

Chelation-Induced Catalytic Multiple Arylation of Allylic 2-Pyridyl Sulfones

Tomás Llamas, Ramón Gómez Arrayás, Juan Carlos Carretero*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid
Cantoblanco, 28049 Madrid, Spain
Fax: (+34)-91-497-3966, e-mail: juancarlos.carretero@uam.es

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Dedicated to the memory of Dr. Juan Carlos del Amo.

Abstract: The development of a chelation-assisted, transition metal-catalyzed protocol for the sequential multiarylation of cyclic allyl sulfones is described. The metal-coordinating ability of the 2-pyridyl group on the sulfone promotes the otherwise difficult intermolecular Heck monoarylation and diarylation of trisubstituted alkenes, as well as the copper-catalyzed allylic arylation with Grignard reagents.

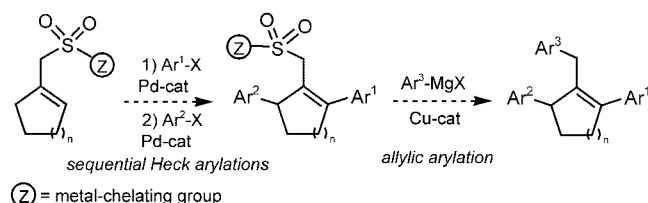
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The Heck and the allylic alkylation reactions have proved to be among the most powerful and versatile C–C bond forming tools.^[1,2] The intermolecular variant of these transformations, however, has some limitations due to its great sensitivity to the substitution pattern of the alkene scaffold, steric factors becoming prevalent over electronics. As a result, the assembly of complex and sterically congested molecules through the Heck reaction of trisubstituted alkenes has been essentially restricted to its intramolecular version.^[1,3] The use of alkenes carrying a removable coordinating group has been reported by several groups,^[4] including ours,^[5] as a successful strategy to overcome the reluctance of substituted alkenes to participate in the intermolecular Heck reaction and/or to control the stereoselectivity of the process. The association of such directing functional-

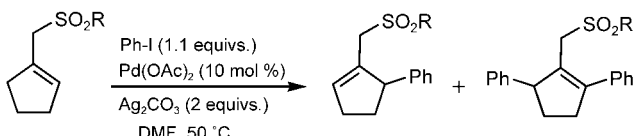
ity, typically a nitrogen-containing group, with the transition metal induces its transfer to the reactive center in an intramolecular fashion.^[6] We envisaged that allylic sulfones bearing a metal coordinating group could function as an excellent platform for the regiocontrolled assembly of structurally complex molecules through sequential Heck reactions and copper-catalyzed allylic arylations (Scheme 1). In this communication we report the crucial role of the metal coordinating 2-pyridylsulfonyl group to accomplish this goal, whereas the typical allyl phenyl sulfones proved unsuccessful.

The starting point of our research was to define an appropriate chelating functionality and to identify the optimal reaction conditions. We chose cyclopentenones **1–3** as model alkene substrates to evaluate potential coordinating groups (Table 1). Compounds **1–3** were readily obtained in good overall yield (65–94%) by condensation of cyclopentanone with the corresponding methyl sulfonyl carbanion (*n*-BuLi, THF, –78 °C), followed by dehydration of the resulting alcohols (TFAA, DMAP, Et₃N, CH₂Cl₂, room temperature) and *in situ* isomerization of the vinyl to the allyl sulfone (DBU, CH₂Cl₂, room temperature).^[7] Examination of the Heck reaction with iodobenzene under different conditions led us to find that a combination of Pd(OAc)₂ as palladium source, Ag₂CO₃ as halide abstractor and base, and DMF or CH₃CN as solvents provided the best results.^[8] Table 1 highlights the crucial role of chelation on the reactivity of substituted cyclopentenones. While the reaction of phenyl sulfone **1** and sulfonamide **2** reached about 50% conversion after 24 h, 2-pyridyl sulfone **3** underwent smooth Heck reaction to afford a 91:9 mixture of the expected product **6** and the diarylated compound **7** within just 2 h (92% conversion). This dramatic acceleration effect, together with the formation of the double-Heck product **7**, suggests a strong chelating interaction of the pyridine moiety with the arylpalladium oxidative addition complex.

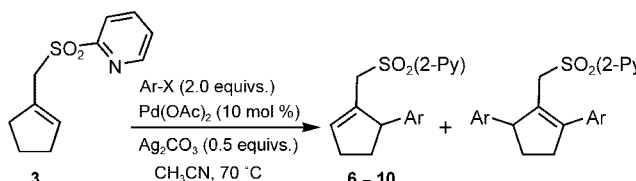
This chelation-assisted Heck protocol was next extended to a range of electronically varied iodoarenes (Table 2). Further optimization of the reaction conditions by means of reducing the amount of Ag₂CO₃ to



Scheme 1. Concept of proposed chelation-assisted multiarylation protocol.

Table 1. Screening of different sulfonyl groups for the Heck arylation.


Entry	Substrate (R)	Time [h]	Conversion [%] ^[a]	Mono-/Diarylation ^[a]
1	1 (Ph)	24	50	4 (100)/–
2	2 (NEt ₂)	24	56	5 (100)/–
3	3 (2-Py)	2	92	6 (91)/ 7 (9)

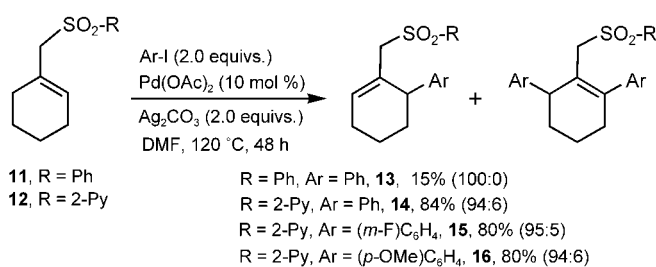
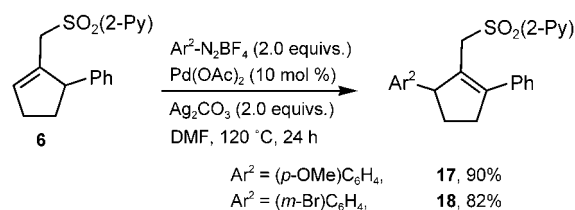
^[a] Measured by ¹H NMR [%].**Table 2.** Heck monoarylation of allylic (2-pyridyl)sulfonylcyclopentenes.


Entry	Ar-X	Yield ^[a]	Mono-/Diarylation ^[b]
1	Ph-I	6 , 92%	98/2
2	(<i>m</i> -F)C ₆ H ₄ -I	8 , 85%	96/4
3	(<i>p</i> -Me)C ₆ H ₄ -I	9 , 89%	93/7
4	(<i>p</i> -OMe)C ₆ H ₄ -I	10 , 89%	95/5
5 ^[c]	(<i>p</i> -OMe)C ₆ H ₄ -N ₂ BF ₄	–	76/24

^[a] Isolated yield after chromatography (mono-/diarylation mixtures).^[b] Measured by ¹H NMR [%].^[c] 1.1 equivalents of diazonium salt at room temperature. 7% of **3** was recovered.

0.5 equivalents led to complete conversion without an increase of the diarylation product (less than 7%). Under these conditions, a number of arylated sulfonylcyclopentenes could be obtained in good yields^[9] regardless of the electronic nature of the iodoarene used. The use of diazonium salts instead of iodoarenes produced an increased amount of the diarylation product (entry 5).

To test the efficiency of this coordinating system toward less reactive substrates, we briefly explored the Heck reaction of cyclohexene derivatives **11** and **12**. These reactions proved to require harsher reaction conditions.^[10] As shown in Scheme 2, phenyl sulfone **11** provided only a 23% conversion after 48 h (15% isolated yield), whereas the pyridyl analogue **12** reached 92% conversion under the same reaction conditions to afford a 94:6 mixture of the mono- and diarylation products, respectively (84% isolated yield). Interestingly, both the electron-deficient (*m*-fluoro)iodobenzene and the electron-rich (*p*-methoxy)iodobenzene participated ef-

**Scheme 2.** Heck monoarylation of cyclohexene derivatives.**Scheme 3.** Heck diarylation of allylic (2-pyridyl)sulfonylcyclopentenes.

ficiently in the Heck arylation reaction with substrate **12** (products **15** and **16**).

Encouraged by the observation of some diarylation during the course of our investigation, especially in the arylation of cyclopentenes with diazonium salts as reagents, we set out to develop a sequential double Heck arylation protocol. Gratifyingly, the Heck reaction of **6** with aryldiazonium salts of varied electronic nature occurred within 24 h at 120 °C, affording 2,5-diarylcyclopentenes in good yield. Disappointingly, the Heck arylation of the cyclohexene derivative **14** did not succeed to a practical extent (30% conversion after 24 h).

To fully realize the synthetic potential of these allyl (2-pyridyl)sulfones, finally we decided to investigate the copper-catalyzed allylic substitutions of such substrates with Grignard reagents.^[11,12] This process would allow the elimination of the sulfonyl group with concomitant formation of a new C–C bond. While allylic halides and allylic alcohol derivatives have been widely used as substrates for copper-catalyzed allylic substitution with non-stabilized nucleophiles,^[13] this transformation

Table 3. Cu-catalyzed substitution of allyl 2-pyridyl sulfones with Grignard reagents.

Entry	Substrate	Ar ¹	R ²	Ar ³	Yield ^[a]
1	6	Ph	H	Ph	19 , 98%
2	6	Ph	H	(<i>p</i> -OMe) ₆ H ₄	20 , 60%
3	6	Ph	H	(<i>p</i> -F) ₆ H ₄	21 , 90%
4	7	Ph	Ph	Ph	22 , 83%
5	17	(<i>p</i> -OMe) ₆ H ₄	Ph	(<i>p</i> -F) ₆ H ₄	23 , 76%
6	18	(<i>m</i> -Br) ₆ H ₄	Ph	(<i>p</i> -OMe) ₆ H ₄	24 , 55%

^[a] Isolated yield after chromatography.

has been little explored in the case of allyl sulfones,^[14] always involving typical non-coordinating phenyl or *p*-toluenesulfonyl derivatives. Allylic substitutions were initially probed on mono-Heck product **6** by addition of PhMgBr (1.5 equivs.) in the presence of a 10 mol % of a copper salt in THF at room temperature. The excellent catalyst-directing aptitude of the 2-pyridylsulfonyl group was also found to be determinant in this copper-catalyzed process.^[15] Whereas phenyl sulfone **1** gave rise to the recovery of unaltered starting material after 24 h, pyridyl sulfone **6** produced a smooth substitution reaction generating with complete selectivity the SN₂-type products **19–21** (Table 3, entries 1–3). As expected, the reaction was completely suppressed in the absence of copper source. The four copper salts examined [CuCN, CuBr·SMe₂, Cu(OAc)₂·(H₂O) and CuTC]^[16] proved to be efficient catalyst for this transformation, the highly soluble CuTC providing slightly better results.^[17] Interestingly, the sterically congested double Heck products were also suitable substrates for the arylation reaction affording the triaryl-substituted cyclopentenes **22–24** (entries 4–6), which clearly shows the efficiency of the allyl (2-pyridyl)sulfonyl moiety in sequential metal-catalyzed arylation processes.

In summary, allyl sulfones bearing a 2-pyridyl group serve as versatile scaffolds for the efficient regiocontrolled construction of highly functionalized cycloalkenes under smooth reaction conditions by means of chelation-assisted intermolecular Heck arylations and further Cu-catalyzed allylic substitution with Grignard reagents.

Experimental Section^[18]

Typical Procedure for the Heck Monoarylation: 5-Phenyl-1-[(2-pyridylsulfonyl)methyl]cyclopent-1-ene (**6**)

To a solution of allyl sulfone **3** (20 mg, 0.089 mmol), Ag₂CO₃ (12.2 mg, 0.044 mmol) and Pd(OAc)₂ (2.0 mg, 0.0089 mmol)

in CH₃CN (1 mL) was added iodobenzene (20 μL, 0.178 mmol). The mixture was stirred at 70 °C for 24 h, then allowed to reach room temperature and Et₂O (10 mL) was added. After filtration through Celite, the filtrate was evaporated and the residue was purified by flash chromatography (*n*-hexane-EtOAc, 4:1) to afford a 98:2 mixture of **6** and **7** (yield: 24.5 mg, 92%) as a solid.

Complete separation by further reverse phase silica (Merck, lichroprep RP-18, MeOH-H₂O, 4:1) afforded pure **6** as a white solid; yield: 15 mg (57%); mp 73–74 °C; ¹H NMR: δ = 8.74–8.79 (m, 1H), 8.07–8.02 (m, 1H), 7.98–7.90 (m, 1H), 7.58–7.51 (m, 1H), 7.33–7.16 (m, 3H), 7.14–7.07 (m, 2H), 5.84 (s, 1H), 4.25 (d, 1H, *J* = 14.1 Hz), 3.97 (m, 1H), 3.72 (d, 1H, *J* = 14.1 Hz), 2.58–2.23 (m, 3H), 1.97–1.78 (m, 1H); ¹³C NMR: δ = 156.8, 149.9, 143.8, 137.7, 136.5, 133.1, 128.4, 127.5, 127.1, 126.3, 122.3, 52.7, 52.1, 33.6, 31.7; MS (APCI+, 60 V): *m/z* = 300 (M⁺ + H, 100), 157 (M⁺ – PySO₂, 50), 144 (88).

Compound 7: yellow solid; mp 139–140 °C; ¹H NMR: δ = 8.43–8.38 (m, 1H), 8.00–7.95 (m, 1H), 7.90–7.82 (m, 1H), 7.45–7.38 (m, 1H), 7.35–7.15 (m, 10H), 4.57 (d, 1H, *J* = 13.9 Hz), 4.38 (m, 1H), 3.72 (d, 1H, *J* = 13.9 Hz), 2.97 (m, 2H), 2.61–2.45 (m, 1H), 2.00–1.86 (m, 1H); ¹³C NMR: δ = 157.3, 150.0, 148.1, 144.3, 137.6, 136.5, 128.7, 128.4, 127.8, 127.7, 127.5, 127.4, 127.1, 126.5, 122.3, 54.1, 51.2, 37.2, 32.7; MS (APCI+, 30 V): *m/z* = 376 (M⁺ + H, 100), 233 (M⁺ – PySO₂, 45), 144 (17).

Typical Procedure for the Cu-Catalyzed Allylic Arylation: 5-Phenyl-1-benzylcyclopent-1-ene (**19**)

To a room temperature solution of allyl sulfone **6** (20 mg, 0.066 mmol) and CuTC^[16] (1.3 mg, 0.0066 mmol) in THF (1 mL) was added a 1 M solution of phenylmagnesium bromide in THF (99 μL, 0.099 mmol). The mixture was stirred at room temperature for 24 h, it was quenched with water (several drops) and CH₂Cl₂ (10 mL) was added. After filtration through Celite, the filtrate was dried (Na₂SO₄) and concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane) to afford **19** as a colourless oil; yield: 15 mg (98%); ¹H NMR: δ = 7.64–7.58 (m, 1H), 7.49–7.42 (m, 1H), 7.39–7.13 (m, 6H), 7.10–7.04 (m, 2H), 5.50 (s, 1H), 3.64 (m, 1H), 3.30 (d, 1H, *J* = 15.3 Hz), 3.00 (d, 1H, *J* = 15.3 Hz), 2.55–2.28 (m, 3H), 1.93–1.78 (m, 1H); ¹³C NMR: δ = 145.6, 129.0, 128.7, 128.4, 128.1, 127.8, 127.2, 126.0, 125.8, 53.1, 36.1, 34.4, 31.4.

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