

Asymmetric Multipoint Control by Diastereo-Differentiative Assembly of Three Components with Palladium Catalyst

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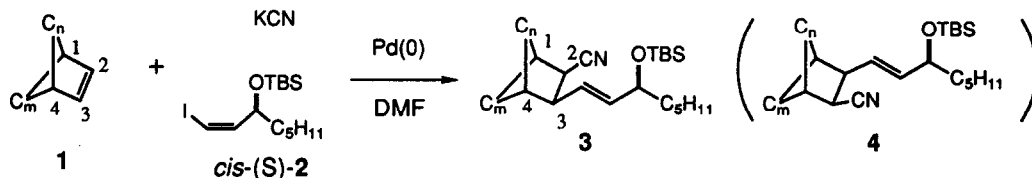
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Key Words: Diastereoselective; Enantioselective; Palladium-catalysis; Three-component assembly; Norbornene

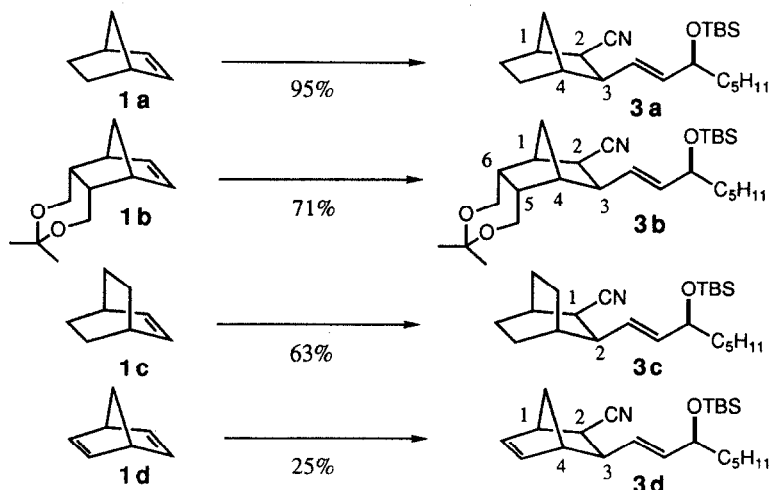
Abstract: Palladium-catalyzed diastereodifferentiative tandem connection of *cis*-alkenyl iodide, norbornene and its homologues, and cyano nucleophile accompanying isomerization of the *cis*-olefin to *trans* was executed, where the diastereotopic face and olefinic carbons of norbornene were discriminated to give 2,3-disubstituted norbornanes.

A diastereoselective addition to a σ -symmetric molecule, particularly *meso*-substrate, is of particular interest, since it involves differentiation of both enantiotopic group and diastereotopic face leading to each of four possible stereoisomers.¹ *Meso*-Substrates contain at least two prochiral centers, all of which can be converted to chiral carbons with addition of other chiralities in a single addition reaction. Our previous effort² along this concept suggests that a chiral palladium species is amenable to such a diastereofacial biasing.

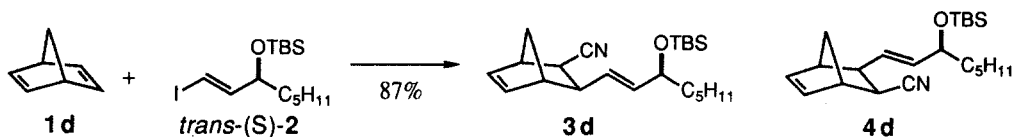
The diastereodifferentiative tandem process with symmetrical compounds **1** has been executed as illustrated below. Employment of the functionalized iodide *cis*-(*S*)-**2**³ enabled the envisioned differentiation of the each side of the symmetrical plane residing in **1**. The efficacy of this methodology is obvious, because the outgrowth of such a stereocontrol followed by the second bond formation results in the incorporation of two chiralities at C2 and C3 with unmasking the two prochiralities at C1 and C4 by asymmetric dissymmetrization.



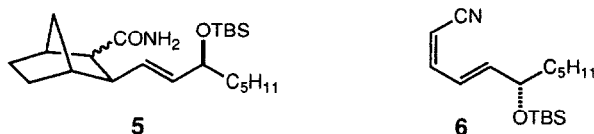
Several bicyclic compounds were examined for this diastereodifferentiative coupling process.⁴ Every substrate predominantly gave the desired cyanides **3** in preference to **4** (3/4:10:1) in good yields as follows. An additionally noteworthy feature is the spontaneous isomerization of the initial *cis*-geometry of **2** to *trans*. The complete isomerization of the olefin was always observed.



The bicyclo[2,2,1] systems **1a** and **1b** involve two and four prochiral centers, respectively. All of them have appeared as the chiral centers in the products **3a** and **3b**, and further two asymmetric centers C2 and C3 have been created by high stereocontrol. Thus, control of totally 4 and 6 chiralities has been achieved by a single chirality of **2** in one pot operation. Other bicyclo-compounds **1c** and **1d** are not meso, however, the diastereoselective addition of two appendages could be performed. Although the reaction of **1d** with *cis*-(*S*)-**2** is sluggish, the assembly with *trans*-(*S*)-**2** readily proceeded to give a 1:1 mixture of **3d** and **4d**. Thus, the diastereoselective reaction relies on the *cis*-nature of **2**.

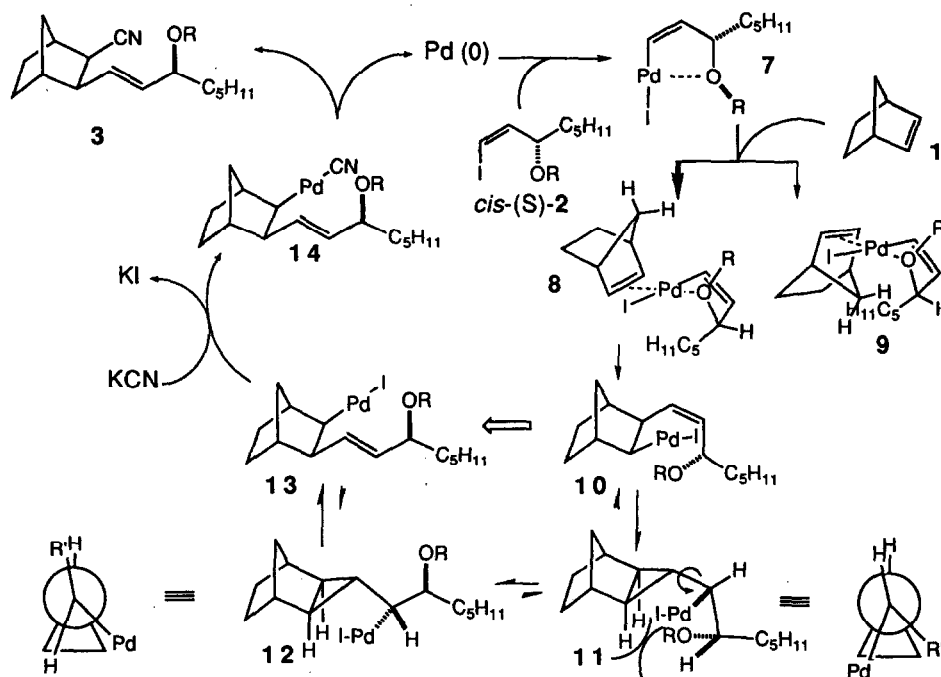


A diverse utility of **3** is conceivable. For example, the conversion of **3a** into **5** was carried out upon treatment with ruthenium complex in 67% yield,⁶ while retro Diels-Alder reaction (180 °C, 5 h) of **3d** and **4d** afforded the corresponding diene **6** in 76% yield. These substrates would entry into the prostaglandin family.⁷



The reaction course is worthy to mention, because the overall reaction involves isomerization of the olefin and **3** showed the opposite stereochemistry to what we expected based on the precedent using *meso*-cyclopentenediol.² A postulated path is illustrated as follows. Vinylpalladium **7** discriminates the diastereotopic face as well as two olefinic carbons of **1**. Previous result² indicates that the insertion of **1** would initially forms **10** through a favorable complex **8**. Since *syn*-elimination of hydridopalladium from **10** is

precluded by the configurational nature, an intramolecular insertion gives **11**,⁸ which is sterically very congested judging from the Newman projection,⁹ Single bond rotation leads to a more preferred conformer **12** and the ensuing ring opening affords the *trans*-olefin **13**.¹⁰ Hence, the isomerization of the olefin involving a bond switching between 2 and 3 positions results in the opposite configuration to the supposed one. Subsequent cyanation¹¹ of **13** followed by a reductive elimination produces the final molecule **3**.¹²



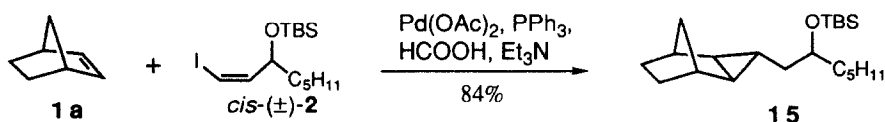
Consequently, various 2,3-disubstituted bicyclo-compounds **3** were obtained, wherein two chiralities were incorporated and plural prochiralities were unmasked by a single chirality. The tandem formation of two carbon-carbon bonds accompanying olefin isomerization were accomplished. This differentiative addition, as a tool of asymmetric induction, containing the discrimination of not only the diastereotopic face and carbon but also the prochiralities in σ -symmetric compounds has proved to be an exceedingly efficient methodology for the stereodefined synthesis, because no fewer than two new chiral centers are created by a single shot.

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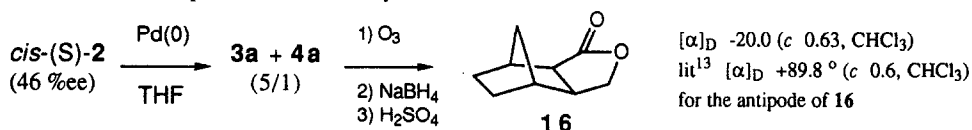
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- In the early stage of this research, the configuration of the product **3a**, obtained by the reaction in THF resulting in a lower ratio (5/1), was determined by the transformation to the known compound **16** and comparison of the specific rotation.¹³ Those of the others were inferred by analogy, since the differentiation step is common in every case.



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