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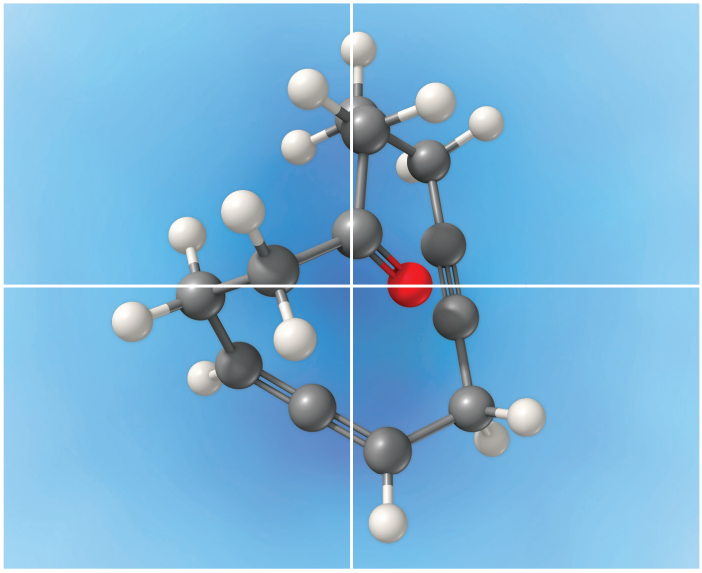

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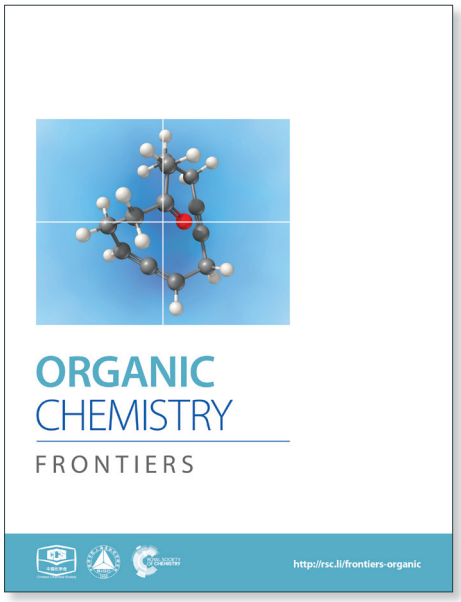

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ARTICLE

Enantioselective Pd-Catalyzed Tandem Allylic Alkylation Reaction Using Monodentate Phosphoramidite Ligands for the Formal Total Synthesis of Huperzine A†‡

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A small library of fine-tunable monodentate phosphoramidite (MPN) ligands was found useful in selecting a highly efficient chiral ligand for the enantioselective Pd-catalyzed tandem allylic alkylation reaction. The reaction gave a critical tricyclic key intermediate with high enantiopurity for the formal total synthesis of (-)-huperzine A, a Lycopodium alkaloid derived from the club moss *Huperaza serrata* that possesses potent inhibitory activity for acetylcholine esterase (AChe).

Introduction

Metal-catalyzed enantioselective reactions serve as one of the most powerful reactions in the modern organic synthesis arsenals, particularly for the synthesis of biologically active compounds.[1-4] Among those reactions, palladium-catalyzed asymmetirc allylic substitution reactions provide unique and powerful methods for the regio- and stereo-controlled formation of carbon-carbon bonds as well as carbon-heteroatom bonds.[5-7]

In order to promote this powerful catalytic process, extensive investigations have been made for the development of efficient chiral ligands.[8] "Modular" diphosphine ligands developed by Trost *et al.*[8, 9] and a series of P-N ligands developed by Pfaltz, Helmchen, and Williams[10, 11] have been among the most successful ligands and widely used. However, these chiral ligands do not always achieve high enantioselectivity and catalyst efficiency in different reaction systems.[5, 12] Accordingly, continued efforts are necessary for the development of new and efficacious chiral ligands in this process.

We have designed and synthesized a series of new chiral biphenols **1** bearing various substituents at the 3,3'-positions,[13] and used them to create the libraries of novel monodentate phosphite (**MPO**) and phosphoramidite (**MPN**) ligands with fine-tuning capabilities.[13-18] These novel monodentate phosphorus ligands have demonstrated excellent efficiency in various transition metal-catalyzed asymmetric transformations.[13-18] We have also developed novel diphosphonite ligands (**BOP**s) with wide bite angles. **BOP** ligands exhibited excellent efficiency in the intermolecular allylic amination reactions.[19-21]

In 1989, Kozikowski applied Pd-catalyzed allylic alkylation as the key step in the total synthesis of racemic huperzine A (Figure 1).[22] This sesiquiterpene alkaloid, derived from the club moss *Huperaza serreta* (Thum. *Lycopodium seratarum*) gained prominence in the 1980's when (-)-huperzine A was identified as a selective and potent inhibitor of acetylcholine esterase (AChe).[23] As a selective inhibitor of AChe, huperzine A has been studied as a clinical agent in the treatment of Alzheimer's Disease (AD). Currently, naturally occurring huperzine A is in clinical use as a treatment mode for AD in China and also advanced to phase III clinical trials in the US.[22, 23] In efficacy studies only (-)-enantiomer was shown to be active against AD.[24] In 1998, Terishima reported the first catalytic asymmetric variant of Kozikowski's proposed route using chiral ferrocenylphosphine ligands,[25] which were able to achieve rather modest enantioselectivity for the formation of a key intermediate to (-)-huperzine A (66% ee). In 2003, Bai achieved 90% ee in the same reaction, using a slightly modified ferrocenylphosphine ligand.[26]

Although the phase III clinical trials did not provide strong enough evidence for FDA approval as drug for treatment of AD,[27] (-)-huperzine A has been attracting considerable interest as neuroprotective agent to counteract against organophosphate chemical weapons such as sarin and VX.[28-31] Thus, several reports on the practical synthesis of (-)-huperzine A have recently published, starting from affordable enantiopure 4-methylcyclohexenones.[32-34] Nevertheless, no new process has been reported on the use of catalytic asymmetric synthesis using transition metal catalysts since Bai's work in 2003 and a practical process development by Azadi-Ardakani's team in 2012 using chiral ferrocenyl-phosphines,[26, 35] although an excellent result was recently reported using an organocatalyst.[36]

Accordingly, we revisited Kozikowski's process, using our monodentate phosphoramidite (**MPN**) ligands (Figure 1), which achieved excellent enantioselectivity (>99% ee) in the short total synthesis of (+)- γ -lycorane using Pd-catalyzed asymmetric allylic alkylation in the key step.[16]

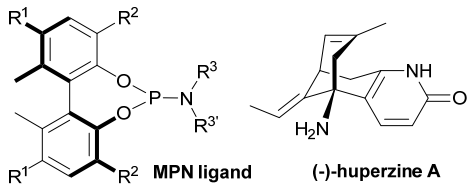
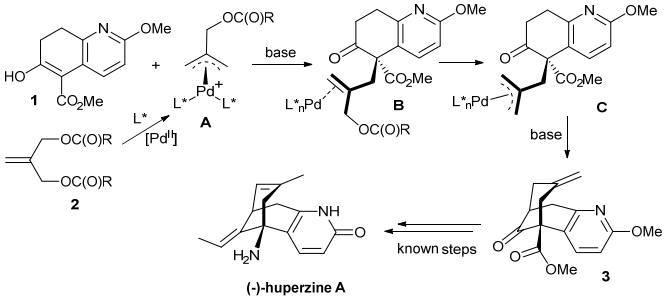


Figure 1. MPN ligand and (-)-huperzine A

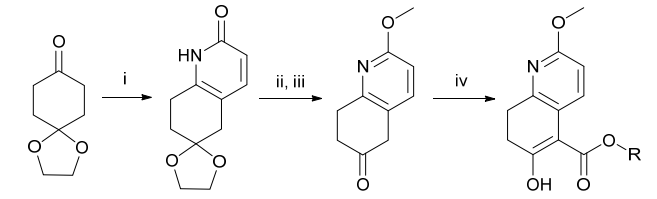
We describe here a successful application of our MPN ligands in the Pd-catalyzed asymmetric tandem allylic alkylation process in the formal total synthesis of huperzine A (Scheme 1).



Scheme 1. Asymmetric tandem allylic alkylation of **1** with **2**

Results and discussion

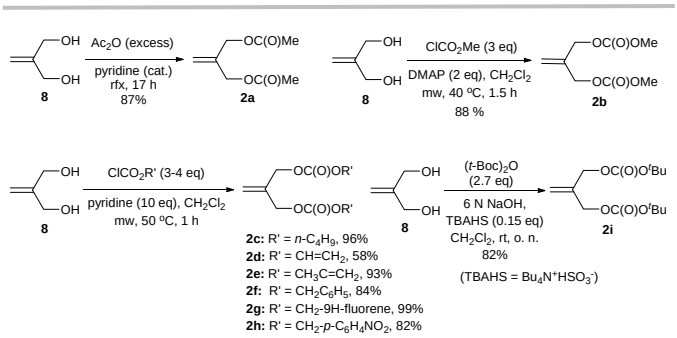
Kozikowski's key nucleophile **1a** was prepared from commercially available mono-protected 1,4-cyclohexanedione (**4**), following the literature method[22] with modifications, as shown in Scheme 2. This preparation features a modified Stork-enamine synthesis with methyl propiolate in the presence of 7 M NH_3 in MeOH to afford compound **5**.[37] The subsequent *O*-methylation and deprotection gave 2-methoxytetrahydroquinolin-6-one (**7**), which was converted to **1a** via carbomethoxylation. It is worthy of note that the enol-tautomer,[38] as shown, was isolated as an exclusive stable species. In a similar manner, four more nucleophiles **1b-e** were prepared by reacting chloroformates with 7 or ester exchange reaction with **1a**, as shown in Scheme 2.



i) methyl propiolate (2 equiv), 7 M NH_3, MeOH, 100 °C, 0.69 Mpa, 15 h, 51-72%; ii) Ag_2CO_3 (2 equiv), MeI (10 equiv), $CHCl_3$, reflux, 3 h, 84%; iii) 5% aq. HCl-acetone (1;1), reflux, 18 h; iv) NaH (4 equiv), (a) $CO(OMe)_2$, reflux, 3 h, 77% for 2 steps, (b) $ClCO_2Ph$, r.t., overnight, 67% for 2 steps, (c) $ClCO_2Bn$, r.t., overnight, 72% for 2 steps, (d) **1a**, Cy-OH, *p*-TsOH, benzene, reflux, 48h, 82%, (e) **1a**, *n*-BuOH, *p*-TsOH, benzene, reflux, 48h, 75%.

Scheme 2. Preparation of nucleophile **1**

A series allylic substrates **2** for tandem dialkylation was prepared from commercially available 2-methylene-1,3-propane-diol (**8**) and the corresponding acid anhydride or chloroformate. The reactions were carried out under conventional or microwave conditions to afford the corresponding allylic diacetate **2a**[38] and allylic dicarbonates **2b-i**[39] in good to excellent yields (Scheme 3).



Scheme 3. Preparation of allylic substrates **2a-i**

The chiral MPN ligands that were employed in this study are shown in Figure 2. This series of ligands exhibited high to excellent enantioselectivity in the Pd-catalyzed intermolecular asymmetric allylic alkylation reaction in the key step of (+)-lycorane total synthesis.[16]

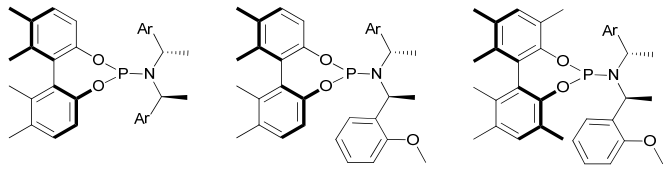


Figure 2. A small library of chiral biphenol-based MPN ligands

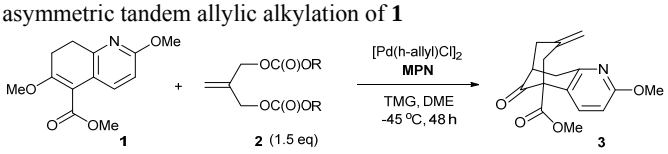
First, we performed a screening of allylic substrates **2** and chiral MPN ligands, using $[Pd(\eta^3\text{-allyl})Cl]_2$ as the catalyst precursor, 1,1,3,3-tetramethylguanidine (TMG) as the base in dimethoxyethane (DME) at -45 °C for 48 h under nitrogen. Results are summarized in Table 1.

For the allylic substrate screening, (*R*,*R*,*R*)-**MPN-L1** ligand was used and **2a-c** and **2i** were examined (entries 1-4). Although only moderate enantioselectivity was observed in those substrates, **2i** gave the best result among them. Thus, we fixed the substrate to **2i** and screened MPN ligands (entries 5-10). As the results clearly indicate, the slight change in the MPN ligand structure exerts dramatic differences in the direction of asymmetric induction, catalytic activity and enantioselectivity. Introduction of 2-Np instead of Ph to C2 symmetrical MPN ligand was detrimental to enantioselectivity (entry 5). Also, a mismatched pair in the chiral amine moiety and axial chirality, i.e., (*R,S,S*)-**MPN-L3**, led to the loss of catalytic activity as well as enantioselectivity (entry 7). Introduction of methyl groups at the 3 and 3′ positions, i.e., (*S,S,S*)-**MPN-L6**, was detrimental to the catalytic activity and enantioselectivity (entry 10). Similarly to the case of (+)-lycorane synthesis, MPN ligands with an asymmetric chiral amine moiety gave substantially better results than those with a symmetrical moiety (entries 6, 8 and 9). Among the MPN ligands examined, (*S,S,S*)-**MPN-L5** gave the best result (76% ee, entry 9). Thus, this MPN ligand was selected as the ligand of choice for optimization.

Then, we examined the effect of allylic substrate structure further with (*S,S,S*)-**MPN-L5**. Thus, the reactions with allylic substrates, **2d**, **2e** and **2f**, were carried out (entries 11-13). It was found that the allylic

dicarbonate bearing benzyl groups, **2f**, gave substantially better results than those bearing ethenyl (**2d**) and 2-propenyl (**2e**) groups, as well as *tert*-butyl groups (**2i**) (entry 13).

Table 1. Screening of allylic substrates **2** and MPN ligands in the asymmetric tandem allylic alkylation of **1**



Entry[a]	Allylic substrate	Ligand (L*)	Conv. %[b]	% ee[c]
1	**2a**	(*R*,*R*,*R*)-**MPN-L1**	100	33 (-)
2	**2b**	(*R*,*R*,*R*)-**MPN-L1**	100	38 (-)
3	**2c**	(*R*,*R*,*R*)-**MPN-L1**	100	36 (-)
4	**2i**	(*R*,*R*,*R*)-**MPN-L1**	100	40 (-)
5	**2i**	(*S*,*S*,*S*)-**MPN-L2**	100	2 (+)
6	**2i**	(*S*,*S*,*S*)-**MPN-L3**	100	49 (-)
7	**2i**	(*R*,*S*,*S*)-**MPN-L3**	<5	n.d.
8	**2i**	(*S*,*S*,*S*)-**MPN-L4**	100	61 (-)
9	**2i**	(*S*,*S*,*S*)-**MPN-L5**	100	76 (-)
10	**2i**	(*S*,*S*,*S*)-**MPN-L6**	<5	n.d.
11	**2d**	(*S*,*S*,*S*)-**MPN-L5**	100	55 (-)
12	**2e**	(*S*,*S*,*S*)-**MPN-L5**	100	54 (-)
13	**2f**	(*S*,*S*,*S*)-**MPN-L5**	100	87 (-)

[a] All reactions were run using $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in DME [0.025] at -45 °C for 48 h under N_2.
[b] Determined by GC-MS.
[c] Determined by HPLC using Chiracel OD-H normal phase column with an eluent of 3% isopropanol in hexanes

Next, we examined the effect of the ester moiety of nucleophile 1 on the reactivity and enantioselectivity. To our surprise, the attempted reactions with phenyl ester **1b** and benzyl ester **1c** did not afford any desirable product **3b** and **3c**, respectively. It was found that **1b** and **1c** existed as keto ester form in sharp contrast with **1a**, **1d** and **1e**, which existed as enol ester form as shown in Scheme 2. This difference in property appears to be a significant factor for the marked contrast in reactivity. The reactions of **1d** and **1e** using (*S*,*S*,*S*)-**MPN-L5** ligand under the same conditions as those shown in Table 1 gave the corresponding products **3d** and **3e** with 59% ee (with **2a**) and 82% ee (with **2f**; 67% ee with **2a**), respectively. Thus, **2a** was selected as the best nucleophile among those examined.

We also examined the effects of solvent and reaction temperature on enantioselectivity and reaction rate. Results are summarized in Table 2. Among the five common solvents employed, DME, dichloromethane and DMF gave comparable results, i.e., 87-89 % ee (entries 1-3) and dichloromethane was so far the best (89% ee, entry 2). Toluene gave lower enantioselectivity (entry 4) and ether was even worse (entry 5).

The effect of temperature on enantioselectivity was found to be rather unexpected, although reaction rate was temperature dependent as anticipated. As Table 2 shows (entries 2, 6-8), the enantioselectivity appears to be optimal at or around -45 °C, and it goes down either higher or lower temperatures. The result implies that the mechanism is not entropy dependent and thus rather sophisticated.

Table 2. Effects of solvent and temperature on enantioselecitivty

Entry[a]	Solvent	Temp (°C)	Time (h)	Conv. %[b]	%ee[c]
1	DME	-45	48	100	87 (-)
2	CH_2Cl_2	-45	48	100	89 (-)
3	DMF	-45	48	100	88 (-)
4	toluene	-45	48	100	81 (-)
5	Et_2O	-45	48	100	70 (-)
6	CH_2Cl_2	-25	24	100	85 (-)
7	CH_2Cl_2	-55	48	100	86 (-)
8	CH_2Cl_2	-78	96	100	68 (-)

[a] All reactions were run using $[[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in a solvent under N_2.
[b,c] See the footnote of Table 1.

Since dibenzyl dicarbonate **2f** was the best allylic substrates thus far, additional allylic dicarbonates, **2g** (9H-fluorenylmethyl) and **2h** (4-nitrobenzyl), were prepared and compared with **2f** in dichloromethane at -45 °C. Results are shown in Table 3.

Allylic dicarbonate **2g** gave virtually the same results (89.0% ee, entry 2) as **2f** (89.2% ee, entry 1). Thus, the table shows the enantioselectivity with one decimal. Introduction of a 4-nitro group to the benzyl ester moiety slightly lowered enantioselectiivty (87.4% ee, entry 3). However, it is not clear if this is an electronic effect or steric effect at present.

Table 3. Effects of the allylic substrates **2** on tandem asymmetric allylic alkylations with **1**

Entry[a]	Allyl substrate	Conv. %[b]	%ee[c]
1	**2f**	100	89.2 (-)
2	**2g**	100	89.0 (-)
3	**2h**	100	87.4 (-)

[a] All reactions were run using $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (2.5 mol%) with **MPN-L5** (15 mol%) and TMG (2.5 eq) in CH_2Cl_2 at -45 °C for 48 h under N_2.
[b,c] See the footnote of Table 1.

Since the mechanism of asymmetric induction in this reaction is rather unique, i.e., π-allyl-Pd complex **A** (Scheme 1) generated as the key intermediate possesses a carbobenzoxymethyl group at the C2 carbon of the π-allyl system as shown in Figure 3. Then, the first carbon-carbon bond formation takes place between the C5 (*) of nucleophile **1** and either C1 or C3 of the allyl moiety, generating the corresponding π-olefin-Pd complex **B** (Scheme 1). The second carbon-carbon bond formation occurs intramolecularly at the C7 (**) of the second π-allyl-Pd complex **C** (Scheme 1). Although the second allylic alkylation reaction creates a chiral carbon center, the overall stereochemistry is already determined in the first reaction. Thus, the absolute configuration of the product is solely determined by the enantioface differentiation of nucleophile **1** in the first allylic alkylation reaction. As Figure 3 illustrates, there are four possible scenarios for this process, i.e., Pro-*S* or Pro-*R* face of **1** reacts with either the C1 or C3 carbon of the π-allyl-Pd complex **A**, generating *S* or *R* product.

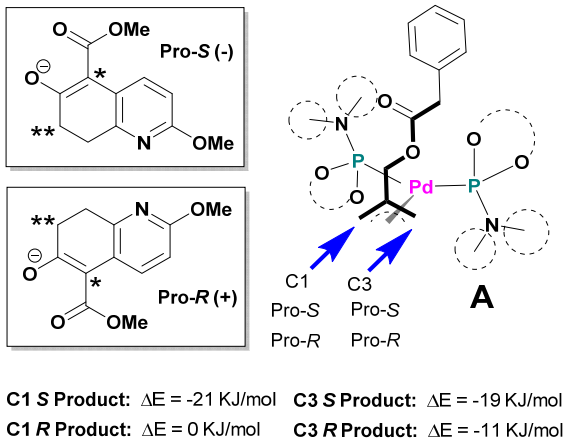


Figure 3. Mechanism of asymmetric induction

As we have successfully analysed the mode of enantioselection in the intramolecular and intermolecular asymmetric allylic substitution reactions,[18, 19] we have performed molecular modeling study using Spartan program (PM3). From our previous studies,[14, 15, 18, 19] it is reasonable to assume that the active chiral catalyst species bears two MPN ligands on the Pd metal, forming pseudo-C2-symmetrical π-allyl-Pd complex. When this Pd-complex reacts with an allylic dicarbonate, it generates the putative π-allyl-Pd complex **A** (Figure 3). We have assumed that this allylic alkylation reaction goes through late transition state, which is product-like. Then, we calculated the relative energy for four possible products, i.e., π-olefin-Pd complexes **B**. The results are shown in Figure 3. The calculations suggest that nucleophile **1** reacts with both C1 and C3, but the *S* product is substantially more favorable over the *R* product in both cases, and the C1 site has higher selectivity. It is worthy of note that the molecular modeling study has shed light on an interesting aspect of the mechanism of asymmetric induction in this reaction.

Conclusions

(*S,S,S*)-**MPN-L5**, selected from fine-tunable MPN ligands, was found to be an excellent chiral ligand for the Pd-catalyzed tandem asymmetric allylic alkylation reaction to afford **3** with high enantiopurity (89.2% ee), which is a critical key intermediate for the formal total synthesis (-)-huperzine. Logical optimization of reaction variables was carried out together with the screening of MPN ligands and allylic substrates **2**. The mechanism of asymmetric induction was investigated and discussed based on the molecular modeling of key Pd-complex species involved in the catalyst cycle using Spartan program. The molecular modeling analysis correctly indicated that *S* enantiomer should be the predominant product. Further studies on the applications of fine-tunable biphenol-based MPN and BOP ligands are activity underway in our laboratory.

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Notes and references

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† Dedicated to Professor Max Malacria on the occasion of his 65th birthday.
‡Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

Experimental

A typical procedure for asymmetric tandem allylic alkylations:
The chiral ligand (*S,S,S*)-**MPN-L5** (17.2 mg, 15 mol%), and a catalyst $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (1.8 mg, 2.5 mol%) and 2-methylenepropane-1,3-diyl dibenzyl dicarbonate (**2f**) (107 mg, 0.30 mmol, 1.5 eq) and **1** (47 mg, 0.20 mmol) were dissolved in 8 mL of dry CH_2Cl_2 in a 35 mL Schlenck tube. The mixture was then stirred at room temperature for 30 min and cooled to -45 °C for 30 min. Then, tetramethylguanidine (TMG) (57.6 mg, 0.50 mmol) was slowly added to this solution and the reaction mixture was stirred at -45 °C for 48 h. The solvent was evaporated and the resulting yellow oil was submitted to normal phase chiral HPLC column (Chiracel OD-H) with an eluent of 3% ispropanol in hexanes (tR = 19.0 and 24.2 mins) to determine the enantiopurity. The crude product was submitted to flash column chromatography on silica gel (hexanes/EtOAc = 20:1→10:1) to give **3** as a light yellow oil (26 mg, 70% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (2H, m), 2.75 (1H, m), 2.92 (m, 1H), 3.06 (2H, m), 3.40 (1H, dd, J = 18.4, J = 6.8), 3.78 (3H, s), 3.86 (3H, s), 4.47 (1H, s), 4.80 (1H, s), 6.54 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.4, 43.9, 45.6, 47.8, 52.6, 53.4, 62.0, 109.5, 116.3, 124.7, 137.5, 138.9, 151.3, 162.9, 171.3, 208.3. All data are consistent with the literature values.

References

1. B. C. G. Söderberg, *Coord. Chem. Rev.*, 2004, **248**, 1085-1158.
2. J. Terao and N. Kambe, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 663-672.
3. Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222-234.
4. K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442-4489.
5. B. M. Trost and C. Lee, in *Catalytic Asymmetric Synthesis, Second Edition*, ed. I. Ojima, Wiley-VCH, New York, 2000, pp. 593-649.
6. B. M. Trost, *J Org. Chem.*, 2004, **69**, 5813-5837.
7. B. M. Trost and G. Dong, *J. Am. Chem. Soc.*, 2006, **128**, 6054-6055.
8. B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921-2943.
9. B. M. Trost, *CHem. Pharm. Bull.*, 2002, **50**, 1-14.
10. G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336-345.
11. R. Pretot and A. Pfaltz, *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 323-325.
12. G. Helmchen, U. Kazmater and S. Förster, in *Catalytic Asymmetric Synthesis, Third Edition*, ed. I. Ojima, Wiley, Hoboken, 2010, pp. 497-641.
13. Z. Hua, V. C. Vassar and I. Ojima, *Org. Lett.*, 2003, **5**, 3831-3834.
14. Z. Hua, V. C. Vassar, H. Choi and I. Ojima, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5411-5416.
15. B. D. Chapsal, Z. Hua and I. Ojima, *Tetrahedron: Asymmetry*, 2006, **17**, 642-657.
16. B. D. Chapsal and I. Ojima, *Org. Lett.*, 2006, **8**, 1395-1398.
17. C. Shi and I. Ojima, *Tetrahedron*, 2007, **63**, 8563-8570.
18. C.-W. Chien, C. Shi, C.-F. Lin and I. Ojima, *Tetrahedron*, 2011, **67**, 6513-6523.
19. C. Shi, C.-W. Chien and I. Ojima, *Chem. Asian J.*, 2011, **6**, 674-680.
20. C.-F. Lin and I. Ojima, *J Org. Chem.*, 2011, **76**, 6240-6249.
21. Y. Zang and I. Ojima, *J Org. Chem.*, 2013, **78**, 4013−4018.
22. Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, 1989, **111**, 4116-4117.
23. D. L. Bai, X. C. Tang and X. C. He, *Curr. Med. Chem.*, 2000, **7**, 355-374.
24. X. C. Tang, G. H. Kindel, A. P. Kozikowski and I. Hanin, *J. Enthnopharmacol.*, 1994, **44**, 147-155.

25. S. Kaneko, T. Yoshino, T. Katoh and S. Terashima, *Tetrahedron: Asymmetry*, 1997, **8**, 829-832.
26. X.-C. He, B. Wang, G. Yu and D. Bai, *Tetrahedron: Asymmetry*, 2001, **12**, 3213-3216.
27. G. Yang, Y. Wang, J. Tian and J. Liu, *PLoS ONE* 2013, **8**, e74916.
28. J. Haigh, S. Johnston, A. Peppernay, P. Mattern, G. Garcia, B. Doctor, R. Gordon and P. Aisen, *Chem.-Biol. Interact.*, 2008, **175**, 380–386.
29. J. Z. Karasova, J. Bajgar, L. Novotny and K. Kuca, *Lett. Drug Des. Discovery*, 2009, **6**, 563–567 and references therei.
30. T. Koshiba, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2009, **11**, 5354–5356.
31. J. White, Y. Li, J. Kim and M. Terinek, *Org. Lett.*, 2013, **15**, 882–885.
32. M. K. M. Tun, D. Wüstmann and S. B. Herzon, *Chem. Sci.* , 2011, **2**, 2251-2253.
33. R. Ding, B.-F. Sun and G.-Q. Lin, *Org. Lett.*, 2012, **14**, 4446–4449.
34. R. Ding, J.-G. Fu, G.-Q. Xu, B.-F. Sun and G.-Q. Lin, *J Org. Chem.*, 2014, **79**, 240−250.
35. S. R. Tudhope, J. A. Bellamy, A. Ball, D. Rajasekar, M. Azadi-Ardakani, H. S. Meera, J. M. Gnanadeepam, R. Saiganesh, F. Gibson, L. He, C. H. Behrens, G. Underiner, J. Marfurt and N. Favre, *Org. Process Res. Dev.*, 2012, **16**, 635-642.
36. X. Ding, X. Li, D. Liu, W. Cui, X. Ju, S. Wang and Z. Yao, *Tetrahedron*, 2012, **68**, 6240–6248.
37. A. P. Kozikowski, E. R. Reddy and C. P. Miller, *J. Chem. Soc. Perkin Trans. 1*, 1990, 195-197.
38. G. Campiani, L. Q. Sun, A. P. Kozikowski, P. Aagaard and M. McKinney, *J Org. Chem.*, 1993, **58**, 7660-7669.
39. S. G. Salamone and G. B. Dudley, *Org. Lett.*, 2005, **7**, 4443-4445.