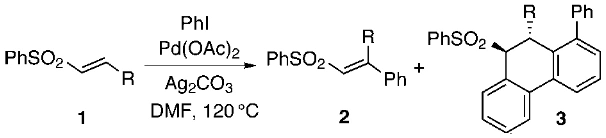
Unusual Palladium-Catalyzed Cascade Arylation of α,β-Unsaturated Phenyl Sulfones under Heck Reaction Conditions**

Pablo Mauleón, Inés Alonso, and Juan C. Carretero*

Over the last two decades the Heck reaction has emerged as one of the most versatile tools for the synthesis of carbon-substituted alkenes.[1] The mechanism of this reaction is generally accepted to proceed through an oxidative addition/*syn*-carbopalladation/*syn*-β-hydrogen elimination sequence. The Heck reaction is also the origin of a fascinating variety of cascade reactions in which the key common feature is the formation, after the carbopalladation step, of a σ-alkylpalladium(II) intermediate lacking a suitable β-hydrogen *syn* with respect to the palladium center.[1, 2] A particularly interesting case is that in which the σ-alkylpalladium(II) complex undergoes an intramolecular C–H activation process to give a palladacycle intermediate.[3]

In our research into the use of substituted vinyl sulfones in stereoselective synthesis,[4] we envisaged that acyclic β,β'-disubstituted-α,β-unsaturated sulfones could be stereoselectively prepared by simple Heck arylation of α,β-unsaturated sulfones through the seemingly evident *syn*-carbopalladation/*syn*-β-hydrogen elimination pathway.[5] However, we describe herein that the palladium-catalyzed reaction of *trans*-α,β-unsaturated phenyl sulfones with excess iodobenzene/Ag$_2$CO$_3$ proceeds by an intermolecular four-component cascade reaction to give 1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrenes in which four C–C bonds are formed in a single step.

To test the behavior of vinyl sulfones in intermolecular Heck reactions,[6] we began by treating the model substrate **1a** (see Eq. (1), Table 1, R = *i*Pr)[7] with iodobenzene under



(1)

typical Heck reaction conditions: Pd(OAc)$_2$ (10 mol %), K$_2$CO$_3$, *N,N*-dimethylformamide (DMF), 120 °C. However, only the base-catalyzed isomerization of the vinyl sulfone to form the corresponding allyl sulfone was observed.[8] Therefore, we turned our attention to the use of Ag$_2$CO$_3$, a milder base that has proved to be very efficient in the Heck reactions of α,β-unsaturated sulfoxides.[9] The reaction of **1a** with iodobenzene (1 equiv) and Ag$_2$CO$_3$ (200 mol %) in DMF at 120 °C for 72 h gave a mixture of four compounds: the starting vinyl sulfone (32 %), the isomerized allyl sulfone (30 %), the expected Heck product **2a** (26 %), and, quite surprisingly, the dihydrophenanthrene **3a** (21 %; Eq. (1)). The yield of **3a** improved progressively in the presence of increasing amounts of iodobenzene since the formation of **3a** requires the participation of three molecules of iodobenzene. The optimal **2a**:**3a** ratio was obtained in the presence of ten equivalents of iodobenzene[10] (**2a**:**3a** 5:95, Table 1, entry 1).

Table 1. Palladium-catalyzed reaction of *trans*-α,β-unsaturated sulfones **1** with iodobenzene.

Entry[a]	Olefin	R	**2**:**3**[b]	Yield[c] [%] (**3**[d] [%])
1	**1a**	*i*Pr	**2a**:**3a** 5:95	86 (69)
2	**1b**	*n*Pent	**2b**:**3b** 12:88	82[e]
3	**1c**	Cy	**2c**:**3c** 10:90	84[e]
4	**1d**	Ph	**2d**:**3d** 3:97	82 (63)
5	**1e**	β-Naph	**2e**:**3e** 8:92	85 (61)
6[f]	**1f**	H	**2d**:**3d** 4:96	78 (60)

[a] Reaction conditions: PhI (10 equiv), Pd(OAc)$_2$ (10 mol %), Ag$_2$CO$_3$ (200 mol %), DMF, 120 °C, 3–5 days. [b] Determined by ^{1}H NMR spectroscopy of the crude mixtures. [c] Yields of mixtures of **2** and **3** after flash chromatography (compound **3** was only partially separated). [d] Yield of pure compound **3** after recrystallization. [e] Dihydrophenanthrenes **3b** and **3c** could not be crystallized. About 10–15 % of pure **3b** or **3c** was obtained after flash chromatography (toluene:*i*Pr$_2$O 100:1). [f] 250 mol % of Ag$_2$CO$_3$ was used.

In order to determine the versatility of this unprecedented Heck-type cascade process on acyclic alkenes, the arylation of several *trans*-α,β-unsaturated phenyl sulfones **1**[7] was studied (Table 1, entries 1–5).

Remarkably, the cascade product **3** predominated largely over the Heck product **2** (**2**:**3** ratio from 12:88 to 3:97, 82–86 % yields of mixtures of **2** and **3**) with both β-alkyl- (Table 1, entries 1–3) and β-aryl-substituted vinyl sulfones (Table 1, entries 4–5). Although compounds **2** and **3** could not be completely separated by standard flash chromatography because of their very similar chromatographic mobilities (R_f values), pure compounds **3** were readily obtained in most cases by further recrystallizations (61–69 % yields in pure crystalline form). The structure of the dihydrophenanthrenes **3** was first studied by NMR spectroscopy and mass spectrometry, and the *trans* configuration at C9–C10 was unambiguously proved by the X-ray structure analyses[11] of **3a** and **3d** (Figure 1).

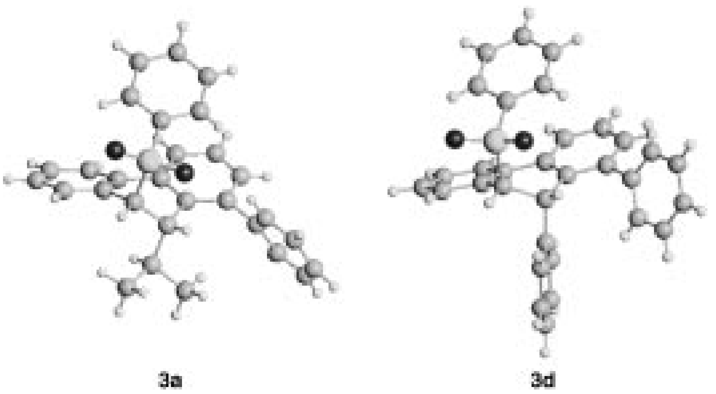

3a **3d**

Figure 1. Crystal structures of **3a** and **3d**.

---

[*] Prof. J. C. Carretero, P. Mauleón, I. Alonso
Departamento de Química Orgánica
Facultad de Ciencias, Universidad Autónoma de Madrid
28049 Madrid (Spain)
Fax: (+34) 913973966
E-mail: juancarlos.carretero@uam.es

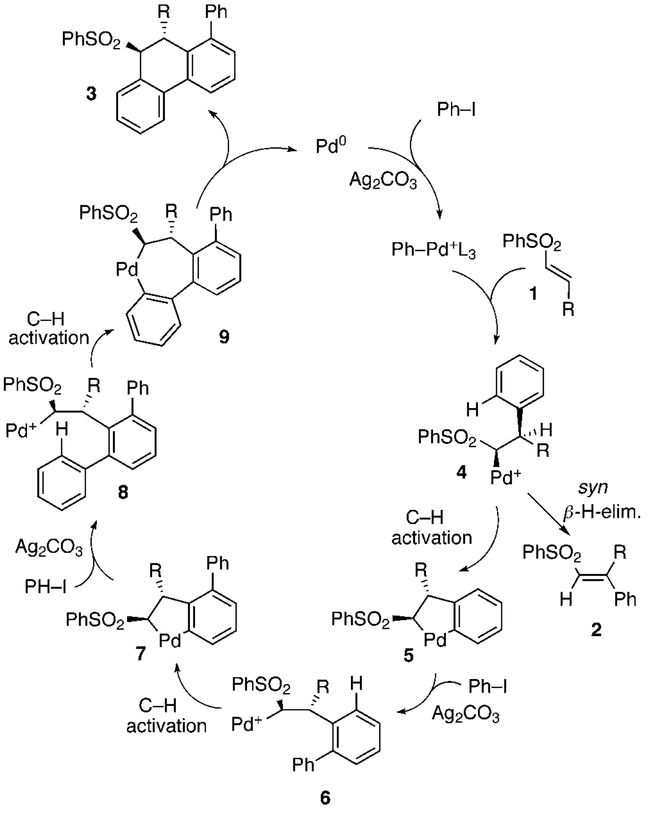
[**] Financial support for this work by the Ministerio de Educación y Cultura (DGES, project PB96-0021), Ministerio de Ciencia y Tecnología (project BQU2000-0226), and Comunidad de Madrid (project 07B/28/1999) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

We were delighted to observe that even the simple phenyl vinyl sulfone **1f** (entry 6) reacted with iodobenzene to give mainly the dihydrophenanthrene **3d**, which showed that four molecules of iodobenzene took part in an even more elaborate cascade process involving the formation of five C–C bonds. This result can be readily explained by assuming that the β-unhindered vinyl sulfone **1f** first undergoes a fast Heck reaction to give the *trans*-disubstituted olefin intermediate **1d**, which then reacts in situ with iodobenzene to afford **3d** through the four-component cascade process (entry 4). Accordingly, **1d** was isolated in 82% yield when the palladium-catalyzed reaction of **1f** was carried out in the presence of a stoichiometric amount of iodobenzene instead of a large excess (10 equiv).

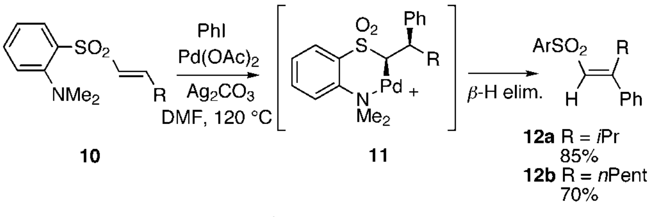
This cascade reaction is similar to the palladacycle-mediated formation of 2:1 and 3:1 coupling products described by Catellani et al.[12] and de Meijere and co-workers[13] in the palladium-catalyzed reactions of halobenzenes with norbornene, a cyclic alkene widely used in interrupted Heck reactions because the *syn*-β-hydrogen elimination step is not feasible. Taking these precedents into account, Scheme 1 outlines a simplified mechanistic hypothesis for the formation of the dihydrophenanthrenes **3**.

The first step after the oxidative addition of iodobenzene to the Pd^0 catalyst would be the regioselective *syn*-insertion of the cationic phenylpalladium species into the C–C double bond in the presence of Ag_2CO_3 to form the sulfonylalkylpalladium intermediate **4**. Unlike the usual behavior of acyclic alkenes, the complex **4** would evolve faster through a C–H activation process, to give the five-membered palladacycle[14] **5**, than by *syn* β-hydrogen elimination to yield the Heck product **2**. The intermediate **5** could react further with iodobenzene to give the σ-alkylpalladium intermediate **6**, possibly through an oxidative addition/reductive elimination pathway via a Pd^{IV} palladacycle intermediate.[15, 16] The repetition of the same mechanistic sequence at the next available *ortho* positions would lead successively to the formation of the intermediates **7** and **8**. Finally, a third C–H activation process would give the seven-membered palladacycle[17] **9**, which would afford the main product **3** after reductive elimination.



Scheme 1. Mechanistic proposal for the palladium-catalyzed cascade reaction of vinyl sulfones **1** with iodobenzene. (The ligands at the palladium center have been omitted for clarity.)

In this cascade process the intramolecular C–H activation steps seem to require the participation of highly electrophilic σ-alkylpalladium(II) species, as it is necessary to use Ag_2CO_3 as a base. Furthermore, the *trans*-α,β-unsaturated 2-(*N*,*N*-dimethylamino)phenyl sulfones **10**[7], which can potentially coordinate palladium, exclusively underwent a normal Heck reaction to give the *E*-trisubstituted olefins **12**,[18] possibly via Pd–N coordinated intermediates[19] **11** (Scheme 2).



Scheme 2. Heck reaction of α,β-unsaturated sulfones **10** with iodobenzene (Ar = *o*-(Me_2N)C_6H_4).

In conclusion, the behavior of *trans* α,β-unsaturated phenyl sulfones under arylation Heck conditions differs from that of all previously studied acyclic 1,2-disubstituted alkenes. In the presence of Ag_2CO_3 the palladium-catalyzed reactions with iodobenzene occur through an intermolecular four-component cascade process, which involves one unit of vinyl sulfone and three units of iodobenzene, rather than by a normal Heck arylation. Further synthetic transformations of the resulting 9,10-dihydrophenanthrenes **3**, as well as studies to ascertain the steric and electronic requirements of this type of cascade reaction with acyclic alkenes are in progress.

Experimental Section

3a: A mixture of *trans* 1-phenylsulfonyl-3-methyl-1-butene (**1a**; 81 mg, 0.38 mmol), silver carbonate (213 mg, 0.77 mmol, 200 mol%), Pd(OAc)$_2$ (8.7 mg, 0.038 mmol, 10 mol%), iodobenzene (0.43 mL, 3.86 mmol, 1000 mol%), and DMF (2 mL) was heated at 120°C under an argon atmosphere and stirred vigorously. After 72 h (thin-layer chromatography control), the mixture was allowed to cool to room temperature, diluted with Et_2O (20 mL), filtered through celite, and washed with water (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was analyzed by ^1H NMR spectroscopy and purified by flash chromatography (hexane/diethyl ether 10:1) to give a 5:95 mixture of **2a**:**3a** (86% yield). This mixture was recrystallized from diethyl ether to afford 10-isopropyl-1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrene (**3a**, 117 mg, 69% yield).

Received: November 15, 2000 [Z16112]

1433-7851/01/4007-1292 $ 17.50+.50/0

[1] For some recent reviews on the Heck reaction, see a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; b) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314; c) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427; d) M. Shibasaki, C. D. J. Boden, A. Kojima, *Tetrahedron* **1997**, *53*, 7371; e) S. E. Gibson, R. J. Middleton, *Contemp. Org. Synth.* **1996**, *3*, 447; f) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2; g) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.

[2] For some very recent reviews on Heck-like palladium-mediated cascade reactions, see a) G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959; b) R. Grigg, V. Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65; c) A. de Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88.

[3] For reviews on palladacycles in cascade reactions, see a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698; b) G. Dyker, *Chem. Ber.* **1997**, *130*, 1567; c) M. Catellani, G. P. Chiusoli, *Gazz. Chim. Ital.* **1993**, *123*, 1; see also ref. [2c].

[4] For a recent reference, see J. Adrio, M. Rodríguez, J. C. Carretero, *Angew. Chem.* **2000**, *112*, 3028; *Angew. Chem. Int. Ed.* **2000**, *39*, 2906.

[5] For recent references on the synthesis of trisubstituted olefins by the Heck reaction of β-substituted α,β-unsaturated esters, nitriles, aldehydes, or ketones, see a) C. Gürtler, S. L. Buchwald, *Chem. Eur. J.* **1999**, *5*, 3107; b) W. A. König, W. Stenzel, T. Schotten, *Tetrahedron Lett.* **1999**, *40*, 2101; c) M. Moreno-Mañas, R. Pleixats, A. Roglans, *Synlett* **1997**, 1157; d) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Tetrahedron* **1996**, *52*, 6983.

[6] For intramolecular Heck arylations of α,β-unsaturated sulfones, see Z. Jin, P. L. Fuchs, *Tetrahedron Lett.* **1993**, *34*, 5205.

[7] The α,β-unsaturated aryl sulfones **1** and **12** were readily prepared by Horner–Wadsworth–Emmons olefination (see, for example, G. H. Posner, D. J. Brunelle, *J. Org. Chem.* **1972**, *37*, 3547) or by condensation of the carbanion of the aryl methyl sulfone with the aldehyde, and further dehydration (MsCl, Et$_3$N, CH$_2$Cl$_2$; Ms = methanesulfonyl).

[8] Allyl sulfones tend to be thermodynamically more stable than vinyl sulfones. For vinyl/allyl isomerization in unsaturated sulfones, see, for example, N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**.

[9] N. Díaz, I. Alonso, J. C. Carretero, *J. Am. Chem. Soc.* **1998**, *120*, 7129.

[10] A significant decrease in the yield of **3a** was observed in the presence of lower amounts of iodobenzene or Ag$_2$CO$_3$. For example, the **2a**:**3a** ratio was 8:92 when five equivalents of iodobenzene (instead of 10 equiv) were used, and 31:69 in the presence of 100 mol% of Ag$_2$CO$_3$ (instead of 200 mol%).

[11] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151679 (**3a**) and -151680 (**3d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] For a recent publication, see M. Catellani, E. Motti, L. Paterlini, *J. Organomet. Chem.* **2000**, *593*, 240, and references therein. See also: a) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem.* **1997**, *109*, 142; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119; b) M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1985**, *286*, C13.

[13] a) K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere, *Tetrahedron* **1994**, *50*, 383; b) O. Reiser, M. Weber, A. de Meijere, *Angew. Chem.* **1989**, *101*, 1071; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1037; see also: c) G. Dyker, J. Körning, P. G. Jones, P. Bubenitschek, *Angew. Chem.* **1993**, *105*, 1805; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1733.

[14] For the isolation of five-membered carbon-substituted palladacycles, see, for example, a) C. Mateo, D. J. Cárdenas, C. Fernández-Rivas, A. M. Echavarren, *Chem. Eur. J.* **1996**, *2*, 1596; b) C.-H. Liu, C.-S. Li, C.-H. Cheng, *Organometallics* **1994**, *13*, 18.

[15] Organopalladium(IV) chemistry: A. J. Canty, *Acc. Chem. Res.* **1992**, *25*, 83. Isolation of a Pd^{IV} palladacycle: J. M. Brunel, M.-H. Hirlemann, A. Heumann, G. Buono, *Chem. Commun.* **2000**, 1869; see also refs. [12, 13].

[16] For a mechanistic alternative avoiding Pd^{IV} intermediates, but requiring ligand-exchange reactions between two Pd^{II} complexes, see: G. Dyker, *Chem. Ber.* **1994**, *127*, 739.

[17] For the isolation of seven-membered palladacycles, see A. S. K. Hashmi, A. R. Nass, J. W. Bats, M. Bolte, *Angew. Chem.* **1999**, *111*, 3565; *Angew. Chem. Int. Ed.* **1999**, *38*, 3370.

[18] The stereochemistry of the trisubstituted olefins **2** and **12** was established by NOESY experiments.

[19] For the Pd–N coordinated complexes proposed in the Heck reaction of nitrogen-containing vinyl ethers, see M. Larhed, C. Andersson, A. Hallberg, *Tetrahedron* **1994**, *50*, 285; see also ref. [9].

Enantioselective Hydrogen Atom Transfer Reactions: Synthesis of *N*-Acyl-α-Amino Acid Esters**

Mukund P. Sibi,* Yasutomi Asano, and
Justin B. Sausker

Enantioselective proton-transfer reactions (enolate protonations) have been investigated in detail for over a decade and even catalytic variants have been demonstrated.[1] In contrast, enantioselective hydrogen atom transfer reactions have begun to emerge only recently.[2] In principle, these reactions can be carried out in two distinct ways: 1) by H-atom transfer from a chiral reagent to a radical, or alternatively 2) by H-atom transfer from an achiral reagent to a radical complexed to a chiral source. Nanni and Curran,[3a] Metzger and co-workers,[3b,c] Roberts and co-workers,[3d] and Schiesser and co-workers[3e] have reported examples of reactions using chiral H-atom transfer reagents. On the other hand, only a few examples of H-atom transfer to radicals complexed to chiral Lewis acids have been noted in the literature.[4] We have shown that enantioselective conjugate additions proceed with high chemical efficiency and selectivity using a chiral Lewis acid derived from M^{2+} metal salts in conjunction with a bisoxazoline prepared from aminoindanol.[5] Herein we show that conjugate radical addition to *N*-acylamido acrylates **1** mediated by a chiral Lewis acid followed by an enantioselective H-atom transfer furnishes a variety of α-amino acid derivatives (**2** or **3**) with good to excellent efficiency [Eq. (1)].

Diastereoselective H-atom transfer reactions to captodative radicals derived from *N*-acylamido acrylates in both acyclic[6] and cyclic[7] systems proceed with moderate to good selectivity.[8] In contrast, enantioselective variants of these reactions have not been reported and this work constitutes the first example of such a process. We began our experiments

---

[*] Prof. M. P. Sibi, Dr. Y. Asano, J. B. Sausker
Department of Chemistry
North Dakota State University
Fargo, ND 58105-5516 (USA)
Fax: (+1)701-231-8831
E-mail: Mukund Sibi@ndsu.nodak.edu

[**] This work was supported by the National Institutes of Health (NIH-GM-54656).

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.