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Asymmetric Multipoint Control by Palladium-catalyzed Diastereoselective Tandem Carbon-Carbon Bond Formation

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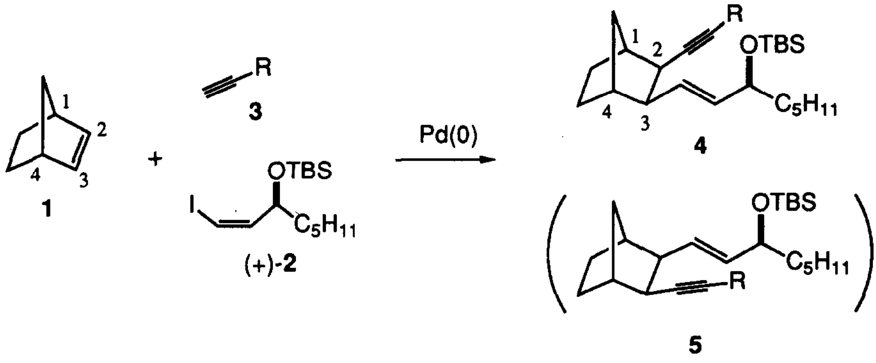
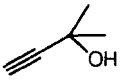
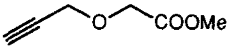
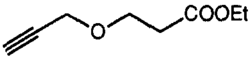
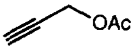
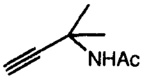
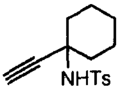
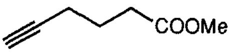
Abstract: *Palladium-catalyzed diastereo-differentiative tandem connection of cis-alkenyl iodide, cyclic fragment, and terminal acetylene was executed. The discrimination of the diastereotopic face and olefinic carbons of norbornene was achieved with accompanying isomerization of the cis-geometry of the olefin to trans in good yields.*

When a bifunctional molecule has an internal mirror, the two halves are enantiotopic. Differentiation of the each side of the plane is a current topic of a number of transformations in which achiral bifunctional compounds are converted into chiral products.[1] Our previous investigations[2] suggest that diastereodifferentiative tandem introduction of two side chains onto norbornene (**1**) is feasible as illustrated below. As the preceding report[3] demonstrated, such a stereocontrolled bond formation leads to the creation of four chiralities by breaking the σ-symmetry of **1**. Although various nonselective assembly with **1** have been reported,[4] the previous catalytic processes require a tedious workup. We found that the envisaged tandem assembly smoothly proceeds by the employment of copper(I) iodide as a co-catalyst, known as a usual catalyst system for the coupling of acetylene and vinyl halide.[5]



The stereodefined coupling of **1**, *cis*-(+)-**2**, and various terminal acetylenes **3** has been executed and the results are collected in Table 1.[6] Interestingly, the envisioned diastereodifferentiation takes place with a satisfactory diastereoselectivity (**4**/**5** : 8/1-10/1) and the initial *cis*-geometry of **2** spontaneously isomerizes to the *trans*-olefin as expected based on the preceding result.[3] The stereoselection is again responsible for the *cis*-geometry of **2**. Thus obtained **4** equips both the proper stereochemistry and appendages of PGH analogues, which are now under intensive research.[4,7]

Table 1. Palladium-catalyzed Tandem Assembly [a]

Entry	Acetylene, 3		Yield, % (4 + 5)
1	**a**		(87)
2	**b**		(84)
3	**c**		(64)
4	**d**		(82)
5	**e**		(60)[b]
6	**f**		(57)
7	**g**		(37)
8	**h**		(44)

a) Carried out using **1** (5 mmol), (+)-**2** (0.5 mmol), **3** (0.55 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.4 mmol), CuI (0.05 mmol), Bu_4NCl (0.5 mmol), Et_2NH (0.75 mmol) in DMF (3 mL), 80 °C for 12 h. Diastereomer ratio (**4**/**5** : 8/1~10/1) was determined by ^1H NMR analysis (500 MHz). b) Stirred for 24 h.

When the acetylene **3** contains a hetero atom at the propargylic position, the three-component assembly readily occurred to give **4** in high yields (Entries 1-6), even if the alcohol is not protected (Entry 1). On the other hand, the reaction with normal chain acetylenes was sluggish and lower yields were obtained with recovering starting materials (Entries 7,8).[8] The diastereomer ratio between **4** and **5** (8/1-10/1) was constant in every attempt and the olefin always isomerized. The configuration and the sense of chirality are assigned by the analogy with the preceding reaction, since the step of the stereoselection is considered to be same.[3,9]

Consequently, a number of 2,3-disubstituted bicyclo[2,2,1]heptanes **4**, pivotal to PGH analogues, were constructed, wherein two chiralities were incorporated and two prochiralities were unmasked, and tandem formation of two carbon-carbon bonds accompanying isomerization of the olefin was accomplished. The asymmetric dissymmetrization by differentiative addition to *meso*-substrates has been demonstrated to become a highly efficient methodology with regard to the asymmetric synthesis, because an asymmetric control at multipoint has been enabled by a single catalysis, a single chirality, and a single operation.

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4. Many examples on non-selective contiguous carbon-carbon bond attachment onto norbornene with stoichiometric or catalytic Pd reagents are known. Larock, R. C.; Narayanan, K. *Tetrahedron* **1988**, *44*, 6995. Larock, R. C.; Hsu, M. H.; Narayanan, K. *Tetrahedron* **1987**, *43*, 2891. Larock, R. C.; Babu, S. *Tetrahedron* **1987**, *43*, 2013. Larock, R. C.; Narayanan, K.; Carlson, R. K.; Ward, J. A. *J. Org. Chem.* **1987**, *52*, 1364. Larock, R. C.; Takagi, K.; Burkhart, J. P.; Herschberger, S. S. *Tetrahedron* **1986**, *42*, 3759. Larock, R. C.; Leach, D. R.; Bjorge, S. M. *J. Org. Chem.* **1986**, *51*, 5221. Larock, R. C.; Herschberger, S. S.; Takagi, K.; Mitchell, M. A. *J. Org. Chem.* **1986**, *51*, 2450. Larock, R. C.; Leach, D. R. *J. Org. Chem.* **1984**, *49*, 2144.; Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1985**, *26*, 2763. Larock, R. C.; Burkhart, J. P.; Oertel, K. *Tetrahedron Lett.* **1982**, *23*, 1071. Larock, R. C.; Leach, D. R.; Bjorge, S. M. *Tetrahedron Lett.* **1982**, *23*, 715. Larock, R. C.; Takagi, K.; Herschberger, S. S.; Mitchell, M. A. *Tetrahedron Lett.* **1981**, *22*, 5231. Catellani, M.; Chiusoli, G. P.; Costa, M. *Pure & Appl. Chem.* **1990**, *62*, 623. Catellani, M.; Chiusoli, G. P.; Corcari, S. *Tetrahedron* **1989**, *45*, 5263. Robert, D.; Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1988**, *29*, 2115. Amari, E.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *285*, 389. Catellani, M.; Chiusoli, G. P.; Mari, A. *J. Organomet. Chem.* **1984**, *275*, 129. Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1983**, *250*, 509. Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *240*, 311. Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1982**, *23*, 4517. u Kosugi, M.; Tamura, H.; Sano, H.; Migita, T. *Tetrahedron* **1989**, *45*, 961. Kosugi, M.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1987**, 193.
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6. The general procedure is as follows. A mixture of $Pd(OAc)_2$ (12 mg, 0.05 mmol), PPh_3 (105 mg, 0.40 mmol), CuI (10 mg, 0.05 mmol), and Bu_4NCl (140 mg, 0.50 mmol) was dissolved in DMF (1 mL). To the above solution was added a solution of **1** (471 mg, 5.00 mmol), *cis*-(+)-**2** (90 %ee, 129 mg, 0.50 mmol), terminal acetylene **3** (0.55 mmol), and Et_2NH (0.08 mL, 0.77 mmol) in DMF (2 mL). The resulting mixture was heated at 80 °C for *ca.* 12 h. After a usual workup, the residue was treated

with H_2O_2 (30 wt%, 5 drops) in MeOH (3 mL) for 2 h at ambient temperature to remove phosphine. A usual workup followed by column chromatography afforded the desired coupling products as a diastereomeric mixture in a ratio of *ca.* 8/1-10/1. Each diastereomer could not be separated but the ratios were determined by the ^{1}H NMR spectra (500 MHz). The physical data (specific rotation, IR, ^{1}H and ^{13}C NMR, and HRMS or MS) of the products are consistent with the structure.

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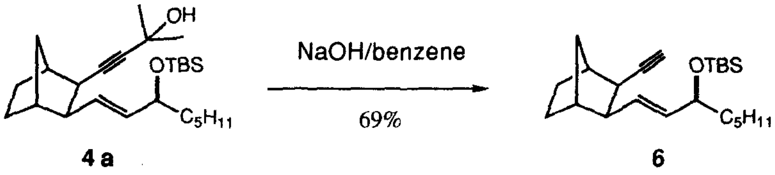
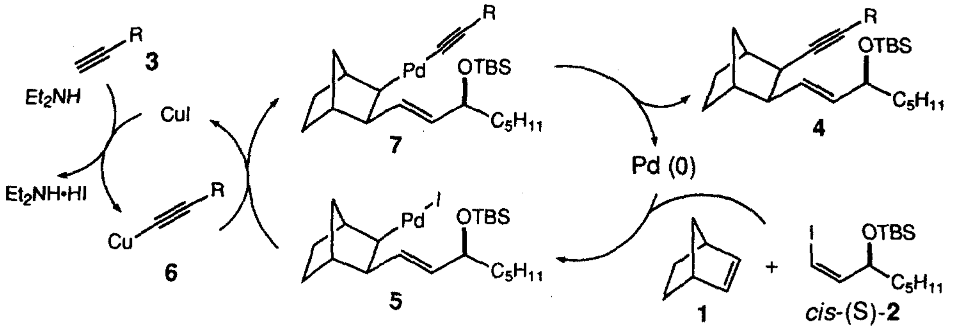
8. Treatment of the acetylene alcohol **4a** with NaOH under refluxing in benzene releases the acetylene **6** in 69% yield, from which a variety of transformations are conceivable to obtain various derivatives.[7]



9. A following path is plausible. Transmetalation of the intermediate **5**[3] with copper acetylide **6**, arising from **3**, CuI, and Et_2NH,[5] produces **7** with regeneration of CuI. The reductive elimination of **4** closes the catalytic cycle.



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