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Chiral Phosphoric Acid Catalyzed Diastereo- and Enantioselective Mannich-Type Reaction between Enamides and Thiazolones

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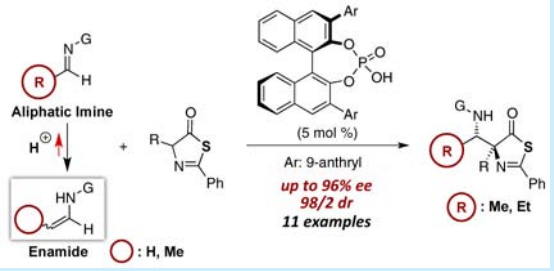
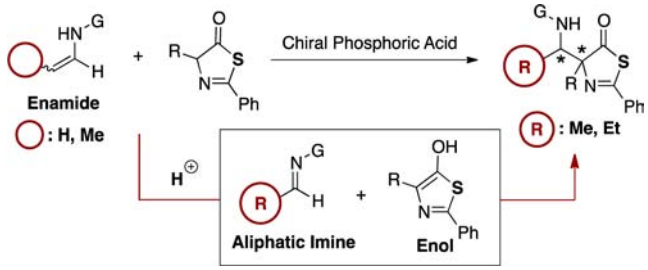
Supporting Information

ABSTRACT: An enantioselective Mannich-type reaction between enamides, serving as aliphatic imine equivalents, and thiazolones or an azlactone, serving as α-amino acid derived pronucleophiles, was investigated using a chiral phosphoric acid catalyst. By using thiazolones, Mannich adducts with a tetrasubstituted chiral carbon center at the α-position and an aliphatic substituent at the β-position were efficiently obtained with high diastereo- and enantioselectivities.



Enantiomerically enriched α,β-diamino acids and their derivatives are important structural motifs because these units are present in a number of natural products and biologically active compounds.[1] Thus far, various approaches for synthesizing these molecules have been reported. One of the most efficient methods is the enantioselective Mannich-type reaction of imines with α-amino acid derivatives as pronucleophiles[2] to form a carbon−carbon bond, as well as vicinal stereogenic centers, in a single step. Among various pronucleophiles, azlactones[3] and their sulfur analogues, thiazolones,[4] are attractive synthons as α-amino acid derived pronucleophiles. Several studies have reported the efficient syntheses of α,β-diamino acid equivalents by enantioselective Mannich-type reactions between imines and azlactones[5,6] or thiazolones.[7] For example, Amarante and co-workers recently reported the direct use of aryl imines in the Mannich-type reaction of azlactones for efficient synthesis of enantiomerically enriched α,β-diamino acid equivalents using a chiral phosphoric acid catalyst.[5f] Although excellent progress has been made in the catalytic asymmetric Mannich-type reaction of aryl imines, the success of this reaction using aliphatic imines, in particular, acetaldehyde-derived compounds, has been extremely limited because of their low stability and high reactivity.[5a,c,d] Based on previous studies,[8] we envisioned that an acetaldehyde imine would be generated in situ from an enamide in the presence of a chiral phosphoric acid[9] catalyst, which would allow us to access the Mannich-type reaction of aliphatic imines. To develop a method for efficiently synthesizing α,β-diamino acid equivalents with an aliphatic substituent at the β-position, we focused our attention on the use of thiazolones. We expected the α-proton of thiazolones to be more acidic than that of azlactones, allowing ready tautomerization to the enol form; hence, an in situ generated acetaldehyde imine easily reacts with thiazolones without side reactions with the enamide itself. Despite the fact that thiazolones are potentially useful pronucleophiles under acidic conditions, the Brønsted acid catalyzed reaction of thiazolones has not been reported so far. Herein, we describe the Mannich-type reaction between enamides and thiazolones catalyzed by a chiral phosphoric acid (Scheme 1).

Scheme 1. Mannich-Type Reaction between Enamides and Thiazolones under Acidic Conditions



To prove the utility of thiazolones, the Mannich-type reaction was initially performed using benzoyl-protected enamide **2a**,[10] phenylglycine-derived thiazolone **3a** or azlactone **3b**, and 5 mol % of catalyst **1a** (Ar = 9-anthryl) at 0 °C in THF (Table 1, entries 1−3). The Mannich-type reactions of **3a** proceeded with considerably higher yield than that of **3b**. These results clearly indicate the utility of thiazolones in the present Mannich-type reaction. We considered that the facile tautomerization of thiazolones to the enol form may contribute to facilitating the reaction of **3a** when compared with that of **3b**.[11] Importantly, Mannich adduct **4aa** was obtained in good

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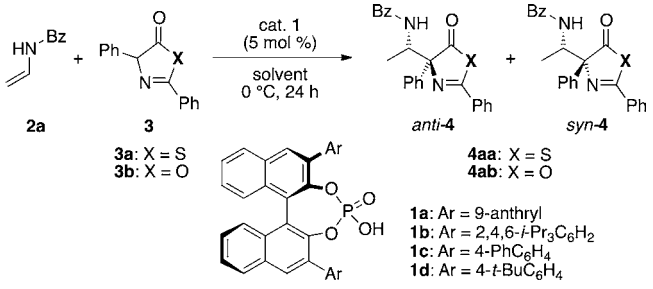
Table 1. Diastereo- and Enantioselective Mannich-Type Reaction between Enamide and Thiazolone or Azlactone[a]



entry	1	3	solvent	yield[b] (%)	anti/syn[c]	ee (%) of 4[d] anti-4/syn-4
1[e]	1a	3a	THF	~75	98/2	96/–
2[f]	1a	3b	THF	18	57/43	67/21
3[g]	1a	3a	THF	82	98/2	96/–
4	1b	3a	THF	58	91/9	71/–
5	1c	3a	THF	60	98/2	49/–
6	1d	3a	THF	65	96/4	51/–
7	1a	3a	CH_2Cl_2	40	84/16	22/–
8	1a	3a	EtOAc	72	92/8	59/–
9	1a	3a	toluene	63	89/11	9/–

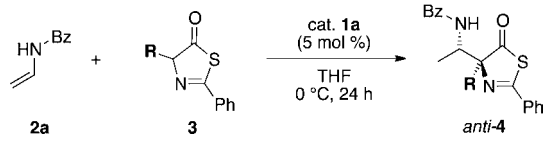
[a]Experimental conditions unless otherwise noted: a mixture of **1** (0.01 mmol), **2a** (0.2 mmol), and **3** (0.2 mmol) in THF (0.4 mL) was stirred at 0 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]Yield of **4aa** was determined on the basis of ^{1}H NMR and weight for the mixture of **2a** and **4aa** due to inseparable **2a**. [f]Stereochemistry of **4ab** was not determined. [g]1.2 equiv of **3a** was used.

yield with excellent diastereo- and enantioselectivities (*anti*/*syn* ratio of 98/2, 96% ee for the anti isomer). An investigation of the effect of the aryl substituents at the 3,3′-positions of **1** showed substantial differences in enantioselectivities even though high diastereoselectivities were observed in all cases (entries 4−6). Solvent screening revealed that the use of dichloromethane, ethyl acetate, and toluene decreased the yield as well as the diastereo- and enantioselectivities (entries 7−9). Consequently, chiral phosphoric acid **1a** possessing a 9-anthryl group as the aryl unit and THF as the solvent were identified as optimal for excellent relative and absolute stereocontrol (entry 3).

With the optimized catalyst and reaction conditions in hand, the scope of thiazolones was examined (Table 2). Although moderate yields were obtained in some cases, various thiazolones with an aryl substituent at the *ortho*-, *meta*-, or *para*-position (**3c−i**) underwent the reaction to afford desired products **4ac−ai** in high diastereo- and enantioselectivities, regardless of the electronic properties of the aryl substituents (entries 2−8). Naphthyl-substituted thiazolone **3j** was also tolerated with high stereoselectivities (entry 9). Isopropyl-substituted thiazolone **3k** was suitable for this reaction, affording **4ak** in high diastereo- and enantioselectivities, despite the moderate yield (entry 10).

To elucidate the mechanism of this Mannich-type reaction, diastereo- and enantioselective reactions using the (*Z*)- and (*E*)-isomers of enamide **2b**, which can proceed via either a stepwise or a concerted mechanism.[12] The reactions of geometric isomers (*Z*)-**2b** and (*E*)-**2b** gave the same products without a significant difference in diastereo- and enantioselectivities (eq 1). These results suggest that the present

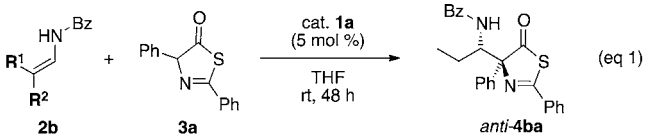
Table 2. Scope of Thiazolone[a]



entry	R	3	yield[b] (%)	anti/syn[c]	ee of anti-4[d] (%)	
1	Ph	3a	82	98/2	96	4aa
2	4-MeC_6H_4	3c	64	98/2	90	4ac
3[e]	4-Br C_6H_4	3d	83	97/3	94	4ad
4	4-$MeOC_6H_4$	3e	56	97/3	89	4ae
5[e]	4-$CF_3C_6H_4$	3f	80	96/4	92	4af
6[e]	3-MeC_6H_4	3g	67	98/2	88	4ag
7[e]	3-BrC_6H_4	3h	79	94/6	87	4ah
8	2-FC_6H_4	3i	51	96/4	88	4ai
9[e]	2-Nap	3j	57	95/5	88	4aj
10[e]	*i*-Pr	3k	44	93/7	88	4ak

[a]Experimental conditions unless otherwise noted: a mixture of **1** (0.01 mmol), **2a** (0.2 mmol), and **3** (0.24 mmol) in THF (0.4 mL) was stirred at 0 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis. [e]**3** (0.28 mmol) was used.

Manich-type reaction between enamides and thiazolones proceeds through a stepwise mechanism via imine generation.

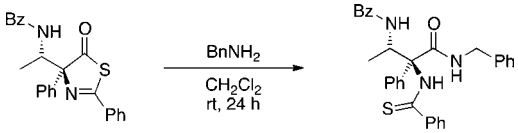


(*Z*)-**2b**: R^1 = Me, R^2 = H
(*E*)-**2b**: R^1 = H, R^2 = Me

from (*Z*)-**2b**: 81% ee (61% yield, 92/8 dr)
from (*E*)-**2b**: 77% ee (68% yield, 91/9 dr)

The ring-opening reaction of the thiazolones demonstrates the potential utility of the present system (Scheme 2).

Scheme 2. Ring Opening of Mannich-Type Reaction Product 4aa



Treatment of **4aa** with benzylamine in dichloromethane afforded α,β-diamino amide **5** without the loss of enantioselectivity. Although we examined further transformations of **5**, unfortunately, we did not realize the removal of the benzoyl group and derivatization of the thioamido unit.

In summary, we have reported the first successful enantioselective Mannich-type reaction between enamides and thiazolones catalyzed by chiral phosphoric acid **1a** containing a 9-anthryl group. The present reaction exhibits the utility of enamides as acetaldehyde imine equivalents, furthering their potential as aliphatic imine equivalents, and thiazolones as α-amino acid-derived pronucleophiles in Mannich-type reactions under acidic conditions. This method allows for the efficient synthesis of α-tetrasubstituted α,β-diamino acid equivalents in a highly diastereo- and enantioselective manner. Currently, further studies for elucidat-

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ing the mechanism and origin of the stereochemical outcome of the present Mannich-type reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00857.

Crystal structure of compound **4ad**(CIF)
Experimental details, characterization data, HPLC enantiomer analysis, NMR spectra for new compounds, and X-ray diffraction analysis(PDF)

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Notes

The authors declare no competing financial interest.

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(10) Although Boc- or Cbz-protected enecarbamates were applicable for the Mannich-type reaction of thiazolone **3a** under the same conditions as in Table 1, enantioselectivities were lower than the reaction with benzoyl-protected enamide **2a**. *N*-Boc-enecarbamate: 90% yield, 87/13 dr, 60% ee. *N*-Cbz-enecarbamate: 56% yield, 93/7 dr, 51% ee.

(11) For NMR studies on the keto−enol form of **3a** and **3b**, see Supporting Information.

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