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Palladium-catalyzed cyclization/cyclopropanation reaction for the synthesis of fused N-containing heterocycles

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ABSTRACT

Palladium-catalyzed cyclization/cyclopropanation can be used to convert a range of substituted cyclic *N*-aryl allyl/methallyl amines efficiently and selectively to the corresponding fused tetrahydropyridine/cyclopropane-fused isoquinoline derivatives via β-hydrogen elimination or a domino sequence.

Among numerous approaches towards the synthesis of heterocycles as well as carbocycles, the palladium-catalyzed cyclization/cyclopropanation has proven to be a novel and versatile method.[1–3] Since several reactions take place in a sequential fashion, cyclopropanation can be used for the synthesis of polycyclic organic molecules. Fused cyclopropane moiety is a basic unit of biologically active natural products such as CC-1065 and duocarmycin.[4] The construction of substituted pyridine frameworks has also been used by numerous groups in the total synthesis of alkaloids and other nitrogen containing natural products such as decumbenine B,[5] carnegine,[6] antidesma[7] and krukovine.[8] Lamellarin D, which is one of the most potent lead candidates for anticancer chemotherapy and is an inhibitor of topoisomerase I, can also be synthesized using the Heck reaction.[9]

Based on these reports we have developed a methodology for the synthesis of fused tetrahydropyridine derivatives via a palladium-catalyzed intramolecular Heck reaction[10] of substituted cyclic derivatives of *N*-aryl allyl amine (**5a**–**5j**) and cyclopropane-fused isoquinoline derivatives via palladium-catalyzed cyclopropanation[11–14] of *N*-aryl methallyl amines (**6a**–**6f**).

The starting materials for this palladium-catalyzed reaction were prepared by alkylation of bromomethylvinyl bromides **3** with monoallylated aniline derivatives **4**. At first the bromovinyl aldehydes **1** were reduced to get bromomethylvinyl alcohols **2** with $NaBH_4$ in CH_3CN at room temperature (25–30 °C). Then these bromomethylvinyl alcohols **2** were brominated using PBr_3 in CCl_4 to get bromomethylvinyl bromides **3**. On the other hand monoallylation of aniline derivatives was achieved from 4-substituted anilines and allyl bromides by using KF-Celite in CH_3CN at reflux temperature. After this, bromomethylvinyl bromides **3** were alkylated with monoallylated aniline derivatives **4** in the presence of Et_3N in DMF at 60 °C to get the precursors **5** and **6** for the Heck reaction (Scheme 1).

The precursors **5a**–**5j** on reaction with $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv) and Cs_2CO_3 (1.2 equiv) in DMF (6 mL) at 90–100 °C yielded the fused tetrahydropyridine derivatives **7a**–**7j** (Table 1) in excellent yield[15] via 6-*exo*-*trig* cyclization (Scheme 2).

But when N-methallylated derivatives **6a**–**6f** were subjected to the Heck reaction under the same reaction conditions[15] they gave cyclopropa[*d*]fused isoquinoline derivatives **8a**–**8f** (Scheme 3, Table 2).

A plausible rationale for the formation of the products (**8a**–**8f**) is shown in Scheme 4. At first an alkenyl palladium intermediate is formed by oxidative addition of Pd(0) to the sp^2 C–Br bond which undergoes addition to the unactivated double bond to produce an alkylpalladium which is again added to the unactivated double bond followed by β-H elimination to afford the cyclopropane-fused compounds[16–18] (Scheme 4).

Both electron-donating and electron-withdrawing substituents are compatible with this reaction except the nitro group. These reactions can also be performed with acetonitrile as a solvent and Et_3N as a base. A reaction temperature of 100 °C and a time of 5–6 h were found to be optimum. Lower temperatures and shorter reaction times lead to incomplete conversion of the starting materials to the products.

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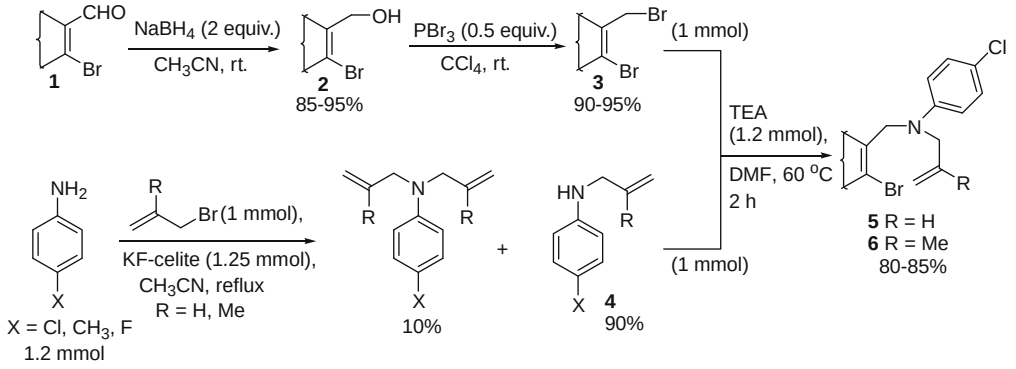


Scheme 1. Alkylation of bromomethylvinyl bromides with monoallylated aniline derivatives.

Table 1
Pd(0)-catalyzed intramolecular reaction of *N*-aryl allyl derivative **5**

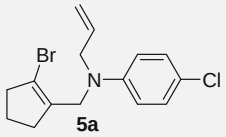
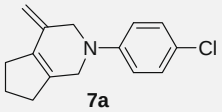
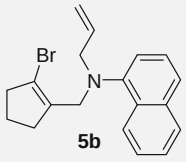
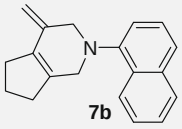
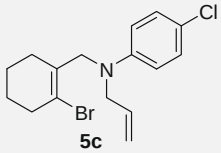
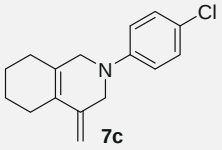
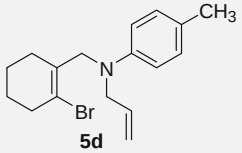
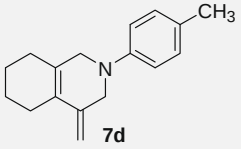
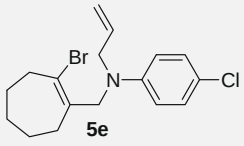
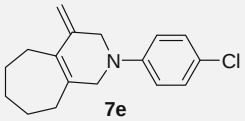
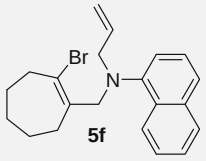
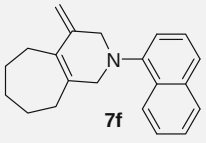
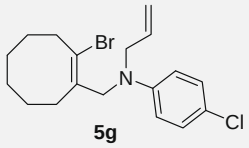
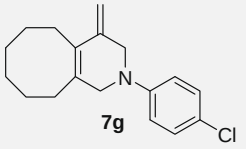
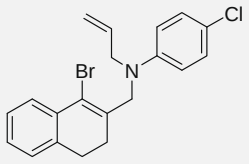
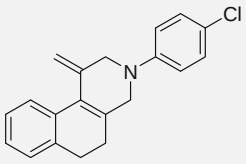
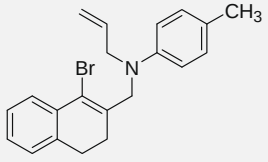
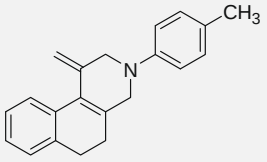
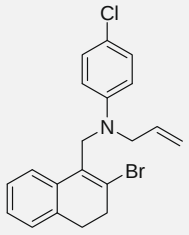
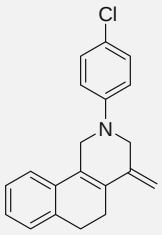
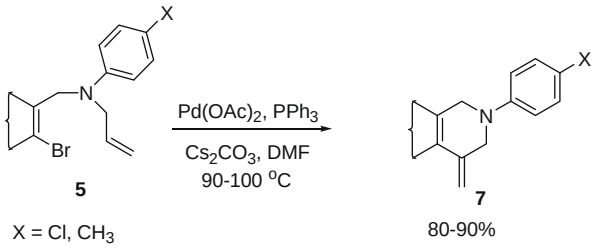
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **5a**	 **7a**	5	82
2	 **5b**	 **7b**	5.5	80
3	 **5c**	 **7c**	5	90
4	 **5d**	 **7d**	5	85
5	 **5e**	 **7e**	6	88
6	 **5f**	 **7f**	5.5	80

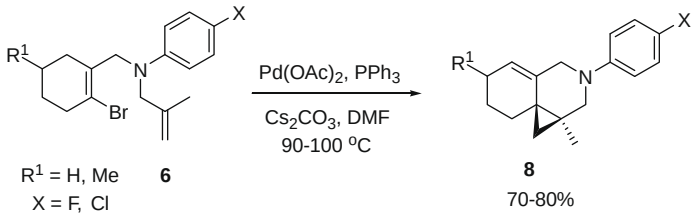
Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)
7	 **5g**	 **7g**	5	90
8	 **5h**	 **7h**	6	81
9	 **5i**	 **7i**	6	80
10	 **5j**	 **7j**	5.5	85



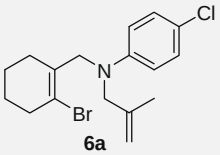
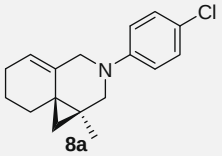
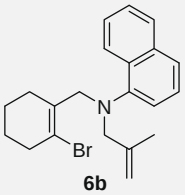
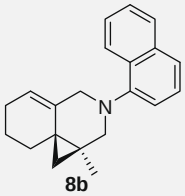
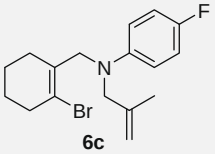
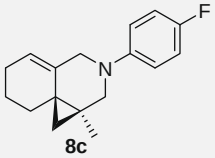
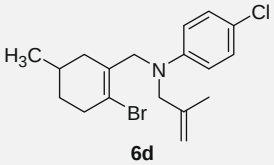
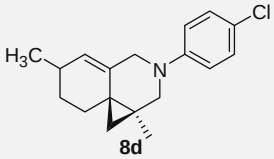
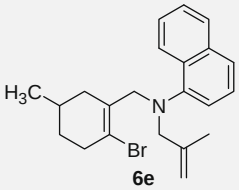
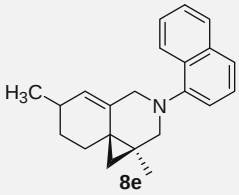
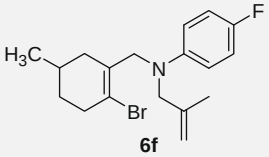
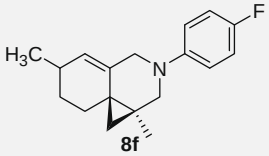
Scheme 2. Pd(0)-catalyzed intramolecular cyclization of *N*-aryl allyl derivative **5**.

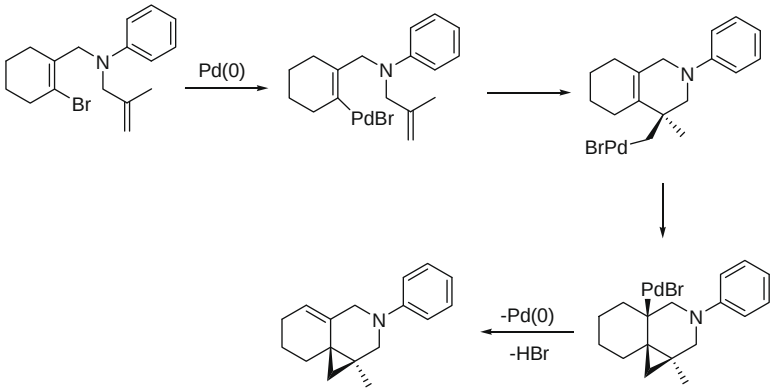
In conclusion, we have developed a general methodology for the synthesis of fused tetrahydropyridine derivatives and cyclopropane-fused compounds by a palladium-catalyzed domino reaction. This methodology can also be used for the synthesis of various types of nitrogen containing natural products and other heterocyclic compounds.



Scheme 3. Pd(0)-catalyzed intramolecular cyclization of *N*-aryl methallyl derivative **6**. Reagents and conditions: **5a**–**5j** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), DMF, 90–100 °C.

Table 2
Pd(0)-catalyzed intramolecular reaction of *N*-aryl methallyl derivative **6**

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **6a**	 **8a**	5	80
2	 **6b**	 **8b**	2.5	73
3	 **6c**	 **8c**	5	75
4	 **6d**	 **8d**	6	70
5	 **6e**	 **8e**	6	65
6	 **6f**	 **8f**	5.5	66



Scheme 4. A plausible rationale for the Pd(0)-catalyzed cyclopropanation reaction. Reagents and conditions: **6a–6f** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), DMF, 90–100 °C.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.156.

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15. *Typical experimental procedure for the Heck reaction*: Compounds **5** or **6** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv) and DMF (6 mL) were placed in a two-neck round-bottomed flask. After degassing with N_2, the mixture was heated at 90–100 °C for 5 h. After cooling, the reaction mixture was diluted with cold water and extracted with ether (30 mL × 3) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by preparative thin layer chromatography.
Spectral data of representative compounds: 2-(4-Chloro-phenyl)-4-methylene-1,2,3,4,5,6-hexahydro-benzo[*h*]isoquinoline (**7j**): Yellow liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.50 (t, 2H, J = 8.4 Hz), 2.84 (t, 2H, J = 8.2 Hz), 4.01 (s, 2H), 4.23 (s, 2H), 5.05 (s, 1H), 5.25 (s, 1H), 6.97 (dd, 2H, J_1 = 2.0 Hz, J_2 = 8.8 Hz), 7.18–7.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: CH_2 at 22.25, 27.77, 50.04, 53.36, 109.05, CH at 117.65 (2C), 121.84, 126.50, 127.27, 127.50, 128.94 (2C), qC at 128.91, 129.01, 130.46, 133.78, 136.12, 139.74, 149.05; Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; N, 4.55. Found: C, 78.20; H, 6.0; N, 4.41; HRMS calcd for $C_{20}H_{19}ClN$ [M^++H]: 308.1206, found: 308.1104.
3-(4-Chloro-phenyl)-1a-methyl-1,1a,2,3,4,6,7,8-octahydro-3-aza-cyclopropa[d]naphthalene (**8a**): Yellow liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.29 (d, 1H, J = 4.6 Hz), 1.16 (d, 1H, J = 4.6 Hz), 1.19 (s, 3H), 1.68–1.78 (m, 4H), 2.09 (br s, 2H), 3.07 (d, 1H, J = 12 Hz), 3.51 (t, 2H, J = 11.6 Hz), 3.82–3.92 (m, 1H), 5.59–5.63 (m, 1H), 6.63 (dd, 2H, J_1 = 2.0 Hz, J_2 = 7 Hz), 7.15 (dd, 2H, J_1 = 2.2 Hz, J_2 = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: CH_3 at 17.28, CH_2 at 21.84, 22.20, 25.27, 28.96, 51.0, 51.96, CH at 113.97 (2C), 121.36, 128.72 (2C), qC at 23.90, 25.40, 121.53, 134.24, 148.48; Anal. Calcd for $C_{17}H_{20}ClN$: C, 74.57; H, 7.36; N, 5.12. Found: C, 74.69; H, 7.49; N, 4.99; HRMS calcd for $C_{17}H_{21}ClN$ [M^++H]: 274.1363, found: 274.1355.
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