Highly Enantioselective Catalytic 1,3-Dipolar Cycloaddition Involving 2,3-Allenoate Dipolarophiles

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ABSTRACT



A bisphosphoric acid-catalyzed 1,3-dipolar cycloaddition of buta-2,3-dienoates with azomethine ylides yields 3-methylenepyrrolidine derivatives with excellent enantioselectivity (up to 97% ee).

Due to the widespread application of pyrrolidine-containing compounds in the synthesis of important biologically active natural and unnatural molecules, the development of efficient synthetic methods to access this structural motif in an optically active form has long been an important project in organic chemistry.¹ The enantioselective synthetic methods commonly used include 1,3-dipolar addition reactions of azomethine ylides to electronically deficient alkenes using chiral auxiliaries, chiral metal complex catalysts, and re-

cently, chiral organocatalysts.^{2,3} These methods provide elegant entries to pyrrolidine derivatives substituted with saturated C–C chemical bonds. 3-Methylene-pyrrolidine derivatives containing a C–C double bond that increases the structural flexibility in view of a tremendous number of reactions associated with olefins are undoubtedly important in synthetic chemistry either as building blocks or as intermediates.

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2,3-Allenoates, activated by nucleophilic catalysts such as organic phosphines and amines to form dipoles, commonly participated in [3 + 2] cycloaddition reactions with electronically deficient olefins and imines.⁴ In contrast, relatively few reports described the cycloaddition reactions involving 2,3allenoates as dipolarophiles.^{5,6} Very recently, we found that the chiral Brønsted acid bonded azomethine ylides could undergo smooth 1.3-dipolar addition reactions with electronically deficient olefins and imines, yielding five-membered nitrogenous heterocycles with high enantiopurity and structural diversity.⁷ To address the long-standing issues concerning no readily available methods to access optically active 3-methylenepyrrolidine derivatives, we had great interest in the development of 1,3-dipolar cycloaddition reaction between 2,3-allenoates and azomethine ylides (Scheme 1). Herein, we report our preliminary results.



The initial experiments included a reaction of 9-anthracenylmethyl buta-2,3-dienoate (**3a**, 9-AnCH₂) with 4-nitrobenzaldehyde and diethyl 2-aminomalonate (**5**) in the presence of structurally diverse binol-based phosphoric acids (Table 1). Although either of the monophosphoric acids⁸ examined afforded a smooth cyclization reaction yielding a 3-methylenepyrrolidine derivative, they provided poor enantioselectivity ranging from 4% to 33% ee (entries 1–7). Under similar conditions, the bisphosphoric acid **2** delivered an almost quantitative yield of 98% and excellent enantioselectivity of 90% ee (entry 8).^{7a} Variation of the substituent at the ester moiety of buta-2,3dienoates led to a conclusion that the introduction of a bulky substituent was beneficial to stereochemical control

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entry	3	catalyst	solvent	yield (%) ^b	ee (%) ^c		
1	3a	1a	$PhCH_3$	86	11		
2	3a	1b	$PhCH_3$	86	33		
3	3a	1c	$PhCH_3$	80	17		
4	3a	1d	$PhCH_3$	62	13		
5	3a	1e	$PhCH_3$	92	4		
6	3a	$\mathbf{1f}$	$PhCH_3$	79	26		
7	3a	1 g	$PhCH_3$	81	11		
8	3a	2	$PhCH_3$	98	90		
9	3b	2	$PhCH_3$	85	50		
10	3c	2	$PhCH_3$	68	88		
11	3a	2	$PhCH_3$	96	91^d		
12	3a	2	$PhCH_3$	95	92^e		
13	3a	2	$PhCH_3$	95	93^{f}		
14	3a	2	$PhCH_3$	93	93^g		
15	3a	2	$\mathrm{CH}_2\mathrm{Cl}_2$	96	$94^{g,h}$		
16	3a	2	$CHCl_3$	90	$92^{g,h}$		
17	3a	2	$Cl(CH_2)_2Cl \\$	86	$93^{g,h}$		

(entries 8–10). Tuning the ratio of buta-2,3-dienoate **3a** had little effect on the stereochemistry and the reaction conversion, and thus, only 1.2 equiv of **3a** to **5** was sufficient for a complete reaction (entries 12-14). A survey of the solvents indicated that halogen-containing solvents were also suitable in terms of the enantioselectivity, but the reaction proceeded relatively slower than those in nonpolar solvents (entries 15-17).



Having the optimized conditions in hand, we investigated the generality for the aldehyde component (Table 2). The protocol tolerated a wide range of aldehyde substrates. Generally, the aromatic aldehydes gave higher enantioselectivity than aliphatic aldehydes. The electronic feature of the substituent on the aryl ring did not have a significant effect on the stereoselectivity. Thus, high enantioselectivity was observed for either the electronrich, neutral, or electron-poor aromatic aldehydes (89%-96% ee, entries 1-11). An electronically rich cinnamaldehyde afforded a high yield and excellent enantioselectivity (93% yield, 95% ee, entry 12). 2-Furanylaldehyde participated in a clean reaction but with a moderate
 Table 2. Scope of Aldehydes of 1,3-Dipolar Addition

 Reactions^a

3a, R' = 9-A	DR' + nCH ₂	$\begin{array}{c} \text{RCHO} + \text{H}_2\text{N} \\ \textbf{4} \\ \textbf{5} \\ \textbf{5} \end{array} \begin{array}{c} \text{CO}_2\text{Et} \\ \text{CO}_2\text{Et} \\ \textbf{3A} \\ \textbf{4} \\ \textbf{5} \end{array} \begin{array}{c} 10 \\ \text{CO}_2\text{Et} \\ \textbf{3A} \\ \textbf{2} \end{array}$	0 mol % 2 EtO ₂ MS, PhCH ₃ EtO ₂ / 5 °C, 36 h	
entry	6	R	yield $(\%)^b$	ee (%) ^c
1	6a	$4-NO_2C_6H_4$	93	93
2	6d	$3-NO_2C_6H_4$	89	96
3	6e	$2-\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4$	79	91
4	6f	$4\text{-}\mathrm{CNC_6H_4}$	94	94
5	6g	$4-MeO_2CC_6H_4$	96	89
6	6h	$4\text{-BrC}_6\text{H}_4$	99	95
7	6i	$4-ClC_6H_4$	85	94
8	6j	$2,3$ - $Cl_2C_6H_4$	92	93
9	6k	Ph	84	92
10	61	$4-MeOC_6H_4$	74	95
11	6m	2-Naphthyl.	97	92
12	6n	$4-MeOC_6H_3CH=CH$	93	95
13	60	2-Furan	98	75
14	6p	2-Thiophen	67	91
15	6 q	c-Propane	90	$69^{d,e}$
16	6r	<i>c</i> -Hexane	87	$28^{d,e}$
17	6s	n-C ₃ H ₇	29	17^{f}

^{*a*} The reaction was carried out in 0.1 mmol scale in PhCH₃ (1 mL) with 3 Å MS (100 mg), and the ratio of **3a/4/5** is 1.2/1.2/1. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC. ^{*d*} The ratio of **3a/4/5** is 5/1.2/1. ^{*e*} The reaction was performed for 60 h. ^{*f*} The reaction was performed for 6 days.

enantioselectivity (entry 13). Although thiophene-2-carbaldehyde gave a comparably lower yield (67%), the enantioselectivity was high (entry 14, 91% ee). α -Branched aliphatic aldehydes proceeded with cleaner reaction than linear aliphatic aldehydes. However, the stereoselectivity was always low in the cycloaddition reactions involving aliphatic aldehydes (entries 15–17).

The generality for the scope of buta-2,3-dienoate derivatives was finally explored (Table 3). The substituents at either

Table 3. Scope of Allene of 1,3-Dipolar Addition Reactions^a

$\begin{array}{c} 1 \\ 2^2 \\ 2^2 \end{array}$	₹ ³ + CO ₂ Ar	R−CHO [⊣] 4a	- (H ₂ N	CO₂Et <u>10 mol % 2</u> CO₂Et 3 A MS.PhCI 5 25 °C	$H_{3,}$ R^{2} R^{3} R^{3} R^{2} R^{3} R^{2} R^{3} R^{2} R^{3} R^{2} R^{2} R^{3} R^{2} R^{3} R^{2} R^{3} R^{2} R^{3} R^{3} R^{4} R^{2} R^{3} R^{4} R^{2} R^{3} R^{4} R^{3} R^{4} $R^{$	-R ¹ CO ₂ Et CO ₂ Et racenyl)methy
entry	7	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	yield $(\%)^b$	ee (%) ^c
1	7a	Ph	Η	Н	68	6
2	7 b	Me	Me	Н		n.d.
3	7c	Η	Η	$\rm CH_2\rm CO_2\rm Bn$	86	88
4	7d	Η	Η	Me	79	92
5	7e	Η	Η	Bn	45	94

^{*a*} The reaction was carried out in 0.1 mmol scale in PhCH₃ (1 mL) with 3 Å MS (100 mg), and the ratio of **3/4/5** is 1.2/1.2/1. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC.

carbon of the allene have considerable influence on the reaction performance. 9-Anthracenylmethyl 4-phenyl buta-

2,3-dienoate underwent a good reaction but gave a low enantiomeric excess (entry 1). No reaction was observed for 4,4-dimethyl variant (entry 2). Interestingly, the presence of a substituent at C2 of the allene was tolerable, leading to the desired cycloaddition products with high stereochemical outcomes (entries 3-5).

Preliminary studies on the kinetic resolution of racemic 4-ethyl buta-2,3-dienoates that bear a alkyl substituent at C2 by the cycloaddition reaction with the azomethine ylides were preformed (Table 4).⁹ These buta-2,3-dienoates reacted

Table 4. Studies on the Kinetic Resolution of the RacemicButa-2,3-dienoates a



^{*a*} The reaction was carried out in 0.1 mmol scale in PhCH₃ (1 mL) with 3 Å MS (100 mg), and the ratio of **3/4/5** is 2/1.2/1. ^{*b*} Isolated yield based on the amino ester **5**. ^{*c*} Isolated yield based on the allenoate **3**. ^{*d*} Determined by HPLC.

readily with the azomethine ylide derived from 4-bromobenzaldehyde to yield the desired cyclic compounds of type **7** as sole products with high enantiomeric excess (89–97% ee). Indeed, the racemic 4-ethyl buta-2,3-dienoates could be resolved, but only moderated enantiomeric purity was observed for the recovered starting materials.

The absolute configuration of the product was accessed by X-ray crystallography analysis. As all the cycloaddition products





failed to grow crystal, we transformed **6h** to a solid derivative. The compound **6h** was reduced with LiAlH₄ and followed by an acylation with 4-chlorobenzoyl chloride, giving a product **8** in overall 12% yield. The compound **8** could be grown to a crystal suitable for X-ray analysis (Scheme 2). The X-ray structure of **8** revealed an assignment of the configuration of the stereogenic centers to be (4R, 5S).¹⁰

In summary, we have disclosed an unprecedented 1,3dipolar cycloaddition of buta-2,3-dienoates with azomethine ylides, yielding 3-methylenepyrrolidine derivatives with excellent enantioselectivity. Notably, the protocol is potentially applicable to the kinetic resolution of racemic 4-alkyl buta-2,3-dienoates. The presence of a carbon–carbon double bond at the pyrrolidine ring would be useful in the structurally diverse five-membered nitrogenous molecules.

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

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