Tetrahedron Letters, Vol. 33, No. 18, pp. 2589-2592, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

FURTHER STUDIES ON A CATALYTIC ASYMMETRIC SYNTHESIS OF DECALIN DERIVATIVES

Yoshihiro Sato,[a] Shoko Watanabe,[a] and Masakatsu Shibasaki[b]*

[a] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan
[b] Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: The decalin derivatives **2** (92% ee) and **18c** (92% ee) were synthesized from the corresponding prochiral substrates **7b** and **17a** by an asymmetric Heck reaction.

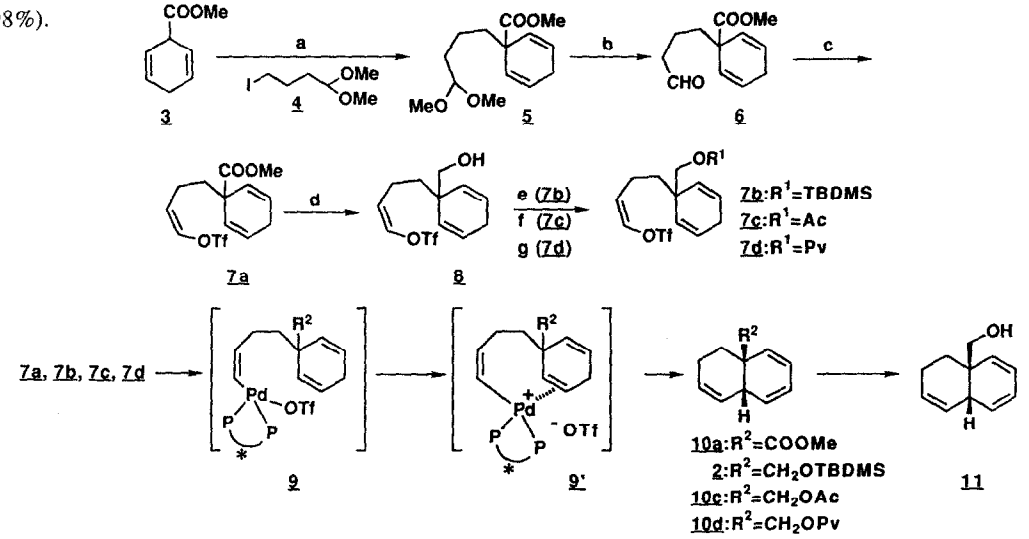
A lot of successful studies on catalytic asymmetric epoxidation,[1] hydrogenation,[2] and their synthetic application have been reported. However, there are only a few excellent catalytic asymmetric C-C bond-forming reactions.[3] We recently reported the first example of an asymmetric Heck reaction, in which the decalin derivative **2** was constructed in up to 80% ee starting with the prochiral alkenyl iodide **1**.[4,5] In order to achieve an asymmetric synthesis of other decalin derivatives, which would find immediate application in the synthesis of bioactive molecules, as well as to improve the above-mentioned decalin formation to synthetically useful levels, we have further studied on a catalytic asymmetric synthesis of decalin derivatives. In this communication, we report an improved catalytic asymmetric synthesis of **2** (92% ee) and a catalytic asymmetric synthesis of the more complex decalin derivative **18c** (92% ee).

1 **2**

TBDMS=*tert*-butyldimethylsilyl

In the previous paper,[4] the decalin derivative **2** with 80% ee was constructed from the alkenyl iodide **1** by treatment with $PdCl_2$[(*R*)-BINAP] (10 mol %), Ag_3PO_4 (2 molar equiv) and $CaCO_3$ (2.2 molar equiv) in 1-methyl-2-pyrrolidinone (NMP) at 60 °C for 84 hr. There are several reasons why Ag_3PO_4 was used as a base. First, a silver salt enhances the reaction rate and prevents deactivation of the palladium catalyst. Second, a silver salt prevents isomerization of the product. Third, a silver salt produces the 16-electron Pd^+ intermediate, leading to the product with high ee. Among a variety of silver salts examined, Ag_3PO_4 gave the highest ee. We thought that use of the alkenyl triflate **7** instead of **1** would afford **2** with high ee even in the absence of a silver salt, because **9** was expected to produce the 16-electron Pd^+ intermediate **9'** spontaneously.[6] The requisite *cis*-alkenyl triflates **7a** ~ **7d** were first prepared as follows. Treatment of the lithium ester enolate generated from **3** (LDA, 0 °C, THF) with the iodide **4**[7] (1.1 equiv) at 0 °C furnished the coupling product **5** in 76% yield. After deprotection of an acetal functionality (TsOH, acetone, r.t., 100%), the resultant aldehyde **6** was converted to the alkenyl triflate **7a** in 63% yield together with the corresponding *trans*-isomer (12%) on exposure to trifluoromethanesulfonic anhydride (1.2 equiv) and 2,6-di-*tert*-butylpyridine (1.8 equiv) in 1,2-dichloroethane (reflux, 20 min).[8] The more polar alkenyl triflate **7a** was readily separated by silica gel column chromatography

(hexane-Et_2O, 9:1) and reduced with lithium aluminum hydride in ether at -78 °C to give the alcohol **8** (85%). The alcohol **8** was further converted to the silyl ether **7b** (95%), the acetate **7c** (96%) and the pivaloyl ester **7d** (98%).



Scheme 1. a. LDA, THF, 0 °C (76%); b. TsOH, acetone, r.t. (100%); c. Tf_2O, 2,6-di-*tert*-butylpyridine, 1,2-dichloroethane, reflux (63%); d. $LiAlH_4$, Et_2O, -78 °C (85%); e. TBDMSCl, imidazole, DMF (95%); f. Ac_2O, pyridine, DMAP, CH_2Cl_2 (96%); g. PvCl, pyridine, DMAP, CH_2Cl_2 (98%).

With the prochiral alkenyl triflates **7a~7d** available, first of all, a catalytic asymmetric synthesis of **10a** using $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (5.5 mol %) and *N*,*N*-diisopropylethylamine (2 equiv) was investigated.

Table 1. Catalytic Asymmetric Synthesis of 2 and 10a~10d from 7a~7d

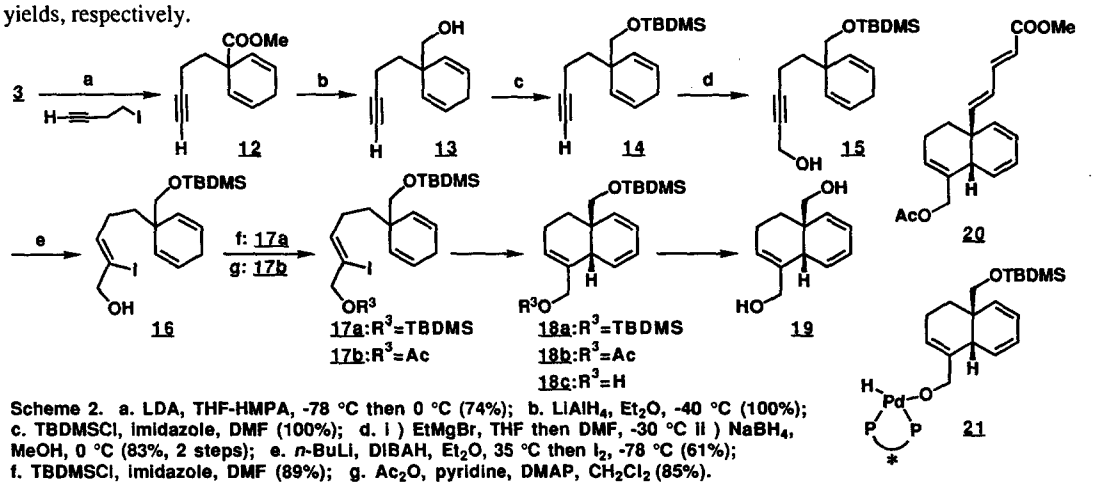
prochiral substrate	product	yield (%)	ee (%)
7a	10a	54	91[a]
7b	2	35	92
7c	10c	44	89
7d	10d	60	91

[a] A trace amount of 7a was recovered.

Although the optically active decalin derivative **10a** with 82% ee was formed in toluene (60 °C, 31 hr, 20%), deactivation of the catalyst occurred gradually, the starting material **7a** being recovered (39%). After several attempts, it was found that treatment of **7a** with $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %) and K_2CO_3 (2 molar equiv) in toluene at 60 °C for 55 hr gave **10a** with 91% ee in 54% yield together with the recovery of **7a** (trace).[9] Furthermore, reaction of **7d** under the same conditions as described above (27 hr) afforded **10d** with 91% ee in 60% yield. The results are summarized in Table 1. The enantiomeric excess (ee) was unequivocally determined by the HPLC analysis (DAICEL CHIRALCEL OJ, hexane–2-propanol, 9:1) of **11** obtainable from **2**, **10a**, **10c**, and **10d**, respectively. Thus, a catalytic asymmetric synthesis of the decalin derivatives **2** and **10a~d** has been greatly improved on two points. That is, addition of a silver salt is not necessary anymore to acquire high ee and higher ee (>90%) has been realized.

Next we became interested in a catalytic asymmetric synthesis of more functionalized decalin derivatives, which would find immediate application in the synthesis of bioactive natural products. Herein, a catalytic asymmetric synthesis of the decalin derivatives **18a**, **18b** and **18c** is described. Treatment of the lithium ester enolate generated from **3** (LDA, -78 °C, THF-HMPA, 7.5:1) with 4-iodo-1-butyne at 0 °C gave **12** in 74% yield, which underwent reduction by lithium aluminum hydride in ether at -40 °C to afford **13** in quantitative yield.

Protection of **13** as a silyl ether (*tert*-butyldimethylsilyl chloride, imidazole, DMF) furnished **14** in nearly quantitative yield. Reaction of **14** with EtMgBr in THF, followed by treatment with DMF (3 equiv) at -30 °C, gave the aldehyde, which was immediately reduced with $NaBH_4$ in MeOH at 0 °C to furnish the acetylenic alcohol **15** in 83% yield. Hydroalumination of **15** (*n*-BuLi-diisobutylaluminum hydride, 35 °C, 36 hr),[10] followed by being quenched with I_2, provided the alkenyl iodide **16** stereospecifically in 61% yield. Silylation (*tert*-butyldimethylsilyl chloride, imidazole) and acetylation (Ac_2O, pyridine) gave **17a** and **17b** in 89% and 85% yields, respectively.



Scheme 2. a. LDA, THF-HMPA, -78 °C then 0 °C (74%); b. $LiAlH_4$, Et_2O, -40 °C (100%); c. TBDMSCl, imidazole, DMF (100%); d. i) EtMgBr, THF then DMF, -30 °C ii) $NaBH_4$, MeOH, 0 °C (83%, 2 steps); e. *n*-BuLi, DIBAH, Et_2O, 35 °C then I_2, -78 °C (61%); f. TBDMSCl, imidazole, DMF (89%); g. Ac_2O, pyridine, DMAP, CH_2Cl_2 (85%).

With the prochiral substrates having a trisubstituted double bond available,[11] a catalytic asymmetric synthesis of **18a** and **18b** was examined. It was found that treatment of **17a** with $PdCl_2$[(*R*)-BINAP] (10 mol %), Ag_3PO_4 (2 molar equiv) and $CaCO_3$ (2.2 molar equiv) in NMP at 60 °C for 41 hr gave the expected product **18a** with 83% ee in 63% yield accompanied with the allylic alcohol **18c** with 92% ee (35% yield).[12] The enantiomeric excess was unequivocally determined by the HPLC analysis (DAICEL CHIRALCEL OJ, hexane–2-propanol, 9:1) of the diol **19** obtainable from **18a** and **18c**, respectively, on exposure to HF in aqueous CH_3CN at 0 °C and assignment of the absolute configuration was achieved by application of the CD exciton chirality method to **20**.[13] In order to understand the mechanism of the formation of **18c** with 92% ee, the following experiments were carried out. First, the prochiral allylic alcohol **16** underwent cyclization under the similar conditions as described above to furnish **18c** with lower ee (71% ee), revealing that **18c** (92% ee) was not produced from **16**.[14] Second, treatment of **18a** with $PdCl_2$[(*R*)-BINAP], Ag_3PO_4, $CaCO_3$ and 1.5 equiv of *n*-Bu_4NOAc in NMP at 60 °C for 44 hr afforded none of **18b**, ruling out a possibility of the formation of the π-allylpalladium complex from **18a**.[14] These results appear to suggest that transmetalation between silicon and (BINAP)Pd$^+$H (**18a**→**21**) plays a key role in the above-mentioned kinetic resolution. Next, a catalytic asymmetric cyclization of the prochiral alkenyl iodide **17b** was also investigated. Exposure of **17b** to $PdCl_2$[(*R*)-BINAP] (10 mol %), Ag_3PO_4 (2 molar equiv) and $CaCO_3$ (2.2 molar equiv) in NMP at 60 °C for 100 hr produced **18b** with 87% ee in 67% yield. In this case, none of the

Table 2. Catalytic Asymmetric Synthesis of 18b from 17b under Various Conditions[a]

silver salt	$CaCO_3$	time (hr)	yield (%)	ee (%)	recovery of SM (%)
Ag_3PO_4	2.2 mol eq	100	67	87	—
Ag_2O	—	90	68	70	—
Ag_2CO_3	—	140	33	65	—
AgOAc	2.2 mol eq	191	47	23	48

[a] 10 mol % $PdCl_2$[(*R*)-BINAP], NMP.

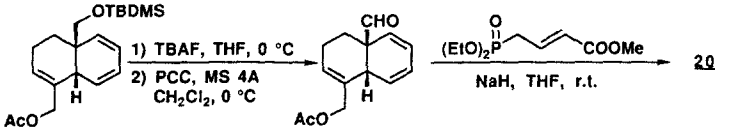
allylic alcohol **18c** was formed. It is interesting to note that there is a similar tendency for silver salts to effect on enantiomeric excess as observed previously.[4] The results are summarized in Table 2. The *cis*-decalin derivatives **18b** and **18c** should be more valuable intermediates for the synthesis of bioactive molecules.[15]

In conclusion, we have succeeded in improving a catalytic asymmetric synthesis of **2** and **10a~d** greatly as well as achieving an efficient catalytic asymmetric synthesis of the more functionalized decalin derivative **18a~c**. Further studies along this line are under investigation.

Acknowledgments : This study was financially supported by Grand-in-Aid for Scientific Research on Priority Areas (Multiplex Organic Synthesis) from the Ministry of Education, Science and Culture, Japan.

References and Notes

1. (a) B. E. Rossiter, In "*Asymmetric Synthesis*", ed. J. D. Morrison, Academic Press, 1985, Vol. 5, p. 193. (b) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980). (c) R. Irie, K. Noda, Y. Ito, and T. Katsuki, *Tetrahedron Lett.*, **32**, 1055 (1991). (d) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc.*, **113**, 7063 (1991).
2. (a) J. Halpern, In "*Asymmetric Synthesis*", ed. J. D. Morrison, Academic Press, 1985, Vol. 5, p. 41. (b).K. E. Koenig, ref. 2a, p. 71. (c) R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990), and references cited therein.
3. (a) T. Hayashi and M. Kumada, In "*Asymmetric Synthesis*", ed. J. D. Morrison, Academic Press, 1985, Vol. 5, p. 147. (b) Y. Ito, M. Sawamura, and T. Hayashi, *J. Am. Chem. Soc*, **108**, 6405 (1986). (c) D. L. Hughes and U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, and E. J. J. Grabowski, *J. Org. Chem.* **52**. 4745 (1987). (d) K. Narasaka, T. Yamada, and H. Minamikawa, *Chem. Lett.*, **1987**, 2073. (e) K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, **109**, 7111 (1987). (f) N. Oguni, Y. Matsuda, and T. Kaneko, *J. Am. Chem. Soc.*, **110**, 7877 (1988). (g). K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, **111**, 1940 (1989). (h) M. Kitamura, S. Okada, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, **111**, 4028 (1989). (i) T. Mukaiyama, S. Kobayashi, H. Uchiro, and I. Shiina, *Chem. Lett.*, **1990**, 129. (j) M. Hayashi, T. Matsuda, and N. Oguni, *J. Chem. Soc., Chem. Comm.*, **1990**, 1364. (k) K. Narasaka, *Synthesis*, **1991**, 1, and references cited therein. (l). K. Furuta, T. Maruyama, and H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 1041 (1991).
4. (a) Y. Sato, M. Sodeoka, and M. Shibasaki, *J. Org. Chem.*, **54**, 4738 (1989); Idem., *Chem. Lett.*, **1990**, 1953. (b) K. Kagechika and M. Shibasaki, *J. Org. Chem.*, **56**, 4093 (1991).
5. For other asymmetric Heck reaction, see: (a) N. E. Carpenter, D. J. Kucera, and L. E. Overman, *J. Org. Chem.*, **54**, 5846 (1989). (b) F. Ozawa, A. Kubo, and T. Hayashi, *J. Am. Chem. Soc.*, **113**, 1417 (1991).
6. R. J. Hinkle, P. J. Stang, and M. H. Kowalski, *J. Org. Chem.*, **55**, 5033 (1990), and references cited therein.
7. H. Niwa, T. Hasegawa, N. Ban, and K. Yamada, *Tetrahedron*, **43**, 825 (1987).
8. P. J. Stang and W. Treptow, *Synthesis*, **1980**, 283.
9. Treatment of **7a** with $PdCl_2$[(*R*)-BINAP] (5 mol %) and K_2CO_3 (2 molar equiv) in toluene at 60 °C for 68 hr gave the less satisfactory result, **10a** with 72% ee being formed in 28% yield. The reason is not clear at present.
10. E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **92**, 6314 (1970).
11. Attempt to prepare the corresponding alkenyl triflates turned out to be unfruitful.
12. Use of $Pd(OAc)_2$ and (*R*)-BINAP instead of $PdCl_2$[(*R*)-BINAP] gave the less satisfactory result.
13. The compound **20** was synthesized as follows.



14. The allylic alcohol can be produced through the π-allylpalladium complex, because a small amount of H_2O ($CaCO_3$+Ag_3PO_4+HI) should be present in the reaction medium.
15. Transformation of **18** to the western part of azadirachtin is under investigation. See: Y. Nishikimi, T. Iimori, M. Sodeoka, and M. Shibasaki, *J. Org. Chem.*, **54**, 3354 (1989).

(Received in Japan 4 December 1991; accepted 20 January 1992)