Organic Synthesis

Intermolecular Tandem Pd-Catalyzed Cross-Coupling/[4+4] and [4+2] Cycloadditions: A One-Pot, Five-Component Assembly of Bicyclo[6.4.0]dodecanes**

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Tandem reactions have long been established as efficient methods for the rapid synthesis of complex compounds starting from simple, readily available substrates in relatively few steps.[1–3] Although many intramolecular tandem reactions have been reported for constructing complex organic molecules, the corresponding highly efficient intermolecular reactions remain an important challenge for synthetic organic chemists. A range of strategies involving the sequential generation of radical and anionic species has been used for such intermolecular transformations.[4,5] However, relatively few transition-metal-catalyzed intermolecular tandem processes[6] have been developed for the synthesis of complex cyclic compounds.[7] Recently, we reported a method for the synthesis of substituted allenes, polyallenes, and unsymmetrical bis(allenes) from allenylindium reagents generated in situ.[8] With this result in hand, we envisioned that a Pd-catalyzed cascade process involving sequential cross-coupling between vinyl bromides or triflates and propargyl halides followed by [4+4] and [4+2] cycloadditions should provide structurally diverse carbocycles. Herein, we describe the development of tandem Pd-catalyzed cross-coupling/[4+4]

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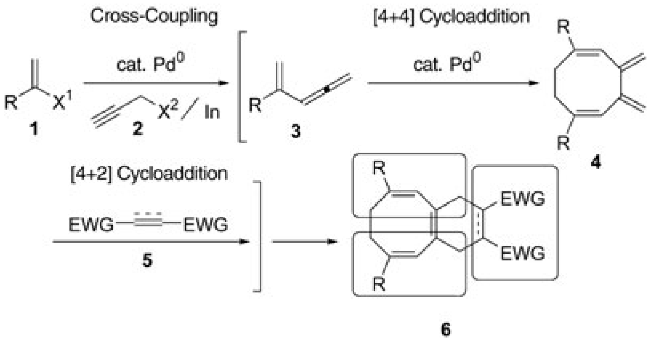
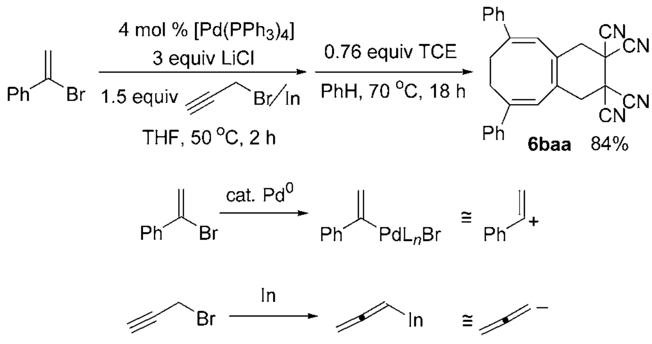
and [4+2] cycloadditions as an efficient approach to bicyclo[6.4.0]dodecane derivatives (Scheme 1).[9]



Scheme 1. EWG = electron-withdrawing group.

The tandem process was first examined with α-bromostyrene, propargyl bromide, and tetracyanoethylene (TCE). The organoindium reagent obtained from one equivalent of indium and 1.5 equivalents of propargyl bromide was added to a solution of one equivalent of α-bromostyrene in the presence of 4 mol% of [Pd(PPh$_3$)$_4$] and three equivalents of LiCl,[8,10] and the solution was stirred at 50 °C for 2 h. In the ^{1}H NMR spectrum of the crude product mixture, 3,4-dimethylene-1,6-diphenyl-1,5-cyclooctadiene (**4ba**) was observed as the major compound, thus indicating that a sequential cross-coupling/[4+4] cycloaddition had taken place to produce **4ba** in 94% yield. Because **4ba** is a 1,3-diene, we further attempted a [4+2] cycloaddition reaction with crude **4ba**. Thus, **4ba** was treated with 1.5 equivalents of TCE (70 °C, benzene, 18 h) to afford **6baa** in 84% yield. This transformation shows that five components can be assembled in an intermolecular cascade cross-coupling/[4+4] and [4+2] cycloaddition sequence (Scheme 2).

A Pd-catalyzed [4+4] cycloaddition reaction with a vinyl allene as the starting material was reported recently.[11] In this reaction, the vinyl allene was obtained from the reaction of 1-phenylvinylmagnesium bromide with propargyl bromide in the presence of a Pd^0 catalyst.[12] However, preparation of the vinyl allene in situ by inversion of the charge polarization of the reaction components (α-bromostyrene and propargyl bromide) was applied in the present method.



Scheme 2.

The results of several one-pot, five-component assembly reactions are summarized in Table 1. With **5b**, **5c**, **5e**, and **5g** as dienophiles, **4ba** gave bicyclo[6.4.0]dodecane derivatives in good yields (entries 2–5). Similarly, **4ba** reacted with maleimide (**5f**) to produce **6baf** in 79% yield (entry 6). For a vast number of α-bromovinylarenes as organic electrophiles, the presence of various substituents, for example, 4-trifluoromethyl, 4-methoxy, and 2-chloro on the aromatic ring, did not affect the efficiency of the tandem reactions. The reaction also worked equally well with α-bromovinylarenes containing free hydroxy and amino groups (entries 9 and 11). Treatment of **4ga** with two equivalents of naphthoquinone afforded **6gad** in 64% yield (entry 7). Reaction of **4da** with glyoxylic acid ethyl ester produced **6dah** in 69% yield, and the enol triflate of 3-bromoacetophenone underwent the cascade reaction to afford **6hae** in 66% yield (entry 12).

(α-Bromovinyl)trimethylsilane reacted with propargyl bromide to produce **4aa** in 71% yield under the optimized conditions. Unfortunately, the desired bicyclo[6.4.0]dodecane derivative was not obtained, because of the instability of **4aa** under the conditions of the [4+2] cycloaddition reaction. With propargyl halides as nucleophilic cross-coupling partners, the presence of a methyl substituent at the α position has little effect on either the reaction rate or the product yield.[13] In the case of 3-chloro-3-methyl-1-butyne (**2b**), **4bb**, **4cb**, **4eb**, and **4gb**, with four methyl substituents on the exocyclic C=C bonds, were obtained in 63–91% yield. However, these compounds did not undergo the [4+2] cycloaddition because of steric hindrance.

Although the mechanism of the present reaction has not been established, a possible reaction pathway is shown in

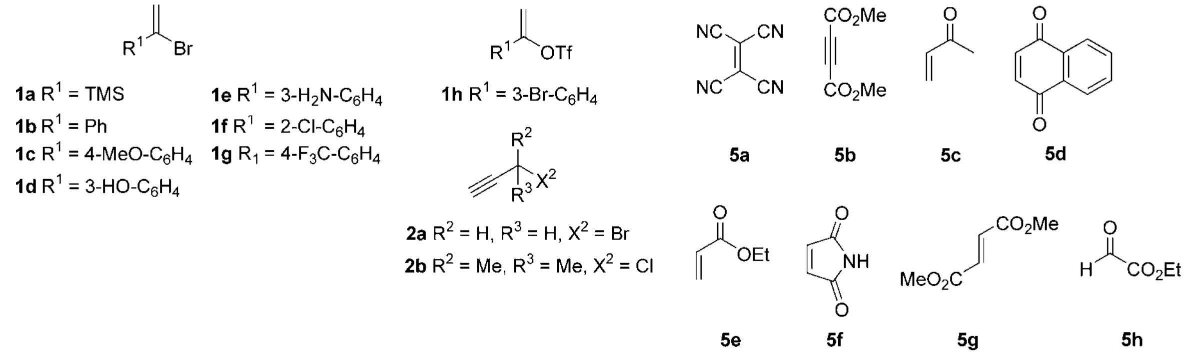
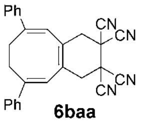
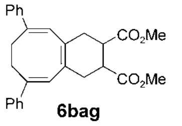
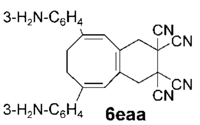
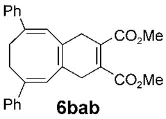
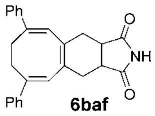
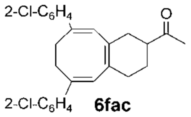
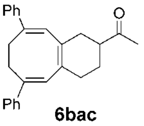
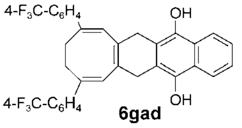
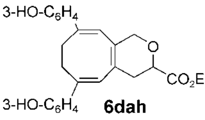
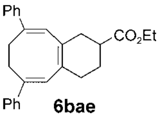
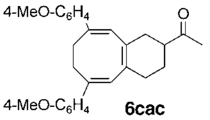
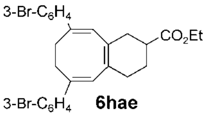
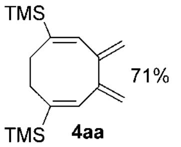


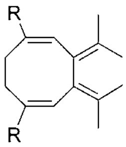
Table 1: Cascade cross-coupling/[4+4] and [4+2] cycloaddition.[a]

Entry	Reagents	Product	Yield [%][b]	Entry	Reagents	Product	Yield [%][b]	Entry	Reagents	Product	Yield [%][b]
1	**1b** **2a** **5a**	 **6baa**	84	5	**1b** **2a** **5g**	 **6bag**	74	9	**1e** **2a** **5a**	 **6eaa**	65
2	**1b** **2a** **5b**	 **6bab**	76	6	**1b** **2a** **5f**	 **6baf**	79	10	**1f** **2a** **5c**	 **6fac**	72[c]
3	**1b** **2a** **5c**	 **6bac**	72[c]	7	**1g** **2a** **5d**	 **6gad**	64	11	**1d** **2a** **5h**	 **6dah**	69
4	**1b** **2a** **5e**	 **6bae**	71	8	**1c** **2a** **5c**	 **6cac**	79[c]	12	**1h** **2a** **5e**	 **6hae**	66

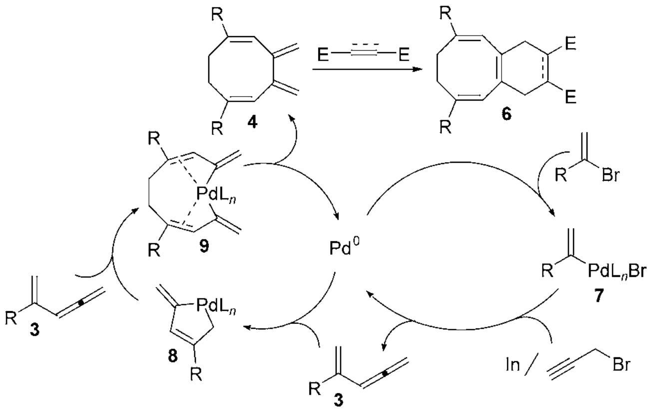
[a] Cross-coupling/[4+4] cycloaddition: Compound **1** (0.5 mmol) was treated with **2** (0.75 mmol) and indium (0.5 mmol) in THF (2 mL), in the presence of 4 mol% of $[Pd(PPh_3)_4]$ and LiCl (1.5 mmol) under N_2 at 50 °C for 2 h. [4+2] Cycloaddition: Crude **4** was treated with **5** (0.38 mmol) in benzene (2 mL) at 70 °C for 18 h. [b] Yield of isolated product. [c] 2.5 equiv of methyl vinyl ketone was used.



4aa



4bb : R = Ph, 91%
4cb : R = 4-MeO-C_6H_4, 79%
4eb : R = 3-H_2N-C_6H_4, 63%
4gb : R = 4-F_3C-C_6H_4, 71%



Scheme 3.

Scheme 3. Oxidative addition of the vinyl bromide to a Pd^0 complex and subsequent transmetalation with the organoindium reagent, followed by reductive elimination, affords the vinylallene **3**. Subsequent insertion of Pd^0 into the vinyl allene produces a five-membered palladacycle **8**, which reacts with another molecule of the vinyl allene to generate the di(σ-alkenyl) palladium complex **9**. Final reductive elimination would then give the 3,4-dimethylene-1,5-cyclooctadiene **4**.[8,11] [4+2] Cycloaddition of the 1,3-diene **4** with representative dienophiles produces the observed bicyclo[6.4.0]dodecane derivatives **6**.

In conclusion, this study has led to the development of a novel tandem Pd-catalyzed cross-coupling/[4+4] and [4+2] cycloaddition sequence that allows the rapid synthesis of bicyclo[6.4.0]dodecane derivatives starting from α-bromovinylarenes, propargyl bromides, and dienophiles in one reaction vessel. It is noteworthy that five components are assembled into one molecule in this procedure. In addition, the present process is one of the comparatively few examples in which a Pd^0 catalyst is simultaneously involved in two catalytic cycles.[2,3]

Experimental Section

Typical experimental procedure: **6baa**: α-Bromostyrene (**1b**, 102.0 mg, 0.5 mmol) was added at room temperature, under nitrogen, to a suspension of $[Pd(PPh_3)_4]$ (4 mol%, 23.1 mg) and lithium chloride (63.5 mg, 1.5 mmol) in dry THF (1 mL). After 15 min the allenylindium reagent, which was generated from propargyl bromide (**2a**, 80% (w/w) in toluene, 89.2 mg, 0.75 mmol) and indium (57.0 mg, 0.5 mmol) in dry THF (1 mL), was added. The solution was stirred at 50 °C under nitrogen for 2 h, and then the solvent was removed under reduced pressure. A solution of tetracyanoethylene (**5a,** 48 mg, 0.38 mmol) in dry benzene (2 mL) was added to the residue. After heating at 70 °C under nitrogen for 18 h, the resulting solution was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic phases were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography with EtOAc/hexane (1:10) as eluent to produce 6,9-diphenyl-7,8-dihydro-1*H*,4*H*-benzocyclooctene-2,2,3,3-tetracarbonitrile (**6baa**; 87.0 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.34$–7.30 (m, 10 H), 5.94 (s, 2 H), 3.28 (s, 4 H), 2.88 ppm (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 147.3, 141.9, 128.6, 128.3, 126.2, 124.2, 124.0, 110.6, 37.9, 36.6, 30.4 ppm; IR (film): $\tilde{\nu} = 3055$, 1941 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{20}N_4M^+$ 412.1688; found 412.1689.

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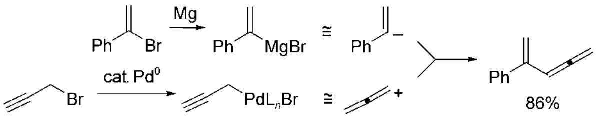

[13] The use of 3-bromo-1-butyne produced the corresponding [4+4] adduct in 90 % yield. The product consisted of three stereoisomers (1.3:1.0:1.3) with respect to the orientation of the two methyl groups on the exocyclic double bonds.