Catalytic Asymmetric Synthesis of Benzylic Quaternary Carbon Centers. An Efficient Synthesis of (–)-Eptazocine

Toshiyasu Takemoto, Mikiko Sodeoka, Hiroaki Sasai, and Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences
University of Tokyo, Hongo
Bunkyo-ku, Tokyo 113, Japan

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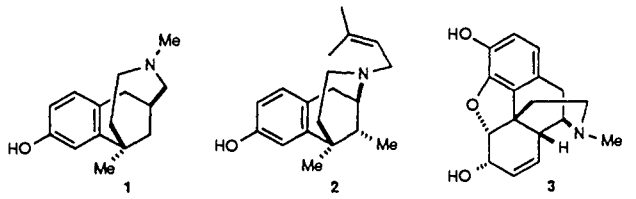
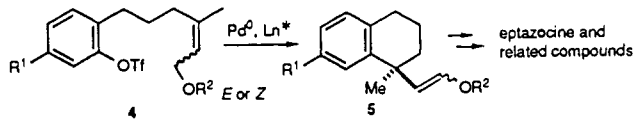
Benzylic quaternary carbon centers are found in various analgesics such as eptazocine(**1**), pentazocine(**2**) and morphine(**3**) (Chart I),[1] and the construction of such centers in a catalytic, enantioselective manner continues to provide an interesting challenge for organic chemists. While elegant catalytic asymmetric syntheses of **2** and **3** have been reported, they rely on the asymmetric hydrogenation of enamides for the introduction of chirality.[2,3] Herein we report a general method for the catalytic asymmetric synthesis of tetralin derivatives having a benzylic quaternary carbon center and demonstrate the efficiency of this asymmetric Heck reaction[4] in the synthesis of (–)-eptazocine.[1a,b] The results described within should also be useful for the synthesis of various analgesics related to **1**.

Our strategy for the construction of benzylic quaternary carbon centers in an optically active form is illustrated in Scheme I. It was expected that the presence of a chiral ligand in the Heck-type arylation of **4** would result in the discrimination of the *Re*- and *Si*- faces of the trisubstituted olefin, but the effect of olefin geometry on the asymmetric induction remained ambiguous. Inspection of possible transition states for the cyclization of both

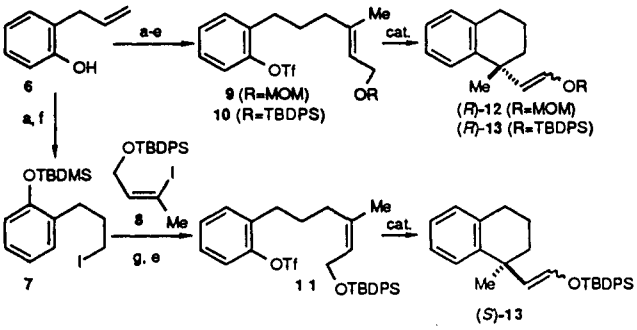
Chart I



Scheme I



Scheme II[a]



[a] Reaction conditions: (a) TBDMSCl, Et_3N, CH_2Cl_2, 23 °C, 100%; (b) OsO_4 (catalyst), $NaIO_4$, THF–H_2O, 23 °C; $Ph_3P{=}CHCOMe$, benzene, 50 °C, 84%; (c) H_2, Pd/C, EtOH, 23 °C; $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 23 °C; Dibal-H, Et_2O, –78 °C, 71%; (d) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 23 °C, 93% (R = MOM); TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 91% (R = TBDPS); (e) TBAF, THF, 0 °C; Tf_2O, Et_3N, CH_2Cl_2, –78 °C–0 °C, 90–95%; (f) BH_3·THF, H_2O_2–NaOH, 0 °C; Ph_3P, I_2, imidazole, benzene, 0 °C, 71%; (g) Zn–Cu, $BrCH_2CH_2Br$ (catalytic amount); **8**, $Pd(PPh_3)_4$ (catalyst), THF, 70 °C, 72%. Cat.: Pd(0)–(*R*)-BINAP complex.

(*E*)- and (*Z*)-**4** suggested that the stereochemistry of the olefin would be crucial, and it was hoped that one of the isomers would provide a product of high ee that could be readily converted to **1** and its analogs.

With these goals in mind, both (*E*)-olefins **9**, **10** and (*Z*)-olefin **11** were prepared in a stereocontrolled manner from the phenol derivative **6**, as shown in Scheme II. The geometry of the (*E*)-olefin was set in a Horner–Emmons reaction, while palladium assisted coupling of **7** and **8**[5] provided the (*Z*)-olefin stereospecifically. The asymmetric Heck reaction of (*E*)-olefins **9** and **10** was first investigated. Treatment of **9** with $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), (*R*)-BINAP[6] (10 mol %), and K_2CO_3 (3 molar equiv)

(1) (a) Shiotani, S.; Kometani, T.; Mitsuhashi, K.; Nozawa, T.; Kurobe, A.; Futsukaichi, O. *J. Med. Chem.* **1976**, *19*, 803. (b) Kameyama, T.; Nabeshima, T.; Yamaguchi, K.; Ukai, M.; Okuyama, S.; Sakakibara, S. *Nippon Yakugaku Zasshi* **1981**, *78*, 599. (c) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. (d) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688 and references cited therein.

(2) (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. (b) Kitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829.

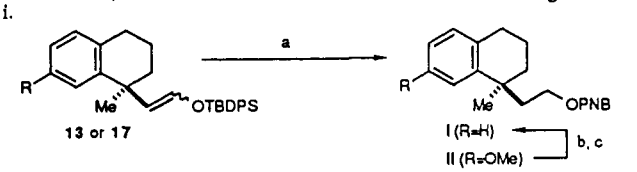
(3) For an elegant example using the diastereoselective alkylation of 1-lithiated tetrahydroisoquinolines, see: (a) Meyers, A. I.; Fuents, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (b) Meyers, A. I.; Fuents, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361. (c) Meyers, A. I. *Aldrichim. Acta* **1985**, *18*, 59. For other asymmetric syntheses of these analgesics, see: (d) Archer, J. F.; Boyd, D. R.; Jackson, W. R.; Grundon, M. F.; Khan, W. A. *J. Chem. Soc. C* **1971**, 2560. (e) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353. (f) Konda, M.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1025. (g) Achiwa, K. *Heterocycles* **1977**, *8*, 247. (h) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, *265*. (i) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1318. (j) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052.

(4) The first example of an asymmetric Heck reaction was reported in 1989. For this and other examples, see: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953. (c) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 4093. (d) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (e) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593. (f) Shibasaki, M.; Sato, Y.; Kagechika, K. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 826. (g) Kagechika, K.; Oshima, T.; Shibasaki, M. *Tetrahedron* **1993**, *49*, 1773. (h) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *26*, 4219. (i) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.*, in press. (j) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (k) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (l) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (m) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421. (n) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (o) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267. (p) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845. For other elegant examples of the construction of racemic quaternary carbon center using intramolecular Heck reactions, see: (q) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (r) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (s) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042.

(5) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. Alkenyl iodide **8** was prepared according to the reported method (Cowell, A.; Stille, J. K. *Tetrahedron Lett.* **1979**, 133), followed by silylation (96%, TBDMSCl, NEt_3, DMAP, CH_2Cl_2, 23 °C, 3 h).

(6) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(7) The ee of **12** was determined by DAICEL CHIRALCEL OJ, hexane–2-propanol, 9:1. On the other hand, those of **13** and **17** were determined by converting to **i** and **ii** (DAICEL CHIRALCEL OD, hexane-2-propanol, 9:1). Furthermore, **ii** was converted to **i** to determine the absolute configuration of **i**.



(a) TBAF, AcOH, THF, 0 °C; $LiAlH_4$, Et_2O; PNBCl, Et_3N, CH_2Cl_2, 89%. (b) BBr_3, CH_2Cl_2; Tf_2O, Et_3N, CH_2Cl_2, 49%. (c) $Pd(OAc)_2$ (catalyst), dppf, Et_3N, HCO_2H, THF, 28%.

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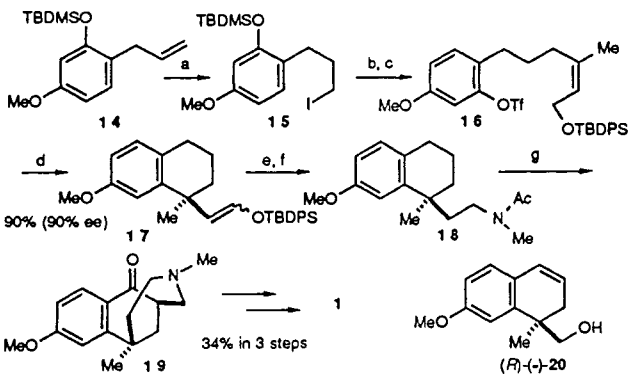
in THF at 70 °C for 87 h was found to give the best results, affording (*R*)-*trans*-**12** of 39% ee as the major product (70% yield) and (*R*)-*cis*-**12** of 32% ee as the minor product (19% yield).[7] A kinetic resolution in the *syn*-β-hydrogen elimination step[8] could easily explain the differences observed in the enantiomeric excesses of *trans*- and *cis*-**12**. The use of other solvents, such as benzene, DMF, 1,2-dichloroethane, and dioxane, and of other ligands, such as CHIRAPHOS, MOD–DIOP, BCPM, and BPPFA, gave less satisfactory results. On the other hand, subjection of **10** to the conditions described above (48 h) resulted in the formation of (*R*)-**13** of 51% ee as a chromatographically inseparable mixture of olefin isomers in 95% yield (*trans:cis* = 84:11).[7] (*Z*)-olefin **11**, which was expected to cyclize with higher selectivity, was examined next. It was found that exposure of **11** to $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), (*R*)-BINAP (10 mol %), and K_2CO_3 (3 molar equiv) in THF at 70 °C for 50 h produced (*S*)-**13** of 80% ee as a chromatographically inseparable mixture of isomers in 97% yield (*trans:cis* = 92:5). Furthermore, treatment of **11** with $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP (20 mol %), and K_2CO_3 (3 molar equiv) in THF at 70 °C for 50 h gave only the (*S*)-*trans*-isomer of 87% ee in 85% yield, and when the reaction was run at 50 °C for 50 h, (*S*)-**13** of 91% ee was obtained in 79% yield (*trans:cis* = 98:2).[9] Apparently, the absolute configuration of the product obtained with the (*R*)-BINAP system is reversed in going from the (*E*)- to (*Z*)-trisubstituted olefin, and the degree of enantioselectivity is influenced significantly by the olefin geometry. With our system, the use of (*Z*)-trisubstituted olefins appears essential for the synthesis of benzylic quaternary carbon centers of high ee.

Having determined the optimal conditions for the catalytic asymmetric synthesis of benzylic quaternary carbon centers, we sought to apply this methodology to the synthesis of (–)-eptazocine (**1**) (Scheme III). The trisubstituted benzene derivative **14** was prepared in three steps (78% overall yield) from 3-methoxyphenol[10] and then converted to **15** in 74% yield by hydroboration–oxidation and treatment with iodine, triphenylphosphine, and imidazole. Cross-coupling[5] of **15** with iodide **8**, deprotection of TBDMS ether, and trifluoromethanesulfonylation afforded **16** in 63% yield. Exposure of **16** to $Pd(OAc)_2$ (7 mol %), (*R*)-BINAP (17 mol %), and K_2CO_3 (3 molar equiv) in THF at 60 °C for 72 h gave the desired cyclized product **17** (*trans:cis* = 21:3) of 90% ee in 90% yield.[7] Moreover, the use of 10 mol % $Pd(OAc)_2$ and 25 mol % (*R*)-BINAP under otherwise identical conditions (48 h) slightly improved the enantiomeric excess (93% ee, 87% yield). With an efficient route to **17**, the synthesis of eptazocine was carried out as follows. Treatment of **17** with TBAF–AcOH in THF gave the corresponding aldehyde in quantitative yield. Subsequent conversion to acetate **18**, $[\alpha]^{24}_D$ +23.20° (*c* 1.60, EtOH), was accomplished in 87% overall yield by exposure to methylamine (MeOH, 23 °C, 1 h), hydrogen–PtO_2 (MeOH, 23 °C, 10 h), and finally acetic anhydride (AcOH, 100 °C, 2 h). Acetate **18** underwent oxidation (CrO_3, AcOH, H_2O) to give the ketone, which was successively treated with KOH and paraformaldehyde to afford tricycle **19** in 90% overall yield.[11] **19** was finally converted to the HBr salt of (–)-eptazocine (**1**), $[\alpha]^{20}_D$ –14.0 °(*c* 1.0, water), according to the reported procedure (34% overall yield, (i) $NaBH_4$, EtOH, (ii) Pd/C–AcOH–H_2, (iii) 48% HBr).[11]

Scheme III[a]



[a] Reaction conditions: (a) BH_3–THF, H_2O_2–NaOH, 0 °C; Ph_3P, I_2, imidazole, benzene, 0 °C, 74%; (b) Zn–Cu, $BrCH_2CH_2Br$ (catalytic amount); **8**, $Pd(PPh_3)_4$ (catalyst), THF, 70 °C, 84%; (c) TBAF, THF, 0 °C; Tf_2O, Et_3N, CH_2Cl_2, –78 °C–0 °C, 88%; (d) Pd(0)–(*R*)-BINAP complex (10 mol %), K_2CO_3, THF, 60 °C; (e) TBAF, AcOH, THF, 0 °C, 100%; (f) $MeNH_2$, MeOH; H_2, PtO_2, MeOH, 23 °C; AcO_2, AcOH, 100 °C, 87%; (g) CrO_3, AcOH, H_2O; KOH, MeOH, reflux; $(CH_2O)_n$, $(CO_2H)_2$, MeOH, 50 °C, 86%.

The absolute configuration of cyclized product was determined by its conversion to the known alcohol (–)-**20**.[12] For therapeutic use, (–)-eptazocine (**1**), the more biologically active enantiomer, is currently prepared through resolution. However, the absolute configuration of (–)-eptazocine has never been reported. Here, we have unequivocally determined the absolute configuration of (–)-eptazocine to be *S*, a result which follows from the configuration of morphine.

In conclusion, we have developed an efficient and general method for the catalytic asymmetric synthesis of a benzylic quaternary carbon center of high enantiomeric excess and applied this methodology to the first catalytic asymmetric synthesis of (–)-eptazocine (**1**).

Acknowledgment. We wish to thank Dr. H. Nakamoto and Mr. O. Futsukaichi of Nihon Iyakuhin Kogyo Co., Ltd., for their helpful discussions.

Supplementary Material Available: Experimental procedures for the synthesis of (–)-eptazocine (**1**) from **14**, and full ^{1}H-NMR spectra for the synthetic intermediates (5 pages). Ordering information is given on any current masthead page.

(8) Use of (*S,S*)-BCPM gave (*R*)-*trans*-**12** of 15% ee in 56% yield, together with (*R*)-*cis*-**12** (84% ee, 11% yield).

(9) Treatment of **11** with $Pd(OAc)_2$ (3 mol %), (*R*)-BINAP (8 mol %), and K_2CO_3 (3 molar equiv) in THF at 50 °C for 14 days afforded only (*S*)-*trans*-**13** of 91% ee in 97% yield.

(10) For the preparation of **14**, see: Borgulya, T.; Madeja, R.; Gahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14.

(11) Nakamoto, H.; Ishizuka, N.; Takeda, S.; Yoshimura, Y. *JP* 01061447, 1989; *Chem. Abstr.* **1989**, *111*, 153380j, *EP* 384917, 1990; *Chem. Abstr.* **1990**, *114*, 185049m.

(12) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290 and a personal communication from Professor K. Ogasawara. The transformation of **17** to (–)-**20**, a key intermediate in the synthesis of (–)-aphanorphine, was achieved in 11 steps (12% overall yield). Thus, a formal catalytic asymmetric synthesis of (–)-aphanorphine has also been achieved.