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Pd-Catalyzed Asymmetric Allylic Alkylation of Pyrazol-5-ones with Allylic Alcohols: The Role of the Chiral Phosphoric Acid in C−O Bond Cleavage and Stereocontrol

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Supporting Information

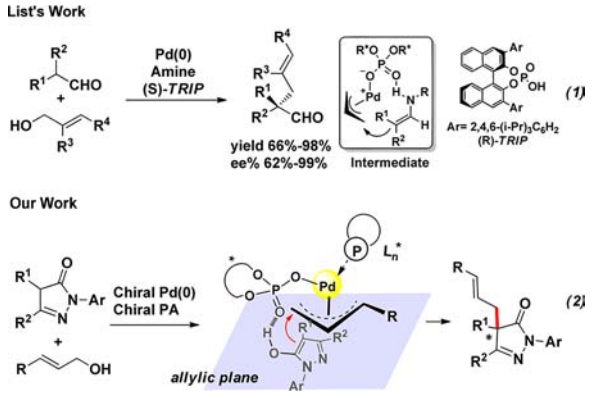
ABSTRACT: The combination of a palladium complex with a chiral phosphoramidite ligand and a chiral phosphoric acid enables the first highly efficient asymmetric allylic alkylation of pyrazol-5-ones with allylic alcohols, affording multiply functionalized heterocyclic products in high yields with excellent enantioselectivities that would be of great potential in the synthesis of pharmaceutically interesting molecules.

Asymmetric catalytic reactions involving C−C bond formation have allowed synthetic access to biologically important molecules. Among these reactions, asymmetric allylic alkylation (AAA)[1] has long been intensely studied for its diversity of bond-forming types and extensive applications in total synthesis. For most of the history of Pd-catalyzed AAA reactions, activated precursors of π-allyl fragments, such as allylic halides, esters, and carbonates, have predominantly been employed to accept the nucleophilic attack of soft or hard nucleophilies (Figure 1a). Nowadays, because of environmental

Figure 1. Profile of the AAA reaction.

issues, alternative sustainable processes are becoming more and more privileged, especially in the field of synthetic chemistry.[2] For this reason, allylic alcohols are considered to be a promising allylic component in AAA because of their wide synthetic reliability and step economy.[3] However, the hydroxyl group is known to be a poor leaving group, which would presumably obstruct the practical use of allylic alcohols in allylic alkylation, particularly the enantioselective variants (Figure 1b). External activators, including Lewis acids[1c,4] and Brønsted acids,[1c,5,6] have been explored to circumvent this formidable challenge. Trost first introduced triethylborane to assist the palladium to break the C−O bond, resulting in the AAA reactions of soft nucleophiles with allylic alcohols.[4a] Recently, List established an AAA reaction of α-enolizable aldehydes with allyl alcohols using the ACDC strategy,[7] in which a catalytic amount of chiral phosphoric acid facilitates the oxidative addition of Pd to allylic alcohols and solely controls the stereochemistry as well (Scheme 1, eq 1). Despite these important advances, a

Scheme 1. Combination of a Pd(0)/Chiral Ligand Complex and a Chiral Brønsted Acid



rejuvenation of the AAA reaction can still be anticipated by the creation of a new strategy capable of overcoming issues associated with limited nucleophile/allylic alcohol pairs in current processes.

Efficient assembly of optically pure multifunctionalized heterocyclic compounds, especially those with quaternary stereocenters,[8] is challenging but would be of great importance. Recently, pyrazol-5-one-derived enantiomers have drawn much attention because they appear prevalently in a collection of nonsteroidal anti-inflammatory drugs[9] such as Analgin, Nifenazone, and Feprazone, leading to an increased demand for efficient synthetic methods. As a result, enantioselective functionalization of pyrazol-5-ones has already been investigated.[10] However, no asymmetric alkylation of pyrazol-5-ones is available to date. Herein we report the first AAA reaction of pyrazol-5-ones using allylic alcohols directly as a reaction component, which was achieved by the combination of a

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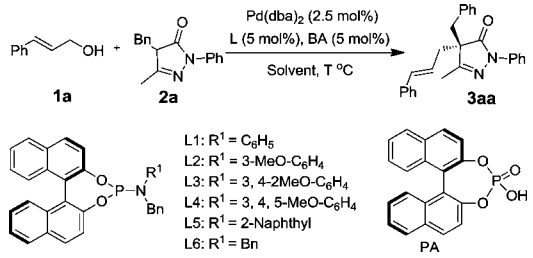
palladium complex with a chiral phosphoramidite ligand[11] and a chiral phosphoric acid.[6,12] In this protocol, the chiral phosphoric acid facilitates the formation of a π-allyl–Pd complex by activation of the C–O bond. Moreover, a remarkable synergistic effect between the ligand and the counteranion was observed (Scheme 1, eq 2).

We initially endeavored to develop a chiral-counteranion-directed AAA reaction using cinnamic alcohol (**1a**) and pyrazol-5-one **2a** as substrates, but the results were disappointing.[13] We then turned our attention to a combination of a chiral phosphoric acid, PA (see Table 1 for the structure), and easily

Table 1. Investigation of Ligands and Brønsted Acids[a]



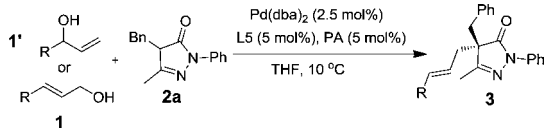
entry	L	BA	solvent	T (°C)	yield (%)[b]	ee (%)[c]
1	Ll	PA	toluene	25	72	49
2	L2	PA	toluene	25	86	77
3	L3	PA	toluene	25	88	88
4	L4	PA	toluene	25	78	78
5	L5	PA	toluene	25	85	90
6	L6	PA	toluene	25	25	84
7	L5	(*S*)-PA	toluene	25	80	81
8	L5	PA	Et_2O	25	91	90
9	L5	PA	CH_2Cl_2	25	17	76
10	L5	PA	THF	25	89	91
11	**L5**	**PA**	**THF**	**10**[d]	**86**	**94**
12	L5	PA	THF	0[e]	50	92
13	L5	TFA	THF	10[d]	58	84
14	L5	*p*-TSA	THF	10[d]	18	84
15	L5	–	THF	10[d]	–	–

[a]Unless indicated otherwise, reactions of **1a** (0.12 mmol), **2a** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), BA (0.005 mmol) and L (0.005 mmol) were carried out in 2 mL of solvent for 16 h. [b]Isolated yields. [c]Determined by HPLC analysis. [d]The reaction was carried out for 36 h. [e]The reaction was carried out for 48 h.

available BINOL-derived chiral phosphoramidite ligands L1–L6 possessing axial chirality only (Table 1, entries 1–6). To our delight, the use of PA and L1 afforded the alkylation product **3aa** in 72% yield with a promising 49% ee (entry 1). Next, various substituents with different electronic effects were placed on the aniline moiety of the ligand (entries 4–6), and **3aa** was obtained in up to 85% yield with a substantially enhanced enantioselectivity of up to 90% ee (entry 5). Notably, (*S*)-PA was found to give a lower enantioselectivity than its enantiomer, suggesting that (*R*)-PA acts as a matched cocatalyst (entry 7). The examination of solvents (entries 8–10) proved that tetrahydrofuran (THF) fitted the reaction best. As one of the determining factors, an appropriate lower temperature (10 °C) was beneficial to the stereochemical control (94% ee) with no significant erosion of the yield (86%) (entry 11). Moreover, two typical achiral Brønsted acids (BAs), trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (*p*-TSA), were employed as activators in place of PA but gave much worse results in terms of yield and enantioselectivity under otherwise identical conditions (entries 13 and 14 vs 11), which indeed suggested the existence of a cooperative effect between the chiral ligand and the counteranion.[14] Finally, the decisive role of the BA in C–O bond cleavage was evidenced by the fact that no starting materials were consumed when the Pd(0) complex was used alone (entry 15).

This combination strategy for the AAA reaction was then subjected to a rigorous test of the substrate scope. First of all, a series of functionalized allylic alcohols **1b–k** were examined using **2a** as the nucleophile, and they furnished the corresponding products **3ba–ka** in 81–98% yield with 90–96% ee (Table 2, entries 1–10). This protocol tolerated a range

Table 2. Scope of Allylic Alcohols[a]



entry	1/1′	R	3	yield (%)[b]	ee (%)[c]
1	**1b**	2-$MeOC_6H_4$	**3ba**	98	91
2	**1c**	3-$MeOC_6H_4$	**3ca**	95	93
3	**1d**	4-$MeOC_6H_4$	**3da**	97	90
4	**1e**	2-BrC_6H_4	**3ea**	86	96
5	**1f**	3-BrC_6H_4	**3fa**	99	95
6	**1g**	4-BrC_6H_4	**3ga**	95	95
7	**1h**	4-FC_6H_4	**3ha**	95	95
8	**1i**	2-$NO_2C_6H_4$	**3ia**	99	96
9	**1j**	$(CH_2)_8CH_3$	**3ja**	81	90
10	**1k**	Me	**3ka**	81	91
11	**1l**	*n*-Pr	**3la**	77	85
12	**1′**	4-MeC_6H_4	**3a′**	94	91

[a]Unless indicated otherwise, reactions of **1** (0.12 mmol), **2a** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), L5 (0.005 mmol), and PA (0.005 mmol) were carried out in 2 mL of THF for 36 h. [b]Isolated yields. [c]Determined by HPLC analysis.

of substituents on the phenyl moiety of allylic alcohols **1**, including those bearing either electron-donating, -neutral, or -withdrawing substituents. Basically, the relatively electron-deficient cinnamic alcohols (**1e–i**, entries 4–8) always exhibited better stereochemical control than the relatively electron-neutral or -rich ones (**1b–d**, entries 1–3). Notably, bromide was surprisingly well tolerated by this Pd(0) catalysis (entries 4–6). Moreover, under the optimized conditions, aliphatic allylic alcohols **1j–l** and the branched substrate **1′** also afforded the corresponding allylic adducts **3ja–3la** and **3a′** with excellent outcomes (entries 9–12). The configuration of **3fa** was determined by X-ray analysis of its crystal (see the Supporting Information).

Next, the generality of pyrazol-5-ones **2** was tested using **1e** as the allylic alcohol (Table 3). The excellent stereocontrol was keenly sensitive to the substituent at the C3 position of the pyrazol-5-one. As a consequence, the replacement of methyl with phenyl or hindered isopropyl led to lower levels of enantioselectivity, while *n*-propyl, ethyl, and H kept the enantioselectivity at similar or even higher levels (entries 1–4 and 15). One of the best results was obtained by introducing a Cl on the benzene ring of the aniline moiety (99% yield, 97% ee; entry 5). Notably, this chiral ligand/conteranion combination strategy allowed a diverse spectrum of substituents at the

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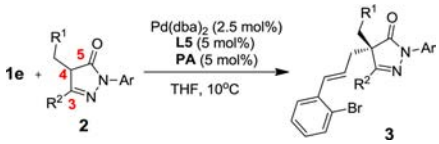
Table 3. Scope of Pyrazol-5-ones[a]



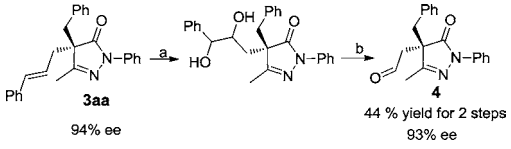
entry	2[b]	R^1	R^2	3	yield (%)[c]	ee (%)[d]
1	**2b**	Ph	Ph	**3eb**	81	66
2	**2c**	Ph	*n*-Pr	**3ec**	97	95
3	**2d**	Ph	*i*-Pr	**3ed**	96	88
4	**2e**	Ph	Et	**3ee**	85	95
5	**2f**[e]	Ph	Me	**3ef**	99	97
6	**2g**	2-FC_6H_4	Me	**3eg**	98	96
7	**2h**	3-FC_6H_4	Me	**3eh**	93	95
8	**2i**	4-FC_6H_4	Me	**3ei**	92	96
9	**2j**	2-$MeOC_6H_4$	Me	**3ej**	99	96
10	**2k**	4-$MeOC_6H_4$	Me	**3ek**	96	95
11	**2l**	α-Naph	Me	**3el**	89	94
12	**2m**	2-thienyl	Me	**3em**	99	97
13	**2n**	Me	Me	**3en**	74	94
14	**2o**	H	Me	**3eo**	90	97
15	**2p**	Ph	H	**3ep**	60	92

[a]Unless indicated otherwise, reactions of **1e** (0.12 mmol), **2** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), L5 (0.005 mmol), and PA (0.005 mmol) were carried out in 2 mL of THF for 36 h. [b]Unless indicated otherwise, Ar = Ph. [c]Isolated yields. [d]Determined by HPLC analysis. [e]Ar = 4-ClC_6H_4

C4 position of the pyrazol-5-one, affording the corresponding products in high yields with excellent enantioselectivities (74–99% yield, 94–97% ee; entries 6–14).

The allylic alkylation products obtained from the AAA reaction can be applied to the synthesis of optically pure and multiply functionalized pyrazol-5-one derivatives. Exposure of pyrazol-5-one derivative **3aa** to a combined dihydroxylation reagent of ruthenium trichloride, sodium periodate, and sulfuric acid in an ethyl acetate/acetonitrile/water solvent mixture followed by oxidation with sodium periodate in a THF/ether/water mixture furnished chiral aldehyde **4** in an overall yield of 44% while maintaining the enantioselectivity (Scheme 2).[15]

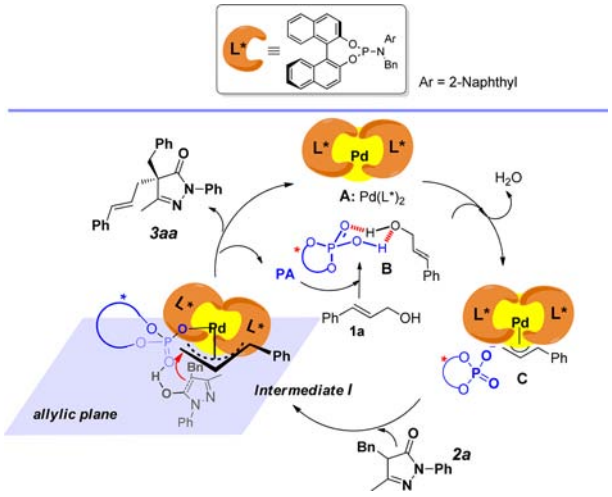
Scheme 2. Synthetic Application of Allylic Adducts of Pyrazol-5-ones[a]



[a]Conditions: (a) 0.5 mol % $RuCl_3$, 1.5 equiv of $NaIO_4$, and 20 mol % H_2SO_4 in 3:3:1 EtOAc/CH_3CN/H_2O at 0 °C overnight; (b) 1.5 equiv of $NaIO_4$ in THF/Et_2O/H_2O at rt for 2 h.

To gain insight into the palladium species in the catalysis, high-resolution mass spectrometry (HRMS) analysis of a reaction mixture of the palladium complex with **1a** and PA was conducted. The results showed that two molecules of the chiral ligand L5 were favorably coordinated to palladium.[16] On the basis of this fact and the experimental observations, a plausible catalytic cycle is proposed (Scheme 3). The $Pd(L^*)_2$ complex **A** initially reacts with PA-activated cinnamic alcohol **B** by hydrogen bonding[7] to expel the hydroxy group, giving the

Scheme 3. Proposed Catalytic Cycle for the Combination of the Chiral Ligand and Chiral Counteranion



crucial cationic π-allylpalladium(II) complex **C** accompanied by the generation of a molecule of water because of the participation of the chiral phosphoric acid. Subsequently, the AAA reaction presumably proceeds with the enolizable pyrazol-5-one **2a** via intermediate **I**, in which the chiral phosphate counteranion is inclined to have a hydrogen-bonding interaction with incoming nucleophile **2a**, which is stereoselectively activated for nucleophilic substitution of π-allyl complex **C**. In this stereochemistry-determining step, the chiral palladium complex and chiral phosphate counteranion work cooperatively to activate the substrates and control the stereochemistry of the AAA reaction, affording the product **3aa** with high enantioselectivity, and simultaneously the parent chiral palladium(0) complex **A** and PA are regenerated for the next catalytic cycle.

In summary, we have demonstrated that the combined use of a palladium complex with a chiral phosphoramidite ligand and a chiral phosphoric acid enables the first highly enantioselective allylic alkylation of pyrazol-5-ones with allylic alcohols. This protocol tolerates a diverse scope of functional groups in both the allylic alcohol and the pyrazol-5-one, furnishing multiply functionalized heterocyclic products in high yields with excellent enantioselectivities that would be of great potential in the synthesis of pharmaceutically interesting molecules. More importantly, the combination of two different simple chiral sources is robust in the creation of a diverse library of chiral elements for the control of stereoselectivity in asymmetric catalysis. Moreover, such a strategy essentially avoids the need for fussy tuning of structurally complicated chiral ligands, which is always encountered in traditional metal-based asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For the first asymmetric allylic alkylation, see: (a) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292. For reviews, see: (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Lu, Z.; Ma, S.-M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(2) (a) Clark, J. *Green Chem.* **1999**, *1*, 1. (b) Sheldon, R. A. *Green Chem.* **2008**, *10*, 359.

(3) For reviews of allylic alcohols, see: (a) Bandini, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 994. (b) Bandini, M.; Cera, G.; Chiarucci, M. *Synthesis* **2012**, *44*, 504. (c) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467. For recent examples, see: (d) Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 13050. (e) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc.* **2013**, *135*, 443.

(4) For the first example of Pd-catalyzed AAA using an allyl alcohol as the electrophile, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. For Ir-catalyzed AAA using allyl alcohols as the electrophile, see: (b) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.

(5) For Pd catalysis, see: (a) Yasuda, S.; Kumagai, N.; Shibasaki, M. *Heterocycles* **2012**, *86*, 745. For Ir catalysis, see: (b) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (c) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5568.

(6) For recent reviews of cooperative catalysis involving Brønsted acids, see: (a) de Armas, P.; Tejedor, D.; García-Tellado, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1013. (b) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (c) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (d) Han, Z.-Y.; Wang, C.; Gong, L.-Z. In *Science of Synthesis: Asymmetric Organocatalysis*; Maruoka, K., Ed.; Georg Thieme Verlag: Stuttgart, 2012; Vol. 2, p 697. (e) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (f) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem.* **2012**, *10*, 211. (g) Du, Z.-T.; Shao, Z.-H. *Chem. Soc. Rev.* **2013**, *42*, 1337.

(7) Jiang, G.-X.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471.

(8) For selected reviews, see: (a) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(9) For selected recent examples, see: (a) Mariappan, G.; Saha, B. P.; Bhuyan, N. R.; Bharti, P. R.; Kumar, D. *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 260. (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053. (c) Chande, M. S.; Barve, P. A.; Suryanarayan, V. *J. Heterocycl. Chem.* **2007**, *44*, 49. (d) Ebner, S.; Wallfisch, B.; Andraos, J.; Aitbaev, I.; Kiselewsky, M.; Bernhardt, P. V.; Kollenz, G.; Wentrup, C. *Org. Biomol. Chem.* **2003**, *1*, 2550.

(10) For recent excellent examples, see: (a) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827. (b) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249. (c) Yang, Z.-G.; Wang, Z.; Bai, S.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Org. Lett.* **2011**, *13*, 596. (d) Wang, Z.; Yang, Z.-G.; Chen, D.-H.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4928. (e) Wang, Z.; Chen, Z.-L.; Bai, S.; Li, W.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2776. (f) Li, F.; Sun, L.; Teng, Y.; Yu, P.; Zhao, C.-G.; Ma, J.-A. *Chem.—Eur. J.* **2012**, *18*, 14255.

(11) For selected reviews, see: (a) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486. (b) Lam, H. W. *Synthesis* **2011**, 2011.

(12) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Synthesis* **2010**, 1929.

(13) For details about the preliminary results for the chiral-counteranion-directed AAA reaction, see the Supporting Information.

(14) For an excellent review, see: (a) Ding, K.-L. *Chem. Commun.* **2008**, 909. For recent examples involving chiral phosphoric acids as part of the strategy, see: (b) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (c) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934. (d) Xie, J.-W.; Huang, X.; Fan, L.-P.; Xu, D.-C.; Li, X.-S.; Su, H.; Wen, Y.-H. *Adv. Synth. Catal.* **2009**, *351*, 3077. (e) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227.

(15) (a) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353. (b) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253.

(16) For HRMS analysis of the intermediate, see the Supporting Information.