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Catalytic Asymmetric Synthesis of *anti*-α,β-Diamino Acid Derivatives

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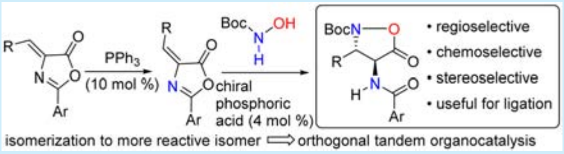
Supporting Information

ABSTRACT: A novel approach to chiral *anti*-α,β-diamino acid derivatives through tandem orthogonal organocatalysis has been developed. Chiral phosphoric acid catalysts control the chemo-, regio-, and stereoselective addition of hydroxylamines to alkylideneoxazolones, while a phosphine catalyst promotes the isomerization of *Z*-alkylideneoxazolones to the more reactive *E*- alkylideneoxazolones.



α,β-Diamino acid derivatives have attracted much attention as important building blocks for the synthesis of various bioactive molecules.[1] In particular, mureidomycins and napsamycins are peptidylnucleoside antibiotics that contain *anti*-α,β-diamino acid residues and show potent antibacterial activity against strains of *Pseudomonas aeruginosa* (Figure 1).[1,2] One of the most useful strategies for the synthesis of α,β-diamino acid derivatives is an asymmetric Mannich reaction using an α-substituted oxazolone.[1] However, in this type of reaction, the product is limited to α,β-diamino acids with an α-tetrasubstituted carbon stereocenter.[3,4] We planned a novel strategy for a catalytic synthesis of chiral *anti*-α,β-diamino acid derivatives with an α-trisubstituted carbon stereocenter[5] using 4-alkylideneoxazolones **A** and hydroxylamine derivatives as substrates (Scheme 1).

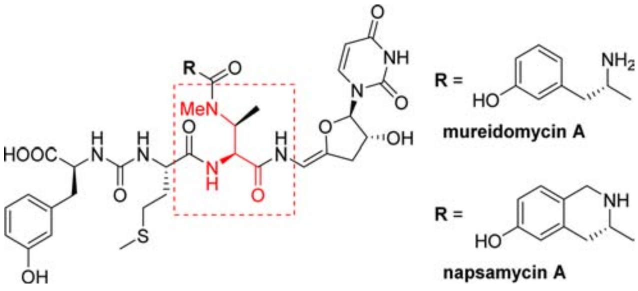
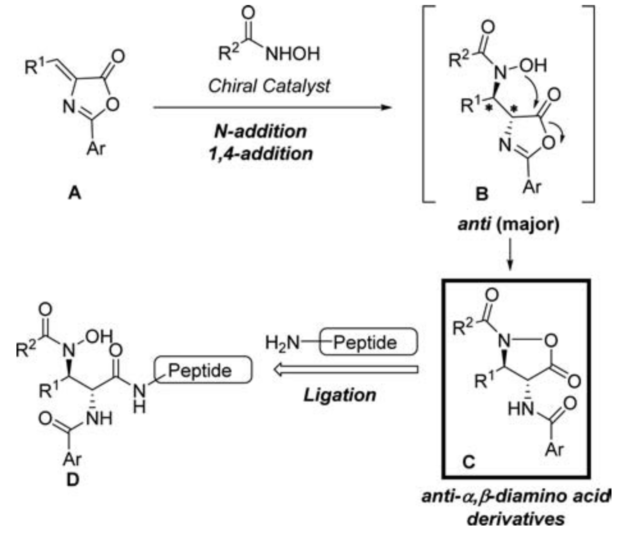


Figure 1. *anti*-α,β-Diamino acid derivatives.

The salient features of this method are as follows. (i) The stereochemistry of the two vicinal chiral centers would be controlled via aza-Michael adduct **B**, where a subsequent ring-opening reaction[6] of the *anti*-isomer should be favored, affording the *anti*-isoxazolidinone **C**. Epimerization of *syn*-isomer to the more stable *anti*-isomer would also be expected. (ii) Intermediate **C** could also be used for peptide ligation to give adduct **D**, whose hydroxylamine moiety could be further elaborated for another peptide ligation.[7] (iii) In the first step, competitive oxa-Michael reaction and 1,2-addition[8] of the hydroxylamine would be fully regulated by a catalyst, resulting in only the desired aza-Michael reaction.

Scheme 1. Synthetic Strategy



We initially sought efficient catalysts that promoted the aza-Michael reaction of alkylideneoxazolone (*Z*)-**1a** with BocNHOH (**2**) (Table 1). No reaction occurred in the absence of a catalyst (Table 1, entry 1). Unfortunately, thiourea catalyst **5**[9] that our laboratory had previously developed promoted the undesired *O*-1,2-addition reaction (Table 1, entry 2),[10] presumably owing to activation of the more acidic OH[8] group of **2** with the tertiary amine moiety of the catalyst. We then screened various organocatalysts without tertiary amine moieties and found that racemic phosphoric acid catalyst **7a** provided the desired product, 5-oxoisoxazolidine (*anti*-**4a**), whose structure was determined by X-ray crystallographic analysis.[10] This indicated that the aza-Michael reaction had occurred, followed by ring opening of oxazolone intermediate **B** (Table 1, entry 4). Interestingly, other possible products such as the oxa-Michael and 1,2-addition adducts were not observed, and only *syn*-**4a** was detected as a minor component. After

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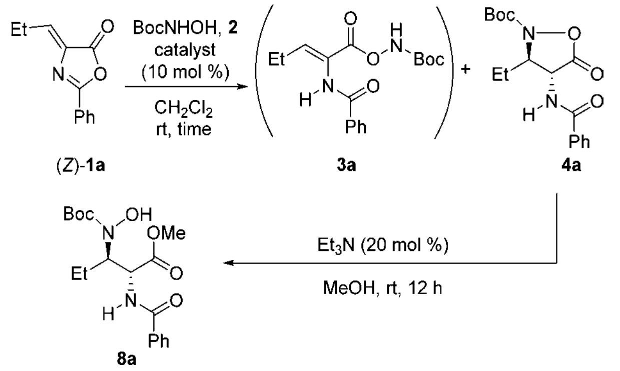
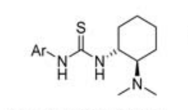
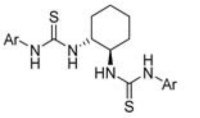
Table 1. Screening of the Reaction Conditions



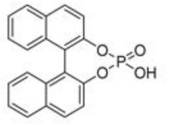
entry	catalyst	t (h)	4a, yield (%)[a]	8a, yield (%)[a]	*anti*/*syn*
1	none	69	N. R.[b]	-	-
2	5	2.5	0[c]	-	-
3[d]	6	74	N. R.[b]	-	-
4	7a	24	72[e]	-	84:16[f]
5	7a	24	n.d.[e,g]	92	80:20[h]


Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$-

5



6



7a

[a] Isolated yields. [b] No reaction. [c] 53% of **3a** was obtained. [d] 5 mol % of **6** was used as catalyst. [e] **3a** was not observed. [f] The ratio was determined on the basis of isolated yields of **4a**. [g] Not determined. [h] The ratio was determined based on isolated yields of **8a**.

several attempts at isolation, product **4a** was shown to be unstable in silica gel, which led to investigations into derivatizing **4a**. Eventually, we successfully obtained stable *anti-α,β*-diamino acid derivative **8a** via a ring-opening reaction of **4** using methanol (Table 1, entry 5).

Encouraged by these results, we next attempted an asymmetric reaction using chiral phosphoric acid **7b** (Scheme 2). We were interested in the differing reactivity between the *E*- and *Z*-isomers,[11,12] so (*Z*)-**1a** and (*E*)-**1a**[10] were investigated under the same reaction conditions. In the presence of 4 mol % of **7b**, the reaction of (*Z*)-**1a** proceeded slowly to furnish the desired compound **8a** in 72% yield (*anti*/*syn* = 74:26) with 25% ee (major *anti* isomer) after ring opening with methanol. The absolute configuration of both *anti*-**4a** and *syn*-**4a** was determined by derivatization to known compounds.[13] Very interestingly, the reaction of (*E*)-**1a** occurred much faster than (*Z*)-**1a** to give *ent*-**8a** in higher enantioselectivity. To confirm the reaction rate of each of the isomers, time course analysis of product formation by ^{1}H NMR was conducted, indicating that the reactivity of (*E*)-**1** was much higher.[10] More importantly, the isomerization of each isomer occurred under the reaction conditions, leading to an equilibrium mixture (*Z*/*E* = ca. 89:11).[10] This made us revise our strategy to achieve high yield and stereoselectivity: (i) *E*-isomers would be a suitable substrate for achieving excellent stereoselectivity, although suppression of the reaction from the *Z*-isomer would be necessary (Table 2); and (ii) the more stable *Z*-isomers could be used as substrates if an additional catalyst could enable isomerization to the *E*-isomers during the reaction, maintaining high stereoselectivities (Table 3).

Scheme 2. Aza-Michael/Ring Opening of (*Z*)- and (*E*)-1a

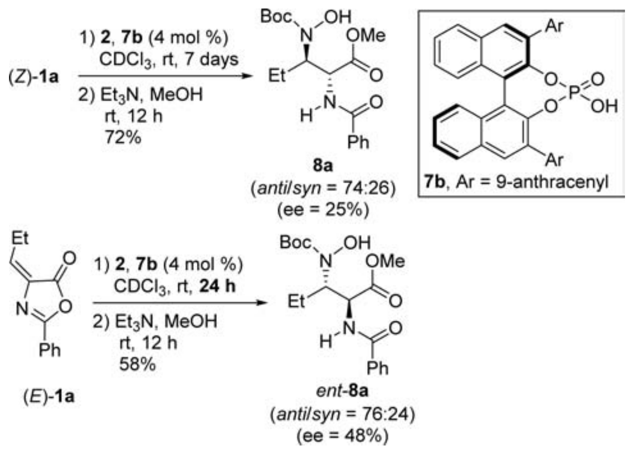
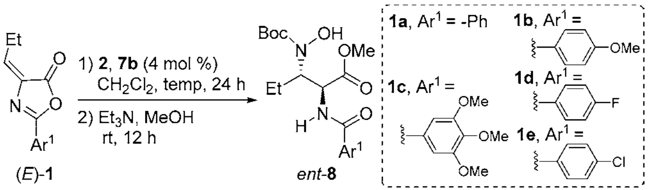
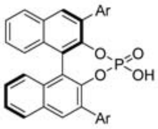


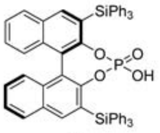
Table 2. Phosphoric Acid Catalyzed Aza-Michael/Ring Opening of Propylideneoxazolone (*E*)-1



entry	1	cat.	temp	*ent*-8 (yield, %)[a]	8, *anti*/*syn*[b]	8, ee[c] (%)
1	1a	7b	rt	*ent*-8a (50)	65:35	58
2	1a	7c	rt	*ent*-8a (70)	65:35	10
3	1a	7d	rt	*ent*-8a (67)	64:36	15
4	1a	7e	rt	*ent*-8a (50)	76:24	68
5	1a	7f	rt	*ent*-8a (53)	75:25	76
6	1a	7f	0 °C	*ent*-8a (56)	76:24	90
7	1b	7f	0 °C	*ent*-8b (48)	81:19	98
8	1c	7f	0 °C	*ent*-8c (59)	71:29	91
9	1d	7f	0 °C	*ent*-8d (44)	75:25	94
10	1e	7f	0 °C	*ent*-8e (46)	70:30	85



7c, Ar = C$_6$F$_5$
7d, Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
7e, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

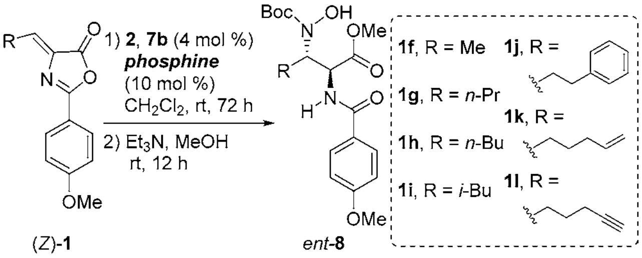


7f

[a] Isolated yields of *ent*-**8** in two steps. [b] The ratio was determined by isolated yields. [c] Determined by chiral HPLC analyses.

Thus, we moved on to investigate the reaction of *E*-isomers (Table 2). First, we screened several chiral phosphoric acids **7b**–**f** at room temperature (Table 2, entries 1–5) and found that **7f** gave the product in 53% yield with 76% ee (Table 2, entry 5). Lowering the reaction temperature improved the enantioselectivity to 90% ee, possibly because of suppression of the isomerization of (*E*)-**1** to (*Z*)-**1** and the direct reaction of (*Z*)-**1** (Table 2, entry 5 vs 6). We next investigated the effect of the aryl substituent on the oxazolone (Table 2, entries 7–10).[1] Although the reaction rate was not affected by the presence of either electron-donating or -withdrawing groups, 4-methoxy

Table 3. Phosphoric Acid Catalyzed Aza-Michael/Ring Opening of Propylideneoxazolone (Z)-1 with 2



entry	1	phosphine	*ent*-8 (yield, %)[a]	8, *anti*/*syn*[b]	8, ee[c] (%)
1[d]	**1b**	Ph_3P	***ent*-8b** (52)	83:17	78
2[d]	**1b**	dppf	***ent*-8b** (38)	72:28	79
3	**1b**	Ph_3P	***ent*-8b** (70)	75:25	71
4	**1f**	Ph_3P	***ent*-8f** (88)	64:36	52
5	**1g**	Ph_3P	***ent*-8g** (60)	75:25	78
6	**1h**	Ph_3P	***ent*-8h** (64)	72:28	84
7[e]	**1i**	Ph_3P	***ent*-8i** (44)	71:29	81
8	**1j**	Ph_3P	***ent*-8j** (60)	73:27	69
9	**1k**	Ph_3P	***ent*-8k** (39)	73:27	80
10	**1l**	Ph_3P	***ent*-8l** (62)	70:30	78

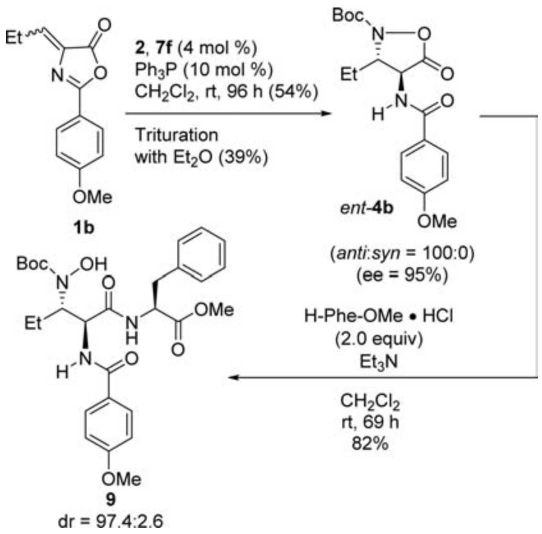
[a] Isolated yields of *ent*-**8** over two steps. [b] The ratio was determined by isolated yields. [c] Determined by chiral HPLC analyses. [d] The reaction (first step) was performed at 0 °C for 120 h. [e] 10 mol % of **7f** was used.

analogue (*E*)-**1b** was found to be an excellent substrate in terms of enantioselectivity (98% ee, Table 2, entry 7), and the diastereoselectivities were slightly improved as well (*anti*/*syn* = 81:19).

Although high enantioselectivities were achieved using the *E*-isomers as substrates (Table 2), unfortunately these were difficult to prepare.[11] A method using readily available (*Z*)-**1** would therefore be attractive. To solve this problem, we focused on finding a co-catalyst that promoted isomerization of the alkylideneoxazolone (Table 3).[14,15] After testing various organic molecules, iodine was found to promote the reaction. However, ^{1}H NMR experiments showed that iodine itself also catalyzed the racemic aza-Michael/ring opening reaction, which led to only modest enantioselectivities.[10,16] Further investigations into the orthogonal tandem catalysts led to the discovery that phosphines such as $(4\text{-MeOC}_6H_4)_3P$ and $CyPh_2P$ catalyzed not only the isomerization but also the undesired 1,2-addition reaction. However, Ph_3P only catalyzed the isomerization reaction, and was chosen as the catalyst for the reaction, affording *ent*-**8b** in 52% yield and in 78% ee (Table 3, entry 1 vs 2).[10] This result strongly suggests that the reaction proceeded mainly through (*E*)-**1b**, which was produced by phosphine-catalyzed isomerization of (*Z*)-**1b**. After optimization of the reaction temperature, this orthogonal tandem reaction was shown to proceed faster at room temperature than at 0 °C without much loss of ee (Table 3, entry 1 vs 3), probably because the isomerization reaction catalyzed by Ph_3P occurred smoothly at room temperature. The substrate scope of (*Z*)-**1** was then examined under the optimized conditions. Substrates with bulky substitution were likely to provide relatively high enantioselectivity, albeit with slightly decreased yields (Table 3, entries 3–7). The reactivity of (*Z*)-**1f** itself was high enough to react with **2** without Ph_3P,[10] which decreased the selectivity although the yield of *ent*-**8f** was excellent (Table 3, entry 4). (*Z*)-**1j**–**l** with phenyl, alkenyl, and alkynyl groups were also tolerated in this reaction (Table 3, entries 8–10).

Finally, the coupling reaction of *ent*-**4b** with an *α*-amino acid was investigated (Scheme 3).[17] In this reaction, **1b** was used without separating the *Z*- and *E*-isomers (*Z*/*E* = 81:19). As *ent*-**4b** has a tendency to yield racemic crystals, the filtrate obtained by trituration with ether provided *ent*,*anti*-**4b** with high ee. In this case, 95% ee of *ent*-**4b** was obtained and was used for the coupling reaction. Instead of MeOH, 2 equiv of phenylalanine methyl ester hydrochloride was used in the ring-opening reaction and gave the desired product **9** in 82% yield (dr =97.4:2.6) without any epimerization, indicating that **4** can be used as a substrate for peptide ligations.

Scheme 3. Coupling Reaction



In conclusion, we have developed a novel method for the asymmetric synthesis of *anti*-*α*,*β*-diamino acid derivatives with an *α*-trisubstituted carbon stereocenter using alkylideneoxazolones **1** and a hydroxylamine as substrates through chiral phosphoric acid catalyzed[18] tandem aza-Michael/ring-opening reaction. We investigated the difference in the reactivity of both *E*- and *Z*-isomers of **1**. To overcome the low reactivity of (*Z*)-**1**, a phosphine was used to catalyze the isomerization of (*Z*)-**1** to (*E*)-**1**. We believe that the present reaction offers an efficient method for the synthesis of peptide-based bioactive compounds through ligation. This is now under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03666.

Experimental details, compound characterization data for all new compounds, and complete NMR and HPLC spectra (PDF)

X-ray data for *anti*-**4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for details of the product characterization data. CCDC 1442977 (*anti*-**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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