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Palladium-Catalyzed Heck Reaction on 1-Alkoxy-1,3-dienes: A Regioselective γ-Arylation of α,β-Unsaturated Carbonyl Compounds

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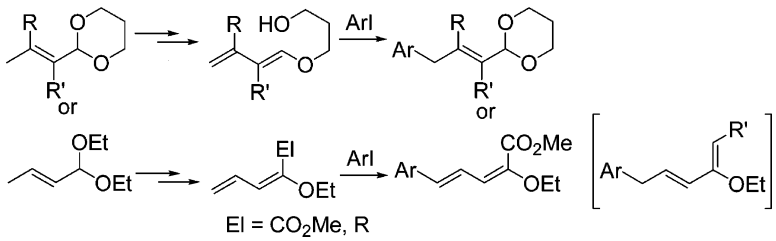
ABSTRACT



α,β-Unsaturated acetals afford, in the presence of the LIC−KOR superbase, 1-alkoxybuta-1,3-dienes. These substrates cross couple with aryl derivatives in the presence of Pd catalyst (Heck conditions) in a regio- and stereoselective mode. With dialkyl acetals, the reaction affords arylated dienes; on the other hand, in the case of 1,3-dioxane derivatives, the final outcome of the process formally corresponds to the direct γ-arylation reaction of the starting α,β-unsaturated material.

Metal-catalyzed coupling reactions are very efficient and reliable procedures for the construction of new carbon−carbon bonds.[1] In particular, the Heck reaction has been used extensively over the past three decades for the elaboration of alkenes.[2] The reaction is a straightforward way to achieve substituted alkenes, dienes, and other unsaturated structures, many of which are important intermediates for the preparation of dyes, UV screens, and drugs.[3] Although arylation of two-carbon vinyl fragments might sometimes result in scarcely regioselective reactions,[4,5] highly regioselective α-arylation and α-vinylation procedures have been reported under specific experimental conditions.[6] In particular, 100% regioselective α-functionalization of vinyl ethers can be achieved by favoring the coordination of the Pd complex to

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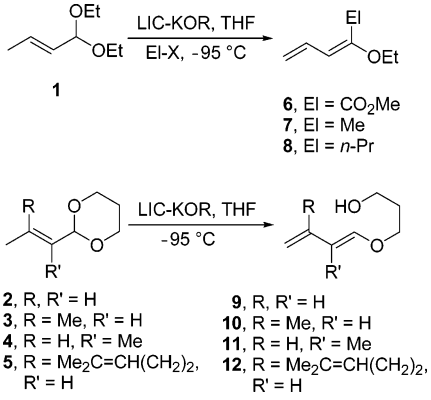
the carbon−carbon double bond via dissociation of the anion ligand. Such a mechanism can be promoted by using triflate as a leaving group or adding a sequestering agent of halide anions.[7] Otherwise, a mixture of isomers is obtained when the coordination−insertion process proceeds via dissociation of one neutral ligand. On the other hand, regioselective β-arylation of vinyl ethers have been achieved when the olefinic substrate contains groups that control the palladium-catalyzed reaction through chelation. Such a procedure has been reported as a useful access to arylethylamines or arylacetic acids of significant pharmaceutical value.[8]

Our interest in the synthesis of stereodefined substituted dienes requires the development of protocols for the preparation of key building blocks. In the present communication, we wish to report the results that we have obtained studying the arylation reaction of 1-alkoxy-1,3-butadienes obtained by conjugate elimination promoted by the LIC−KOR super base.

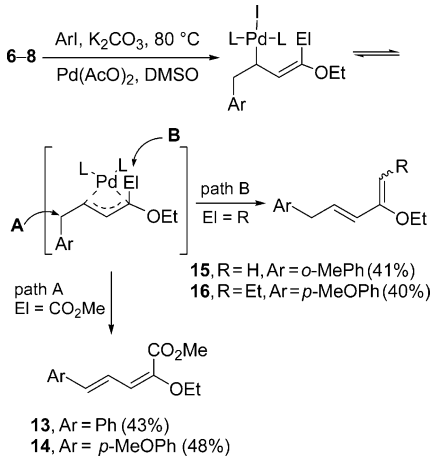
Treatment of α,β-unsaturated acetals **1**−**5** at −95 °C with Schlosser's LIC−KOR superbase (LIC, butyllithium; KOR, potassium *tert*-butoxide)[9] readily promotes a conjugate elimination reaction that gives 1-alkoxy-1,3-butadienes **6**−**12**. In particular, in the presence of an excess of base, the metalation reaction gives α-metalated 1-alkoxybuta-1,3-dienes.[10] Subsequent quenching with a suitable electrophile leads to α-functionalized unsaturated derivatives **6**−**8** (Scheme 1).

Scheme 1. LIC−KOR-Promoted Conjugate Elimination Reaction of α,β-Unsaturated Acetals **1**−**5**: Syntheses of 1-Ethoxybuta-1,3-dienes **6**−**8** and 1-(3-Hydropropoxy)buta-1,3-dienes **9**−**12**



As shown in Scheme 2, the cross-coupling reaction of diene **6** affords arylated products **13** and **14** in a regio- and stereoselective manner (path A). Only 4-aryl derivatives have been isolated with (1*E*,3*E*)-configuration. Reaction yields are reported in Scheme 2.[11] The regio- and stereoselective outcome of the arylation process is clearly suggested by the presence in the ^{1}H NMR spectrum of the crude reaction mixture of a single doublet of doublets centered at 6.86 ppm (J = 15.7, 11.5 Hz, derivative **13** as an example).

Scheme 2. Heck Reaction on 1-Ethoxybuta-1,3-dienes



On the other hand, derivatives **15** and **16** were isolated in the cross coupling process of dienes **7** and **8** (Scheme 2). These products (path B) are isomers of the expected dienes.[12] Derivatives **13**, **14** and **15**, **16** probably come from the common π-allylpalladium intermediate shown in Scheme 2, which undergoes β-hydride elimination at two different sites.[13] In particular, in case B, the structure of diene **15** has been confirmed on the basis of the following ^{1}H NMR data: two broad singlets centered at 3.95 and 3.98 ppm, a doublet at 5.65 ppm (J = 15.0 Hz), and a doublet of triplets centered at 6.21 ppm (J = 15.0, 6.6). In contrast, diene **13**, coming from path A, shows two doublets centered at 6.80 and 6.92 ppm (J = 15.7 and 11.1, respectively) and a doublet of doublets at 7.20 ppm (J = 15.7, 11.1). The π-allylpalladium intermediate that leads to dienes **15** and **16** could, in principle, undergo β-hydride elimination according to either pathway A or B. The B pathway prevails probably due to steric reasons. In the case of dienes **13** and **14**, β-hydride elimination at the B site is clearly impossible because of the lack of a C−H bond.

Moreover, when the Heck cross-coupling is carried out on 1-(3-hydropropoxy)buta-1,3-dienes **9**−**12** obtained from

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(11) Reaction yields range from 41 to 48% (pure isolated products, by column chromatography); on the other hand, reaction conversions, determined on the crude reaction mixture, are higher and range from 95 to 100%.

(12) In the case of diene **15**, a Diels−Alder reaction has been carried out using *N*-methylmaleimide as a dienophile. The corresponding cycloaddition product has been isolated in quantitative yield and an endo:exo ratio of 80:20.

(13) Chemo-, regio-, and stereoselective palladium-catalyzed arylation of 1,3-dienes has been reported. See, for example: Jeffery, T. *Tetrahedron Lett.* **1992**, *33*, 1989−1992. Also, those results are consistent with a β-elimination step proceeding from the π-allylpalladium complex derived from the σ-complex, which is obtained by the carbopalladation of the terminal double bond of the diene.

cyclic acetals, the reaction follows a different pathway, probably promoted by the presence of the hydroxy group: the 1,3-dioxane ring is reformed, and the the process formally leads to γ-arylation of the α,β-unsaturated protected carbonyl compound.[14] For example, in the case of product **19**, the crude reaction mixture shows a doublet of triplets (6.00 ppm, $J = 15.4$, 6.6 Hz) and a doublet of doublets (5.45 ppm, $J = 15.4$, 5.4 Hz). The reaction products are shown in Scheme 3, and Table 1 reports reaction yields.

Scheme 3. Heck Reaction on 1-(3-Hydropropoxy)buta-1,3-dienes

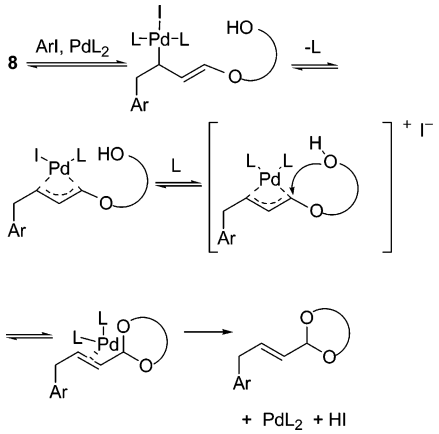
It was previously reported that the Heck reaction allows the formation of several new bonds in a domino reaction mode.[15] More recently, intramolecular variants were developed by several groups. In Scheme 4, a possible mechanism is suggested that takes into account the γ-arylation of conjugate dienes and the closure to the 1,3-dioxane ring. The formation of the product can be explained on the basis of the addition of the arylpalladium intermediate to the terminal double bond of the diene followed by the arrangement to the π-allylic complex and iodide ion−acetate ligand exchange. The final attack of the hydroxy group upon the complex with displacement of the palladium complex gives the cyclic acetal, while palladium catalyst oxidatively adds more aryl halide to start the catalytic cycle once more.[16]

Table 1. Heck Reaction of 1-(3-Hydropropoxy)buta-1,3-dienes **7**−**9** with Various Aryl Iodides

diene	ArI	product	*E*/*Z*	yield (%)
9	PhI	17	100/0	60
9	*p*-MeOPhI	18	100/0	66
9	*o*-MeOPhI	19	100/0	68
9	*m*-EtCO$_2$PhI	20	100/0	73
9	1-NaphI	21	100/0	70
10	PhI	22	83/17[a]	50
10	*o*-MePhI	23	79/21[a]	83
10	*o*-MeOPhI	24	100/0[a]	78
10	*m*-EtCO$_2$PhI	25	75/25[b]	70
10	*p*-MeCO$_2$PhI	26	77/23[a]	72
10	1-NaphI	27	79/21[a]	90
11	PhI	28	100/0[a]	65
11	*o*-MePhI	29	100/0	87
11	*m*-MePhI	30	100/0	80
11	*p*-MeOPhI	31	100/0	70
11	*p*-MeCO$_2$PhI	32	100/0	80
12	PhI	33	100/0	76

[a] Determined on the basis of the ratio between the pure isolated isomers. [b] By ^{1}H NMR analysis on the crude reaction mixture.

Scheme 4. Proposed Mechanism that Takes into Account the γ-Arylation of 1-(3-Hydropropoxy)buta-1,3-dienes



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Supporting Information Available: Experimental details for the chromatographic purification procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, MS, IR, and C,H analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Typical Procedure.** 3-(2-Methyl-buta-1,3-dienyloxy)propan-1-ol (**9**) (0.28 g, 2.0 mmol) was added to a mixture of 4-iodobenzoic acid methyl ester (0.52 g, 1.0 mmol), Pd(AcO)$_2$ (1.12 10^{-3} g, 5.0 10^{-3} mmol), and K_2CO_3 (1 mmol) in 6.0 mL of anhydrous DMSO degassed with argon for 10 min. The reaction mixture was stirred under argon in a sealed tube for 16 h at 85 °C. Samples were periodically taken and partitioned between Et_2O and H_2O. The organic layer was analyzed by GC and TLC. After complete consumption of the starting aryl halide, the reaction was cooled to room temperature and H_2O was added (10 mL). The reaction was worked up by extraction with Et_2O (3 × 20 mL), and the organic phases were washed three times with brine (10 mL). Drying (K_2CO_3) and removal of the solvent gave the crude reaction mixture that was purified by column chromatography on silica gel deactivated with Et_3N (1%) (eluent: petroleum ether/diethyl ether, 90/10), affording 0.22 g (80%) of pure 4-(3-[1,3]dioxan-2-yl-but-2-enyl)benzoic acid methyl ester (**26**) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10−2.20 (m, 2 H), 1.72 (s, 3 H), 3.38 (d, $J = 7.3$ Hz, 2 H), 3.70−3.95 (m, 5 H), 4.08 (m, 2 H), 4.78 (s, 1 H), 5.72 (t, $J = 7.3$ Hz, 2 H), 7.15 (d, $J = 7.2$ Hz, 2 H), 7.80 (d, $J = 7.2$ Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.34, 26.42, 34.40, 52.65, 67.71, 105.15, 126.41, 127.44, 128.74, 130.87, 135.38, 146.64, 167.79; MS (EI, 70 eV) *m*/*z* 276 (M^+, 48), 261 (100), 203 (46), 159 (53), 59 (58); ν_{max} (neat; cm^{-1}) 3020, 1721, 1609, 1280, 1238, 1108, 840, 760. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 70.05; H, 7.26.

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(16) An analogous mechanism was first proposed by F. Heck himself upon studying the palladium-catalyzed vinylation of conjugate dienes in the presence of morpholine or piperidine that affords 2,5-dienylamines: Patel, B. A.; Kao, L.-C; Cortese, N. A.; Minkiewicz, J. V.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 918−921.