Regioselective Olefin Insertion in Asymmetric Heck Reaction. Catalytic Asymmetric Synthesis of a Versatile Intermediate for Diterpene Syntheses

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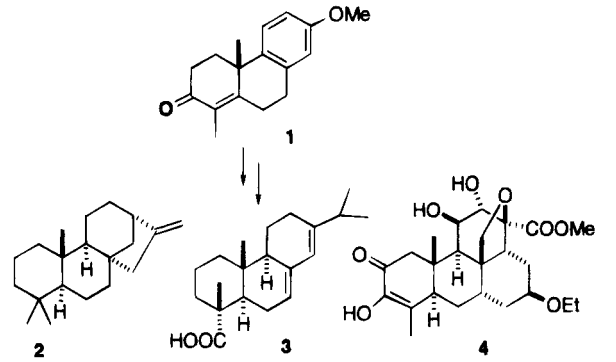
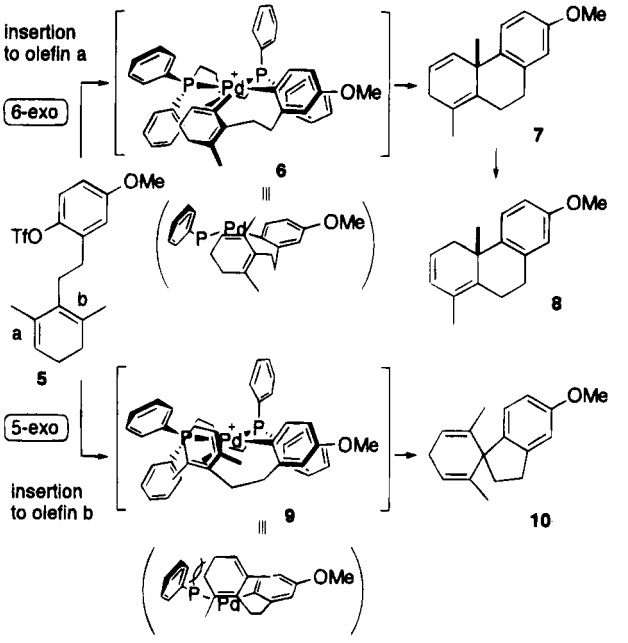
Since our first report on the asymmetric Heck reaction in 1989, we[1] and others[2] have demonstrated that this carbon–carbon bond-forming reaction is quite useful for the highly enantioselective synthesis of various compounds. The construction of polycyclic skeletons via the intramolecular Heck reaction is a particularly powerful application and has been used in the asymmetric synthesis of several complex natural products.[1c,f,g,k,p,q,2i] In these cases, however, there has been no issue of regioselectivity in the cyclization with only the 5-exo or 6-exo mode possible. The question remains as to whether regioselectivity in the cyclization of substrates containing both possible reaction pathways can be controlled and predicted. Herein, we describe the regioselective asymmetric cyclization of **5** to optically active **8** (95% ee) and the use of this tricyclic compound in the asymmetric synthesis of various diterpenes.

The enone **1** is a versatile synthetic intermediate for a number of diterpenes such as kaurene (**2**), abietic acid (**3**), and bruceantin analog (**4**) (Scheme 1).[3] We planned

Scheme 1



Scheme 2



the asymmetric synthesis of enone **1** from **5**, a substrate expected to yield the tetrahydrophenanthrene derivative **7** or its isomerized product **8** in a regioselective, asymmetric Heck cyclization. The 6-exo-cyclization was predicted using a molecular model with the assumptions that (1) cyclization of the aryl triflate would proceed via a squareplanar cationic Pd(II) intermediate with a 16-electron configuration[1f,o] and that (2) the insertion step would proceed through "in-plane" coordination of the olefin as suggested by Hoffmann *et al.*[4] In principle, four insertion modes, 6-exo, 7-endo, 5-exo, and 6-endo, are possible for diene **5**; however, the 7-endo and 6-endo modes are disfavored by the severe tortional strain that results on "in-plane" coordination. As shown in Scheme 2, "in-plane" coordination leading to both the 6-exo and 5-exo products, **7** and **10**, respectively are possible.

Discrimination between the remaining two pathways relies on consideration of the steric environment generated by the chiral ligand. Extrapolating from the X-ray crystal structure of $PdCl_2$[(*R*)-binap], one would expect that the (*R*)-BINAP ligand forms an asymmetric environment about Pd with a phenyl group placed in close proximity to the olefin coordinating site.[2k] More steric repulsion would thus result between the phenyl group and the tetrasubstituted olefin **b** (in **9**) than the trisub-

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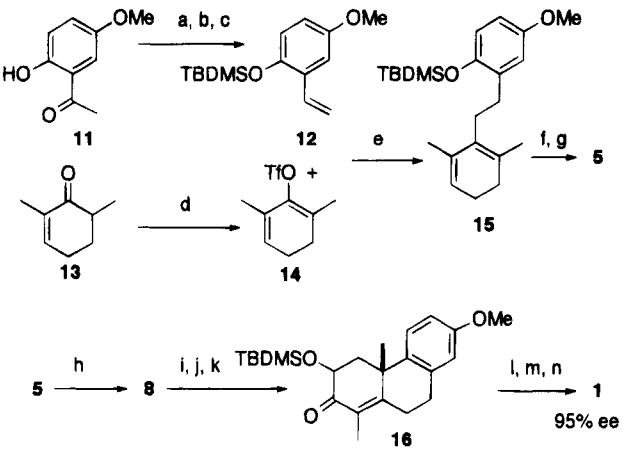
Scheme 3



stituted olefin **a** (in **6**), and this was expected to give preferred formation of the desired optically active tricyclic compound **7**. To verify this prediction, the asymmetric Heck cyclization of **5** using (*R*)-BINAP was examined.

Substrate **5** was prepared as shown in Scheme 3. Suzuki coupling[5] of vinyl phenol derivative **12** and triflate **14**, prepared from **11** and **13**,[6] respectively, gave desired diene **15** in 72% yield. Addition of water to the reaction mixture after the hydroboration of **12** was found to be essential for clean conversion to **15**.[7] Silyl ether **15** was then converted to triflate **5** in 63% yield by deprotection of the *tert*-butyldimethylsilyl group and trifluoromethanesulfonylation. With the desired substrate **5** in hand, we began to test reaction conditions for the asymmetric Heck reaction. Treatment of diene **5** with $Pd(OAc)_2$ (9 mol %), (*R*)-BINAP[8] (18 mol %), and K_2CO_3 (3 mol equiv) in toluene at 80 °C for 12 h gave the desired 6-endo-cyclized product **7** of 94% ee[9] in 36% chemical yield. A small amount of **5** (16%) was also recovered. Prolonged reaction at this temperature did not improve the chemical yield of **7**, possibly because of decomposition of the products and/or starting material. The use of other solvents, such as THF, DMF, and 1,2-dichloroethane, and of another palladium complex, $Pd_2(dba)_3{\cdot}CHCl_3$, gave less satisfactory results.[10] When the reaction temperature was decreased to 60 °C, the conjugated diene **8** was formed in 8% yield in addition to **7** (38%). Reaction at 50 °C gave the best results with the combined yield of the desired 6-exo-cyclized products **7** and **8** increasing to 62% (**7**:**8** = 3:1) (**7**: $[\alpha]^{24}_D$ +174° (*c* 0.60, $CHCl_3$); **8**: $[\alpha]^{27}_D$ +363° (*c* 4.67, $CHCl_3$)).[11] *Asymmetric induction in this cyclization was 95% ee.*[9] The nonconjugated diene **7** (or a mixture of **7** and **8**) was cleanly isomerized to conjugated diene **8** in quantitative yield using catalytic naphthalene·$Cr(CO)_3$.[12] The optical rotation of **8** from this isomerization reaction was identical to that of the product from the Heck reaction, suggesting no kinetic resolution occurred during the Pd-catalyzed isomerization process.[13] Thus, 6-exo selective cyclization of **5** to **8** has been achieved with excellent enantioselectivity. The 5-exo-cyclized product **10** was not isolated in any case.

Conjugated diene **8** has also been successfully converted to enone **1** ($[\alpha]^{27}_D$ +149° (*c* 1.21, $CHCl_3$), 95% ee).[9] As shown in Scheme 3, a diastereomeric mixture of the *cis*-diols obtained by the regioselective dihydroxylation of **8** was converted to the α-(silyloxy)enone **16** in good yield after selective protection and oxidation. Removal of the silyloxy group from **16** afforded enone **1**, with spectral data identical to that reported. The absolute stereochemistry of **1** was unequivocally determined to be (*S*) by comparison of its optical rotation with the reported value.[3d]

In conclusion, we have shown that a highly regio- and enantioselective intramolecular Heck reacition of **5** can be achieved, and conversion of the cyclized products to **1** provides a simple route to a useful intermediate for diterpene syntheses. This example suggests that consideration of the interactions resulting on "in-plane" olefin coordination in cationic complexes may be useful for the prediction of the regio- and enantioselectivity in asymmetric Heck reactions.

Supporting Information Available: Experimental procedure and spectral data (26 pages).

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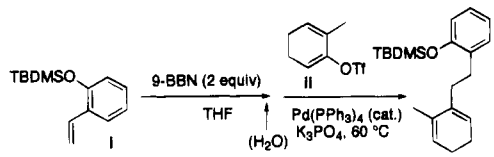
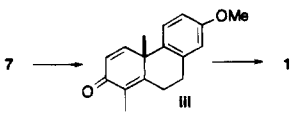
(7) Initial examinations of this coupling reaction using model substrates **i** and **ii** were problematic. Excess 9-BBN was necessary for the complete conversion of **i** to its hydroboration product but caused formation of the reduced product, 2-methylcyclohexa-1,3-diene, as well. Formation of this byproduct suggests that the hydridoalkenylpalladium intermediate is formed on transmetalation with 9-BBN. Addition of water after hydroboration of **i** efficiently hydrolyzed the residual 9-BBN, increasing the yield of the coupling product from 13% to 67%.



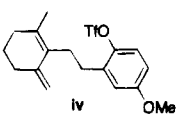
(8) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(9) The enantiomeric excesses of **7** and **8** were determined by HPLC analysis after conversion to **1** (DAICEL CHIRALPAK AS, hexane:2-propanol, 9:1). Nonconjugated diene **7** was also converted to **1** via dienone **iii** in two steps (CrO_3–3,5-dimethylpyrazole, CH_2Cl_2, −78 °C, 43% conversion yield; H_2, cat. $RhCl(PPh_3)_3$, 79% yield). The enantiomeric excess of **7** was also confirmed by HPLC analysis of **iii** (DAICEL CHIRALCEL OJ, hexane:2-propanol, 9:1), and the ee of **iii** was identical with that of **1**.



(10) Reaction using achiral diphenylphosphinopropane or triphenylphosphine as a ligand was quite slow (ca. 50% yield of the starting material was recovered after 72 h at 80 °C), and no cyclized product was isolated.

(11) Starting material **5** (3%) and its olefin-isomerized product **iv** (4%) were also recovered, and formation of some highly polar materials was observed. These polar byproducts may be formed by thermal decomposition of **5** and/or the cyclized products. It is unlikely that a significant amount of the 5-*exo*-product **10** was formed, and only this compound was selectively decomposed to the highly polar materials; however, there might be a possibility that a small amount of **10** was formed and decomposed under the reaction conditions.



(12) Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823.

(13) Conjugated diene **8** could be formed by olefin isomerization through the hydridopalladium intermediate as shown below.