

Enantioselective Synthesis of α -Amino Phosphonates via Pd-Catalyzed Asymmetric Hydrogenation

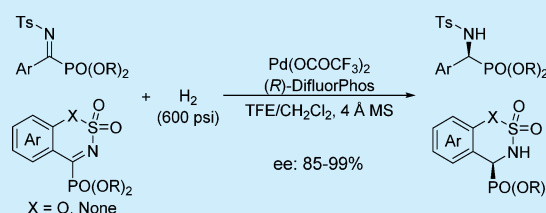
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S Supporting Information

ABSTRACT: A highly enantioselective palladium-catalyzed hydrogenation of a series of linear and cyclic α -iminophosphonates has been achieved, providing efficient access to optically active α -amino phosphonates with up to 99% ee.



α -Aminophosphonic acids are valuable and prevalent substructures with important biological and pharmacological properties.¹ Owing to their structural analogy to α -amino acids, optically active α -aminophosphonic acids have found widespread applications as potentially active substrates, including enzyme inhibitors,² antibacterial agents,³ and herbicides.⁴ Notably, the biological properties of α -aminophosphonic acids are closely linked with the absolute configuration of the stereogenic α -carbon to phosphorus. For example, (S,R)-alafosfalin serves as a better antibacterial reagent against both Gram-positive and Gram-negative microorganisms than the other three diastereoisomers,⁵ and (R)-1-amino-3,4-dichlorobenzylphosphonic acid exhibits more potent inhibition on phenylalanine ammonia-lyase than the S enantiomer (Figure 1).⁶ Therefore, developing an efficient and convenient method to optically active α -aminophosphonic acids is of great significance and highly desirable.

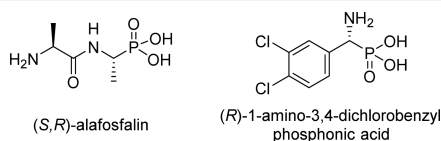


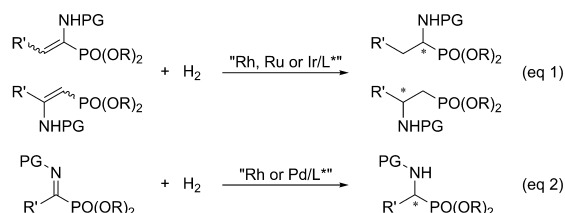
Figure 1. Selected biologically active molecules containing chiral α -aminophosphonic acid motif.

In the past decades, organic chemists have developed several catalytic asymmetric protocols for the synthesis of optically active α -aminophosphonic acids and their derivatives.⁷ Most enantioselective methods rely on the construction of stereoselective C–C, C–N, C–P, and C–H bond formation. Among these protocols, transition-metal-catalyzed asymmetric hydrogenation is particularly attractive and convenient from an atom efficiency point of view.⁸ However, the asymmetric hydrogenation strategy has only received limited attention to date. In 1985, Schöllkopf's group reported the first asymmetric

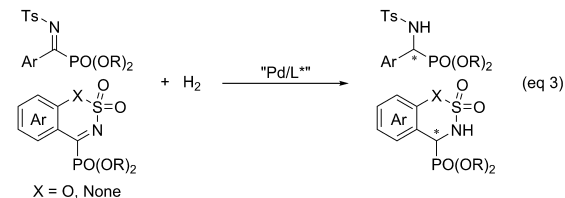
hydrogenation of α,β -dehydroaminophosphonates by using a rhodium catalytic system with up to 76% ee.⁹ Then a plethora of research focused on the Rh-, Ru-, or Ir-catalyzed hydrogenation of the corresponding olefinic precursors that had been described and provided both α - and β -aminophosphonic acid derivatives with good to excellent enantioselectivities (eq 1, Scheme 1).¹⁰ Notably, in 1994, Burk's group documented enantioselective synthesis of α -aminophosphonate through Rh-DuPhos-catalyzed hydrogenation of hydrazone substrate, but only one example was reported.¹¹ Subsequently, Goulioukina's group developed a straightforward strategy for the preparation of optically active α -aminophosphonates via the Rh- or Pd-

Scheme 1. Synthesis of Chiral Aminophosphonates via Asymmetric Hydrogenation

Previous works



This work



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catalyzed asymmetric hydrogenation of α -iminophosphonates with moderate to high ee values (eq 2, Scheme 1).¹² Despite continuing progress in the asymmetric hydrogenation of linear α -iminophosphonates, these reports rarely involve cyclic imine substrates.

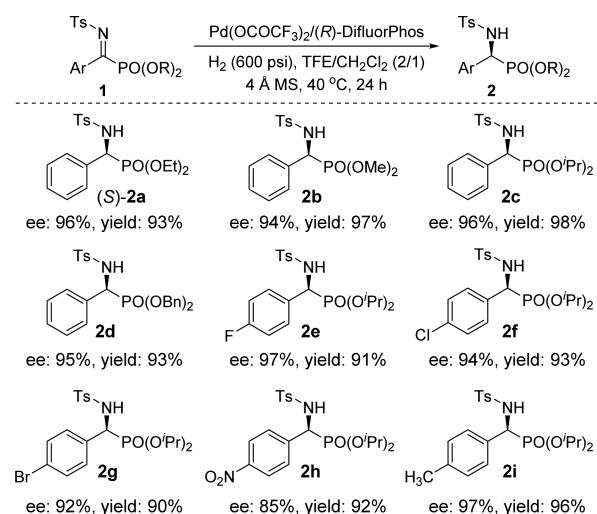
During the past few years, our group has been involved in the development of Pd-catalyzed homogeneous asymmetric hydrogenation of various unsaturated compounds and a series of functional imine substrates with good to excellent enantioselectivities.^{8f,13} Considering the ready availability and easy preparation of *N*-tosyl α -ketiminophosphonates,¹⁴ we envisioned that optically active α -aminophosphonates could be easily synthesized through Pd-catalyzed asymmetric hydrogenation of these compounds. The challenging aspects of this process include the control of enantioselectivity and the improvement of reactivity. Herein, we report a Pd-catalyzed asymmetric hydrogenation of both linear and cyclic α -iminophosphonates with good to excellent enantioselectivities (eq 3, Scheme 1).

Initially, (*E*)-diethyl(phenyl(tosylimino)methyl)phosphonate **1a** was chosen as the model substrate. We tested the hydrogenation of **1a** with Pd(OCOCF₃)₂/(*S*)-SynPhos as catalyst in the presence of 4 Å MS as additive in TFE (600 psi hydrogen gas, 40 °C and 24 h). Gratifyingly, the reaction proceeded smoothly, and moderate 75% ee was obtained (Table 1, entry 1). A variety of solvents were tested under the same conditions. As shown in Table 1, good enantioselectivity but poor reactivity could be obtained in CH₂Cl₂, and the reaction proceeded with no reactivity in toluene and THF (Table 1, entries 2–4). The results suggested that the presence

of TFE was crucial for the reactivity. To further improve the reaction efficiency, an enhanced survey of the mixed solvent was conducted, and TFE/CH₂Cl₂ (1/4) was the optimal reaction medium with 85% ee (Table 1, entries 5–8). We further turned our attention toward chiral ligands (Table 1, entries 8–12). Of various commercially available diphosphine ligands investigated, electron-withdrawing (*R*)-DifluorPhos (**L5**) proved to be the most favorable ligand resulted in 97% ee, albeit with low reactivity (Table 1, entry 12). Fortunately, when we adjusted the ratio of TFE/CH₂Cl₂ to 2/1, the enantioselectivity could be maintained and the reactivity increased obviously at the same time (Table 1, entry 14).

With the optimized reaction conditions in hand, we then investigated the substrate scope of the reaction. The results were summarized in Scheme 2. Pleasingly, a series of aryl-

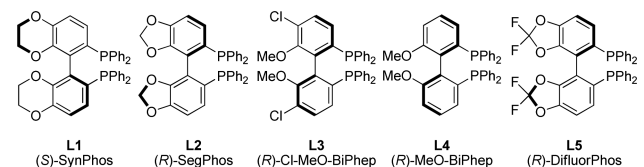
Scheme 2. Substrate Scope: Linear α -Iminophosphonates **1**^a



^aConditions: **1** (0.10 mmol), Pd(OCOCF₃)₂ (2.0 mol %), (*R*)-DifluorPhos (2.4 mol %), 4 Å MS (50 mg), TFE/CH₂Cl₂ (2/1) (1.5 mL), H₂ (600 psi), 40 °C, 24 h.

Table 1. Evaluation of Reaction Parameters^a

entry	solvent	ligand	yield ^b (%)	ee ^c (%)
1	TFE	L1	92	75 (<i>R</i>)
2	CH ₂ Cl ₂	L1	10	90 (<i>R</i>)
3	toluene	L1	NR	NA
4	THF	L1	NR	NA
5	TFE/CH ₂ Cl ₂ (4:1)	L1	93	78 (<i>R</i>)
6	TFE/CH ₂ Cl ₂ (2:1)	L1	95	80 (<i>R</i>)
7	TFE/CH ₂ Cl ₂ (1:2)	L1	98	84 (<i>R</i>)
8	TFE/CH ₂ Cl ₂ (1:4)	L1	97	85 (<i>R</i>)
9	TFE/CH ₂ Cl ₂ (1:4)	L2	88	91 (<i>S</i>)
10	TFE/CH ₂ Cl ₂ (1:4)	L3	75	93 (<i>S</i>)
11	TFE/CH ₂ Cl ₂ (1:4)	L4	97	87 (<i>S</i>)
12	TFE/CH ₂ Cl ₂ (1:4)	L5	81	97 (<i>S</i>)
13	TFE/CH ₂ Cl ₂ (1:2)	L5	89	97 (<i>S</i>)
14	TFE/CH ₂ Cl ₂ (2:1)	L5	93	96 (<i>S</i>)



^aConditions: **1a** (0.10 mmol), Pd(OCOCF₃)₂ (2.0 mol %), **L** (2.4 mol %), 4 Å MS (50 mg), solvent (1.5 mL), H₂ (600 psi), 40 °C, 24 h.

^bIsolated yields. ^cDetermined by chiral HPLC. NR: no reaction. NA: no analysis.

substituted α -ketiminophosphonates were successfully converted to the corresponding α -aminophosphonates with good to excellent ee values (85–97% ee). It was noteworthy that the substrates (**1a–d**) bearing different phosphonate substituents all afforded excellent enantioselectivities. In contrast to ethyl substituent, the length of the alkyl chain had little influence on enantioselectivity, and the high steric hindrance of isopropyl rarely affected the enantiocontrol. Additionally, substrates with different halogen groups on the phenyl ring also proceeded smoothly, giving the desired adducts (**2e–g**) in high ee values and yields. However, the ee value decreased dramatically to 85%, when a strong electron-withdrawing nitro group was introduced (**2h**). In particular, when a methyl group was introduced at the 4-position of the phenyl ring (**2i**), the transformation displayed both high reactivity and enantioselectivity. The absolute configuration of the product **2a** (which can be increased to 99% ee by a simple recrystallization with dichloromethane and *n*-hexane) was unambiguously determined to be *S* by X-ray crystallographic analysis (Figure 2).

Furthermore, in order to demonstrate the versatility of our method, a series of cyclic six- and five-membered ring α -iminophosphonates were also synthesized by the combination of slightly modified literature procedures (Scheme 3).¹⁵ Readily available salicylaldehyde and *N*-*tert*-butylbenzenesulfonamide

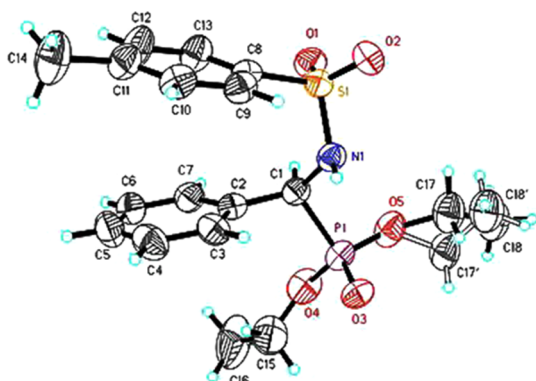
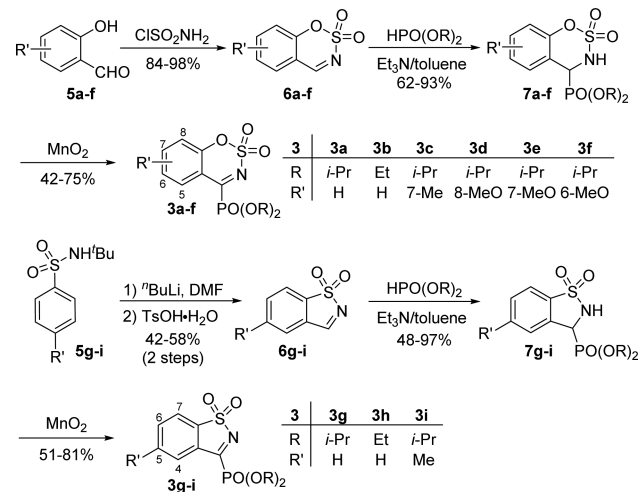


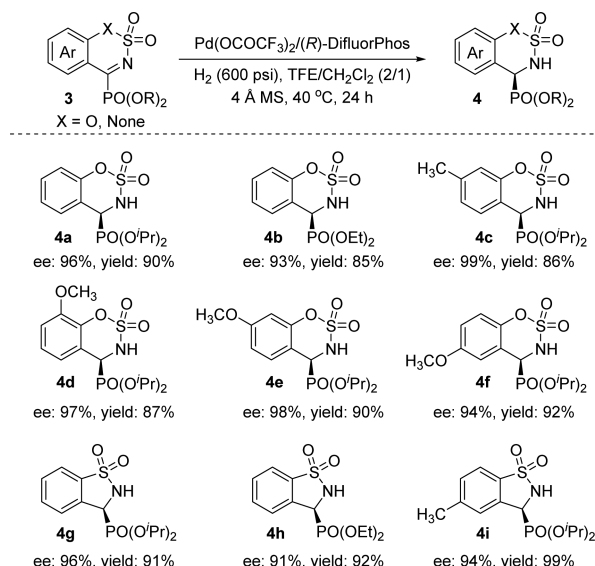
Figure 2. X-ray crystal structure of compound (S)-2a.

Scheme 3. Synthesis of Cyclic α -Iminophosphonates 3

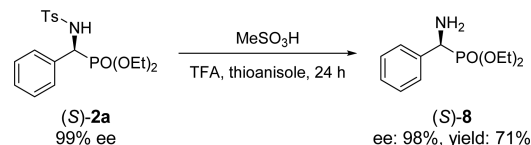
were used as the starting materials and converted to the sulfonylimine intermediates **6**, followed by nucleophilic addition of phosphites to afford α -aminophosphonates **7** and oxidation dehydrogenation. Notably, for the selective dehydrogenation process of α -aminophosphonates **7**, only freshly prepared manganese dioxide gave high yield and selectivity.

Pleasingly, the asymmetric hydrogenation strategy also fit well for those cyclic α -iminophosphonates **3**, and they were successfully converted to the corresponding α -aminophosphonates with excellent ee values (91–99% ee). As shown in Scheme 4, it was noteworthy that the substrates bearing an isopropyl phosphonate substituent afforded higher enantiomeric excess than the diethyl phosphonate substituent. Considering the steric effect of aryl substituents, the substrates (**3d–f**) were synthesized and the slightly higher enantioselectivity was obtained when a methoxy group was introduced on the 7-position of the phenyl ring. Notably, when a methyl group was introduced at the same position (**3c**), the highest 99% ee was obtained. Meanwhile, the five-membered ring α -iminophosphonates were also transformed completely, and excellent ee values were obtained. When the 5-position of the phenyl ring was introduced a methyl group, excellent reactivity could be obtained.

The 4-methylbenzenesulfonyl group could be removed from (S)-**2a** by treatment with methanesulfonic acid in trifluoroacetic acid/thioanisole to provide optically active α -amino phosphonate (S)-**8** (Scheme 5) without racemization.¹⁶

Scheme 4. Substrate Scope: Cyclic α -Iminophosphonates 3^a

^aConditions: **3** (0.10 mmol), Pd(OCOCF₃)₂ (2.0 mol %), (R)-DifluorPhos (2.4 mol %), 4 Å MS (50 mg), TFE/CH₂Cl₂ (2/1) (1.5 mL), H₂ (600 psi), 40 °C, 24 h.

Scheme 5. Desulfonylation of (S)-**2a**

In summary, we have successfully realized the asymmetric hydrogenation of a series of linear and cyclic α -iminophosphonates with a palladium catalyst, providing an efficient access to optically active α -aminophosphonates with up to 99% ee. Further efforts to achieve the asymmetric hydrogenation of other functionalized α -iminophosphonates are ongoing in our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03664.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For reviews, see: (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, 63, 193. (b) McLeod, D. A.; Brinkworth, R. I.; Ashley, J. A.; Janda, K. D.; Wirsching, P. *Bioorg. Med. Chem. Lett.* **1991**, 1, 653.
- (2) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, 32, 1652. (b) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Leo, G. C.; Franz, J. E. *J. Org. Chem.* **1988**, 53, 4069.
- (3) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, 272, 56.
- (4) Mao, M. K.; Franz, J. E. *Synthesis* **1991**, 1991, 920.
- (5) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, 29, 29.
- (6) Zon, J.; Amrhein, N.; Gancarz, R. *Phytochemistry* **2002**, 59, 9.
- (7) (a) Kowalczyk, D.; Albrecht, E. *Chem. Commun.* **2015**, 51, 3981. (b) Ordóñez, M.; Viveros-Ceballos, J. L.; Cativiela, C.; Sayago, F. J. *Tetrahedron* **2015**, 71, 1745. (c) Olszewski, T. K. *Synthesis* **2014**, 46, 403. (d) Turcheniuk, K. V.; Kukhar, V. P.; Röschenthaler, G.-V.; Aceña, J. L.; Soloshonok, V. A.; Sorochinsky, A. E. *RSC Adv.* **2013**, 3, 6693. (e) Ordóñez, M.; Sayago, F. J.; Cativiela, C. *Tetrahedron* **2012**, 68, 6369. (f) Mucha, A. *Molecules* **2012**, 17, 13530. (g) Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Stevens, C. V. *Curr. Org. Chem.* **2011**, 15, 2015. (h) Albrecht, E.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2010**, 16, 28. (i) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, 65, 17. (j) Ma, J.-A. *Chem. Soc. Rev.* **2006**, 35, 630.
- (8) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, 103, 3029. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, 105, 3272. (c) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, 111, 1713. (d) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, 41, 3340. (e) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, 112, 2557. (f) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, 42, 497.
- (9) Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 1985, 555.
- (10) For selected examples of asymmetric hydrogenation of dehydroaminophosphonates, see: (a) Dwars, T.; Schmidt, U.; Fischer, C.; Grassert, I.; Kempe, R.; Fröhlich, R.; Drauz, K.; Oehme, G. *Angew. Chem., Int. Ed.* **1998**, 37, 2851. (b) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, 1, 387. (c) Gridnev, I. D.; Yasutake, M.; Imamoto, T.; Beletskaya, I. P. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 5385. (d) Wang, D.-Y.; Huang, J.-D.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, 73, 2011. (e) Wassenaar, J.; Reek, J. N. H. *J. Org. Chem.* **2009**, 74, 8403. (f) Kadyrov, R.; Holz, J.; Schäffner, B.; Zayas, O.; Almena, J.; Börner, A. *Tetrahedron: Asymmetry* **2008**, 19, 1189. (g) Doherty, S.; Knight, J. G.; Bell, A. L.; El-Menabawey, S.; Vogels, C. M.; Decken, A.; Westcott, S. A. *Tetrahedron: Asymmetry* **2009**, 20, 1437. (h) Lyubimov, S. E.; Rastorguev, E. A.; Verbitskaya, T. A.; Rys, E. G.; Kalinin, V. N.; Davankov, V. A. *Russ. J. Phys. Chem. B* **2010**, 4, 1241. (i) Zhang, J.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2011**, 50, 11743.
- (11) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, 50, 4399.
- (12) (a) Goulioukina, N. S.; Bondarenko, G. N.; Lyubimov, S. E.; Davankov, V. A.; Gavrilov, K. N.; Beletskaya, I. P. *Adv. Synth. Catal.* **2008**, 350, 482. (b) Goulioukina, N. S.; Shergold, I. A.; Bondarenko, G. N.; Ilyin, M. M.; Davankov, V. A.; Beletskaya, I. P. *Adv. Synth. Catal.* **2012**, 354, 2727.
- (13) For selected examples, see: (a) Wang, Y.-Q.; Zhou, Y.-G. *Synlett* **2006**, 2006, 1189. (b) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *J. Org. Chem.* **2007**, 72, 3729. (c) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, 10, 2071. (d) Yu, C.-B.; Wang, D.-W.; Zhou, Y.-G. *J. Org. Chem.* **2009**, 74, 5633. (e) Chen, M.-W.; Duan, Y.; Chen, Q.-A.; Wang, D.-S.; Yu, C.-B.; Zhou, Y.-G. *Org. Lett.* **2010**, 12, 5075. (f) Zhou, X.-Y.; Bao, M.; Zhou, Y.-G. *Adv. Synth. Catal.* **2011**, 353, 84. (g) Chen, Z.-P.; Hu, S.-B.; Zhou, J.; Zhou, Y.-G. *ACS Catal.* **2015**, 5, 6086.
- (14) Vicario, J.; Ortiz, P.; Ezpeleta, J. M.; Palacios, F. *J. Org. Chem.* **2015**, 80, 156.
- (15) (a) Kamal, A.; Sattur, P. B. *Synthesis* **1981**, 1981, 272. (b) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35. (c) Singh, S. K.; Shivaramakrishna, S.; Saibaba, V.; Rao, K. S.; Ganesh, K. R.; Vasudev, R.; Kumar, P. P.; Babu, J. M.; Vyas, K.; Rao, Y. K.; Iqbal, J. *Eur. J. Med. Chem.* **2007**, 42, 456. (d) Batal, D. J.; Madison, S. A. U.S. Patent US5463115 A1, 1995.
- (16) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, 131, 18240.