# Asymmetric synthesis of 1-aryl and 1,3-diarylcyclopentenes by the Heck reaction of 1-sulfinylcyclopentenes with iodoarenes

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**Abstract**

The asymmetric synthesis of 1-aryl and 1,3-diarylcyclopentenes by Heck reaction of (*R*)-1-[*o*-(*N*,*N*-dimethylamino)phenylsufinyl]cyclopentene with iodoarenes is described. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Heck reaction; cyclopentenes; sulfoxides; palladium; asymmetric synthesis.

The palladium-catalyzed arylation and alkenylation of olefins with organic halides (the Heck reaction[1]) has become one of the most useful reactions for the formation of carbon–carbon bonds. Furthermore, in the last decade, the development of new reaction conditions, the use of other types of organic electrophiles, the discovery of new efficient catalysts, and the progress in enantioselective variants have greatly improved its synthetic efficiency.[2] Regarding the asymmetric Heck reaction,[3] we recently described that certain sulfoxides can be used as suitable chiral auxiliaries bonded to the alkene moiety.[4] In particular, the *o*-(*N*,*N*-dimethylamino)phenylsulfinyl group proved to be very efficient in the Heck reaction of sulfinyldihydrofurans with iodoarenes.[4a] We report here that the use of this chiral auxiliary can be extended to less reactive cyclic alkenes, such as cyclopentenes.

First, to study the viability of the Heck reaction, the racemic 1-sulfinylcyclopentene **1** was readily prepared by sulfenylation of cyclopentenyllithium with *o*-(*N*,*N*-dimethylamino)phenyl disulfide[5] and further oxidation at sulfur (MCPBA, 68% overall yield). In Scheme 1 and Table 1 are summarized the results obtained in the Heck reaction of **1** with several iodoarenes under the optimal conditions previously found for other α,β-unsaturated sulfoxides:[4] Pd(OAc)$_2$ 10 mol%, Ag$_2$CO$_3$ 200 mol%, dppp 10 mol%, DMF, 100°C. Interestingly, in spite of the well known sensitivity of the Heck reaction to steric hindrance, the rather bulky trisubstituted alkene[6] **1** reacted completely after several hours (control by TLC), affording cleanly the Heck products **2**–**4** (Table 1) without formation of double bond isomerized cyclopentene by-products[7] (76–83% yields). Concerning the diastereoselectivity of the reaction, the stereochemical behavior of **1** parallels that of sulfinyldihydrofurans.[4a] In all cases, the reaction took

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place with a significant stereocontrol, affording mixtures of **A**+**B** isomers in which the **B** isomer largely predominated.[8] Remarkably, under quite similar experimental conditions, but using longer reaction times (control by TLC), these **A**+**B** mixtures of α,β-unsaturated sulfoxides underwent a second Heck reaction to give 1,3-diarylated products **5–7** in satisfactory yields (50–80% after chromatography) and with very high stereocontrol: a single isomer was detected by ^{1}H NMR regardless the starting ratio of **A**+**B** isomers (Scheme 1 and Table 2). The (3R*,SR*) configuration of these compounds was unequivocally established in the case of **5** (in optically pure form) by X-ray difraction.[9] In agreement with these results, the 1,3-diphenylcyclopentene **5** was directly obtained from **1** (81% yield) by monitoring the progress of the Heck reaction by TLC until the complete disappearance of the intermediate phenylcyclopentenes **2**.



Structure of (3R,SR)-**5**
In the crystal[9]
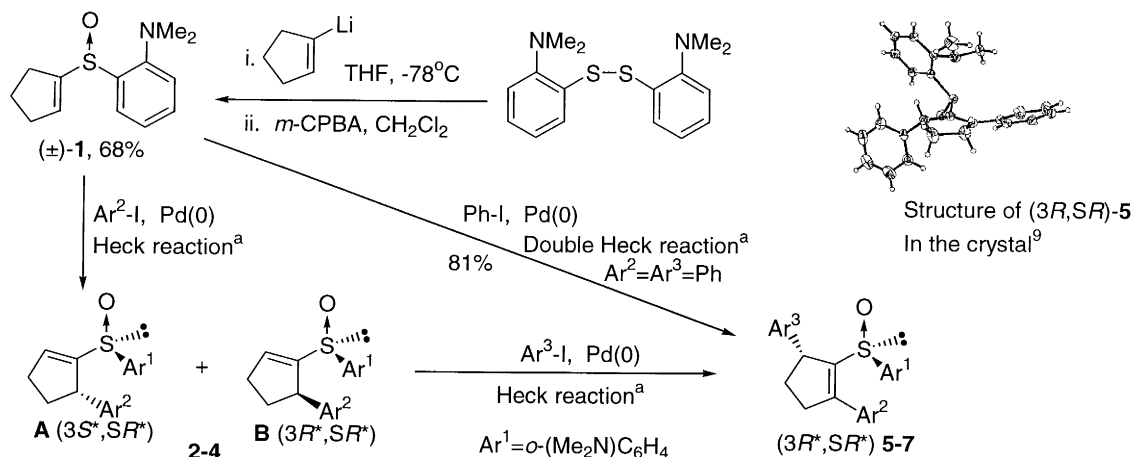
[a] Reaction conditions: Ar²-I 300 mol%, Pd(OAc)₂ 10 mol%, Ag₂CO₃ 200 mol%, dppp 10 mol%, DMF, 100°C, (control by TLC).

Scheme 1.

Table 1
First Heck reaction

| Ar² | Product | A:B[a] | Yield (%)[b] |
|---|---|---|---|
| Ph | **2** | 8:92 | 76 |
| p-(MeO)C₆H₄ | **3** | 25:75 | 77 |
| p-(NO₂)C₆H₄ | **4** | 12:83 | 83 |

[a] Determined by ^{1}H-NMR on the crude mixtures.
[b] In pure **A**+**B** mixture.

Table 2
Second Heck reaction

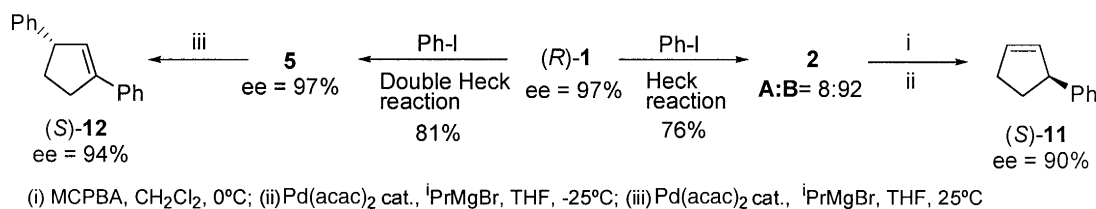| Ar² | Ar³ | Product | Yield (%)[a] |
|---|---|---|---|
| Ph | Ph | **5** | 75 |
| Ph | p-(MeO)C₆H₄ | **6** | 80 |
| p-(NO₂)C₆H₄ | Ph | **7** | 50 |

[a] In pure product.

Next, in order to apply these diastereoselective Heck reactions in asymmetric synthesis, the sulfinyl-cyclopentene **1** had to be prepared in enantiomerically pure form. Unlike the widely applied synthesis of enantiopure p-tolylsulfoxides by reaction of carbon nucleophiles with menthyl p-tolylsulfinate, the preparation of other types of substituted sulfoxides is frequently much complicated.[10] Among the

methods displaying some structural flexibility, we focused our attention on Kagan's procedure based on the reaction of the enantiopure cyclic sulfite **8** with organometallic reagents.[11] The reaction of commercially available **8** with o-(N,N-dimethylamino)phenyllithium (generated in situ by treatment of the corresponding iodide with n-BuLi) in diethyl ether at −78°C led to a 3:1 mixture of the sulfinates **9**:**10**, which were readily separated by flash chromatography (61 and 21% yields, respectively). The further reaction of **9** with the cyclopentenyl organometallic reagent furnished in good yields the required sulfoxide (R)-**1**.[12] However, it is important to note that while this second substitution at sulfur occurred with a little racemization when cyclopentenyllithium was used as nucleophile (ee=88%, HPLC, Chiralcel OD column), (R)-**1** was obtained in very high optical purity by reaction with the corresponding Grignard reagent (ee=97%) (Scheme 2).



| M | T (°C) | Yield (%)[a] | e e (%)[b] |
|---|---|---|---|
| Li | -78°C | 79 | 88 |
| MgBr | 25°C | 85 | 97 |

[a] In pure product. [b] Determined by HPLC (Chiralcel OD column).
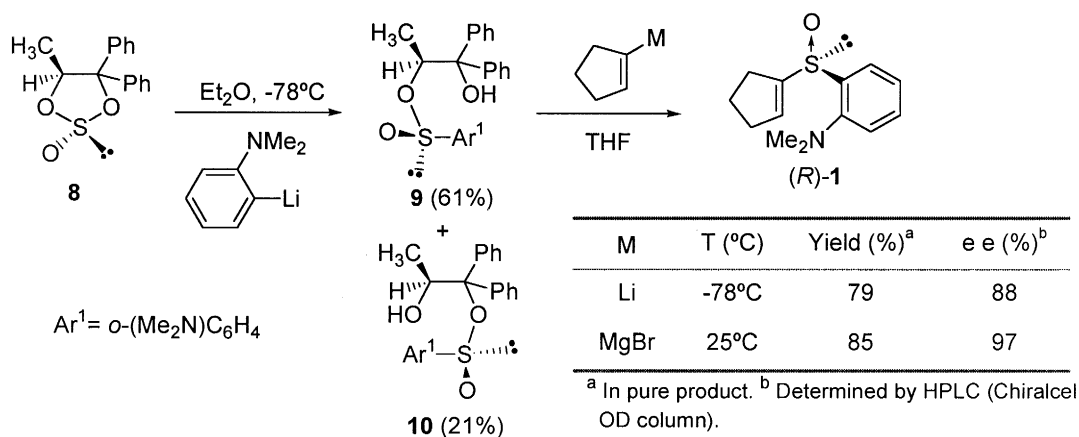
Scheme 2.

The application of (R)-**1** to the enantioselective synthesis of substituted cyclopentenes, in particular to the preparation of (S) 3-phenylcyclopentene **11**[7a] and (S) 1,3-diphenylcyclopentene **12**, is shown in Scheme 3. As indicated before, the Heck reaction of (R)-**1** with phenyl iodide can be directed either to the preparation of the 3-phenylcyclopentenes **2** (**A**+**B** isomers) or to the 1,3-diphenylcyclopentane **5**, both in high optical purity as it was confirmed in the case of (3R,SR)-**5**[12] (ee=97%, HPLC, Chiralcel OD column), which proved otherwise that sulfoxide (R)-**1** is configurationally stable under the experimental conditions of the Heck reaction. Finally, we found that an appropriate method for the cleavage of the chiral auxiliary was the palladium catalyzed reductive desulfurization [Pd(acac)$_2$ 5 mol%, $^i$PrMgBr 300 mol%, THF][13] of either the sulfoxide **5** or the sulfones derived from **2**. Thus, the **A**+**B** mixture of isomers **2** was transformed into (S)-**11**[12] (55% yield, ee=90%, GC Cyclosilb column), while (3R,SR)-**5** afforded (S)-**12**[12] (77%, ee=94%, HPLC, Chiralpak AS column).



(i) MCPBA, CH$_2$Cl$_2$, 0°C; (ii) Pd(acac)$_2$ cat., $^i$PrMgBr, THF, -25°C; (iii) Pd(acac)$_2$ cat., $^i$PrMgBr, THF, 25°C

Scheme 3.

In summary, the results shown here indicate that the Heck reactions of the sulfinylcyclopentene (R)-**1**

with iodoarenes occur with a synthetically useful stereoselectivity. 3-Arylated or 1,3-diarylated cyclopentenes can be selectively prepared in high optical purity after Heck reaction and further desulfinylation.

## Acknowledgements

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8. The chemical shifts differences of the protons contiguous to the sulfur atom ($H_1$ and $H_3$) in both **A** and **B** isomers constitute an excellent criteria for its configurational assignment (Ref. 4). Thus, due to the highly deshielding effect induced by the sulfinylic oxygen on the hydrogens in 1,3-parallel relationship, $H_1$ appears significantly more deshielded in isomers **A** than in isomers **B**, whereas the opposite was observed for $H_3$ (figures below). On the other hand, this stereochemical assignment was confirmed by chemical correlation of optically pure **2B** (3*R*,S*R* configuration) into (*S*) 3-phenylcyclopentene (Scheme 3). The high reactivity and stereoselectivity of the tribustituted alkenes **1–4** in Heck reactions could be attributed to a intramolecular like process facilitated by the previous coordination of the dimethylamino group to the palladium cationic species prior to the insertion step (see graphic for (*R*)–**1** and Ref. 4a). For the participation of Pd–N coordinated complexes in the Heck reaction of amino olefins, see: Larhed, M.; Andersson, C.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285 (and references cited therein).
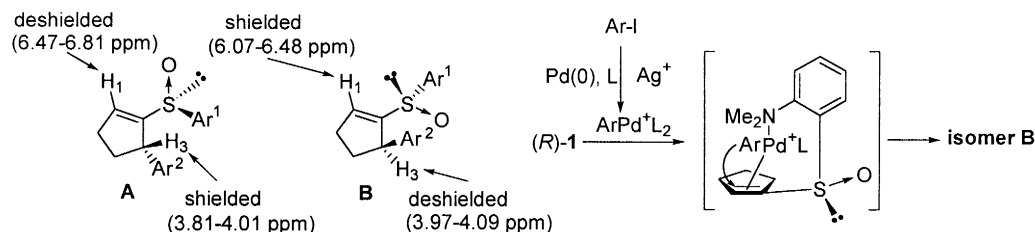
9. X-Ray data of (3$R$,S$R$)-**5** ($C_{25}H_{35}NOS$): monoclinic, space group P2$_1$, $a$=8.431 (2), $b$=14.141 (3), $c$=8.867 (2) Å, $V$=1033 Å$^3$, $Z$=2, $M_{calcd}$=387.52, $\rho_{calcd}$=1.245 Mg/m$^3$. Crystals were obtained from dichloromethane/$n$-hexane, crystal dimensions 0.17×0.25×0.25 mm. $\theta$ max=57.14°, Cu$_{k\alpha}$ radiation ($\lambda$=1.54178 Å). The scan mode was Omega. T=296 K. Reflections collected 1972, independent reflections 1595 (R$_{int}$=0.0279). Empirical absorption correction. The structure was solved with program SHELXTL, version 5.1, Bruker AXS. Refinement method full-matrix least-squares on F$^2$. Automatic treatment of H atoms. Parameters refined: 254. Final $R$ indices [I>2$\sigma$($I$)]: $R$1=0.0327, $wR$2=0.1052. $R$ indices (all data): $R$1=0.0329, $wR$2=0.1056. Residual electron density: 0.275 and –0.185 e Å$^{-3}$.

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