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Pd^{II}-Catalyzed Domino Heterocyclization/Cross-Coupling of α-Allenols and α-Allenic Esters: Efficient Preparation of Functionalized Buta-1,3-dienyl Dihydrofurans

Benito Alcaide,*[a] Pedro Almendros,*[b] Teresa Martínez del Campo,[a] and Rocío Carrascosa[a]

Abstract: A mild, palladium(II)-catalyzed reaction of α-allenols with α-allenic esters in a heterocyclization/cross-coupling sequence, applicable to a wide range of substitution patterns, has been developed for the preparation of 2,3,4-trifunctionalized 2,5-dihydrofurans. Our studies indicate high levels of chemo- and regiocontrol. The possibility of using optically active substrates as well as substrates of increased steric demand, such as tertiary α-allenols, makes this novel sequence of heterocyclization/cross-coupling an attractive method in organic synthesis. The current mechanistic hypothesis invokes a regiocontrolled palladium(II)-mediated intramolecular oxypalladation of the free allenol component, that then undergoes a cross-coupling reaction with the allenic ester partner, followed by a *trans*-β-deacyloxypalladation with concomitant regeneration of the Pd^{II} species.

Keywords: allenes · cyclization · heterocycles · palladium · regioselectivity

Introduction

For a long period of time, allenes were considered as highly unstable, which hindered development of the chemistry of allenes. However, during the past decade the allene moiety has developed from almost a rarity to an established member of the weaponry utilized in modern organic synthetic chemistry.[1] Although many efforts have been made for transition-metal-catalyzed cyclization of functionalized allenes,[2] cross-coupling reactions of two different allenes are almost unexplored. Ma et al. have reported the coupling of 2,3-allenoic acids with 2,3-allenols, 1,2-allenyl ketones, or simple allenes,[3] while we recently communicated the cross-coupling reaction between two different secondary α-allenol derivatives.[4] On the other hand, 2,5-dihydrofurans, in addition to being structural motifs that are frequent in a wide variety of natural products exhibiting interesting biological activity,[5] are useful building blocks in organic synthesis.[6] As a consequence, the development of practical synthetic routes to access such structures is of major interest. In continuation of our interest in heterocyclic and allene chemistry,[7] we report here full details of the novel heterocyclization/cross-coupling reaction of secondary α-allenols with α-allenic esters,[4] together with its extension to tertiary α-allenols to give, in a single step, highly functionalized monocyclic or spirocyclic 2,5-dihydrofurans.

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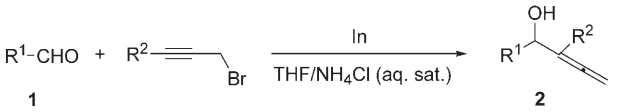
Results and Discussion

Precursors for the dihydrofuran formation, secondary α-allenols **2a–j**, were prepared in good overall yield beginning from the appropriate carbaldehyde **1a–i** (Scheme 1, Table 1) by the regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media.[8] α-Allenols (−)-**2g**, (+)-**2i**, and (+)-**2j** were obtained as single isomers. Total diastereocontrol was not achieved for the indium-mediated allenylation of enantiopure aldehyde (+)-**1h**.



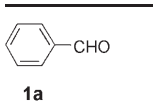
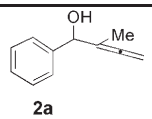
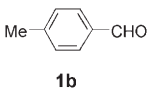
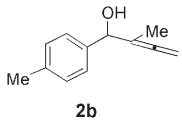
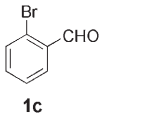
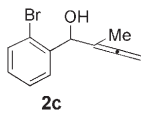
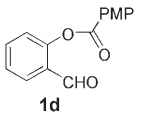
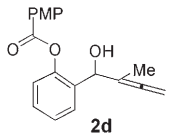
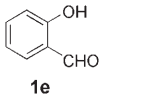
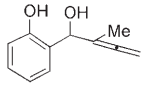
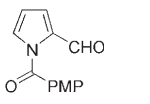
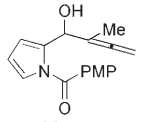
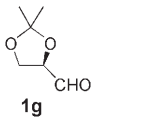
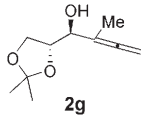
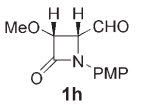
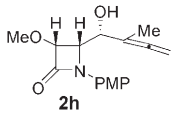
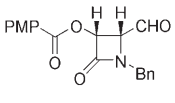
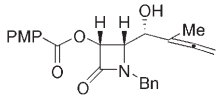
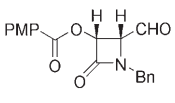
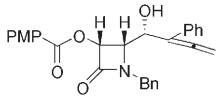
Scheme 1. Indium-mediated Barbier-type carbonyl allenylation of aldehydes **1**. Synthesis of α-allenols **2**.

However, the diastereomeric α-allenols (+)-**2h** and *anti*-(+)-**2h** could be easily separated by gravity flow chromatography. Configuration at the carbinolic chiral center of the enantiopure α-allenols **2g** and **2i** was established using Trost's method by comparison of the ^{1}H NMR chemical shifts of their acetylmandelates **3–6** (Scheme S1 of the Supporting Information).[9] Some α-allenols **2a–j** were protected as the corresponding acetates or *p*-nitrobenzoates **7a–d** using standard chemistry (Scheme S2 of the Supporting Information).

Initial studies evaluated the effectiveness of different α-allenol derivatives and catalysts (Scheme 2, Table 2). Aromatic α-allenols were selected as initial test substrates. Our early efforts focused on the reaction between α-allenol **2d** and α-allenic acetate **7b**. The use of $AuCl_3$ resulted in a complex mixture of unidentified products. Fortunately, palladium-based catalysts, such as $Pd(OAc)_2$ or $PdCl_2$ in the absence of any oxidant, were found to promote (albeit in low yield with $Pd(OAc)_2$) this new heterocyclization/cross-coupling sequence in solvents such as MeCN or DMF at ambient temperature (Table 2). It was discovered that, upon treatment with 5 mol% of $PdCl_2$ in DMF (0.2 M), α-allenol **2d** gave an impressive 90% yield of the desired cyclization adduct **8a** when protected α-allenol **7b** was used as the coupling partner (entry 4, Table 2). No homodimerization products were detected. In addition, the domino cyclization reaction is totally regioselective, giving exclusively the five-membered oxacycle. The free α-allenol component suffered heterocyclization to give a 2,5-dihydrofuran, while the protected α-allenol cross-coupling partner was embodied to the C4 carbon atom of the oxacycle as a 3-methyl-4-phenyl-buta-1,3-diene functionality. When the allenic ester component was suppressed in the $PdCl_2$-catalyzed reaction, the α-allenols **2** suffer a very slow low yielding homodimerization.[3f]

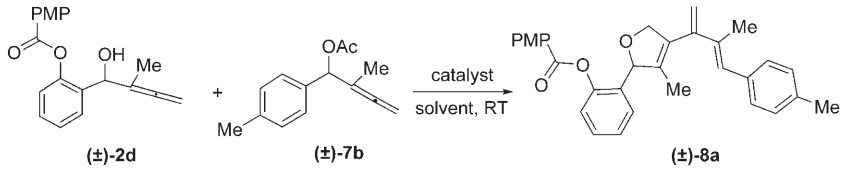
To further probe the scope of this transformation, we tested the tolerance of the Pd^{II}-catalyzed heterocyclizative cross-coupling to structural alterations at both the α-allenol and protected α-allenol moieties. Additionally, γ-allenols were found to be completely unreactive under these conditions, and it was possible to chemoselectively couple α-allenic acetate **7b** and α-allenol **2e**, which bears an α- and a γ-allenol functionality on the same molecule. None of the coupled phenolic γ-allenol was obtained, giving exclusively the product **8b** by selective coupling to the α-allenol moiety (Scheme 3). Since cyclization to the seven-membered ring is

Table 1. Preparation of α-allenic alcohols **2**.

Aldehyde	α-Allenol	Yield [%][a]
 **1a**	 **2a**	99
 **1b**	 **2b**	66
 **1c**	 **2c**	97
 **1d**	 **2d**	77
 **1e**	 **2e**	96
 **1f**	 **2f**	58
 **1g**	 **2g**	67
 **1h**	 **2h**	70[b]
 **1i**	 **2i**	68
 **1i**	 **2j**	74

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] 5 mg (7%) of the epimeric compound *anti*-(+)-**2h** was also obtained. Configuration at the carbinolic chiral center of the enantiopure α-allenol (+)-**2h** was assumed to be the same as that for α-allenol (+)-**2i**; which is in agreement with previous results in our group. PMP = 4-$MeOC_6H_4$.

Abstract in Spanish: Se ha desarrollado un nuevo proceso de heterociclación/acoplamiento cruzado de dos α-alenoles diferentes que permite obtener 2,5-dihidrofuranos 2,3,4-trifuncionalizados, compatible con una gran variedad de funcionalidades en cualquiera de las agrupaciones alenólicas. El proceso tándem ocurre con total regio- y estereoselectividad, así como con conservación de la integridad estereoquímica cuando se utilizan sustratos óptimamente activos. La utilidad de esta nueva metodología se ha demostrado con la síntesis de β-lactamas y oxindoles espiránicos, ambas estructuras de relevancia biológica.



Scheme 2. Reaction between α-allenol **2d** and α-allenic acetate **7b** under modified metal-catalyzed heterocyclization/cross-coupling. PMP = 4-$MeOC_6H_4$.

Table 2. Metal-catalyzed heterocyclization/cross-coupling sequence of α-allenol **2d** and α-allenic acetate **7b**.

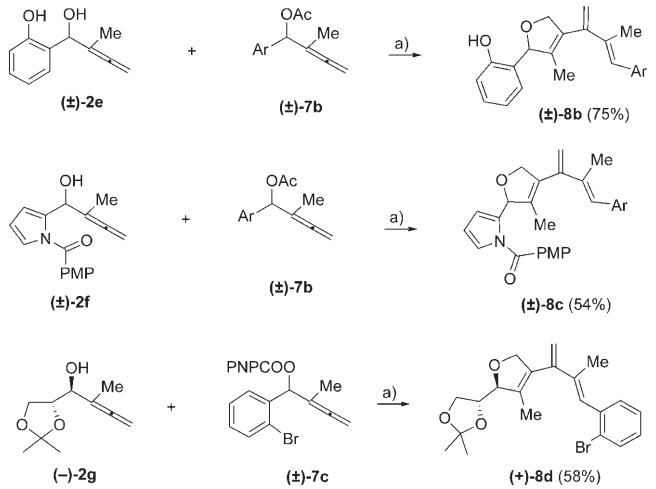
Entry	Catalyst[a]	Solvent	Time [h]	Yield [%][b]
1	$AuCl_3$	CH_2Cl_2	24	–[c]
2	$Pd(OAc)_2$	DMF	24	10
3	$Pd(OAc)_2$	MeCN	48	–[c]
4	$PdCl_2$	DMF	4	90
5	$PdCl_2$	MeCN	9	55

[a] All reactions were conducted using 5 mol% of catalyst. [b] Yield of pure, isolated product with correct analytical and spectral data. Disappearance of starting **2d** was observed in all cases. [c] A complex mixture of unidentified products was obtained.

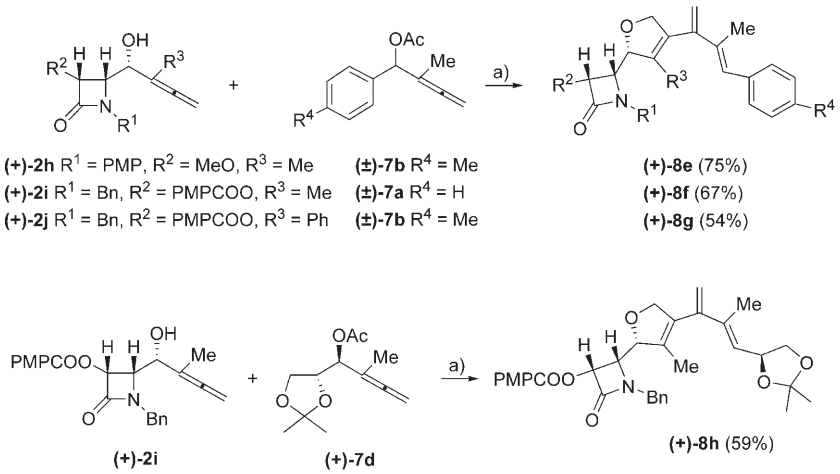
slower, it is also unable to compete. Next, we decided to use heteroaromatic α-allenol derivatives as the reactants (Scheme 3). Gratifyingly, buta-1,3-dienyl dihydrofuran **8c** was obtained in reasonable yield. Therefore, we set out to evaluate the tolerance of the cross-coupling process toward the presence of stereocenters. Conversion of α-allenol **2g** to the desired functionalized optically active dihydrofuran derivative **8d** was smoothly accomplished. This result indicates that the stereochemical integrity at the carbinolic allenol carbon atom as well as the proximal stereocenter was retained in the course of the allene–allene cross-coupling process. No efforts have yet been made to develop the heterocyclization/cross-coupling reaction for allenes bearing substituents at the terminal position. Therefore, the reaction may only be limited to terminal allenes where chirality transfer is not involved.

The development of new synthetic methods for the efficient construction of biologically active compounds is an important field in organic chemistry. In this context, natural products are of particular interest as leading structures. However, the isolation of new natural products is rather difficult and time consuming. Therefore, the concept of synthesizing natural product hybrids and analogues, containing two different pharmacophoric subunits, has been recently devised.[10] Thus, we decided to explore the above coupling sequence for the preparation of 2-azetidinone-tethered buta-1,3-dienyl 2,5-dihydrofurans, which can be regarded as hybrids of the pharmacologically relevant subunits of β-lactam and dihydrofuran. Remarkably, the heterocyclizative cross-coupling between 2-azetidinone-tethered allenols **2h–j** and α-allenic acetates **7** resulted in the achievement of β-lactam–dihydrofuran hybrids **8e–h** in good yields (Scheme 4). Thus, it was shown that the heterocyclization/cross-coupling of two different α-allenol derivatives can be considered in a complex synthetic planning.

Extrapolation of the coupling sequence of secondary α-allenols to sterically more encumbered tertiary allenic alco-

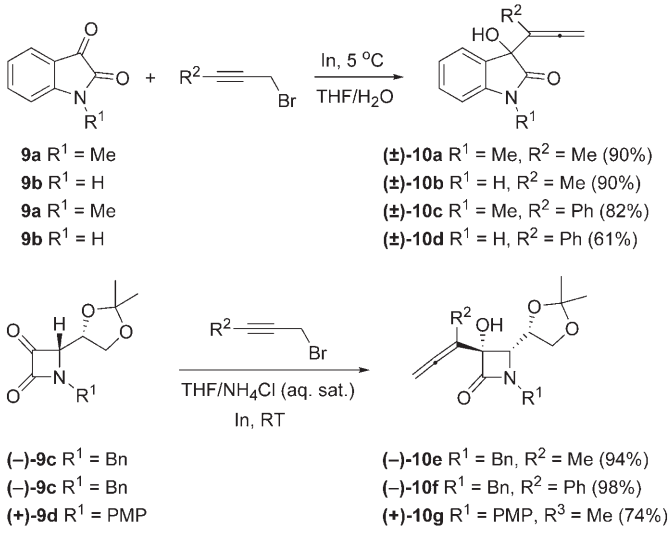


Scheme 3. Palladium-promoted preparation of five-membered oxacycles **8b–d**. Reagents and conditions: a) 5 mol% $PdCl_2$, DMF, RT; **8b**: 6 h (the reaction was carried out at 0 °C); **8c**: 2.5 h; **8d**: 4 h. Ar = *p*-tolyl. PNP = 4-$NO_2C_6H_4$.



Scheme 4. Palladium-promoted preparation of 2-azetidinone-tethered buta-1,3-dienyl 2,5-dihydrofurans **8e–h**. Reagents and conditions: a) 5 mol% $PdCl_2$, DMF, RT; **8e**: 4 h; **8f**: 2.5 h; **8g**: 4 h (the reaction was carried out at 0 °C); **8h**: 5 h.

hols is not obvious.[11] Having in hand the precursors, α-allenols **10a–g**, which can be made in aqueous media starting from α-oxolactams **9a–d** by the indium-mediated Barbier-type ketone–allenylation reaction (Scheme 5),[12] we decided



9a R^1 = Me
9b R^1 = H
9a R^1 = Me
9b R^1 = H

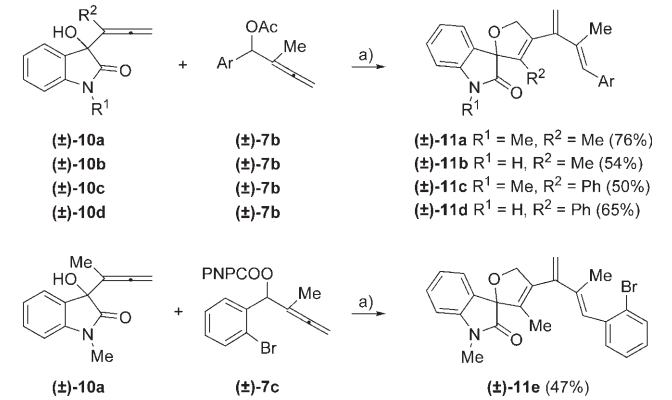
(±)-10a R^1 = Me, R^2 = Me (90%)
(±)-10b R^1 = H, R^2 = Me (90%)
(±)-10c R^1 = Me, R^2 = Ph (82%)
(±)-10d R^1 = H, R^2 = Ph (61%)

(–)-9c R^1 = Bn
(–)-9c R^1 = Bn
(+)-9d R^1 = PMP

(–)-10e R^1 = Bn, R^2 = Me (94%)
(–)-10f R^1 = Bn, R^2 = Ph (98%)
(+)-10g R^1 = PMP, R^3 = Me (74%)

Scheme 5. Indium-mediated Barbier-type carbonyl allenylation of ketones **9**. Synthesis of tertiary α-allenols **10a–g**.

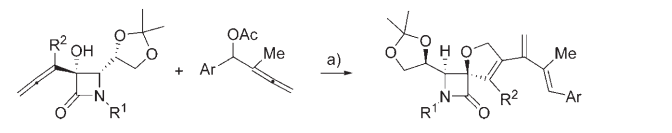
to undertake a study of the potential use of more diverse allenols in this novel domino reaction. Schemes 6 and 7 illus-



(±)-10a **(±)-7b** **(±)-11a** R^1 = Me, R^2 = Me (76%)
(±)-10b **(±)-7b** **(±)-11b** R^1 = H, R^2 = Me (54%)
(±)-10c **(±)-7b** **(±)-11c** R^1 = Me, R^2 = Ph (50%)
(±)-10d **(±)-7b** **(±)-11d** R^1 = H, R^2 = Ph (65%)

(±)-10a **(±)-7c** **(±)-11e** (47%)

Scheme 6. Palladium-promoted preparation of spirocyclic oxindoles **11a–e**. Reagents and conditions: a) 5 mol% $PdCl_2$, DMF, RT; **11a**: 2 h; **11b**: 2 h; **11c**: 1.5 h; **11d**: 4.5 h; **11e**: 3.5 h. Ar = *p*-tolyl.



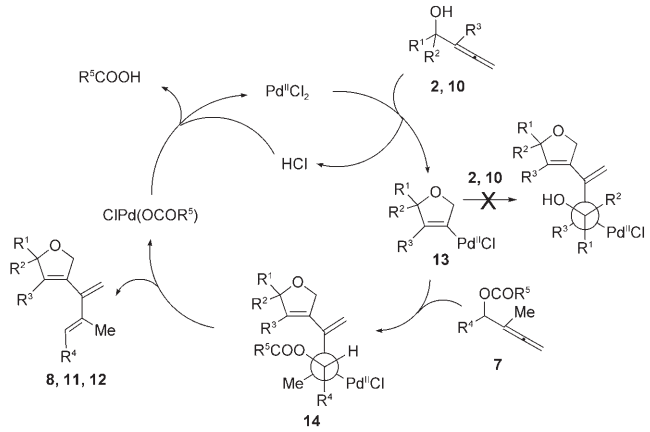
(–)-10e **(±)-7a** **(–)-12a** R^1 = Bn, R^2 = Me, Ar = Ph (51%)
(–)-10e **(±)-7b** **(–)-12b** R^1 = Bn, R^2 = Me, Ar = *p*-tolyl (75%)
(–)-10f **(±)-7b** **(+)-12c** R^1 = Bn, R^2 = Ph, Ar = *p*-tolyl (47%)
(+)-10g **(±)-7b** **(+)-12d** R^1 = PMP, R^2 = Me, Ar = *p*-tolyl (57%)

Scheme 7. Palladium-promoted preparation of spirocyclic β-lactams **12a–d**. Reagents and conditions: a) 5 mol% $PdCl_2$, DMF, 0 °C; **12a**: 3 h; **12b**: 4.5 h; **12c**: 24 h; **12d**: 4 h.

trate several examples of the heterocyclization/cross-coupling methodology on tertiary α-allenols **10**. All substrates reacted efficiently to afford high yields of the isolated corresponding spiro adducts **11** and **12**. This provides a new mild method for the synthesis of the spirocyclic β-lactam and oxindole frameworks, which are important structural motifs in biologically relevant compounds as natural products and pharmaceuticals.[13] Noteworthy cases include the chemoselective cross-coupling in the presence of the NH-lactam moiety, which remains unchanged, and the heterocyclization of hindered phenyl-substituted allenols.

Importantly, all products were obtained as single isomers, that is, with complete *E* selectivity with regard to the newly established C=C double bond. The cyclic structure (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry of the substituted alkene moiety (by qualitative homonuclear NOE difference spectra) of (*E*)-buta-1,3-dienyl dihydrofurans **8**, **11**, and **12** were established by one- and two-dimensional NMR techniques.

The formation of dihydrofurans **8**, **11**, and **12** can be rationalized through a novel heterocyclization/cross-coupling reaction between α-allenols and protected allenols. A possible catalytic cycle is shown in Scheme 8. Regiocontrolled



Scheme 8. Mechanistic explanation for the palladium-catalyzed heterocyclization/cross-coupling reaction.

palladium(II)-mediated intramolecular oxypalladation of the free allenol component **2** or **10** generates a palladadihydrofuran intermediate **13** that then undergoes a cross-coupling reaction with the protected allenol partner **7**. The coupling of vinyl palladium(II) intermediates **13** with protected allenols **7** leading to species **14** takes place regioselectively at the central allene carbon atom of **7**. Finally, *trans*-β-deacyloxypalladation generates, in a highly stereoselective manner, buta-1,3-dienyl dihydrofurans **8**, **11**, and **12** as single *E* isomers with concomitant regeneration of the Pd^{II} species. It should be noted that the carbopalladation of 2,5-dihydrofuranyl palladium intermediate **13** to form the corresponding π-allylic palladium intermediate is totally chemoselective toward the allenic acetate **7**; since homodimerization from the coupling with another molecule of free allenol

did not occur. Probably, the central allene carbon atom in allenic esters **7** is more activated than in free allenols **2** or **10** because of the presence of the acetate group.

Conclusions

In conclusion, an atom-economic, selective, and highly practical one-pot synthesis of 2,3,4-trifunctionalized heterocycles has been developed that efficiently affords racemic and enantiopure (*E*)-buta-1,3-dienyl dihydrofurans. This mild 2,5-dihydrofuran-forming palladium(II)-catalyzed reaction of α-allenols with α-allenic esters in a heterocyclization/cross-coupling sequence is applicable to a wide range of substitution patterns. Finally, the utility of this novel heterocyclization/cross-coupling sequence was demonstrated through the preparation of spiro β-lactams and oxindoles, which are both chemically and biologically relevant moieties.

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken on a HP5989 A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General Procedure for the Heterocyclizative Cross-Coupling between α-Allenols and Protected α-Allenols

Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding α-allenol **2** or **10** (0.10 mmol) and the appropriate α-allenic acetate or *p*-nitrobenzoate **7** (0.30 mmol) in *N*,*N*-dimethylformamide (1.0 mL). The reaction was stirred under argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being 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 eluting with hexanes/ethyl acetate mixtures gave analytically pure 2,3,4-trisubstituted 2,5-dihydrofurans **8**, **11**, or **12**.[14]

(±)-8a: α-Allenol (±)-**2d** (50 mg, 0.16 mmol), after chromatography of the residue using hexanes/ethyl acetate (10:1) as eluent, afforded compound (±)-**8a** (68 mg, 90%) as a colorless oil; IR ($CHCl_3$): $\tilde{\nu}$ = 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.20 and 7.00 (d, *J* = 9.0 Hz, each 2H), 7.32 (m, 8H), 6.60 (br s, 1H), 5.99 (m, 1H), 5.36 (d, *J* = 1.5 Hz, 1H), 5.00 (d, *J* = 1.0 Hz, 1H), 4.87 (m, 2H), 3.91 (s, 3H), 2.36 (s, 3H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.53 ppm (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 164.8, 164.0, 148.8, 144.6, 136.4, 135.2, 134.9, 133.8, 133.7, 133.0, 132.4, 129.1, 128.8, 128.4, 128.3, 126.4, 122.8, 121.6, 114.4, 113.9, 86.7, 78.7, 55.5, 21.2, 15.8, 10.9 ppm; MS (ES): *m/z* (%) 467 (100) $[M+H]^+$, 466 (14) $[M]^+$; elemental analysis calcd (%) for $C_{31}H_{30}O_4$ (466.6): C 79.80, H 6.48; found C 79.94, H 6.44.

(+)-8e: α-Allenol (+)-**2h** (55 mg, 0.19 mmol), and after chromatography of the residue using hexanes/ethyl acetate (20:1) as eluent, gave compound (+)-**8e** (64 mg, 75%) as a colorless oil; $[\alpha]_D$ = +45.5 (*c* = 2.1, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 1742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.48 and 6.79 (d, *J* = 9.0 Hz, each 2H), 7.11 and 6.97 (d, *J* = 8.0 Hz, each 2H), 6.17 (br s, 1H), 5.29 (m, 1H), 5.21 and 4.58 (d, *J* = 1.2 Hz, each 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 4.68 (m, 2H), 4.56 (m, 1H), 3.67 and 3.65 (s, each 3H), 2.33 (d, *J* = 0.7 Hz, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.67 ppm (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 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; MS (ES): *m/z* (%): 446 (100) $[M+H]^+$, 445 (11) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{31}NO_4$ (445.6): C 75.48, H 7.01, N 3.14; found C 75.72, H 7.06, N 3.10.

(±)-11a: α-Allenol (±)-**10a** (50 mg, 0.23 mmol), after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent, afforded compound (±)-**11a** (66 mg, 76%) as a colorless oil; IR ($CHCl_3$): $\tilde{\nu}$ = 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.24 (m, 5H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.78 (br s, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 5.20 (br s, 1H), 5.16 and 5.03 (dq, *J* = 11.7, 2.0 Hz, each 1H), 3.23 (s, 3H), 2.37 (s, 3H), 2.10 (d, *J* = 1.2 Hz, 3H), 1.35 ppm (t, *J* = 1.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 171.0, 144.0, 137.3, 136.5, 136.2, 135.0, 134.5, 131.2, 130.1, 129.6, 129.3, 128.9, 124.5, 123.2, 117.6, 114.9, 108.3, 105.0, 79.5, 26.3, 21.2, 15.5, 9.7 ppm; MS (ES): *m/z* (%): 372 (100) $[M+H]^+$, 371 (15) $[M]^+$; elemental analysis calcd (%) for $C_{25}H_{25}NO_2$ (371.5): C 80.83, H 6.78, N 3.77; found C 80.70, H 6.83, N 3.80.

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