Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5677–5681

The highly enantioselective Diels–Alder reaction of 1,2-dihydropyridine using chiral cationic palladium–phosphinooxazolidine catalyst for the synthesis of chiral isoquinuclidines

Hiroto Nakano,* Natsumi Tsugawa and Reiko Fujita

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

Received 14 May 2005; revised 13 June 2005; accepted 17 June 2005
Available online 5 July 2005

Abstract—The enantioselective Diels–Alder reactions of 1-phenoxycarbonyl-1,2-dihydropyridine with 1-alkylated acryloyl-pyrazolidin-3-ones using chiral cationic palladium–phosphinooxazolidine (Pd–POZ) catalyst afforded chiral isoquinuclidines with excellent enantioselectivity (up to 97% ee).

The 2-azabicyclo[2.2.2]octanes (isoquinuclidines) are found widely in natural products, particularly among the iboga-type indole alkaloids, members of which have varied and interesting biological properties.[1] In particular, there are pharmacologically important vinca alkaloids such as vinblastine and vincristine, which are created through the coupling of catharanthine **1**, which possesses isoquinuclidines, with the aspidosperma portion (Fig. 1).[2] Most recently, it was also indicated that ibogaine **2** reduces cravings for alcohol and other drugs of abuse by its ability to boost levels of a growth factor known as glial cell line-derived neurotrophic factor (GDNF) (Fig. 1).[3] Furthermore, isoquinuclidines are also valuable intermediates in the synthesis of other alkaloids[4] and in medicinal chemistry.[5] Therefore, it is meaningful to establish an effective asymmetric synthetic methodology of chiral isoquinuclidines. A well-established route to this ring system is through the Diels–Alder (DA) reaction of 1,2-dihydropyridines with dienophiles. However, there has been little work to date on the asymmetric version of this reaction and almost all examples of asymmetric DA reactions of 1,2-dihydropyridines are a diastereoselective version in which a diene or dienophile has a chiral auxiliary.[6] Despite its obvious advantages, to the best of our knowledge, only one example employing a Cr–BINAM catalyst has been reported to date by Rawal et al. for the catalytic enantioselective version of the DA reaction, but nevertheless, this afforded only modest asymmetric induction (up to 85% ee).[7] Recently, we reported that the cationic Pd–POZ complex **A** is an effective catalyst in the DA reaction of cyclic or acyclic dienes with oxazolidone dienophiles.[8] Therefore, we applied cationic Pd–POZ catalysts to the enantioselective DA reactions of 1,2-dihydropyridines with imide dienophiles such as acryloyl-1,3-oxazolidin-2-one and 1-substituted acryloyl-pyrazolidin-3-ones (Fig. 1).

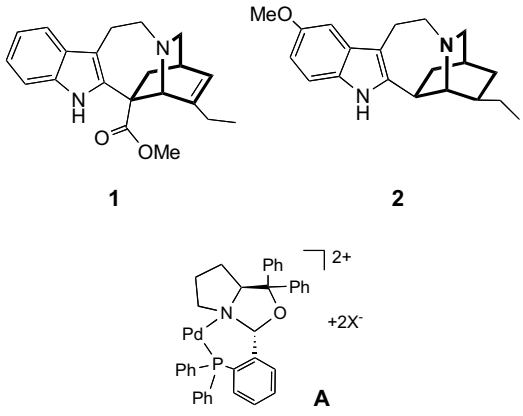


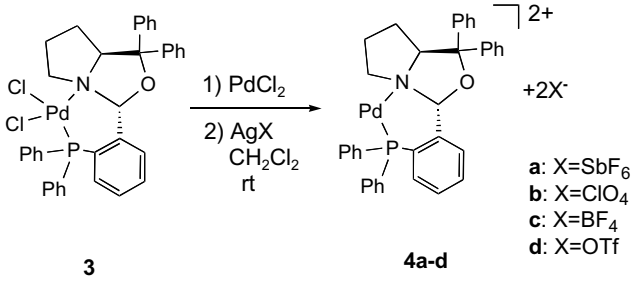
Figure 1. Cationic Pd–POZ catalyst.

Keywords: Enantioselective Diels–Alder reaction; 1,2-Dihydropyridine; Chiral cationic palladium–phosphinooxazolidine catalyst; Chiral isoquinuclidines.
* Corresponding author. Tel.: +81 22 234 4181; fax: +81 22 275 2013; e-mail: hnakano@tohoku-pharm.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.089

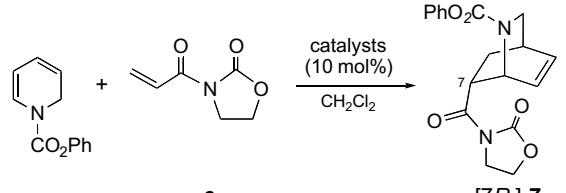
Herein, we wish to report the successful enantioselective DA reaction of 1,2-dihydropyridine as a diene, giving chiral isoquinuclidines at synthetically useful levels of enantiomeric excess (ee). Thus, the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **5** with 1-benzyl-2-acryloyl-pyrazolidin-3-one **8a** using chiral cationic Pd–POZ catalyst **4a** afforded chiral isoquinuclidines with a good chemical yield (80%) and excellent enantioselectivity (97% ee).

For the catalytic enantioselective version of the DA reaction, we first tested the reaction of common acryloyl-1,3-oxazolidine-2-one **6** with 1-phenoxycarbonyl-1,2-dihydropyridine **5**. The cationic Pd–POZ catalysts **4a–d** were prepared by the reactions of $PdCl_2$–POZ **3** and the corresponding AgX (X = SF_6, ClO_4, BF_4, OTf) in dry CH_2Cl_2 using our previously reported procedure (Scheme 1).[8] The DA reaction of diene **5** with dienophile **6** was carried out at 0 °C in CH_2Cl_2 in the presence of 10 mol % of the prepared cationic Pd–POZ catalysts **4a–d** to give DA adduct **7**. The results are summarized in Table 1. The obtained DA adduct **7** was exclusively the *endo*-form.[7] The reaction catalyzed by the antimonate complex **4a** gave DA adduct **7** in excellent isolated yield (98%) and with moderate enantioselectivity (76% ee, entry 1). Cooling to −25 °C led to a slight increase in enantioselectivity (82% ee), but the chemical yield decreased to 84% (entry 2). The use of perchlorate complex **4b** brought about a slight decrease in chemical yield (90%), but DA adduct **7** was obtained at 84% ee (entry 3). Unfortunately, the reaction at −25 °C did not show an increase in enantioselectivity (entry 4). On the other hand, tetrafluoroborate complex **4c** afforded the highest enantioselectivity (88% ee), but chemical yield was poor (46%, entry 5). Triflate complex **4d** did not show satisfactory catalytic activity (37%, 74% ee, entry 6).



Scheme 1.

Table 1. Enantioselective DA reaction of **5** with **6**



Entry	Catalyst	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4a**	0	24	98	76
2	**4a**	−25	48	84	82
3	**4b**	0	24	90	84
4	**4b**	−25	48	73	82
5	**4c**	0	24	46	88
6	**4d**	0	24	37	74

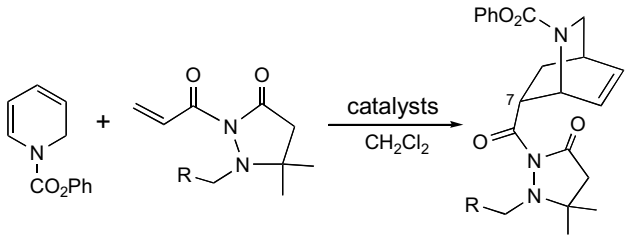
[a] Isolated yields.
[b] ee of *endo* isomer was Determined by HPLC analysis using a Daicel Chiralcel AD column.[7]

In order to improve enantioselectivity in the reaction, we explored the possibilities presented in a report by Sibi et al.,[9] who examined a novel 1-substituted 2-crotonyl-pyrazolidin-3-one as a dienophile based on the concept of 'chiral relay', and reported that the combination of this dienophile and nonoptimized Cu-bis-oxazoline catalyst can bring about an excellent asymmetric induction in the DA reaction with cyclopentadiene as a diene. We applied the 1-substituted 2-crotonyl-pyrazolidin-3-one dienophile to the DA reaction of 1,2-dihydropyridine **5** using cationic Pd–POZ catalysts **4a–d**. New 1-substituted 2-crotonyl-pyrazolidin-3-ones **8a–c** were prepared following the procedure reported by Sibi et al.[9]

First, we examined the effectiveness of dienophiles **8a–c** using superior antimonate catalyst **4a**. The reactions of diene **5** with dienophiles **8a–c** were carried out at 0 °C in the presence of 10 mol % of the prepared Pd–POZ catalysts **4a–d** to give the corresponding *endo*-DA adducts **9a–c**.[10] The results are summarized in Table 2. A significant difference was observed in chemical yield and enantioselectivity corresponding to the different substituent groups on the nitrogen at the 1-position. When 1-benzyl substituted derivative **8a** was used, a dramatic increase in enantioselectivity to 97% ee was observed with good chemical yield (80%, entry 1). Despite our expectations, the reaction with the bulkier 1-naphthylmethyl derivative **8b** was slow and brought about a decrease in both chemical yield and enantioselectivity (entry 2). Similarly, the reaction with 1-ethyl substituted derivative **8c** was also sluggish and did not give satisfactory results, although the reasons for this remain unclear (entry 3).

Next, we examined the effects of other counterions in the reaction with superior dienophile **8a**. Cationic perchlorate catalyst **4b** gave DA adduct **9a** in good chemical yield (87%) and with fairly good enantioselectivity (94%, entry 4). Tetrafluoroborate catalyst **4c** afforded the best enantioselectivity (97% ee) with good chemical yield (76%, entry 5) in results almost identical to those achieved with antimonate catalyst **4a**. However, triflate catalyst **4d** did not give satisfactory reactivity or enantioselectivity (60%, 89% ee, entry 6). The reactions with superior cationic catalysts **4a** and **4c** at −25 °C did not afford better results for chemical yields and enantioselectivities than the results at 0 °C (entries 7 and 8). Furthermore, the effect of reducing the molar ratio of catalyst **4a** was examined. At low catalytic loading to 5 mol % of

Table 2. Enantioselective DA reaction of diene **5** with **8a–c**[a]



5 **8a-c** [7*R*]-**9a-c**[a]

a: R=Ph
b: R=1-Naph
c: R=Me

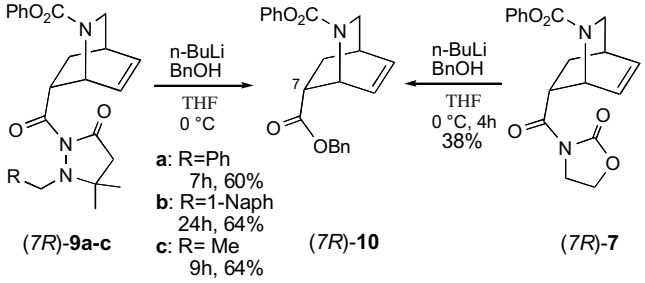
a: R=Ph
b: R=1-Naph
c: R=Me

Entry	Dienophile	Catalyst	Ligand (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**8a**	**4a**	10	0	24	80	97
2	**8b**	**4a**	10	0	72	47	33
3	**8c**	**4a**	10	0	72	42	43
4	**8a**	**4b**	10	0	24	87	94
5	**8a**	**4c**	10	0	24	76	97
6	**8a**	**4d**	10	0	24	60	89
7	**8a**	**4a**	10	−25	48	76	95
8	**8a**	**4c**	10	−25	48	76	89
9	**8a**	**4a**	5	0	24	78	95
10	**8a**	**4a**	2.5	0	24	59	84

[a] After conversion to benzyl ester [7*R*]-**10**, the absolute configuration were determined.
[b] Isolated yields.
[c] ee of *endo* isomer was determined by HPLC analysis using a Daicel Chiralcel AD column.

4a, equally satisfactory results (78%, 95% ee) were obtained, but the use of 2.5 mol % greatly decreased both the chemical yield and enantioselectivity (59% and 84% ee, entries 9 and 10). These results indicate that the antimonate POZ catalyst **4a** and 1-benzylpyrazolidin-3-one dienophile **8a** were most effective in obtaining chiral isoquinuclidines **9a** with excellent enantioselectivity.

For the absolute stereochemistry assignments of the new DA adducts, both the obtained **9a–c** and the known (7*R*)-**7** were converted to benzyl ester **10** (Scheme 2). Thus, the reactions of **9a–c** or (7*R*)-**7** with BnOH using *n*-BuLi as a base in THF afforded (7*R*)-benzyl ester **10**[11] in moderate yields (**9a**: 60%; **9b**: 64%; **9c**: 64%; **7**: 38%). The obtained **10** is expected to serve as an effective chiral synthetic intermediate.



Scheme 2.

Finally, we also examined the effectiveness of four kinds of chiral catalysts (Cu–bis-oxazoline–**11**,[9] Pd–BINAP–**12**,[12] Pd–POZ–**13**[13] and 2-azanorbornane-based Pd–POZ–**14**[8] complexes) in the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **5** with 1-benzyl-2-pyrazolidin-3-one dienophile **8a**. The reactions were carried out at 0 °C in the presence of 10 mol % of catalysts **11**–**14** to give the corresponding DA adduct **9a**. The results are shown in Table 3. The effective complex **11** in Sibi's experiment[9] did not show catalytic activity (entry 1). Complex **11**, acting as superior catalyst in many reactions, had low reactivity and afforded only moderate chemical yield (57%) even at 72 h of reaction time, although it gave excellent enantioselectivity (96% ee, entry 2). Furthermore, catalyst **13** gave DA adduct **9a** in low chemical yield (35%), but with 85% ee (entry 3). Unfortunately, our developed norbornane-based POZ catalyst **14** did not work well in this reaction (entry 4).

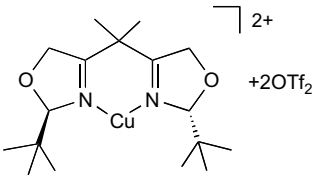
In conclusion, we have developed the high enantioselective Diels–Alder reaction of 1,2-dihydropyridine that provides an efficient methodology for obtaining pharmacologically important chiral isoquinuclidines. In the reaction, the combination of cationic Pd–POZ catalyst **4a** with SbF_6 counterion and 1-benzyl-2-acryloyl-pyrazolidin-3-one dienophile **8a** as a dienophile is most effective, affording the corresponding DA adduct **9a** at 97% ee. These results indicate that the combination of Pd–POZ catalyst **4** with 1-substituted pyrazolidin-3-one dienophile **8** is useful not only in the DA reaction of 1,2-dihydropyridine but also in other DA reactions with

Table 3. Catalyst screen

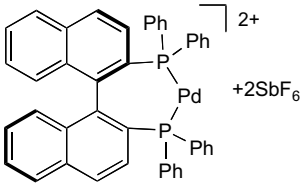
$$\mathbf{5} + \mathbf{8a} \xrightarrow[CH_2Cl_2\ \ 0^\circ C]{\text{catalysts (10 mol\%)}} \mathbf{9a}$$

Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	**11**	72	No reaction	—	—
2	**12**	72	57	96	7*R*
3	**13**	24	31	85	7*S*
4	**14**	24	54	10	7*S*

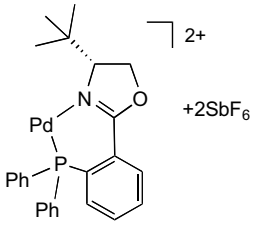
[a] Isolated yields.
[b] ee of *endo* isomer was determined by HPLC analysis using a Daicel Chiralcel AD column.
[c] After conversion to benzyl ester [7*R*]-**10**, the absolute configuration were determined.



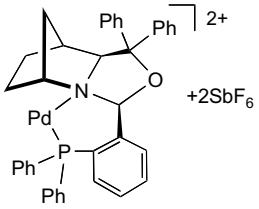
11



12



13



14

other dienes and in other asymmetric processes. Further studies to examine the scope and limitations of this combination system for the catalytic asymmetric version of the DA reactions of 1,2-dihydropyridines are now in progress.

References and notes

1. (a) Kuehne, M. E.; Marko, I. In *Syntheses of Vinblastine-type Alkaloids. The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37, pp 77–131; (b) Popik, P.; Skolnick, P. In *Pharmacology of Ibogaine and Ibogaine-related Alkaloids. The Alkaloids. Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1999; Vol. 52, pp 197–231; (c) Glick, S. D.; Maisonneuve, I. M.; Szumlinski, K. K. In *Mechanisms of Action of Ibogaine: Relevance to Putative Therapeutic Effects and Development of a Safer Iboga Alkaloid Congener. The Alkaloids*; Alper, K. R., Glick, S. D., Cordell, G. A., Eds.; Academic Press: San Diego, 2001; Vol. 56, pp 39–53.
2. (a) Buchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099–3109; (b) Marazano, C.; LeGoff, M.; Fourrey, J.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389–391; (c) Redding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973–976.
3. He, D. Y.; McGough, N. N.; Ravindranathan, A.; Jeanblanc, J.; Logrip, M. L.; Phamluong, K.; Janak, P. H.; Pon, D. *J. Neurosci.* **2005**, *25*, 619–628.
4. Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124–6134.
5. (a) Mitch, C. H. U.S. Patent 5,834,458, 1998; *Chem. Abstr.* **1999**, *129*, 343498; (b) Mitch, C. H. U.S. Patent 5,889,019, 1999; *Chem. Abstr.* **1999**, *130*, 252363; (c) Krow, G. R.; Cheung, O. H.; Hu, Z.; Huang, Q.; Hutchinson, J.; Liu, N.; Nguyen, K. T.; Ulrich, S.; Yuan, J.; Xiao, Y.; Wypij, D. M.; Zuo, F.; Carroll, P. J. *Tetrahedron* **1999**, *5*, 7747–7756.
6. (a) dos Santos, D. C.; de Freitas Gil, R. P.; Gil, L.; Marazano, C. *Tetrahedron Lett.* **2001**, *42*, 6109–6111; (b) Matsumura, Y.; Nakamura, Y.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 7685–7689; (c) Ho, G.; Mather, D. J. *J. Org. Chem.* **1995**, *60*, 2271–2273; (d) Marazano, C.; Yannic, Y.; Mehmandoust, M.; Das, B. C. *Tetrahedron Lett.* **1990**, *31*, 1995–1998; (e) Kouklovsky, C.; Pouilhes, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672–6679; (f) Campbell, M. M.; Mahon, M. F.; Sainsbury, M.; Searle, P. A.; Davies, G. M. *Tetrahedron Lett.* **1991**, *32*, 951–954; (g) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836–4842.
7. Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299–8305.
8. (a) Nakano, H.; Okuyama, Y.; Suzuki, Y.; Fujita, R.; Kabuto, C. *Chem. Commun.* **2002**, 1146–1147; (b) Nakano, H.; Takahashi, K.; Okuyama, Y.; Senoo, C.; Tsugawa, N.; Suzuki, Y.; Fujita, R.; Sasaki, K.; Kabuto, C. *J. Org. Chem.* **2004**, *69*, 7092–7100.
9. Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444–8445.
10. A representative procedure for the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **5** with 1-substituted 2-acryloyl-5,5-dimethyl-pyrazolidin-3-ones **8** using cationic Pd–POZ complex **4a**: a suspension of $PdCl_2$–POZ

complex **3** (28.1 mg, 0.07 mmol) and $AgSbF_6$ (27.4 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled at 0 °C and diene **5** (402.0 mg, 2 mmol) and 1-benzyl-2-acryloyl-5,5-dimethyl-pyrazolidin-3-one **8a** (103.3 mg, 0.4 mmol) were added. The reaction mixture was stirred under Ar at 0 °C for 24 h. The mixture was then quenched with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with hexane–AcOEt = 1:1 to afford **9a** (147 mg, 80%). Colourless prism. Mp 165–168 °C. $[\alpha]_D^{20} = -52.95$ (*c* 0.68, $CHCl_3$). ^1H NMR ($CDCl_3$) δ : 1.12–1.24 (m, 6H), 1.53–1.64 (m, 3H), 1.94–2.18 (m, 1H), 2.56–2.59 (m, 1H), 2.64–2.69 (m, 1H), 2.84 (br s, 1H), 3.06 (d, 1/2H, J = 10.6), 3.18 (d, 1/2H, J = 10.3), 3.35 (d, 1/2H, J = 10.6), 3.50 (d, 1/2H, J = 10.3), 4.00 (br s, 1H), 4.03 (br s, 2H), 5.07 (br s, 1H), 6.39–6.44 (m, 2H), 7.12–7.13 (m, 1H), 7.13–7.38 (m, 7H), 7.43–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.80, 26.65, 27.51, 30.76, 43.50, 45.54, 46.79, 47.20, 57.10, 60.93, 121.78, 121.83, 125.13, 127.45, 127.50, 128.37, 128.88, 128.99, 129.18, 129.23, 130.84, 133.65, 137.58, 151.36, 153.38, 169.68, 173.91. HRMS (EI) *m*/*z* calcd for $C_{27}H_{29}N_3O_4$ (M^+) 459.2158. Found 459.2176.

11. Conversion from DA adduct **9a** to benzyl ester **10**: *n*-BuLi (0.73 mL, 1.0 M in hexane, 0.78 mmol) was added to a cooled (−78 °C) solution of benzylalcohol (0.1 mL, 1.0 mmol) in 6 mL of THF. The resulting solution was stirred for 5 min and a solution of DA adduct **9a** (97% ee, 240 mg, 0.52 mmol) in THF was added. The solution was warmed to 0 °C and stirred for 3 h. The mixture was then quenched with saturated NH_4Cl solution and the solvent was evaporated under reduced pressure. H_2O was added to the residue and extracted with $CHCl_3$. The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on a column of silica gel with AcOEt–$CHCl_3$ = 1:3 to afford [7*R*]-benzyl ester **10** (113 mg, 60%). Colourless oil. $[\alpha]_D^{20} = -59.92$ (*c* 2.52, DMSO). ^1H NMR ($CDCl_3$): δ 1.91–2.07 (m, 2H), 2.91 (br s, 1H), 3.05 (d, 1/2H, J = 10.6), 3.16 (d, 1/2H, J = 10.3), 3.22–3.26 (m, 1H), 3.35 (d, 1/2H, J = 10.6), 3.49 (d, 1/2H, J = 10.3), 5.07–5.16 (m, 2H), 5.24–5.27 (m, 1H), 6.34–6.38 (m, 1H), 6.48–6.54 (m, 1H), 7.04–7.13 (m, 2H), 7.17–7.20 (m, 1H), 7.30–7.41 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 26.00, 30.67, 43.87, 46.96, 47.58, 66.61, 121.69, 121.76, 125.22, 128.11, 128.20, 128.25, 128.55, 128.59, 129.21, 129.25, 130.15, 135.26, 151.27, 153.06, 153.62, 172.36. HRMS (EI) *m*/*z* calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471. Found 363.1471.
12. Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157–2159.
13. Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841–1843.