Cross-Coupling Reactions

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Reaction of Two Different α-Allenols in a Heterocyclization/Cross-Coupling Sequence: Convenient Access to Functionalized Buta-1,3-dienyl Dihydrofurans**

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In memory of Marcial Moreno-Mañas

Dihydrofurans are an important class of oxygenated heterocycles that have attracted much interest because of the biological activity of naturally occurring representatives. They

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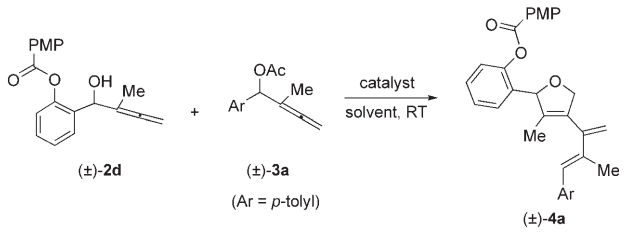
are also useful building blocks in organic synthesis.[1] Allenes, once a rarity, have become established as an extremely useful functional group in modern synthetic organic chemistry.[2] In particular, the transition-metal-catalyzed cyclization of functionalized allenes that contain a nucleophilic center has attracted much attention.[3] However, the cross-coupling of two different allenes has scarcely been mentioned; only Ma and co-workers have described reactions of this type in recent reports on the coupling of 2,3-allenoic acids with 2,3-allenols or 1,2-allenyl ketones.[4] In continuation of our research in heterocyclic and allene chemistry,[5] we report herein an efficient cross-coupling reaction between two different α-allenol derivatives to give functionalized dihydrofurans in a single step.

The precursors for dihydrofuran formation, α-allenols **2a–j**, were readily prepared in good overall yield from the appropriate carbaldehyde **1a–i** (Table 1) through a regioselective indium-mediated Barbier-type carbonyl-allenylation reaction in an aqueous medium.[6] When the indium-mediated allenylation of enantiomerically pure aldehydes **1** did not take place with complete diastereoselectivity, the diastereomeric α-allenols **2** and *anti*-**2** could be separated readily by gravity flow chromatography.[7,8]

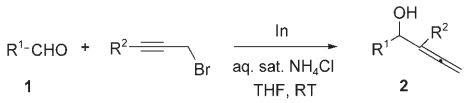
Some α-allenols **2** were protected as the corresponding acetates or *p*-nitrobenzoate **3a–c** by using standard procedures. Initial studies evaluated the effectiveness of different α-allenol derivatives and catalysts. Aromatic α-allenols were selected as initial test substrates. Our early efforts focused on the reaction between α-allenol **2d** and α-allenol **2b** protected as its acetate **3a** (Ar = *p*-MeC_6H_4). The use of $AuCl_3$ resulted in a complex mixture of unidentified products. Fortunately, palladium catalysts such as $Pd(OAc)_2$ and $PdCl_2$ in the absence of an oxidant effectively promoted this new heterocyclization/cross-coupling sequence in solvents such as MeCN and DMF at ambient temperature (Scheme 1, Table 2). It was

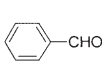
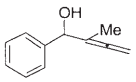
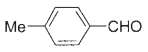
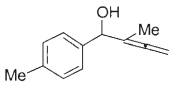
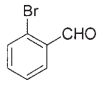
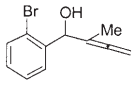
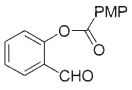
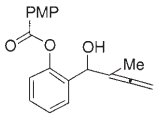
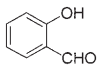
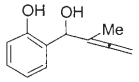
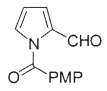
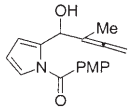
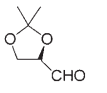
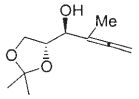
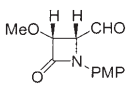
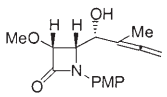
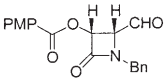
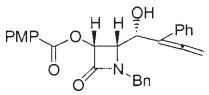
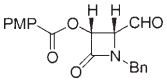
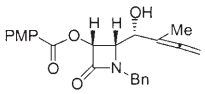


Scheme 1. Synthesis of the 2,3,4-trisubstituted 2,5-dihydrofuran **4a** through palladium(II)-catalyzed heterocyclization/cross-coupling of α-allenol derivatives **2d** and **3a**. PMP = 4-$MeOC_6H_4$.

discovered that the treatment of α-allenol **2d** with $PdCl_2$ (5 mol%) in DMF (0.2 M) led to the desired cyclization adduct **4a** in an impressive 90% yield when the protected α-allenol **3a** was used as the coupling partner (Table 2, entry 4). No homodimerization products were detected. Furthermore, the domino cyclization reaction is totally regioselective, with exclusive formation of the five-membered oxacycle. The free α-allenol component undergoes heterocyclization to give a 2,5-dihydrofuran, and the protected α-allenol cross-coupling partner becomes attached to the C4 carbon atom of the oxacycle as a substituted buta-1,3-diene functionality.

Table 1: Indium-mediated Barbier-type carbonyl allenylation of aldehydes **1**.



Entry	R^1CHO	R^2	Product	Yield [%][a]
1	 **1a**	Me	 (±)-**2a**	99
2	 **1b**	Me	 (±)-**2b**	66
3	 **1c**	Me	 (±)-**2c**	97
4	 **1d**	Me	 (±)-**2d**	77
5	 **1e**	Me	 (±)-**2e**	96
6	 **1f**	Me	 (±)-**2f**	58
7	 (−)-**1g**	Me	 (−)-**2g**	67
8	 (+)-**1h**	Me	 (+)-**2h**	70
9	 (−)-**1i**	Ph	 (+)-**2i**	74
10	 (−)-**1i**	Me	 (+)-**2j**	68

[a] Yield of the pure, isolated product with correct analytical and spectral data. Bn = benzyl, PMP = 4-$MeOC_6H_4$.

Table 2: Reaction of α-allenol derivatives **2d** and **3a** under different conditions: palladium(II)-catalyzed heterocyclization/cross-coupling.[a]

Entry	Catalyst[a]	Solvent	*t* [h]	Yield [%][b]
1	$AuCl_3$	CH_2Cl_2	24	[c]
2	$Pd(OAc)_2$	DMF	24	10
3	$Pd(OAc)_2$	MeCN	48	[c]
4	$PdCl_2$	DMF	4	90
5	$PdCl_2$	MeCN	9	55

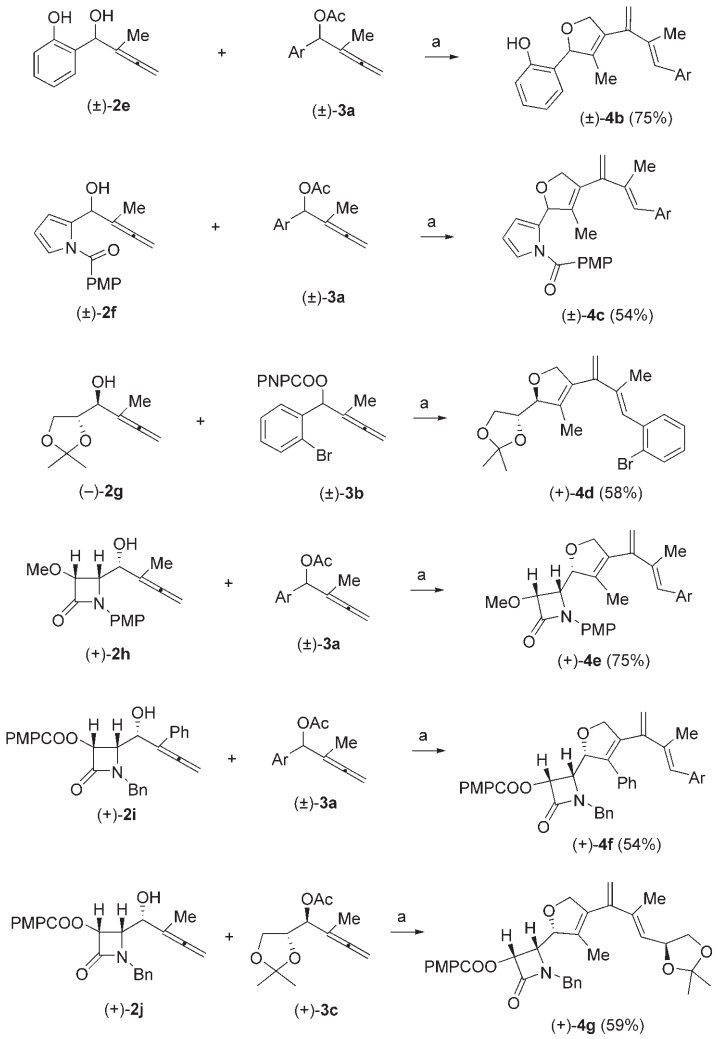
[a] All reactions were conducted with 5 mol% of the catalyst. [b] Yield of the pure, isolated product with correct analytical and spectral data. The disappearance of the starting material **2d** was observed in all cases. [c] A complex mixture of unidentified products was obtained. DMF = *N*,*N*-dimethylformamide.

To further probe the scope of this transformation, we tested the tolerance of the Pd^{II}-catalyzed heterocyclization/cross-coupling to structural alterations to both the α-allenol and protected α-allenol moieties. As expected, γ-allenols were found to be completely unreactive under these conditions. It was possible to couple chemoselectively the protected α-allenol **3a** with compound **2e**, which contains both α- and γ-allenol functionalities. None of the coupled γ-allenol was obtained, but instead the product **4b** was formed exclusively by selective coupling to the α-allenol moiety (Scheme 2). Next, we decided to use heteroaromatic α-allenol derivatives as the reactants (Scheme 2). Buta-1,3-dienyl dihydrofuran **4c** was obtained in a reasonable yield from **2f** and **3a**.

Satisfied with the above results, we set out to evaluate the cross-coupling process for substrates that contain stereocenters. Thus, a series of aliphatic enantiomerically pure α-allenol derivatives were tested (Scheme 2). The α-allenols **2g–j** were converted smoothly into the desired functionalized optically active dihydrofuran derivatives **4d–g**. These results indicate that stereochemical integrity is conserved at the carbinol carbon atom of the allenol as well as at the distal stereocenters in the course of the allene–allene cross-coupling process. The sterically more encumbered phenyl-substituted allenol derivative **2i** readily underwent the cyclization/coupling sequence under identical conditions. Remarkably, the heterocyclization/cross-coupling reaction between the 2-azetidinone-tethered allenol **2j** and the 1,3-dioxolane-tethered protected allenol **3c** gave the β-lactam–dihydrofuran hybrid **4g** in 59% yield. Thus, it was shown that the heterocyclization/cross-coupling of two different α-allenol derivatives can be considered in the planning of a complex synthetic route.

In this study, the assignment of the configuration of the newly formed 1,3-diene moiety of dihydrofurans **4** was a crucial problem, which we thought we might solve conveniently by means of X-ray crystallography. However, the reluctance of most of these compounds to form suitable crystals for X-ray analysis prompted us to consider an alternative method. We focused our attention on NMR spectroscopic methods for the determination of the geometry of substituted alkenes. Indeed, qualitative homonuclear NOE difference spectra allowed us to assign the *E* configuration as depicted in Schemes 1 and 2.

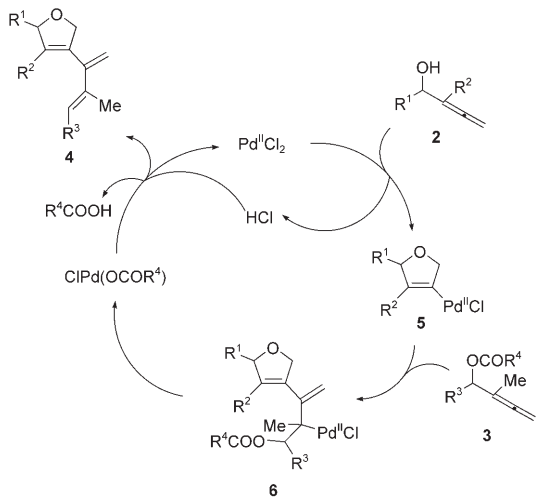
The formation of buta-1,3-dienyl dihydrofurans **4** can be rationalized through a novel heterocyclization/cross-coupling



Scheme 2. Synthesis of 2,3,4-trisubstituted 2,5-dihydrofurans **4b–g** through palladium(II)-catalyzed heterocyclization/cross-coupling of α-allenol derivatives **2** and **3**. Reagents and conditions: a) $PdCl_2$ (5 mol%), DMF, RT; **4b**: 6 h (at 0°C); **4c**: 2.5 h; **4d**: 4 h; **4e**: 4 h; **4f**: 4 h (at 0°C); **4g**: 5 h. Ar = *p*-tolyl, PMP = 4-$MeOC_6H_4$, PNP = 4-$NO_2C_6H_4$.

reaction between α-allenols and protected allenols. A possible catalytic cycle is shown in Scheme 3. Regioselective palladium(II)-mediated intramolecular oxypalladation of the free allenol component **2** generates a palladadihydrofuran intermediate **5**, which then undergoes a cross-coupling reaction with the protected allenol partner **3**. The coupling of vinyl palladium(II) intermediates **5** with protected allenols **3** to give species **6** takes place regioselectively at the central allene carbon atom of **3**. Finally, *trans*-β-deacyloxypalladation generates a buta-1,3-dienyl dihydrofuran **4** in a highly stereoselective manner with exclusive formation of the *E* isomer and concomitant regeneration of the palladium(II) species.

In conclusion, we have developed a mild, palladium(II)-catalyzed heterocyclization/cross-coupling reaction to form 2,3,4-trifunctionalized 2,5-dihydrofurans from two different α-allenols that is applicable to compounds with a wide range of substitution patterns. As our studies indicate high levels of regioselectivity as well as the possibility of using optically



Scheme 3. Mechanistic explanation for the Pd^{II}-catalyzed heterocyclization/cross-coupling of α-allenols and protected α-allenols.

active substrates, this is a potentially attractive method for organic synthesis. Current work is aimed at exploring the scope of the reaction with respect to both α-allenols and protected α-allenols, and identifying applications in complex-molecule synthesis.

Experimental Section

General procedure: $PdCl_2$ (0.005 mmol) was added to a stirred solution of an α-allenol **2** (0.10 mmol) and the appropriate protected α-allenol **3** (0.30 mmol) in *N*,*N*-dimethylformamide (1.0 mL). The reaction mixture was stirred under an argon atmosphere until the starting material had disappeared (monitored by TLC). Water (0.5 mL) was then added, and the reaction mixture was extracted with ethyl acetate (3 × 4 mL). The organic phase was washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with mixtures of hexanes and ethyl acetate as the eluent gave analytically pure 2,3,4-trisubstituted 2,5-dihydrofurans **4**. (+)-**4e**: Prepared from (+)-**2h** (55 mg, 0.19 mmol); chromatographic purification of the crude product (hexanes/ethyl acetate 20:1) gave (+)-**4e** (64 mg, 75%) as a colorless oil; $[\alpha]_D = +45.5$ ($c = 2.1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.48$ (d, $J = 9.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.0$ Hz, 2H), 6.79 (d, $J = 9.0$ Hz, 2H), 6.17 (br s, 1H), 5.28–5.30 (m, 1H), 5.21 (d, $J = 1.2$ Hz, 1H), 4.72 (d, $J = 5.6$ Hz, 1H), 4.67–4.69 (m, 2H), 4.58 (d, $J = 1.2$ Hz, 1H), 4.55–4.57 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 2.33 (d, $J = 0.7$ Hz, 3H), 1.84 (d, $J = 1.2$ Hz, 3H), 1.66–1.68 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 164.9$, 156.3, 144.2, 136.2, 135.9, 134.9, 134.5, 133.5, 130.4, 129.3, 129.1, 128.6, 118.9, 114.2, 114.1, 86.9, 82.7, 77.6, 61.7, 59.4, 55.3, 21.1, 15.1, 12.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1742$ cm^{-1}; MS (ESI): *m*/*z* (%): 446 (100) $[M+H]^+$, 445 (11) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{31}NO_4$ (445.5): C 75.48, H 7.01, N 3.14; found: C 75.72, H 7.06, N 3.10.

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