Advanced Synthesis & Catalysis

Accepted Article

Title: Enantioselective Synthesis of β-Aminotetralins via Chiral Phosphoric Acid-catalyzed Reductive Amination of β-Tetralones

Authors: Do Young Park, Kyung-Hee Kim, and Cheol-Hong Cheon

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701198

Link to VoR: http://dx.doi.org/10.1002/adsc.201701198

10.1002/adsc.201701198

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective Synthesis of β-Aminotetralins via Chiral Phosphoric Acid-catalyzed Reductive Amination of β-Tetralones

Do Young Park[a,†], Kyung-Hee Kim [a,†] and Cheol-Hong Cheon[a]*

[a] Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea
Tel: (+82)-2-3290-3147; Fax: (+82)-2-3290-3121; e-mail: cheon@korea.ac.kr
[†] These authors contributed equally to this work.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A new protocol for the synthesis of chiral β-aminotetralins has been developed via chiral phosphoric acid-catalyzed asymmetric reductive amination of β-tetralones using a Hantzsch ester as an organic hydride donor. Various chiral β-aminotetralins were obtained in good yields with good to high enantioselectivities. Furthermore, the utility of our new protocol was successfully demonstrated in the enantioselective synthesis of rotigotine.

Keywords: β-Aminotetralins; Asymmetric reductive amination; Chiral phosphoric acid catalysis; Rotigotine; β-Tetralones

Chiral β-aminotetralin scaffolds have been found in various biologically active compounds and pharmaceuticals, several of which are currently marketed or are under development (Figure 1).[1]

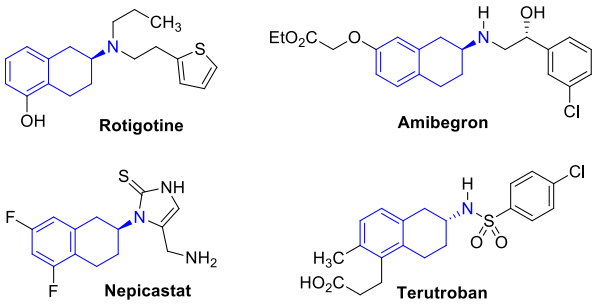
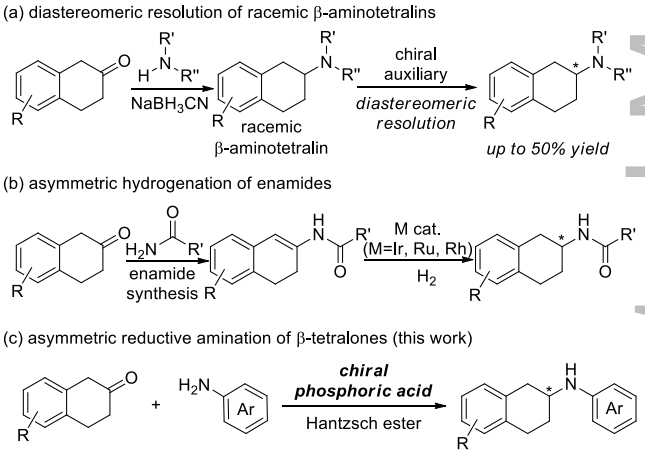


Figure 1. Representative examples of pharmaceutical products bearing a chiral β-aminotetralin scaffold.

For example, rotigotine is a dopamine agonist of the non-ergoline class of medication used for the treatment of Parkinson's disease and restless legs syndrome.[1a-1d] Thus, the development of efficient methods for the synthesis of chiral β-aminotetralins has been considered the research of importance and a number of efforts has been made to control the stereochemistry of the amine moiety to date.[2,3]

The majority of reported syntheses of chiral β-aminotetralins involve the classical diastereomeric resolution of racemic β-aminotetralins with a chiral auxiliary.[2] However, diastereomeric resolution requires a stoichiometric amount of a chiral auxiliary and the maximum yield of the desired β-aminotetralins cannot exceed 50% (Scheme 1a).



Scheme 1. General strategies for the synthesis of chiral β-aminotetralins.

To overcome these limitations, new catalytic asymmetric protocols to access these chiral β-aminotetralins have been developed. Most of the previous catalytic protocols have relied on the asymmetric hydrogenation of cyclic enamides derived from β-tetralones in the presence of transition metals, such as iridium, ruthenium, and rhodium (Scheme 1b).[3] However, these methods involve expensive and toxic transition metals, which can often cause additional problems associated with the residual transition metal catalysts.[4] Thus, the development of a protocol to access these building blocks without

10.1002/adsc.201701198

using toxic transition metal catalysts is highly desirable.

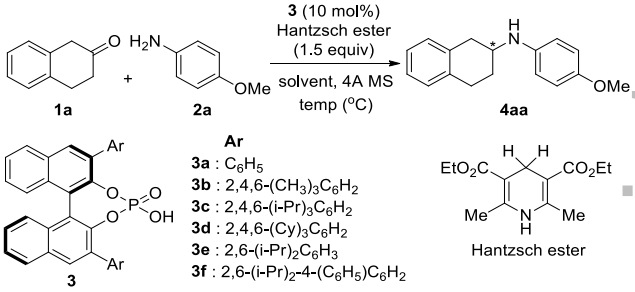
During the past decade, chiral phosphoric acid catalysis has become one of the most rapidly growing fields in asymmetric catalysis.[5] Among the various asymmetric transformations developed with chiral phosphoric acids, the enantioselective synthesis of chiral amines via the asymmetric reduction of ketimines and/or the asymmetric reductive amination of ketones has been considered one of the most popular methods.[6] However, the previously reported chiral phosphoric acid-catalyzed asymmetric reduction of ketimines and/or reductive amination of ketones have been limited to the preparation of chiral acyclic amines from acyclic ketones, and the chiral phosphoric acid-catalyzed asymmetric reductive amination of cyclic ketones has remained unexplored.[7] Considering the biological and pharmaceutical importance of chiral cyclic amines and the lack of protocols to access these important building blocks using chiral phosphoric acids, we strongly felt the need to develop a new method for the enantioselective synthesis of cyclic amines via chiral phosphoric acid-catalyzed asymmetric reductive amination of cyclic ketones as an alternative to asymmetric hydrogenation.

We herein report the enantioselective synthesis of β-aminotetralins via chiral phosphoric acid-catalyzed asymmetric reductive amination of β-tetralones with anilines using a Hantzsch ester as an organic hydride donor (Scheme 1c).[8] This protocol can be applied to various β-tetralones and anilines, providing the corresponding β-aminotetralins in good yields with good to high enantioselectivities. Furthermore, the usefulness of this protocol was demonstrated in the enantioselective synthesis of rotigotine, one of the representative pharmaceuticals bearing a β-aminotetralin scaffold.

Recently, our group has initiated a program for the enantioselective synthesis of chiral β-arylamines via chiral phosphoric acid-catalyzed reductive amination of benzyl methyl ketones.[9,10,11] As a continuing effort to develop protocols to access chiral β-arylamines via chiral phosphoric acid-catalyzed asymmetric reductive amination, we further attempted to develop a protocol for the synthesis of chiral cyclic β-arylamines by reductive amination of benzofused cyclic β-ketones.

Based on this idea, we began our research with the investigation of the reaction conditions required for the synthesis of chiral cyclic β-arylamines via chiral phosphoric acid-catalyzed asymmetric reductive amination, using β-tetralone **1a** as a model benzofused cyclic β-ketone in the presence of a chiral phosphoric acid **3** (Table 1). When β-tetralone **1a** and *para*-anisidine **2a** were subjected to asymmetric reductive amination with a Hantzsch ester as an organic hydride donor in the presence of the chiral phosphoric acid **3a**, the desired β-aminotetralin **4aa** was obtained in 71% yield but with low enantioselectivity (entry 1). With this result in hand, other chiral phosphoric acids **3** derived from BINOL derivatives, bearing different aryl substituents at the 3,3'-position on the BINOL scaffold, were investigated. Interestingly, the introduction of bulky substituents on the 2,6-positions of the aryl group turned out to have a beneficial effect on the enantioselectivity of this transformation (entries 1-4). The reaction with phosphoric acid **3c** bearing 2,4,6-tri(isopropyl)phenyl groups at the 3,3'-positions of the BINOL scaffold provided **4aa** in 84% yield and 72% ee (entry 3).

Table 1. Optimization of reaction conditions.



entry	CPA (3)	solvent	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**3a**	toluene	60	20	71	7
2	**3b**	toluene	60	20	83	51
3	**3c**	toluene	60	20	84	72
4	**3d**	toluene	60	20	80	70
5	**3e**	toluene	60	20	72	60
6	**3f**	toluene	60	20	72	43
7	**3c**	m-xylene	60	20	88	72
8	**3c**	fluorobenzene	60	20	80	69
9	**3c**	TBME	60	20	87	71
10	**3c**	CPME	60	20	80	72
11	**3c**	DCE	60	28	64	63
12	**3c**	toluene	50	25	82	75
13	**3c**	toluene	40	32	79	77
14	**3c**	toluene	30	54	84	78
15	**3c**	toluene	25	72	84	81

[a] Isolated yield of **4aa**.
[b] Enantiomeric excess (ee) was determined by a chiral HPLC analysis.

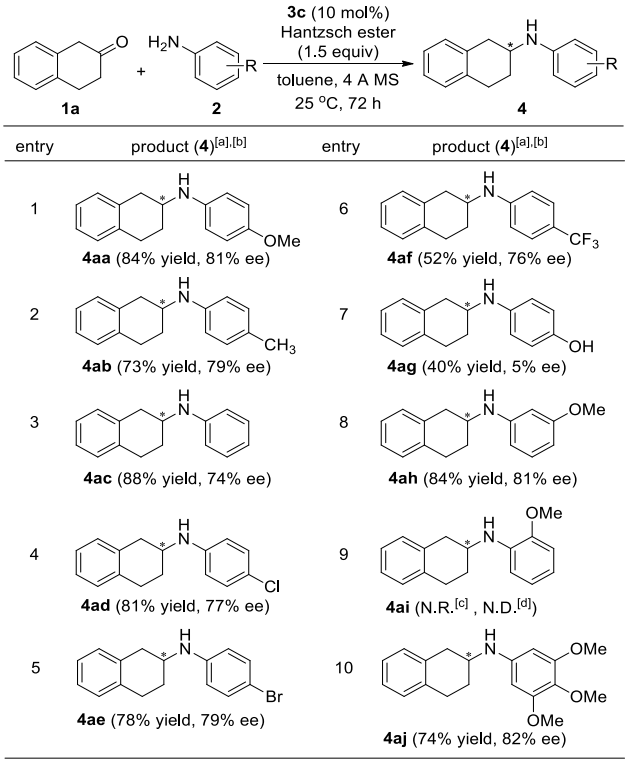
Then, the effect of a substituent at the *para*-position of the aryl substituent was investigated and the size of the substituent was found to have a considerable influence on the enantioselectivity (entries 3, 5-6); enantioselectivity increased with increasing size of the substituent (entries 3 and 5), whereas the introduction of a bulky phenyl substituent at the *para*-position was found to have a detrimental effect on the enantioselectivity (entries 3 and 6). Since **3c** gave the best result among the chiral phosphoric acids tested, **3c** was chosen as the optimal catalyst.

We next explored the effect of reaction media. It was found that the choice of the solvent had only a

10.1002/adsc.201701198

slight influence on the outcome of this transformation (entries 3, 7-11). Reactions in aromatic hydrocarbons and non-polar etherated solvents afforded the desired product **4aa** in similar enantioselectivities (entries 3, 7-10), while the enantioselectivity slightly decreased in the reaction using a halogenated solvent (entry 11). Among the solvents tested, toluene was chosen as the optimal solvent. Next, screening the reaction temperature (entries 3, 12-15) revealed that enantioselectivity increased when the reaction was carried out at lower temperatures. Since the reaction at room temperature yielded **4aa** in the best enantioselectivity (entry 15), we decided to perform this transformation at room temperature.[12]

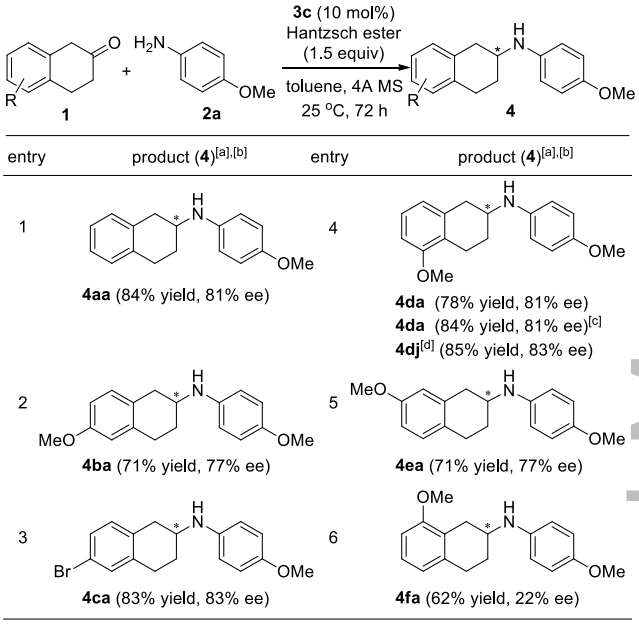
Table 2. Substrate scope of aniline derivatives **2** in reductive amination of β-tetralone **1a**



[a] Isolated yield of **4**.
[b] Ee was determined by a chiral HPLC analysis.
[c] N.R. means no reaction.
[d] N.D. means not determined.

Under these optimized conditions, the substrate scope of aniline derivatives **2** was explored in this transformation with β-tetralone **1a** (Table 2). The electronic effect of the aniline derivatives had negligible effect on the enantioselectivity (entries 1-6). Generally, aniline derivatives **2** carrying either an electron-donating or an electron-withdrawing substituent provided β-aminotetralins **4** in similar enantioselectivities. However, aniline **2g** bearing a free hydroxy group provided the desired product **4ag** in much lower yield and enantioselectivity (entry 7). Next, the steric bulk of the aniline derivatives was found to have a considerable influence on the outcome of this transformation. *Para*- and *meta*-anisidines provided the corresponding β-aminotetralins (**4aa** and **4ah**) with similar efficiencies (entries 1 and 8), while *ortho*-anisidine was not suitable for this transformation and no formation of β-aminotetralin **4ai** was observed with *ortho*-anisidine (entry 9). Furthermore, the more electron-rich 3,4,5-trimethoxyaniline **2j** was applicable to this protocol and the desired product **4aj** was obtained in 82% ee (entry 10). Among the aniline derivatives **2** tested, *para*-anisidine **2a** was chosen as the optimal protected ammonia surrogate because 1) the reaction with **2a** provided the best results in terms of the yield and enantioselectivity of the desired β-aminotetralin, and 2) the *para*-methoxyphenyl (PMP) group could be removed under oxidative conditions to generate a free amine.[13]

Table 3. Scope of β-tetralone derivatives **1** in reductive amination of *para*-anisidine **2a**

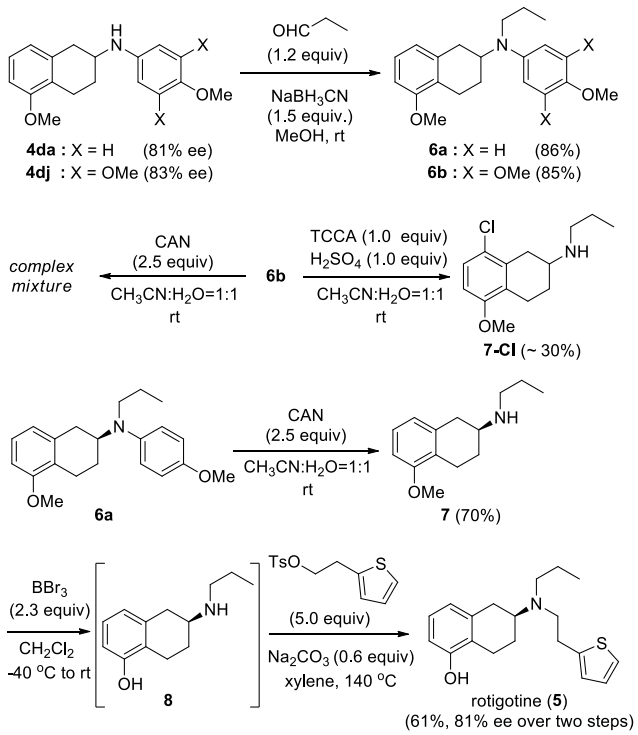


[a] Isolated yield of **4**.
[b] Ee was determined by a chiral HPLC analysis.
[c] 1.5 mmol scale.
[d] 3,4,5-Trimethoxyaniline **2j** was used.

Next, we investigated the substrate scope of β-tetralone derivatives **1** in this transformation with *para*-anisidine **2a** (Table 3). First, the electronic effect of the phenyl ring in β-tetralones **1** was investigated and found to exert little influence on the efficiency of this asymmetric transformation; β-tetralone derivatives bearing either an electron-donating or an electron-withdrawing substituent on the phenyl ring provided the desired β-aminotetralin derivatives **4** with similar enantioselectivities (entries 1-3). However, the position of a substituent on the β-tetralone scaffold affected the efficiency of this transformation. β-Tetralones bearing a methoxy group at either 5-, 6-, or 7-position provided the β-tetralin products **4** in similar yields and enantioselectivities regardless of the position of the substituent (entries 2, 4 and 5), while β-tetralone **1f** bearing a methoxy

group at the 8-position provided the desired product **4fa** with much lower efficiency (entry 6). Furthermore, this transformation could be carried out on a relatively large scale (1.5 mmol) without any loss of efficiency. In addition, the asymmetric reductive amination of **1d** with 3,4,5-trimethoxyaniline **2j** proceeded smoothly to provide β-aminotetralin **4dj** in 85% yield and 83% ee. Unfortunately, however, our attempts to extend this protocol to the synthesis of other cyclic amines, such as α-aminotetralins, via enantioselective reductive amination of α-tetralones was unsuccessful.[14]

With these results in hand, we further attempted to demonstrate the utility of this protocol in the enantioselective synthesis of rotigotine (**5**) (Scheme 2).[15]



Scheme 2. Synthesis of rotigotine (**5**)

Since β-aminotetralin **4dj** bearing a 3,4,5-trimethylphenyl group has a slightly better enantioselectivity than **4da** carrying a PMP group (entry 4, Table 3), we first attempted to complete the synthesis of rotigotine (**5**) with **4dj**. Reductive amination of **4dj** with propanal afforded the tertiary amine **6b** in 85% yield. However, deprotection of the 3,4,5-methoxyphenyl group present in **6b** was challenging. Deprotection of the 3,4,5-trimethoxyphenyl group with cerium ammonium nitrate (CAN)[16] provided a complex mixture, while the reaction of **6b** with trichloroisocyanuric acid (TCCA) yielded the unwanted side product **7-Cl** containing one chlorine atom on the phenyl ring in a low yield.[17]

Thus, we focused our efforts on the completion of the asymmetric synthesis of rotigotine (**5**) with **4da**. The reductive amination of **4da** with propanal yielded the desired tertiary amine **6a** in 86% yield. Treatment of **6a** with CAN successfully provided the desired secondary amine **7** in 70% yield through oxidative removal of the PMP moiety.[13] Deprotection of the methoxy group with BBr_3, followed by reaction with 2-thienylethanol tosylate provided rotigotine (**5**) in 61% yield and with 81% ee over two steps. It should be noted that all these transformations could be accomplished without any loss in enantiopurity. Furthermore, the absolute stereochemistry of rotigotine **5** was assigned as (*S*) by comparing the optical rotation of each HCl salt of compounds **5** and **7**, respectively, with the reported value in the literature.[18]

In conclusion, we have reported the first chiral phosphoric acid-catalyzed reductive amination of β-tetralones leading to chiral β-aminotetralins. This protocol could be applied to various β-tetralones and aniline derivatives and the desired β-aminotetralins were obtained in good yields with good to high enantioselectivities. Furthermore, the utility of this transformation was successfully demonstrated by the enantioselective synthesis of rotigotine. The absolute stereochemistry of the resulting β-aminotetralins could be assigned as (*S*) by the comparison of the optical rotation with the reported value in the literature. Further application of this method to the preparation of other biologically important compounds and detailed mechanistic studies are currently underway in our laboratory and will be reported in due course.

Experimental Section

General procedure for the asymmetric reductive amination of β-tetralones with anilines (Tables 2 and 3).

To a test tube equipped with a stirring bar were added β-tetralone derivative **1** (0.10 mmol; 1.0 equiv), aniline derivative **2** (0.12 mmol; 1.2 equiv), Hantzsch ester (0.15 mmol; 1.5 equiv), catalyst **3c** (0.010 mmol; 10 mol%) and 4 Å molecular sieves. Then, toluene (1.0 mL) was added to the above mixture. The reaction mixture was stirred at room temperature and monitored by TLC. After complete consumption of the tetralone derivative **1**, the reaction mixture was filtered to remove molecular sieves. The filtrate was purified by column chromatography on silica to provide the desired product **4**.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-20100020209 and NRF-2015R1D1A1A01057200). C.-H.C. also thanks for a financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis). We also thank Professor Jianwei Sun for providing us with SP-CPA.

References

[1] For examples of bioactive compounds bearing a chiral β-aminotetralin moiety, see: for rotigotine, a) G. Zareba, *Drugs Today* **2006,** *42*, 21−28; b) D. Q. Pham, A. Nogid, *Clin. Ther*. **2008**, *30*, 813−824; c) S. Davies, *Drugs Today* **2009,** *45*, 663−668; d) J. J. Chen, D. M. Swope, K. Dashtipour, K. E. Lyons, *Pharmacotherapy* **2009**, *29*, 1452−1467; for amibegron, e) D. H. Overstreet, J. Stemmelin, G. Griebel, *Pharmacol., Biochem. Behav*. **2008**, *89*, 623–626; for nepicastat: f) W. C. Stanley, B. Li, D. W. Bonhaus, L. G. Johnson, K. Lee, S. Porter, K. Walker, G. Martinez, R. M. Eglen, R. L. Whiting, S. S. Hegde, *Br. J. Pharmacol.* **1997**, *121*, 1803−1809; for terutroban: g) J. I. Osende, D. Shimbo, V. Fuster, M. Dubar, J. J. Badimon, *J. Thromb. Haemost.* **2004**, *2*, 492–498; h) L. A. Sorbera, N. Serradell, J. Bolos, M. Bayes, *Drugs Future* **2006**, *31*, 867–873.

[2] For the synthesis of β-aminotetralins via diastereomeric resolution, see: a) V. Bakthavachalam, N. Baindur, B. K. Madras, J. L. Neumeyer, *J. Med. Chem*. **1991**, *34*, 3235−3241; b) C. Sonesson, T. Barf, J. Nilsson, D. Dijkstra, A. Carlsson, K. Svensson, M. W. Smith, I. J. Martin, J. N. Duncan, *J. Med. Chem.* **1995**, *38*, 1319–1329; c) S. Biswas, S. Zhang, F. Fernandez, B. Ghosh, J. Zhen, E. Kuzhikandathil, M. E. A. Reith, A. K. Dutta, *J. Med. Chem.* **2008**, *51*, 101–117; d) B. Ghosh, T. Antonio, J. Zhen, P. Kharkar, M. E. A. Reith, A. K. Dutta, *J. Med. Chem.* **2010**, *53*, 1023–1037; e) B. Ghosh, T. Antonio, B. Gopishetty, M. Reith, A. Dutta, *Bioorg. Med. Chem.* **2010**, *18*, 5661–5674.

[3] For the synthesis of β-aminotetralins via catalytic asymmetric hydrogenation of enamides derived from β-tetralones, see: a) I. Arribas, M. Rubio, P. Kleman, A. Pizzano, *J. Org. Chem.* **2013**, *78*, 3997–4005; b) E. Salomó, S. Orgué, A. Riera, X. Verdaguer, *Angew. Chem.* **2016**, *128*, 8120–8124; *Angew. Chem. Int. Ed.* **2016**, *55*, 7988–7992; c) C. J. Cobley, G. Evans, T. Fanjul, S. Simmonds, A. Woods, *Tetrahedron Lett.* **2016**, *57* 986–989; d) M. Magre, O. Pàmies, M. Diéguez, *ACS Catal.* **2016**, *6*, 5186–5190.

[4]a) C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889–900; b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DeSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang, *Org. Process Res. Dev.* **2005**, *9*, 198–205; c) A. Thayer, *Chem. Eng. News* **2005**, *83*, 55–58.

[5] For reviews on chiral phosphoric acid catalysis, see: a) T. Akiyama, *Chem. Rev.* **2007**, 107, 5744–5758; b) M. Terada, *Chem. Commun.* **2008**, 4097–4112; c) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153; d) T. Akiyama, K. Mori, *Chem. Rev.* **2015**, *115*, 9277–9306.

[6] For reviews on asymmetric reduction of ketimines and/or reductive amination of ketones with Hantzsch ester, see: a) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; b) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407–3417; c) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820–827; d) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084–1105.

[7] The List group reported an excellent example of the chiral phosphoric acid-catalyzed asymmetric amination of α-branched cyclic ketones. See: V. N. Wakchaure, J. Zhau, S. Hoffmann, B. List, *Angew. Chem.* **2010**, *122*, 4716–4718; *Angew. Chem. Int. Ed.* **2010**, *49*, 4612–4614.

[8] Prior to this report, there was only one patent on the preparation of chiral β-aminotetralins via diastereoselective reduction of imines derived from β-aminotetralones and chiral α-methylbenzylamine, see: Q. Huang, Q, Huang, M. Lou, US20140446096.

[9] Before we started this program about the synthesis of chiral β-aryl amines by chiral phosphoric acid-catalyzed reductive amination of benzyl methyl ketones, only one example was reported in the literature. See: D. Enders, J. X. Liebich, G. Raabe, *Chem. Eur. J.* **2010**, *16*, 9763–9766.

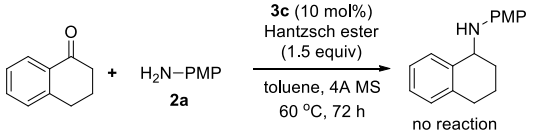
[10] K.-H. Kim, C.-Y. Lee, C.-H. Cheon, *J. Org. Chem.* **2015**, *80*, 6367–6374.

[11] We successfully applied the chiral phosphoric acid-catalyzed reductive amination of a benzyl methyl ketone derivative to total synthesis of ancistrocladinium A, see: a) K.-H. Kim, C.-H. Cheon, *Adv. Synth. Catal.* **2016**, *358*, 2883–2888; b) K.-H. Kim, C.-H. Cheon, *Org. Chem. Front.* **2017**, *4*, 1341–1349.

[12] For further optimization of other reaction parameters, see Supporting Information.

[13] For examples on the oxidative cleavage of a PMP group, see: a) A. Cordova, *Synlett* **2003**, 1651–1654; b) M. Shimizu, M. Kimura, T. Watanabe, Y. Tamaru, *Org. Lett.* **2005**, *7*, 637–640; c) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delfta, F. P. J. T. Rutjesa, *Tetrahedron Lett.* **2006,** 47, 8109–8113; d) A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem.* **2011,** *123*, 8330–8333; *Angew. Chem. Int. Ed.* **2011,** *50*, 8180–8183; e) Y. Jiang, S. E. Schaus, *Angew. Chem.* **2017**, *129*, 1566–1570; *Angew. Chem. Int. Ed.* **2017**, *56*, 1544–1548.

[14] Unlike β-tetralones, the reductive amination of α-tetralone with *para*-anisidine **2a** did not proceed at all and the starting α-tetralone remained unreacted.



[15] For previous reports on the synthesis of rotigotine (**5**), see: a) R. Webster, A. Boyer, M. J. Fleming, M. Lautens, *Org. Lett.* **2010**, *12*, 5418–5421; b) see ref 3c.

[16] For the oxidative removal of a 3,4,5-trimethoxyphenyl group with CAN, see: a) T. B. Nguyen, H. Bousserouel, Q. Wang, F. Guéritte, *Adv. Synth. Catal.* **2011**, *353*, 257–262; b) S. A. Morris, T. H. Nguyen, N. Zheng, *Adv. Synth. Catal.* **2015**, *357*, 2311–2316.

[17] Based on the spectroscopic data, we confirmed that the product **7-Cl** has one chlorine atom either *ortho* or

10.1002/adsc.201701198

para to the methoxy group. However, we did not fully analyze the position of the chlorine atom in **7-Cl** because it was not the desired product and the yield was poor.

[18] Optical rotation ($[\alpha]_D^{20}$) values of HCl salts of rotigotine (**5**) and **7** were found to be -38.3 (c = 1.0, CH_3OH) and -26.1 (c = 1.0, CH_3OH), respectively. Since these values have the same sign with the reference values of HCl salts of (*S*)-**5** {-54.6 (c = 1.0, CH_3OH)} and (*S*)-**7** {-71.5 (c = 1.0, CH_3OH)}, respectively, we assigned the absolute stereochemistry at the C-2 in rotigotine (**5**) as (*S*), although there were some discrepancies in $[\alpha]_D^{20}$ between the measured values and the reported ones. For the reported $[\alpha]_D^{20}$ values in literature, see ref 2d.

10.1002/adsc.201701198

COMMUNICATION

Enantioselective Synthesis of β-Aminotetralins via Chiral Phosphoric Acid-catalyzed Reductive Amination of β-Tetralones

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Do Young Park, Kyung-Hee Kim, Cheol-Hong Cheon*