

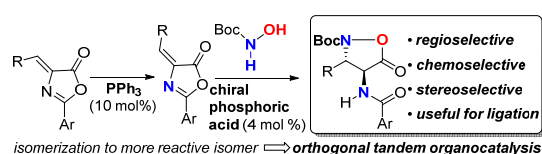
Title	Catalytic Asymmetric Synthesis of anti- , -Diamino Acid Derivatives
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# Catalytic Asymmetric Synthesis of *anti*- $\alpha,\beta$ -Diamino Acid Derivatives

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Supporting Information



**ABSTRACT:** A novel approach to chiral *anti*- $\alpha,\beta$ -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.

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

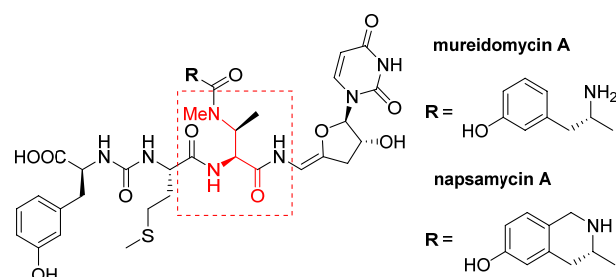
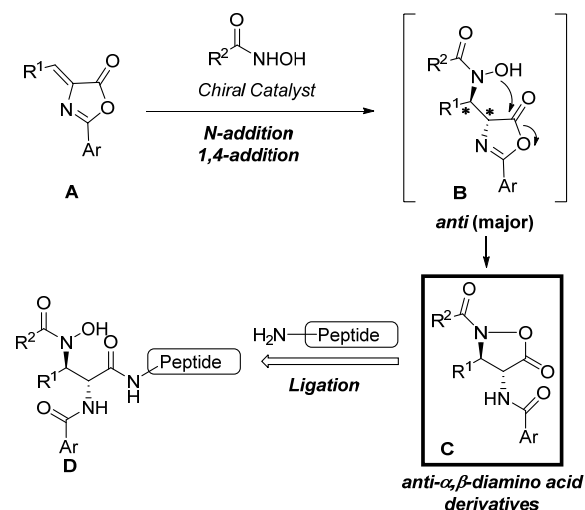


Figure 1. *anti*- $\alpha,\beta$ -Diamino acid derivatives

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<sup>6</sup> 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;<sup>7</sup> (iii) in the first step, com-

petitive oxa-Michael reaction<sup>8</sup> and 1,2-addition<sup>9</sup> of the hydroxylamine would be fully regulated by a catalyst, resulting in only the desired aza-Michael reaction.

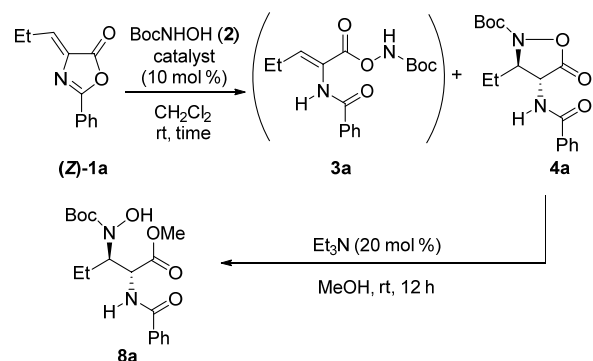
## Scheme 1. Synthetic strategy



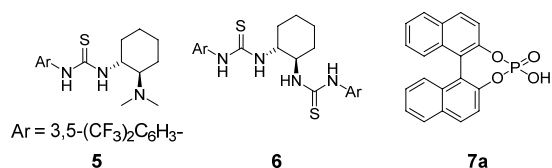
We initially sought efficient catalysts that promoted the aza-Michael reaction of alkylideneoxazolone (**Z**-**1a**) with Boc-NHOH (Table 1). No reaction occurred in the absence of a catalyst (entry 1). Unfortunately, thiourea catalyst **5** that our laboratory had previously developed promoted the undesired *O*-1,2-addition reaction (entry 2),<sup>10</sup> presumably owing to activation of the more acidic OH<sup>8</sup> 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.<sup>10</sup> This indicated that the aza-Michael reaction had occurred, followed by ring

opening of oxazolone intermediate **B** (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 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*- $\alpha,\beta$ -diamino acid derivative **8a** via a ring-opening reaction of **4** using methanol (entry 5).

**Table 1. Screening of the reaction condition**



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

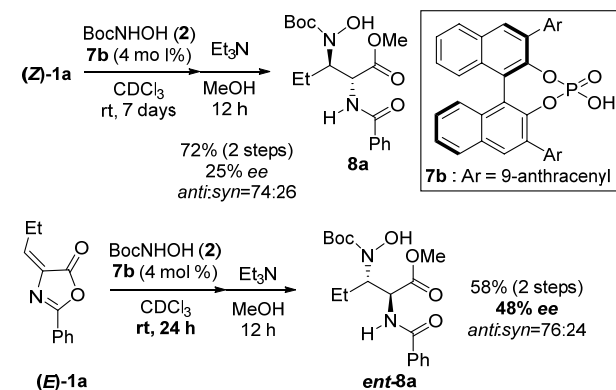


<sup>a</sup> Isolated yields. <sup>b</sup> No reaction. <sup>c</sup> 53% of **3a** was obtained. <sup>d</sup> 5 mol % of **6** was used as catalyst. <sup>e</sup> **3a** was not observed. <sup>f</sup> The ratio was determined based on isolated yields of **4a**. <sup>g</sup> Not determined. <sup>h</sup>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

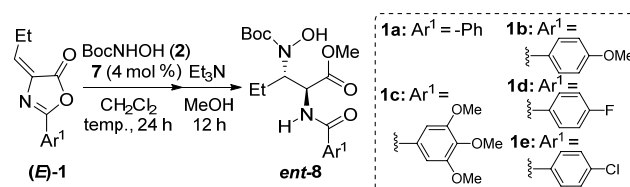
Encouraged by these results, we next tried an asymmetric reaction using chiral phosphoric acid **7b** (Scheme 2). We were interested in the differing reactivity between the *E*- and *Z*-isomers,<sup>11,12</sup> so (*Z*)-**1a** and (*E*)-**1a**<sup>10</sup> were investigated under the same reaction conditions. 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.<sup>13</sup> 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 <sup>1</sup>H NMR was conducted, indicating that the reactivity of (*E*)-**1** was much higher.<sup>10</sup> More importantly, the isomerization of each isomer occurred under the reaction conditions, leading to an equilibrium mixture (*Z*:*E* ca. 89:11).<sup>10</sup> 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); (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).

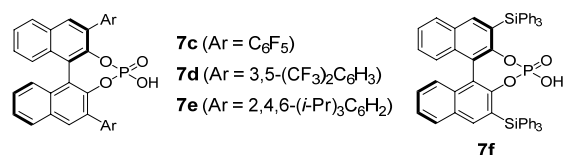
**Scheme 2. Aza-Michael/ring-opening of *Z*- and *E*-**1a****



**Table 2. Phosphoric acid-catalyzed aza-Michael/ring opening of propylideneoxazolone (*E*)-**1****



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

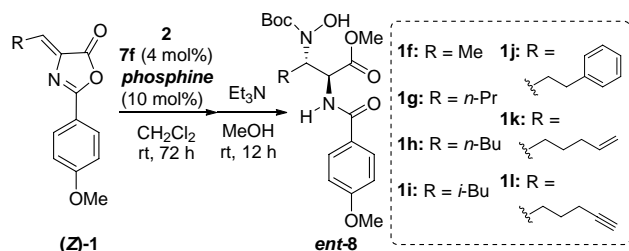


<sup>a</sup> Isolated yields of *ent*-**8** in 2 steps. <sup>b</sup> The ratio was determined by isolated yields. <sup>c</sup> Determined by chiral HPLC analyses.

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 (entries 1–5), and found that **7f** gave the product in 53% yield with 76% ee (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** (entry 5 vs 6). We next investigated the effect of the aryl substituent on the oxazolone (entries 7–10).<sup>1</sup> Although the reaction rate was not affected by the presence of either electron-donating or -withdrawing groups, 4-methoxy analog (*E*)-**1b** was found to be an excellent substrate in terms of enantioselectivity (98% ee, entry 7), and the diastereoselectivities were slightly improved as well (*anti*:*syn*=81:19).

**Table 3. Phosphoric acid-catalyzed aza-Michael/ring opening of propylideneoxazolone (*Z*)-**1** with **2****



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

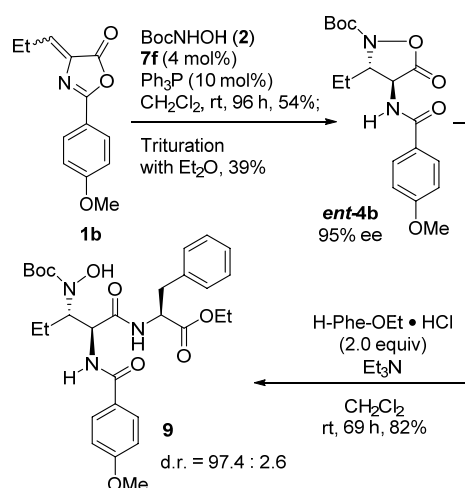
<sup>a</sup> Isolated yields of *ent*-**8** over 2 steps. <sup>b</sup> The ratio was determined by isolated yields. <sup>c</sup> Determined by chiral HPLC analyses. <sup>d</sup> The reaction (first step) was performed at 0 °C for 120 h. <sup>e</sup> 10 mol % of **7f** was used.

Although high enantioselectivities were achieved using the *E*-isomers as substrates (Table 2), unfortunately these were difficult to prepare.<sup>11</sup> 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).<sup>14,15</sup> After testing various organic molecules, iodine was found to promote the reaction. However, <sup>1</sup>H NMR experiments showed that iodine itself also catalyzed the racemic aza-Michael/ring opening reaction, which led to only modest enantioselectivities.<sup>10,16</sup> Further investigations into the orthogonal tandem catalysts led to the discovery that phosphines such as (4-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P and CyPh<sub>2</sub>P catalyzed not only the isomerization, but also the undesired 1,2-addition reaction. However, Ph<sub>3</sub>P only catalyzed the isomerization reaction, and was chosen as the catalyst for the reaction, affording *ent*-**8b** in 52% yield and in 78% ee (entry 1 vs 2).<sup>10</sup> 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 (entry 1 vs 3), probably because the isomerization reaction catalyzed by Ph<sub>3</sub>P occurred smoothly at room temper-

ature. 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 (entries 3–7). The reactivity of (*Z*)-**1f** itself was high enough to react with **2** without Ph<sub>3</sub>P,<sup>10</sup> which decreased the selectivity though the yield of *ent*-**8f** was excellent (entry 4). (*Z*)-**1j–l** with phenyl, alkenyl, and alkynyl groups were also tolerated in this reaction (entries 8–10).

Finally, the coupling reaction of *ent*-**4b** with an  $\alpha$ -amino acid was investigated.<sup>17</sup> 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 equivalents of phenylalanine ethyl ester hydrochloride were used in the ring-opening reaction, and gave the desired product **9** in 82% yield (d.r. = 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*- $\alpha,\beta$ -diamino acid derivatives with an  $\alpha$ -trisubstituted carbon stereocenter using alkylideneoxazolones **1** and a hydroxylamine as substrates, through chiral phosphoric acid-catalyzed<sup>18</sup> 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 experimental details, compound characterization data for all new compounds, the complete copies of NMR and HPLC charts, and CIF file of *anti*-**4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## REFERENCES

- (1) (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (b) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1.
- (2) Okamoto, K.; Sakagami, M.; Feng, F.; Togame, H.; Takemoto, H.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2012**, *77*, 1367.
- (3) For catalytic asymmetric Mannich reactions using  $\alpha$ -substituted oxazolone nucleophiles, see (a) Ávila, E. P.; Justo, R. M. S.; Gonçalves, V. P.; Pereira, A. A.; Diniz, R.; Amarante, G. W. *J. Org. Chem.* **2015**, *80*, 590. (b) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 4085. (c) Shi, S.-H.; Huang, F.-P.; Zhu, P.; Yan, W.; Dong, Z.-W.; Hui, X.-P. *Org. Lett.* **2012**, *14*, 2010. (d) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517. (e) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876. (f) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088.
- (4) Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun.* **2010**, *46*, 300.
- (5) (a) Liang, G.; Tong, M.-C.; Tao, H.; Wang, C.-J.; *Adv. Synth. Catal.* **2010**, *352*, 1851. (b) Shang, D.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 3678. (c) Hernández-Toribio, J.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (d) Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362.
- (6) For Michael addition/ring opening reactions with other nucleophiles, see (a) Cui, B.-D.; Zuo, J.; Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2014**, *79*, 5305. (b) Geng, Z.-C.; Li, N.; Chen, J.; Huang, X.-F.; Wu, B.; Liu, G.-G.; Wang, X.-W. *Chem. Commun.* **2012**, *48*, 4713.
- (7) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.
- (8) (a) Noël, R.; Gembus, V.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2014**, *12*, 1245. (b) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 5762. (c) Pohjakallio, A.; Pihko, P. M. *Chem.-Eur. J.* **2009**, *15*, 3960. (d) Ibrahim, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**, 849.
- (9) Kumar, S. V.; Saraiah, B.; Misra, N. C.; Ila, H. *J. Org. Chem.* **2012**, *77*, 10752.
- (10) 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](http://www.ccdc.cam.ac.uk/data_request/cif). See the Supporting Information for details of the product characterization data.
- (11) Rao, Y. S.; Filler, R. *Synthesis* **1975**, *12*, 749.
- (12) (a) Bianco-Lomas, M.; Funes-Ardoiz, I.; Campos, P. J.; Sampedro, D. *Eur. J. Org. Chem.* **2013**, 6611. (b) Bianco-Lomas, M.; Campos, P. J.; Sampedro, D. *Org. Lett.* **2012**, *14*, 4334.
- (13) Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148.
- (14) Lohr, T. L.; Marks, T. J. *Nature Chem.* **2015**, *7*, 477.
- (15) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171.
- (16) Ahmed, N.; Babu, B. V. *Synth. Commun.* **2013**, *43*, 3044.
- (17) (a) Azumaya, I.; Aebi, R.; Kubik, S.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12013. (b) Obrecht, D.; Karajannis, H.; Lehmann, C.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 703.
- (18) (a) For reviews, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5173. (c) Terada, M. *Chem. Commun.* **2008**, 4097. (d) Rueping, M.; Kuenkel, A.; Atodiresei, I.; *Chem. Soc. Rev.* **2011**, *40*, 4539. (e) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.