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Communication

# Desymmetrisation of bicyclo[4.4.0]decadienes: A planar-chiral complex proved to be most effective in an asymmetric Heck reaction

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**Abstract**

The synthesis and desymmetrisation of bicyclo[4.4.0]decadienes is described; the enantioselective Heck reaction using JOSIPHOS as a planar-chiral complex produces a tetracyclic system with three stereogenic centers in up to 84% enantiomeric purity.


*Keywords:* Heck reaction; Desymmetrisation; JOSIPHOS

The desymmetrisation of achiral compounds is an indispensable tool for the synthesis of chiral compounds [1]. Nature uses desymmetrisation to build up complex molecules. While the ring opening of epoxides [2] and oxidation of double bonds are well established approaches in desymmetrisation strategies [3], the formation of carbon–carbon bonds by asymmetric transition-metal catalysis has not been exhaustively examined [3]. Nevertheless, this method remains viable because both enantiomers of the complex molecule are accessible. In particular, the asymmetric intramolecular Heck reaction [4], pioneered by Kagechika and Shibasaki [5a], Ashimori and Overman [5b], and used by others [4,5c,5d], would result in the formation of complex molecules.

We were intrigued by the fact that desymmetrisation of a bicyclic system gives rise to tricyclic systems. The required bicyclic system was assembled as followed. Starting from naphthalene (**1**), Birch reduction, epoxidation and ring-opening led to alcohol **4** [6]. Alkylation was performed with functionalised benzyl bromides to obtain the required starting materials **5**-X (X = I, Br) in good overall yields. The triflate **5**-OTf and nonaflate **5**-ONf were prepared starting from **5**-Br by conversion into the phenol derivate **5**-OH and subsequent conversion with trifluoromethanesulfonic acid anhydride or nonafluorobutanesulfonic fluoride, to the desired products **5**-OTf and **5**-ONf, respectively (Scheme 1).

Heck reaction with iodide **5**-I, bromide **5**-Br and triflate **5**-OTf under various conditions led to the formation of **6** with different results. Its relative stereochemistry was proven by X-ray crystallography (Fig. 1) [7]. The usual ligands for asymmetric Heck reactions, BINAP or the oxazoline **9**, led to very low enantioselection or no conversion at all (Table 1; Scheme 2).

The conversion rates could be increased by the addition of silver carbonate, but this had almost no positive effect on the enantiomeric excess. Other ligands ((*R*)-PHANEPHOS, (*S*,*S*)ET-BPE, ligand **11**) were either inactive or produced tricycles with low stereoinduction (Fig. 2).

The use of the JOSIPHOS ligand, employed primarily in hydrogenation reactions, gave a remarkably high enantiomeric excess. Recrystallisation of this product gave a virtually enantiopure material (Table 1, entry 17). Additionally, the use of bromide **5**-Br gave almost the same

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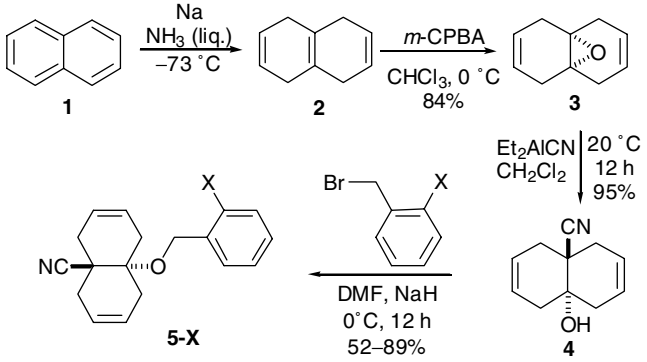
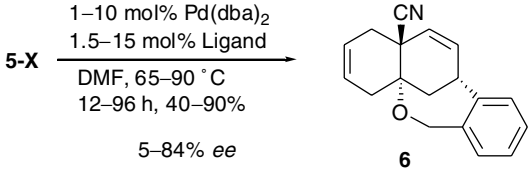



Scheme 1. Synthesis of 8a-benzyloxy-1,5,8,8a-tetrahydro-4*H*-naphthalene-4a-carbonitriles **5**-X.




Scheme 2. Asymmetric intramolecular Heck reactions.

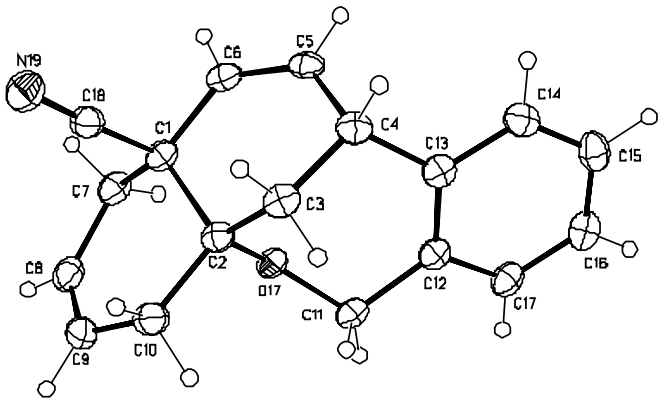



Fig. 1. X-ray structure of **6**.

enantiomeric excess but with lesser yield than the use of **5**-I (entry 12). However, in this case, the conversion of starting material was complete. The reaction gave rise to the hydrogenated product **5**-H, which in the case of the iodide was only observed with an addition of silver carbonate. The change from a bromide to a triflate or non-aflate leaving group had almost no effect on the stereoinduction of the product (entries 17 and 18), although the yields were relatively lower. Therefore, other ligands were not examined in this case. The use of silver salts, which are known to have positive effects on conversion rates and stereoinduction [4], created no significant change in the product but made workup more difficult. They are not needed in this case. Bases, apart from $Et_3N$, had no advantageous effects in this reaction.

Research is still on-going to discover the reason behind the high stereoselectivity with JOSIPHOS as a chiral complex.

In conclusion, we demonstrated the successful use of bicyclic systems in an asymmetric Heck reaction to create the product with excellent yields and good enantiomeric excess, thus forming three new chiral centers in one step. It is remarkable that the hydrogenation catalyst JOSIPHOS [8,9] is the best complex for this approach.

Table 1
Desymmetrisation of dienes **5**-X

| Entry | X | Palladium precursor | Ligand/additive (solvent) | mol% (ligand) | Time (h) | Yield (%) | e.e. |
|---|---|---|---|---|---|---|---|
| 1 | **5**-I | $Pd(dba)_2$ | (*R*)-BINAP/$Ag_2CO_3$ (DMF) | 10 | 48 | Traces | 16[a] |
| 2 | **5**-I | $Pd(dba)_2$ | (*R*)-PHANEPHOS (DMF) | 10 | 24 | 82 | 3 |
| 3 | **5**-I | $Pd(dba)_2$ | (*R*)-PHANEPHOS/$Ag_2CO_3$ (DMF) | 10 | 48 | 52 | 4 |
| 4 | **5**-I | $Pd(dba)_2$ | (*S*)-oxazoline (**9**)/$Ag_2CO_3$ (DMF) | 10 | 48 | 31 | 10 |
| 5 | **5**-I | $Pd(dba)_2$ | (*R*,*R*)-DIOP (**8**) (DMF) | 10 | 6 | 98 | 6 |
| 6 | **5**-I | $Pd(dba)_2$ | (*R*,*R*)-DIOP (THF) | 10 | 24 | 31 | 17 |
| 7 | **5**-I | $Pd(dba)_2$ | KW 247 (**11**) (DMF) [10] | 1 | 48 | 43[b] | 0 |
| 8 | **5**-I | $Pd(dba)_2$ | (*R*,*S*)-JOSIPHOS (**10**) (DMF) | 10 | 24 | 92 | 84 |
| 9 | **5**-I | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 10 | 24 | 90 | 78 |
| 10 | **5**-I | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 1 | 250 | 75 | 27 |
| 11 | **5**-I | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS/$AgBF_4$ (DMF) | 10 | 12 | 68[c] | 35 |
| 12 | **5**-Br | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 10 | 72 | 56[c] | 82 |
| 13 | **5**-Br | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 1 | 250 | 24 | 71 |
| 14 | **5**-Br | $Pd(dba)_2$ | (*R*,*R*)-DIOP (**8**) (DMF) | 10 | 72 | Quant. | 5 |
| 15 | **5**-Br | $Pd(dba)_2$ | (*R*,*R*)-NORPHOS (DMF) | 10 | 24 | 64 | 20 |
| 16 | **5**-Br | $Pd(dba)_2$ | (*S*,*R*)-$Cy_4$Josiphos (DMF) | 10 | 24 | 41 | 36 |
| 17 | **5**-OTf | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 10 | 24 | 42 | 80 (99)[d] |
| 18 | **5**-ONf | $Pd(dba)_2$ | (*S*,*R*)-JOSIPHOS (**10**) (DMF) | 10 | 16 | 40 | 81 |

[a] The enantiomeric excess was determined by GC on chiral stationary columns.
[b] Used for X-Ray analysis.
[c] Reduction to give **5**-H was also observed.
[d] After recrystallisation >99.5% e.e.

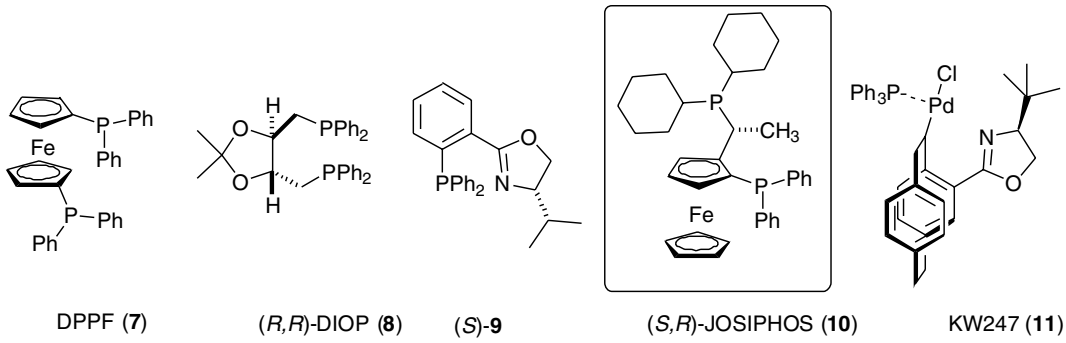



Fig. 2. Ligands and complexes examined.

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