Asymmetric Heck Reaction of (R) 1-tert-Butylsulfinylcyclopentene with Arenediazonium Salts

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Abstract: The asymmetric Heck reaction of the readily available (*R*) 1-*tert*-butylsulfinyl-1-cyclopentene with a variety of *para*- and *meta*- substituted arenediazonium tetrafluoroborates is described. In the presence of Ag_2CO_3 as base, in CH₃CN at rt, the reactions occur in good yields (72-79%) with high diastereoselectivities (de = 82-92%) to afford (3*S*, *SR*)-3-aryl-2-*tert*-butylsulfinyl-1-cyclopentenes as the major adducts. In contrast, poor results were obtained from *ortho*-substituted arenediazonium salts.

Key words: Heck reaction, asymmetric synthesis, sulfoxides, diazoniums salts, chiral cyclopentenes

The impressive development achieved over the last two decades in the palladium-catalyzed arylation and alkenylation of olefins (the Heck reaction) demonstrates the versatility of such reactions in organic synthesis.¹ However, efficient enantioselective variants of this process (asymmetric Heck reactions) have only been developed during the last decade, mainly using enantiopure phosphane ligands as source of chiral induction.² Motivated by our recent results on the use of substituted aryl sulfoxides as chiral auxiliaries in the asymmetric Heck reactions of 4arylsulfinyl-2,3-dihydrofurans with iodoarenes,³ we envisaged that the use of sterically more demanding sulfoxides, such as the *tert*-butylsulfinyl group, could afford even higher diastereoselectivities.⁴

To test this hypothesis, (R) 1-tert-butylsulfinyl-1-cyclopentene (1) was readily prepared in 67% yield with high optical purity (ee = 96% by HPLC, Chiralpak AS) by sulfinylation of cyclopentenyllithium (generated in situ from 1-bromocyclopentene and t-BuLi in THF at -78°C) with (*R*) *tert*-butyl *tert*-butanethiosulfinate⁵ (ee = 97% by HPLC, Chiralpak AS). Disappointingly, the reaction of 1 with aryl iodides under the optimum conditions previously found for the Heck reactions of 4-arylsulfinyl-2,3dihydrofurans³ [Pd(OAc)₂, Ag₂CO₃, dppp, DMF, 100°C] gave a complex mixture of products, due in part to the thermal instability of the alkyl sulfoxides. On the other hand, at lower temperatures (60°C) a very sluggish reaction was observed even after several days.⁶ Taking into account the reluctance of the hindered substituted cyclopentene 1 to undergo Heck reactions with iodoarenes, we turned towards the use of the more reactive arenediazonium salts.7

The results obtained for palladium catalyzed $[Pd(OAc)_2]$ reaction of **1** with *p*-methoxyphenyldiazonium tetrafluoroborate (2.0 equiv) under different experimental conditions are shown in Table 1.
 Table 1 Reaction of 1 with p-methoxyphenyldiazonium tetrafluoroborate under various conditions.

1 ee = 96%	MeO- <u></u> -N ₂ ⁺ O (2.0 equiv) Pd(OAc) ₂ 10 mc Base, Solven rt, 24 h	BF4 1 2 1 %	t-Bu 3 0 0 0 0 0 0 0 0 0 0 0 0 0	^{t-Bu} S O OMe 2B S, S <i>R</i>)
Entry	Base (2.0 equiv)	Solvent	Conversion (%) ^a	2A : 2B ratio ^a
1	-	MeOH	-	-
2	-	CH ₃ CN	11	-
3	NaOAc	CH ₃ CN	27	-
4	K ₂ CO ₃	CH ₃ CN	-	-
5	AgBF ₄	CH ₃ CN	23	20 : 80
6	Tl(OAc) ₃	CH ₃ CN	23	22 : 78
7	Ag ₂ CO ₃	CH ₃ CN	>98	9:91
8	Ag ₂ CO ₃	DMF	>98	37 : 63
9	Ag ₂ CO ₃	DMSO	27	48 : 52

^a Determined by ¹H NMR on the crude mixtures

Despite the fact that the Heck reactions of arenediazonium salts with unhindered alkenes usually occur rapidly in alcoholic solvents in the absence of added bases,⁷ no reaction was observed after treatment of 1 with pmethoxyphenyldiazonium tetrafluoroborate in the presence of 10 mol% Pd(OAc)₂ in methanol at rt for 24 h (entry 1), whereas only a sluggish reaction was detected in acetonitrile (entry 2). The use of different bases, such as NaOAc, K₂CO₃, AgBF₄ and Tl(OAc)₃ gave no reaction at all or very low conversions (entries 3-6). Most gratifying, using Ag_2CO_3 (2.0 equiv.) as base⁸ and CH_3CN as solvent (entry 7), a clean and complete reaction took place, leading to the Heck adducts 2 in good yield (78%) and in a highly stereoselective manner (2A:2B = 9:91, entry 7). Further studies showed the solvent dependence of this reaction with regard to both the stereoselectivity (2A:2B = 37:63 in DMF, entry 8) and the reactivity (27%)conversion in DMSO, entry 9) of the process.⁹

The scope of this reaction was studied with a wide array of electronically and structurally diverse arenediazonium salts under the optimum conditions¹⁰ $[Pd(OAc)_2 (20)]$ mol%),¹¹ Ag₂CO₃ (2.0 equiv.), CH₃CN, rt]. As described in Table 2, the Heck reaction occurred cleanly using phenyldiazonium tetrafluoroborate (entry 2) or the para-substituted arenediazonium salts bearing either electrondonating (entries 1 and 3) or weakly electron-withdrawing functional groups (entry 4). In all these cases we observed complete disappearance of 1 (conversion >98% after 8-10h) and the formation of the Heck adducts as the main products (72-79% yields after chromatographic purification) devoid of any double bond isomerized cyclopentene byproducts.¹² However, the most interesting result concerns the remarkable stereoselectivity of the process, which affords stereoisomer **B** as the major adduct¹³ (**A:B**) ratio ranging from 9:91 to 4:96).

Table 2 Heck reactions of 1 with arenediazonium tetrafluoroborates.^a



5	$p-NO_2C_6H_4$	24	18	6	-	-
6	m-MeC ₆ H ₄	24	64	7	7 : 93	54 (73) ^e
7	o-MeC ₆ H ₄	24	16	8	-	-
8	o-ClC ₆ H ₄	24	<2	9	-	-

equiv), CH₃CN, rt, vigorous stirring. ^b With regard to 1. Determined by ¹H NMR on the crude mixtures. ^c Determined by ¹H NMR. ^d In pure adducts after flash chromatography. ^e Conversion yield.

The stereochemical assignments of **A** and **B** isomers were first established by ¹H NMR¹⁴ and later confirmed by conversion of **3B** (ee = 96% by HPLC, Chiralcel OD) into the known (*R*) 3-phenylcyclopentene¹⁵ by a two-step reductive cleavage of the sulfinylated chiral auxiliary¹⁶ (Scheme 1). Thus, the oxidation of **3B** with MCPBA (1 equiv, CH₂Cl₂, 0°C) afforded quantitatively the vinyl sulfone **10**, which was reductively desulfonylated by treatment with excess of *i*-PrMgBr in the presence of a catalytic amount of Pd(acac)₂¹⁷ (5 mol%) to give cleanly the (*R*) 3-phenylcyclopentene (**11**) in 53% overall yield¹⁸ and in high optical purity [[α]_D = +194 (*c* 1, CHCl₃), ee = 96%; [α]_D^{Lit. ref 15} = +184 (*c* 1, CHCl₃), ee = 91%].



This high π -facial stereoselectivity could be rationalized on steric grounds invoking that the aryl insertion step would take place from the least hindered face of substrate **1**, that in the face opposite to the bulky *tert*-butyl group, in its most stable *s*-cis conformation¹⁹ (shown in Table 2).

However, very low conversions were observed when *para*-nitrophenyldiazonium tetrafluoroborate²⁰ (entry 5) or *ortho*-substituted arenediazonium salts (entries 7 and 8) were used. In these cases the Heck adducts were detected as minor products (yields $\leq 20\%$) due to the formation of complex mixtures of aromatic compounds, likely as a result of the competitive coupling reaction of arenediazonium salts or other palladium catalyzed side reactions. An intermediate behaviour was observed for the *meta*-tolyl-diazonium tetrafluoroborate (entry 6), which led to the corresponding Heck adducts **7** (**7A:7B** = 7:93) in moderate yield (54%) because of the incomplete consumption of **1** (64% conversion).

In summary, the results shown here indicate the usefulness of the *t*-butylsulfinyl group as a novel chiral auxiliary in asymmetric Heck reactions when arenediazonium salts are used as arylating reagents. Good yields (72-79%) and high diastereoselectivities (de = 82-92%) were obtained in the Heck reactions of 1-sulfinylcyclopentane **1** with a variety of arenediazonium tetrafluoroborates. The extension of this procedure to other cyclic alkenes is in progress in our laboratory.

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References and Notes

- Recent reviews on the Heck reaction: a) Gibson, S. E.; Middleton, R. J. Contemp. Org. Synth., 1996, 3, 447. b) Cabri, W.; Candiani, I. Acc. Chem. Res. 1995, 28, 2. c) de Meijere, A.; Meyer, F. E. Angew. Chem. Int. Ed. Engl. 1994, 36, 2379. d) Bräse, S.; de Meijere, A. In Metal-catalyzed Crosscoupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3.
- (2) For a review on the asymmetric Heck reaction, see: Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* 1997, *53*, 7371. For some recent references, see: a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* 1998, *120*, 6477. b) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *Synthesis* 1998, 581. c) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* 1997, 1338. c) Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. *Tetrahedron Lett.* 1997, *38*, 4571. d) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* 1997, *119*, 6315.

- (3) Díaz Buezo, N.; Alonso, I.; Carretero, J. C. J. Am. Chem. Soc. 1998, 120, 7129.
- (4) For some recent results on the use of the *tert*-butylsulfinyl group as a chiral auxiliary in other reactions, see: a) Cogan D. A.; Ellman, J. A. J. Am. Chem. Soc. 1999, 121, 268. b) Tang, T. P.; Ellman, J. A. J. Org. Chem. 1999, 64, 12. c) Adrio, J.; Carretero, J. C. J. Am. Chem. Soc. 1999, 121, 7411.
- (5) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. J. Am. Chem. Soc. 1998, 120, 8011.
- (6) Only 35% conversion was observed in the reaction of 1 with *p*-methoxyiodobenzene [Pd(OAc)₂ 10 mol%, dppp 10 mol%, Ag₂CO₃ (2 equiv)] in acetonitrile at 60°C for 72h. Furthermore, the stereoselectivity was significantly lower than from *p*-methoxybenzenediazonium tetrafluoroborate (2A:2B = 17:83 instead of 9:91).
- (7) For recent references on aryldiazonium salts in Heck reactions, see: a) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083. b) Sengupta, S.; Sadhukhan, S. K. *Tetrahedron Lett.* **1998**, *39*, 715. c) Sengupta, S.; Bhattacharyya, Sadhukhan, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 275. d) Sengupta, S.; Sadhukhan, S. K.; Bhattacharyya, S. *Tetrahedron* **1997**, *53*, 2213.
- (8) To the best of our knowledge the use of Ag₂CO₃ as additive in the Heck reaction of arenediazonium salts had not been described previously.
- (9) We also found that the addition of a catalytic amount of phosphane ligands (PPh₃ or dppp) had a detrimental effect on the reactivity.
 General procedure: In a one-necked round bottom flask were

sequentially added the sulfinylcyclopentene **1** (172 mg, 1 mmol), *p*-methoxyphenyldiazonium tetrafluoroborate (445 mg, 2 mmol), Ag₂CO₃ (552 mg, 2 mmol), Pd(OAc)₂ (45 mg, 0.2 mmol) and dry acetonitrile (2 mL). The reaction was degassed and stirred vigorously at rt under argon. The reaction was followed by TLC until disappearance of **1** (8-10 h). Then, the mixture was diluted with ether (12 mL), filtered and washed with water. The organic layer was dried (MgSO₄) and evaporated to give the crude Heck adducts **2A**+**2B** (9:91 ratio), which were purified by flash chromatography (2:1 ethyl acetate: CH₂Cl₂ as eluent, 78% yield).

2B. $[\alpha]_{D} = +32.4$ (c 0.46, CHCl₃). Rf = 0.35 (2:1 ethyl acetate: CH₂Cl₂). ¹H NMR (200 MHz, C₆D₆): δ = 7.16 (AA'BB', 2H), 6.83 (AA'BB', 2H), 6.09 (br s, 1H), 4.12 (br s, 1H), 3.37 (s, 3H), 2.29-2.41 (m, 1H), 1.98-2.19 (m, 2H), 1.73-1.81 (m, 1H), 1.03 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ = 158.0, 147.6, 139.0, 135.5, 127.9, 113.7, 56.0, 55.0, 50.7, 34.5, 31.7, 23.1. Anal. Calcd. for C₁₆H₂₂O₂S: C 69.03; H 7.96; S 11.52. Found: C 69.02; H 7.65; S 11.97. **2A**. Rf = 0.29 (2:1 ethyl acetate: CH₂Cl₂). ¹H NMR (200

MHz, C_6D_6), significant signals: $\delta = 6.09$ (br s, 1H), 4.11 (br s, 1H), 1.08 (s, 9H).

- (11) Incomplete conversions were observed in the presence of 10 mol% Pd(OAc)₂ for the case of the diazonium salts of entries 3 and 4 of Table 2.
- (12) For examples of Heck reactions of cyclopentene, see: a) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* 1988, 29, 905.
 b) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.*

1989, *30*, 2603. c) Prashad, M.; Tomesch, J. C.; Wareing, J. R.; Smith, H. C.; Cheon, S. H. *Tetrahedron Lett.* **1989**, *30*, 2877. d) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31

- (13) We confirmed that, as expected, substrate 1 (ee = 96%, HPLC, chiralpak AS) did not suffer racemization at sulfur under these experimental Heck reactions, as it was proved by the preservation of the same high optical purity in the adduct 3B (ee = 96% by HPLC, Chiralcel OD).
- (14) As in the case of Heck adducts of sulfinylated dihydrofuran (reference 3), 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. Thus, H_1 appears significantly more deshielded in isomers **A** than in isomers **B**, whereas the opposite was observed for H_3 . These effects can be explained as shown in the figure below on the basis of the highly deshielding effect induced by the sulfinylic oxygen on the hydrogens in 1,3-parallel relationship in the presumed most stable conformations of isomers **A** and **B** (for NMR effects of the sulfinyl group, see: Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379).



 $\begin{array}{l} \Delta\delta_1=\delta_1 \textbf{A} \mbox{-} \delta_1 \textbf{B}=+\ [0.3\mbox{-} 0.4] \ ppm; \ \Delta\delta_3=\delta_3 \textbf{A} \mbox{-} \delta_3 \textbf{B}=[0.3\mbox{-} 0.5] \\ ppm \ (values \ in \ CDCl_3) \end{array}$

- (15) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. Synthesis 1997, 1338.
- (16) All attempts to remove the *tert*-butylsulfinyl group by reaction with different desulfinylating agents were unsuccessful, due to the competitive reduction to the thioether (activated zinc, NH_4Cl), overreduction to cyclopentanes (Raney Ni, EtOH) or lack of reaction [SmI₂/THF/MeOH or Ni(OAc)₂/NaH/*t*-AmOH].
- (17) Fabre, J. L.; Julia, M. Tetrahedron Lett. 1983, 4311.
- (18) This moderate yield was mainly due to the high volatility of cyclopentene **11**.
- (19) Recent ab initio calculations performed on different substituted α,β–unsaturated sulfoxides indicate that the *s*-cis conformation is significantly more stable than any other (Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952).
- (20) For a similar result in the Heck reactions of nitro-substituted diazonium compounds, see: Sengupta, S.; Bhattacharya, S. J. *Chem. Soc. Perkin Trans. 1* **1993**, 1943.

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