establish the suitable aldehyde substrate for the efficient kinetic resolution, we investigated the 1,3-dipolar cycloaddition reaction of the racemic 9-anthracenylmethyl 2-benzylhexa-2,3-dienoate (**2a**) with azomethine ylides derived from diethyl 2-aminomalonate (**4**) and various aromatic aldehydes in the presence of the bisphosphoric acid **1** (Table 1). The substituent on the aromatic aldehyde proved to have considerable influence on the kinetic resolution, and the use of 4-bromobenzaldehyde gave **6d** in 51% yield and with 96% ee, while remarkably, **5a** was recovered in 48% yield and with 98% ee (Table 1, entries 1−4). Reducing the catalyst loading from 10 mol % to 7.5 mol % led to a subtle enhancement in the enantioselectivity of **5a** (entry 5). However, when catalyst loading was reduced to 5 mol %, slightly diminished ee values were observed for both the recovered substrate and the product (entry 6).

(7) (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357. (c) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (d) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946.

(8) For some reviews of the kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974, and references cited therein. For selected examples of the kinetic resolution of 2,3-allenoic acid, see: (d) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441.

Table 1. Optimization of Reaction Conditions[a]



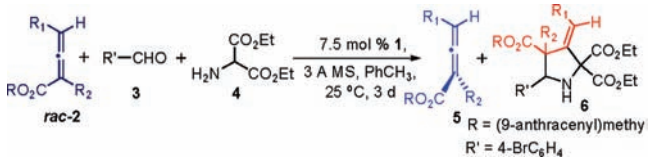
				5a		6	
entry	x	**3**	**2a**: **3**: **4**	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	10	**3a**	1:1.2:1	47	96	50	96
2	10	**3b**	1:1.2:1	43	94	49	95
3	10	**3c**	1:1.2:1	45	99	46	93
4	10	**3d**	1:1.2:1	48	98	51	96
5	7.5	**3d**	1:1.2:1	47	99	52	94
6	5	**3d**	1:1.2:1	46	98	53	92
7[d]	7.5	**3d**	1:1.2:1	47	99	52	94
8[e]	7.5	**3d**	1:1.2:1	50	90	48	96
9	7.5	**3d**	1:1.1:1	45	>99	48	94
10[f]	7.5	**3d**	1:1.1:1	65	24	19	92
11[g]	7.5	**3d**	1:1.1:1	51	33	26	92

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in $PhCH_3$ (1 mL) with 3 Å MS (100 mg) for 3 days. [b] Isolated yield. [c] Determined by HPLC. [d] 4 Å MS was used. [e] 5 Å MS was used. [f] CH_2Cl_2 was used as solvent. [g] $CHCl_3$ was used as solvent.

The variation of molecular sieves afforded no positive effects on the stereoselectivity (entries 7 and 8). Tuning the stoichiometric ratio of 4-bromobenzaldehyde had little effect on the stereoselectivity of **6d** and the recovered **5a**, and thus, addition of only 1.1 equiv of 4-bromobenzaldehyde to **2a** was sufficient for the reaction, generating **5a** with excellent enantioselectivity of >99% ee (entry 9). A comparison of solvents indicated that the reaction proceeded more slowly in halogenated media than in toluene. Additionally, much lower ee values were obtained for the recovered **5a**, when the reaction was conducted in either chloroform or dichloromethane (entries 10 and 11).

With the optimized conditions in hand, the scope of 2,3-allenoates was then examined (Table 2). The protocol tolerated a wide range of allenylic α-substituents on the allenoate **2**, including benzyl, alkyl, and allyl moieties. Generally, the reactions provided cycloaddition products **6** in 39−57% yields and 64−94% ee accompanied by yields of 35−48% for the recovered 2,3-allenoates **5** in 85−99% ee. The substituents at C4 of the 2,3-allenoate (R_1 group) had little effect on the enantioselectivity of recovered 2,3-allenoates **5**. The ee of the products eroded to a small degree when the ethyl group was replaced with a benzyl group at C4 of the allenoates (Table 2, entries 1 vs 11 and 2 vs 10). Variation of the substituent at C2 of the allenoates showed that larger substituents were beneficial to the enantioselectivity of products while high ee values were observed for the recovered allenoates (entries 1−5 and 9−12). The 6-chlorohexa-2,3-dienoate derivatives proved to be more reactive than other alleonates toward azomethine ylides in the 1,3-dipolar cycloaddition, giving products **6** in higher yields under the similar conditions, whereas the

Table 2. Scope for the Kinetic Resolution of the Allenoates **2**[a]



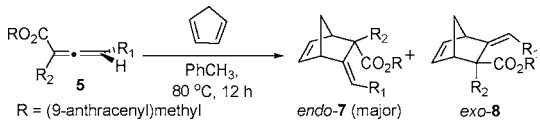
			5		6	
entry	R_1	R_2	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	Et	Bn	45 (**5a**)	>99	48 (**6d**)	94
2	Et	Me	46 (**5b**)	85	49 (**6e**)	84
3	Et	Allyl	48 (**5c**)	89	50 (**6f**)	90
4[d]	Et	H	40 (**5d**)	>99	52 (**6g**)	80
5	Et	CH_2CO_2Bn	41 (**5e**)	99	57 (**6h**)	80
6	$Cl(CH_2)_2$	Me	40 (**5f**)	98	55 (**6i**)	82
7	$Cl(CH_2)_2$	Allyl	43 (**5g**)	>99	54 (**6j**)	81
8	$Cl(CH_2)_2$	Bn	42 (**5h**)	99	55 (**6k**)	81
9[d]	$PhCH_2$	H	35 (**5i**)	>99	54 (**6l**)	64
10	$PhCH_2$	Me	43 (**5j**)	>99	50 (**6m**)	70
11	$PhCH_2$	Bn	47 (**5k**)	98	49 (**6n**)	89
12	$PhCH_2$	$4\text{-}BrC_6H_4CH_2$	40 (**5l**)	>99	39 (**6o**)	89

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in $PhCH_3$ (1 mL) with 3 Å MS (100 mg) for 3 days, and the ratio of **2**/**3**/**4** is 1/1.1/1. [b] Isolated yield. [c] Determined by HPLC. [d] The reaction was performed for 30 h.

enantioselectivities of the products were much lower (entries 6−8). The size of the substituent at C2 of the 6-chlorohexa-2,3-dienoates exerted little effect on the enantioselectivities of both the products and the recovered allenoates. Notably, the reaction of allenoates lacking an α-substitutent, proceeding at a faster rate than that for α-substituted ones, and also gave excellent enantioselectivities (entries 4 and 9).

Allenic esters have served as versatile reactants exhibiting great potential in organic synthesis. For example, the use of allene-containing compounds as dienophiles in Diels−Alder reactions has gained increasing attention.[9] Thus, we investigated the cycloaddition of the 2,3-allenoates **5** with cyclopentadiene. The reaction proceeded smoothly to give the *endo* diastereomer **7** as the major isomer in good yields (Table 3). Significantly, the chirality transfer from the optically pure

Table 3. Cycloadditions of Allenoates **5** with Cyclopentadienes

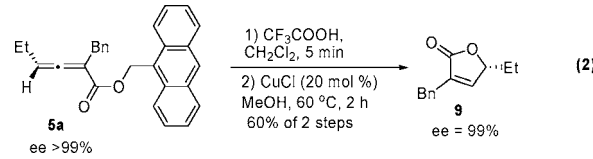


entry	**5** (ee of **5**)	yield[a] (%)	dr[b]	ee[c] (%)
1	**5a** (>99%)	71	3:1	>99 (**7a**), >99 (**8a**)
2	**5d** (99%)	87	3:1	92 (**7b**), 53 (**8b**)
3	**5h** (99%)	69	2.5:1	97 (**7c**), 99 (**8c**)

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Determined by HPLC.

allenoates to the corresponding Diels−Alder adducts was excellent. The relative stereochemistry was determined by NOESY experiments (see the Supporting Information).

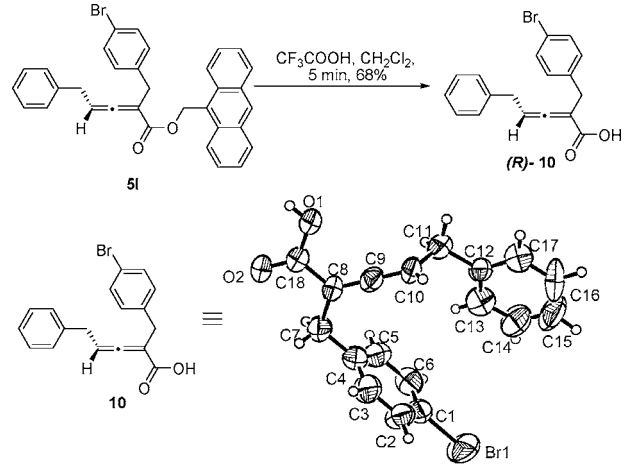
Butenolides commonly appear in natural products and biologically active compounds,[5] and efficient methodologies for the synthesis of β-unsubstituted butenolides from 2,3-allenoic acids have been described.[2h] In our hands, the 2,3-allenoic acid was initially obtained from the optically pure 9-(anthracenyl)methyl allenoic ester (**5a**) by hydrolysis under basic conditions, and the subsequent CuCl-catalyzed cycloisomerization of the 2,3-allenoic acid[10] provided the β-unsubstituted butenolide, but with complete racemization. As the basic hydrolysis of allenoic esters proceeded with racemization,[4a,11] we turned our attention to removal of the 9-(anthracenyl)methyl group of allenoate **5a** by hydrolysis under acidic conditions. Fortunately, the 9-(anthracenyl)methyl protecting group could be removed smoothly with trifluoroacetic acid in dichloromethane over 5 min, and the cyclization reaction readily afforded the β-unsubstituted butenolide **9** with excellent enantioselectivity (eq 2). This observation indicated that the axial chirality in allenes could be efficiently transferred to the stereogenic center in butenolides.



(2)

The absolute configuration of the recovered 2,3-allenoate was determined by X-ray crystallographic analysis. The compound **5l** was hydrolyzed in the presence of trifluoroacetic acid, producing the 2,3-allenoic acid **10** in 68% yield (Scheme 1). The X-ray structure of **10** revealed the assignment of the configuration of the 2,3-allenoate to be *R*.[12]

Scheme 1. Absolute Configuration of the 2,3-Allenoic Acid



In conclusion, we have established a kinetic resolution of the 2,3-allenoates via organocatalytic 1,3-dipolar cycload-

dition enabling access to both 3-methylenepyrrolidine derivatives and the recovered 2,3-allenoates with (*R*)-configuration in high yields and excellent enantiomeric excess. The 9-(anthracenyl)methyl 2,3-allenoates have been effectively transformed to the corresponding allenoic acid by hydrolysis under acidic conditions with high stereochemical outcomes. Moreover, the application of the obtained enantioenriched 2,3-allenoates to the Diels−Alder reaction and lactonization demonstrated the synthetic importance of the current method.

Acknowledgment. We are grateful for financial support from NSFC (20732006), CAS, MOST (973 project 2010CB833300), and the Ministry of Education.

Supporting Information Available: Experimental details, characterization of new compounds, and crystal data of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For recent examples, see: (a) Jung, M. E.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113. (b) Mukherjee, S.; Scopten, A. P.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1836. (c) Henderson, J. R.; Chesterman, J. P.; Parvez, M.; Keay, B. A. *J. Org. Chem.* **2010**, *75*, 988.

(10) Ma, S.; Yu, Z. *Synthesis* **2006**, 3711.

(11) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

(12) CCDC 776658. See the Supporting Information for details.