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Highly Regio- and Stereoselective Synthesis of Nine- to Twelve-Membered Cyclic Compounds by a Pd^0-Catalyzed Cyclization Reaction between Allenes with a Nucleophilic Functionality and Organic Halides

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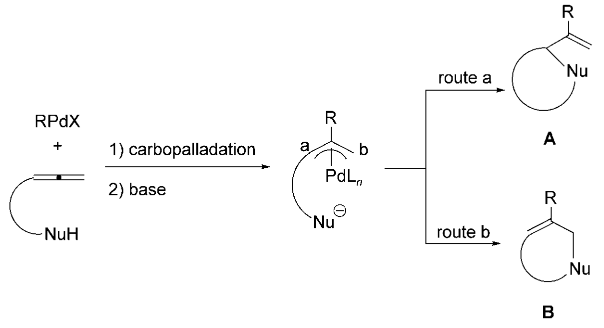
Eight- to twelve-membered carbocycles and heterocycles are extremely important subunits of a large variety of natural products.[1] The attractive properties of these cyclic compounds have encouraged organic chemists to develop various efficient methods for their synthesis.[1,2] However, there are only limited strategies for the preparation of this class of compound, which is mainly due to the fact that their formation is usually hampered by entropic/enthalpic factors.[3]

Recently, the reactions of allenes have attracted much attention due to the interesting chemical properties associated with their cumulated double bonds.[4] Some methodologies have been developed to form eight-membered rings from allenes, the most notable of which are: 1) intramolecular carbopalladation of ω-haloallenes;[5] 2) cyclization of bromoallenes with an oxygen, nitrogen, or carbon nucleophilic functionality;[6] 3) intermolecular heteroannulation of a variety of allenes that have aryl and vinylic iodides with tosylamide and amine functionalities;[7] and 4) base-catalyzed intramolecular Michael addition of carbanion species to sulfonylallenes.[8] In these reports, it was noted that the formation of nine-membered and even larger rings was more sluggish because of competing side reactions, especially dimerization, which were avoided by applying high-dilution conditions[5b] or longer reaction times[7] to obtain reasonable yields. In addition, the cycloisomerization of allenes with carbon nucleophilic functionality was reported to afford 9–17-membered rings under high-dilution conditions.[9] Therefore, it is still of current interest to develop efficient methodologies for the preparation of nine- to twelve-membered ring compounds under mild conditions based on the chemistry on allenes.

It is known that the carbopalladation of allenes may afford a π-allyl palladium intermediate that can easily be further trapped by a nucleophilic unit to provide three- to six-membered carbocycles (Scheme 1).[10] The formidable challenge here is the regioselective formation of cyclic products **A** or **B** and the stereoselectivity for the formation of the C=C bond in **B**. Herein, we wish to disclose our recent observation that this type of transformation may be easily applied for the regioselective synthesis of nine- to twelve-membered cycloalkenes with a stereodefined C=C bond in the ring in high yields (Scheme 1, route b).



Scheme 1.

Initially, we conducted a treatment of methyl 3-{2-[2,2-bis(methoxycarbonyl)hexa-4,5-dienyl]phenyl}-2-(methoxycarbonyl)propionate **1a** with PhI under the conditions we

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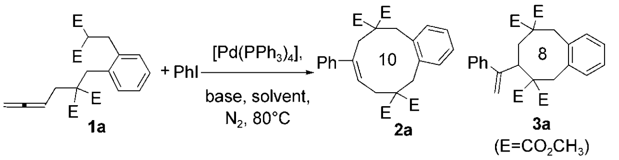
previously used for the cyclization of 2-(2′,3′-allenyl)malonates with aryl halides ([Pd(PPh$_3$)$_4$] (5 mol %) and K$_2$CO$_3$ (4 equiv) in THF, 80 °C).[10e] Unfortunately, the reaction failed to afford expected products **2a** or **3a** after 3 days; 84 % of **1a** was recovered (Table 1, entry 1). Luckily, in other solvents, such as DMSO (Table 1, entry 2) and DMF (Table 1, entry 3), the reaction afforded ten-membered cycloalkene (*E*)-**2a** as the only product in yields of 76 and 69 %, respectively. Surprisingly, when DMA was used, the NMR yield was improved to 93 % (Table 1, entry 4). The configuration of the C=C bond in **2a** was established by a NOE study (Figure 1). It is also worth noting that the formation of eight-membered carbocycle **3a** was not observed, indicating that this reaction is highly regioselective. With the addition of a different base, such as Na$_2$CO$_3$, Cs$_2$CO$_3$, KOAc, and KHCO$_3$ (Table 1, entries 5–8), the reaction afforded (*E*)-**2a** in relatively lower yields. Thus, [Pd(PPh$_3$)$_4$] (5 mol %) and K$_2$CO$_3$ (4 equiv) in DMA at 80 °C were established as the optimized reaction conditions for further study.

Table 1. Effects of solvent and base in [Pd(PPh$_3$)$_4$]-catalyzed coupling cyclization of **1a** with PhI.[a]



Entry	Base	Solvent[b]	*t* [h]	Yield of **2a**[c] [%]
1	K$_2$CO$_3$	THF	72	0[d]
2	K$_2$CO$_3$	DMSO	14.5	76
3	K$_2$CO$_3$	DMF	11	69
4	K$_2$CO$_3$	DMA	11	93 (91)
5	Na$_2$CO$_3$	DMA	24	36[e]
6	Cs$_2$CO$_3$	DMA	11	58
7	KOAc	DMA	24	0
8	KHCO$_3$	DMA	24	43

[a] Reaction conditions: **1a** (0.07 M), PhI (2 equiv), [Pd(PPh$_3$)$_4$] (5 mol %), base (4 equiv). [b] THF = tetrahydrofuran, DMSO = dimethylsulfoxide, DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide. [c] Determined by using ^{1}H NMR (300 MHz) spectroscopy with CH$_2$Br$_2$ as the internal standard; yields of the isolated product are given in parentheses. [d] 84 % of starting material **1a** was recovered. [e] 43 % of starting material **1a** was recovered.

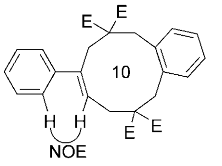
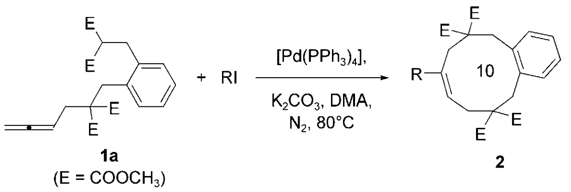


Figure 1. NOE study of (*E*)-**2a** (E = CO$_2$CH$_3$).

The scope of this reaction of **1a** with different organic halides to give ten-membered rings has been demonstrated, with typical results summarized in Table 2. The following issues should be noted: 1) The yields of these reactions range from 60 to 91 %; 2) in addition to electron-deficient (Table 2, entries 2 and 3), electron-rich (Table 2, entry 4), and Cl-substituted aryl iodides (Table 2, entry 5), pyridinyl iodide (Table 2, entry 6), 1-iodohex-1-(*E*)-ene (Table 2, entry 7), and (*E*)-styryl iodide (Table 2, entry 8) may be used to afford the corresponding ten-membered rings with an *E* C=C bond in high regio- and stereoselectivity.

Table 2. [Pd(PPh$_3$)$_4$]-catalyzed coupling cyclization of **1a** with different organic halides under standard conditions.[a]



Entry	R	*t* [h]	Yield of **2**[b] [%]
1	Ph	11	91 (**2a**)
2	*p*-MeOOCC$_6$H$_4$	11.5	84 (**2b**)
3	*p*-MeCOC$_6$H$_4$	14	89 (**2c**)
4	*p*-MeC$_6$H$_4$	12	90 (**2d**)
5	*p*-ClC$_6$H$_4$	17	85 (**2e**)
6	4-pyridinyl	14	84 (**2f**)
7	(*E*)-1-hexenyl[c,b]	72	60 (**2g**)
8	(*E*)-styryl[d]	72	62 (**2h**)

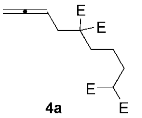
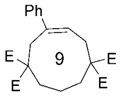
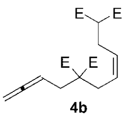
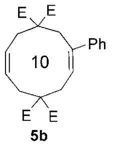
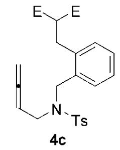
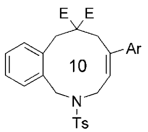
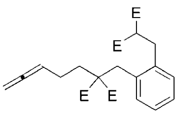
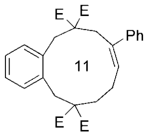
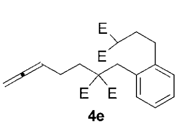
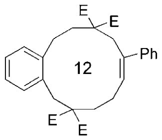
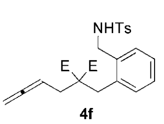
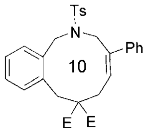
[a] Reaction conditions: **1a** (0.07 M), RI (2 equiv), [Pd(PPh$_3$)$_4$] (5 mol %), K$_2$CO$_3$ (4 equiv). [b] Isolated yield. [c] 1-iodohex-1-(*E*)-ene (3 equiv) was used. [d] (*E*)-styryl iodide (3 equiv).

This set of standard reaction conditions may also be used for the synthesis of nine- to twelve-membered rings (Table 3, entries 1–5). The reaction of **4c** with 4-chlorophenyl iodide gave the medium-sized nitrogen-tethered heterocycle **5c** in 82 % yield (Table 3, entry 3). The structure of this compound was further established by an X-ray diffraction study (Figure 2a).[11] Based on these results, we reasoned that a similar treatment of ω-aminoallene with iodobenzene could also provide an efficient route to similar azacycles. To our delight, under the same conditions, the expected product **5f** was obtained in 83 % yield (Table 3, entry 6), the structure and the configuration of the C=C bond of this compounds was further established by the X-ray diffraction study (Figure 2b).[12]

The stereoselectivity may be explained by the presence of the R group,[13] which leads to the formation of the *anti* intermediate to avoid steric repulsion between the R group and the substituent with the nucleophilic functionality.[14] Subsequent highly regioselective attack of the nucleophilic moiety to the less substituted terminal affords the final cyclic products (see Scheme 2).

In conclusion, we have developed an efficient method for the synthesis of not-readily-available nine- to twelve-membered rings by a [Pd(PPh$_3$)$_4$]-catalyzed coupling cyclization reaction of functionalized allenes with organic halides in highly regio- and stereoselectivity without applying highly diluted technique. Further study in this area is being pursued in our laboratory.

Table 3. [Pd(PPh$_3$)$_4$]-catalyzed coupling cyclization of **4** with PhI under standard conditions.[a]

Entry	**4**[b]	**5**[b]	t [h]	Isolated yield of **5** [%]
1	 **4a**	 **5a**	11.5	70
2	 **4b**	 **5b**	16.7	89
3[c]	 **4c**	 **5c**	8	82
4	 **4d**	 **5d**	11	73
5	 **4e**	 **5e**	13	73
6[d]	 **4f**	 **5f**	16	83

[a] The reactions were carried out at 80 °C in DMA with **4** (c = 0.07 M), K$_2$CO$_3$ (4 equiv) and PhI (2.0 equiv) in the presence of [Pd(PPh$_3$)$_4$] (5 mol %). [b] E = CO$_2$Me. [c] ArI = 4-chlorophenyl iodide (2.0 equiv) was used. [d] E = CO$_2$Et.

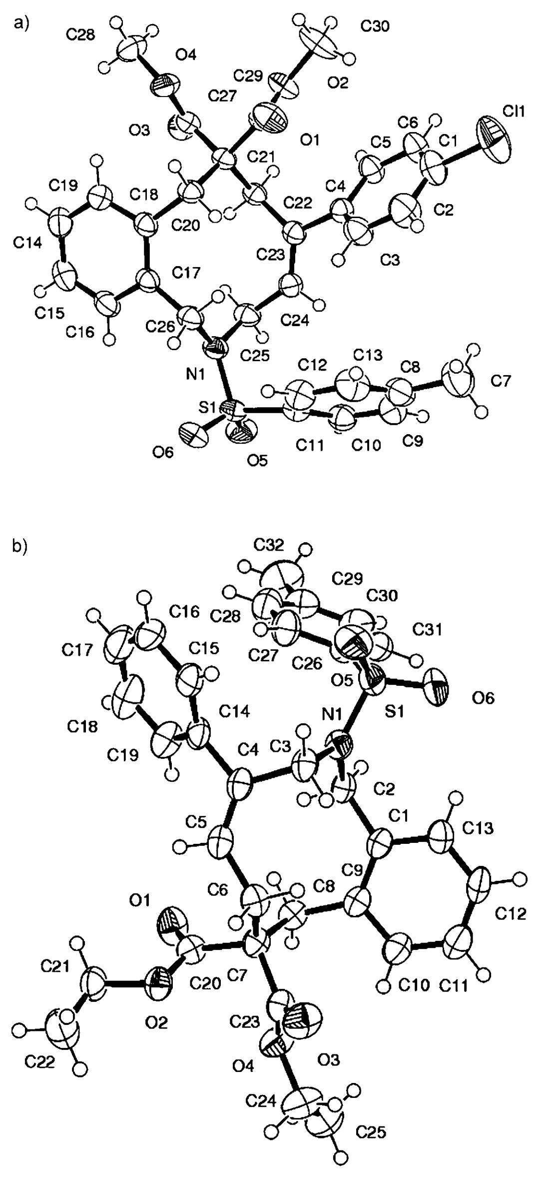
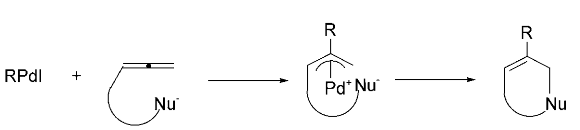


Figure 2. ORTEP drawing of a) **5c** and b) **5f**. Thermal ellipsoids are drawn at the 30 % probability level.



Scheme 2.

Experimental Section

[Pd(PPh$_3$)$_4$] (5.7 mg, 0.005 mmol), **1a** (41.8 mg, 0.1 mmol), iodobenzene (40.9 mg, 0.2 mmol), and DMA (1.5 mL) were added sequentially to a Schlenk tube containing potassium carbonate (55.6 mg, 0.4 mmol) under nitrogen. The Schlenk tube was cooled by using a dry-ice/acetone bath and back-filled with nitrogen three times. The reaction was stirred at 80 °C for 11 h until completion, as monitored by TLC (eluent: petroleum ether/ethyl acetate 5:1). The resulting mixture was quenched with H$_2$O (10 mL) and extracted with diethyl ether (3 × 30 mL), then washed with water and brine and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvent, chromatography on silica gel (eluent: petroleum ether/ethyl acetate/dichloromethane 5:1:1) gave **2a** as a white solid (44.9 mg, 91 %). M.p. 204–205 °C (CH$_2$Cl$_2$/n-hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.34–7.18 (m, 5H), 7.18–7.08 (m, 2H), 6.90–6.78 (m, 2H), 5.19 (dd, J_1 = 12.8, J_2 = 4.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.60 (d, J = 14.7 Hz, 1H), 3.47 (d, J = 15.0 Hz, 1H), 3.29–3.11 (m, 3H), 2.95 (d, J = 14.7 Hz, 1H), 2.88 (s, 3H), 2.63 (dd, J_1 = 14.3 Hz, J_2 = 4.4 Hz, 1H), 2.44 ppm (t, J = 13.4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.2, 171.8, 171.2, 170.8, 142.4, 140.2, 135.6, 135.4, 129.8, 129.41, 129.37, 127.8, 127.6, 127.1, 127.0, 126.9, 58.6, 57.9, 52.8, 52.6, 52.5, 51.8, 33.1, 32.5, 31.2, 30.2 ppm; IR (KBr): ν = 1734, 1496, 1433, 1270, 1206, 1179, 1111, 1068 cm^{-1}; EI MS (70 eV): m/z (%): 494.2 (57.22) [M^+], 115 (100); elemental analysis calcd (%) for C$_{28}$H$_{30}$O$_8$: C 68.00, H 6.11; found: C 68.09, H 6.18.

CCDC 721795 (**5c**) and 702170 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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Keywords: allenes · cyclization · medium-ring compounds · palladium · stereoselectivity

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[11] Crystal data for compound **5c**: formula $C_{30}H_{30}ClNO_6S$; $M_r = 568.07$; crystal system triclinic; space group $P\bar{1}$; final R indices $[I > 2\sigma(I)]$: $R_1 = 0.0345$, $wR_2 = 0.0921$; R indices (all data): $R_1 = 0.0400$, $wR_2 = 0.0977$; $a = 10.5105(2)$, $b = 12.2322(2)$, $c = 12.7448(2)$ Å; $\alpha = 66.541(10)$, $\beta = 89.807(10)$, $\gamma = 71.098(10)°$; $V = 1407.09(4)$ Å^3; $T = 296(2)$ K; $Z = 23$; reflections collected/unique 14963/4947 ($R_{int} = 0.0159$); number of observations $[I > 2\sigma(I)]$: 4320; parameters: 353.

[12] Crystal data for compound **5f**: Formula $C_{32}H_{35}NO_6S$; $M_r = 561.67$; crystal system orthorhombic; space group $P2(1)2(1)2(1)$; final R indices $[I > 2\sigma(I)]$: $R_1 = 0.0525$, $wR_2 = 0.1172$; R indices (all data): $R_1 = 0.0905$, $wR_2 = 0.1305$; $a = 10.329(2)$, $b = 10.473(2)$, $c = 26.552(6)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 2872.2(10)$ Å^3; $T = 293(2)$ K; $Z = 4$; reflections collected/unique 13785/3524 ($R_{int} = 0.1030$); number of observations $[I > 2\sigma(I)]$: 2343; parameters: 364.

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