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Synthesis of Spiroheterocycles by Palladium-Catalyzed Domino Cycloisomerization/Cross-Coupling of α-Allenols and Baylis–Hillman Acetates

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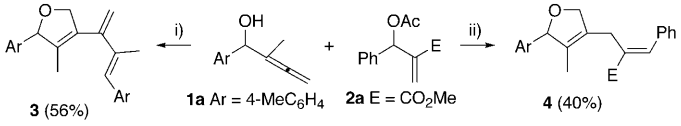
Dedicated to Professor Josep Font on the occasion of his 70th birthday

The Baylis–Hillman (BH) reaction is a straightforward C–C bond forming reaction that affords densely functionalized adducts, which, particularly in the form of acetyl derivatives, are versatile synthetic intermediates.[1] Despite regioselectivity problems, the allene moiety has developed from almost a rarity to an established member of the weaponry utilized in modern organic synthetic chemistry.[2] However, although many efforts have been made in these fields, examples of the reaction between allenes and BH adducts have not been reported yet. In continuation of our interest in heterocyclic and allene chemistry,[3] we now disclose the first examples of the reaction of an allene and a BH adduct, namely the heterocyclization cross-coupling reaction of α-allenols and BH acetates.

Precursors for the heterocycle formation, α-allenols **1a–d**, were readily prepared in good overall yield from the corresponding carbonyl compound by a regiocontrolled indium-mediated Barbier-type carbonyl-allenylation reaction in aqueous media using our previously described methodology.[4] α-Allenol **1a** was selected as a simple model to test the chemical bent for the BH acetate **2a** in the heterocyclization cross-coupling sequence. The search for an effective metal catalyst system for the tandem reaction was performed by using various palladium salts ($PdCl_2$, $[PdCl_2(MeCN)_2]$, and $Pd(OAc)_2$), solvents (*N,N*-dimethylformamide, acetonitrile, and dimethyl sulfoxide), and additives (alkaline carbonates and phosphines). Disappointingly, the $PdCl_2$-catalyzed reaction of α-allenol **1a** and BH acetate **2a** afforded the homodimer **3**, which is the result of an allene oxycyclization followed by coupling with another allene molecule rather than with the BH adduct (Scheme 1).[5] To our delight, the above screening revealed that $Pd(OAc)_2$ was a competent catalyst,



Scheme 1. Palladium-catalyzed reaction of α-allenol **1a** with BH acetate **2a**. Reagents and conditions: i) 5 mol% $PdCl_2$, DMF, RT. ii) 5 mol% $Pd(OAc)_2$, K_2CO_3, TDMPP, DMSO, RT.

and the combination of $Pd(OAc)_2$, K_2CO_3, and tris(2,6-dimethoxyphenyl)phosphine (TDMPP) in DMSO was the most efficient system for the domino coupling. We also examined the use of PPh_3 in this reaction, although the yield of **4** (20%) was not very high in this case; this indicated that an electron-rich phosphine was necessary. Accordingly, the controlled reaction between α-allenol **1a** and BH acetate **2a** selectively gave the [(2,5-dihydrofuran-3-yl)methyl]acrylate **4** (Scheme 1).

Encouraged by this result, tertiary α-allenols **1b–d** were studied to determine the applicability of the tandem sequence for the preparation of spirocycles, which, due to their atypical topologies, have attracted the attention of organic chemists.[6] Pleasingly, 2-indolinone-tethered allenic alcohol **1b** underwent reaction with BH acetates **2a** and **2b**, affording reasonable yields of spiroindolinones **5a** and **5b** (Scheme 2).[7]

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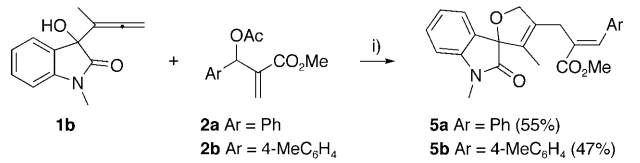
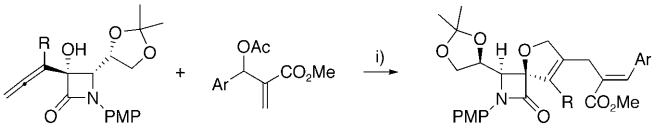


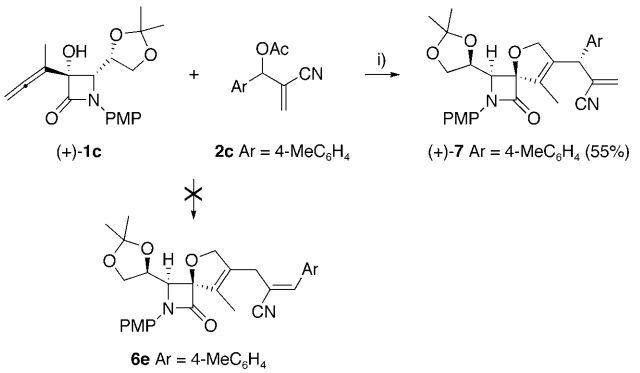
Scheme 2. Palladium-catalyzed preparation of spiroindolinones **5a** and **5b**. Reagents and conditions: i) 5 mol% $Pd(OAc)_2$, K_2CO_3, TDMPP, DMSO, RT.

The above domino reaction provides a facile access to functionalized spiroindolinones, which prompted us to test it using enantiopure 2-azetidinone-tethered allenic alcohols. Pleasingly, α-allenols **1c** and **1d** reacted with BH acetates **2a** and **2b** to furnish selectively the desired spiroazetidinones **6a–d** in moderate to good yields (Scheme 3).[8,9]



Scheme 3. Palladium-catalyzed preparation of enantiopure spiroazetidinones **6a–d**. Reagents and conditions: i) 5 mol% $Pd(OAc)_2$, K_2CO_3, TDMPP, DMSO, RT. PMP = 4-$MeOC_6H_4$.

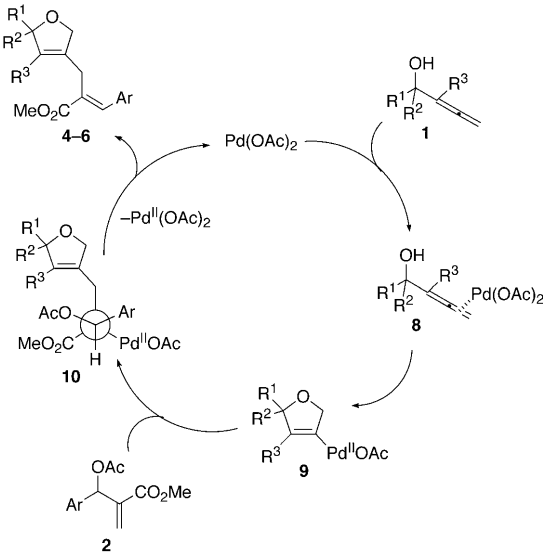
When α-allenol **1c** and BH acetate containing nitrile **2c** were subjected to this Pd^{II}-catalyzed protocol, the reaction did not yield the expected adduct **6e**, which would have arisen by S_N2' substitution by attack at the methylenic position remote from the leaving group, followed by migration of the double bond. Interestingly, under the present conditions the reaction exclusively led to the spiroazetidinone **7**, probably by way of a regio- and diastereospecific S_N1 substitution (Scheme 4).[10] The configurational assignment at the benzylic-like carbon atom in **7** was made taking into account



Scheme 4. Palladium-catalyzed preparation of enantiopure spiroazetidinone **7**. Reagents and conditions: i) 5 mol% $Pd(OAc)_2$, K_2CO_3, TDMPP, DMSO, RT. PMP = 4-$MeOC_6H_4$.

mechanistic considerations. The total diastereoselectivity for the spiroazetidinone **7** could be explained by invoking the hindrance between the incoming pallada-species and the aryl group of the BH acetate; the less sterically demanding group (hydrogen atom) of the β-lactam ring being placed in the same plane as the aryl group. The difference in reactivity between both types of BH acetates could be explained by the different inductive and resonating capacities of the ester and cyano groups. The presence of a cyano substituent in the BH adduct probably strengthened the reactivity of the benzylic-like carbon, thus favoring the S_N1 substitution over the S_N2' substitution.

The catalytic cycle proposed in Scheme 5 appears valid for the formation of products **4–6** by the heterocyclization cross-coupling reaction of α-allenols and BH acetates. Initial



Scheme 5. Mechanistic explanation for the palladium-catalyzed oxycyclization/cross-coupling reaction.

palladium(II) coordination to the 1,2-diene moiety of the α-allenol component **1** gives an allenepalladium complex **8**, which undergoes regiocontrolled intramolecular oxypalladation leading to a palladadihydrofuran intermediate **9**, which, in turn, undergoes a cross-coupling reaction with the BH acetate **2**. The coupling of vinyl palladium(II) intermediates **9** with protected BH adducts **2** that leads to species **10** takes place regioselectively at the methylenic carbon atom of **2**, remote from the acetate group. Finally, *trans*-β-deacetoxypalladation generates [(2,5-dihydrofuran-3-yl)methyl]acrylates **4–6** in a highly steoselective manner as single *E* isomers with concomitant regeneration of the Pd^{II} species.

In summary, we have developed a novel domino heterocyclization/cross-coupling reaction of α-allenols and BH acetates that furnishes [(2,5-dihydrofuran-3-yl)methyl]acrylate derivatives in moderate to good yields. In addition, the present study provides the first insight into the manner in which the allene group and BH adducts undergo reaction.

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Keywords: allenes · heterocycles · palladium · spiro compounds · synthetic methods

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