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Synthesis of functionalized tetrahydroisoquinolines via palladium-catalyzed 6-*exo*-*dig* carbocyclization of 2-bromo-*N*-propargylbenzylamines

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ABSTRACT

An efficient twostep synthetic strategy for tetrahydroisoquinolines has been described. The first step involves CuI catalyzed three-component coupling reaction of terminal alkyne, aldehyde and amine that provides the requisite propargyl amine. Regio- and stereoselective palladium-catalyzed 6-*exo*-*dig* carbocyclization of propargyl amine, which provides a concise access to functionalized tetrahydroisoquinolines in good yields has been developed.

Tetrahydroisoquinolines are an important class of heterocyclic compounds found in a wide range of natural products. They comprise the largest family of alkaloids (Fig. 1),[1] that exhibit important biological activities including antiarrhythmic, angiotensin-converting enzyme inhibition, antihypertensive, antitumor, antimicrobial, antiplasmodial, noncompetitive inhibition to AMPA receptor and antidepression activities[2,3f] furthermore, they are used as synthetic intermediates for an array of substances.[3] The wide range of biological and pharmacological importance of tetrahydroisoquinolinones prompted us to synthesize these heterocycles utilizing a simple and efficient method.

In general, tetrahydroisoquinolines have been constructed through various methods like Bischler–Napieralski reactions which involves cyclization of a β-arylethylamide to a 1-substituted 3,4-dihydroisoquinoline or a corresponding isoquinolinium salt, which is then reduced in the next step,[3h] Pictet–Spengler reaction, which includes the acid-catalyzed cyclization of a β-arylethylamine with an aldehyde,[3h] intramolecular Friedel–Crafts alkylation,[4] acid-catalyzed cyclization of benzalamino acetals in C_4–C_{4a} bond formation,[5] C_1–N_2 connectivity approach by Meyers and Munchhof reaction,[6] transition metal catalyzed C–C bond formation[7] etc.

Among various synthetic strategies, catalytic transformation by means of transition-metal catalysts is one of the modern approaches for the synthesis of substituted tetrahydroisoquinoline derivatives. Due to our interest in developing novel routes to common heterocycles,[8] herein we report a new and efficient two-step protocol for the synthesis of tetrahydroisoquinolines, which involves CuI-catalyzed three component coupling of aldehyde, alkyne and amine (A^3 coupling)[9] providing the required propargylamines, followed by a regio- and stereoselective Pd-catalyzed intramolecular acetylene hydroarylation.

We first investigated the coupling reactions of *N*-(2-bromobenzyl)(phenyl)methanamine **1** (R^1 = H, 1 equiv), aldehyde **2** (R^2 = 4-MePh, 1.2 equiv) and acetylene **3** (R^3 = Ph, 1.5 equiv) using 10 mol % of CuI as catalyst (Scheme 1). It was found that the propargyl amine **4** (R^1 = H, R^2 = 4-MePh, R^3 = Ph) was formed in 76% yield by stirring at 100 °C for 3 h in toluene (Table 1, entry 1). Similarly, when the reaction was run with CuBr, the same propargylic amine was obtained in 70% yield (Table 1, entry 2). It was found that the amount of catalyst also affects the yield of the product. Increasing the catalyst amount to 15 mol % CuI and CuBr resulted in very good yields of 85% and 78%, respectively (Table 1, entries 3 and 4). Further increment of catalyst amount did not alter the reaction yield (Table 1,

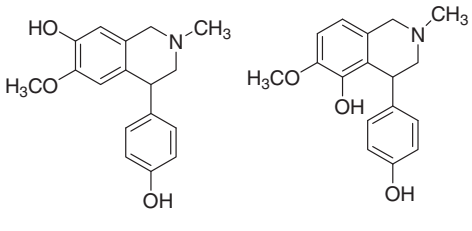

Figure 1. Representative structures of tetrahydroisoquinolines.

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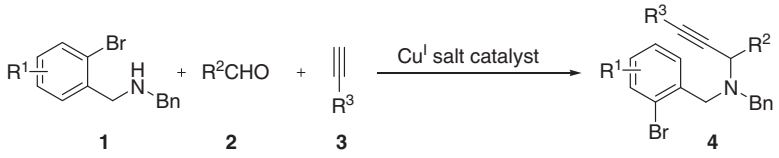


Scheme 1. Optimization of three component coupling reaction.

Table 1
Optimization of three component coupling reaction

Entry	Catalyst	mol %	Temperature (°C)	Yield[a,b] (%)
1	CuI	10	100	76
2	CuBr	10	100	70
3	CuI	15	100	85
4	CuBr	15	100	78
5	CuI	20	100	84
6	CuI	15	70	60
7	CuI	15	rt	0[c]

[a] The reactions were performed with amine **1** (R^1 = H, 0.5 mmol), *p*-tolualdehyde **2** (0.55 mmol) and phenylacetylene (0.75 mmol).
[b] Isolated yields.
[c] Amine **1** remains unconsumed.

entry 5). When the reaction was carried out at a lower temperature of 70 °C, the yield decreased to 60% (Table 1, entry 6). However the reaction at ambient temperature for prolonged time met with failure (Table 1, entry 7).

To generalize the reaction,[11] the coupling of amine with various aldehydes and alkynes, was carried out under optimal conditions (Scheme 2). The results are summarized in Table 2. The results indicated that aromatic aldehydes bearing such functional groups as fluoro, chloro, methyl and methoxy were able to effect the A^3 coupling. Aliphatic aldehydes also displayed clean reactions under this standard condition. Various terminal alkynes were also examined. Both aromatic and aliphatic alkynes reacted smoothly with aldehyde and amine to give the corresponding products in good yields. To expand the scope of amine substrates, we used a substituted aryl amine. The coupling proceeded smoothly to afford the corresponding propargylamines in good yields under standard conditions. Formation of propargylamine derivatives was confirmed by ^{1}H and ^{13}C NMR spectroscopic techniques. The ^{1}H NMR spectra of compound **4d** in $CDCl_3$ consisted of a characteristic singlet due to the methine proton (N–C*H*–) in the region of 4.92 ppm. In the ^{13}C NMR spectra, the appearance of two distinguishable peaks at 85.1 and 88.7 ppm corresponded to two acetylenic carbons. These observations confirmed the formation of propargyl amine (**4d**).[12]

We then investigated the intramolecular cyclization of propargylamine **4** (R^1 = H, R^2 = 4-MePh, R^3 = Ph) using 3 mol % of $Pd(PPh_3)_4$ as catalyst and sodium formate as a reducing agent under conventional heating condition. The optimal solvent system for the cyclization was found to be a DMF/water mixture (3:1). Water was essential to activate the reducing agent in this reaction.[10] The catalytic activity of various palladium catalysts were examined in a model reaction of propargylamine **4** (R^1 = H, R^2 = 4-MePh, R^3 = Ph) in DMF/H_2O solvent system under nitrogen atmosphere at 100 °C for 3 h and the results are summarized in Table 3. To our delight,

Table 2
Synthesis of propargylamines (**4a–l**)

Entry	Substrate			Product (4)	Yield[a,b] (%)
	R^1	R^2	R^3		
1	H	Ph	Ph	**4a**	84
2	H	4-$CH_3C_6H_4$	Ph	**4b**	85
3	H	4-ClC_6H_4	Ph	**4c**	87
4	H	4-$OMeC_6H_4$	Ph	**4d**	80
5	H	2-FC_6H_4	Ph	**4e**	84
6	H	*iso*-Propyl	Ph	**4f**	90
7	H	H	Ph	**4g**	82
8	H	Ph	4-$OMeC_6H_4$	**4h**	86
9	H	4-$CH_3C_6H_4$	*n*-Butyl	**4i**	83
10	4,5-OMe	4-ClC_6H_4	*n*-Butyl	**4j**	85
11	4,5-OMe	H	Ph	**4k**	84
12	4,5-OMe	4-$CH_3C_6H_4$	4-$OMeC_6H_4$	**4l**	83

[a] Isolated yields.
[b] All the compounds were characterized by IR, ^{1}H and ^{13}C NMR and mass spectroscopic techniques.

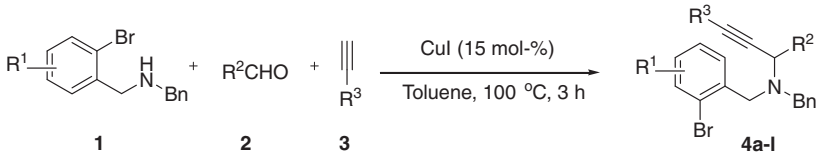
Table 3
Optimization of carbocyclization reaction using different Pd catalysts

Entry	Solvent (v/v)	Catalyst	Time (h)	Yield[a] (%)
1	DMF/H_2O (1:0)	$Pd(PPh_3)_4$	3	55
2	DMF/H_2O (3:1)	$Pd(PPh_3)_4$	3	78
3	DMF/H_2O (4:1)	$Pd(PPh_3)_4$	3	68
4	DMF/H_2O (3:1)	$Pd(OAc)_2$ + $2PPh_3$	3	76
5	DMF/H_2O (3:1)	$PdCl_2$ + $2PPh_3$	3	70
6	DMF/H_2O (3:1)	$Pd(PPh_3)_4$	3	65[b]
7	DMF/H_2O (3:1)	$Pd(PPh_3)_4$	12	62[b]

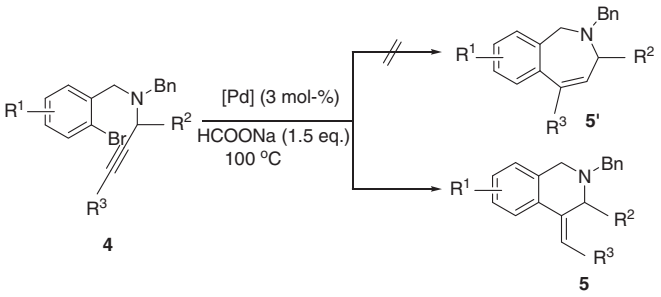
[a] The reactions were carried out with propargylamine **4** (R^1 = H, R^2 = 4-MePh, R^3 = Ph, 0.4 mmol) in the presence of HCOONa (0.6 mmol) and $Pd(PPh_3)_4$ (3 mol %) in DMF/H_2O (3:1) (6 mL) at 100 °C (oil bath temperature) in 70 mM concentration.
[b] The reactions were run in 140 mM concentration.

the intramolecular carbocyclisation reaction proceeded smoothly and generated the desired product **5** (R^1 = H, R^2 = 4-MePh, R^3 = Ph) in 78% yield, representing one of the best results when 3 mol % of $Pd(PPh_3)_4$ was used as the catalyst (Table 3, entry 2). Higher yields for cyclization were generated when a higher dilution (70 mM) was employed (Scheme 3 and Table 3).

Having the optimized conditions in hand,[13] the analogs of tetrahydroisoquinoline **5** were synthesized in good yields and are presented in Table 4 and Scheme 4. The high stereo- and regioselectivity of the cyclization step leading to one isomer exclusively was confirmed with the aid of ^{1}H NMR data. In ^{1}H NMR spectrum, the compound **5d** exhibited two sharp singlets at 4.98 and



Scheme 2. Synthesis of substituted propargylamines.



Scheme 3. Optimization of palladium catalyzed carbocyclization reaction.

7.45 ppm indicated the presence of methine and vinylic protons, respectively. This observation showed that these two protons are not adjacent to each other which ruled out the possibility of formation of a seven-membered ring(Scheme 3). All these findings confirmed the formation of the *exo*-cyclic six-membered ring. The exclusive formation of the *Z*-isomer was attributed to the *syn*-addition of the Pd on to the triple bond. The *(Z)*-stereochemistry of compound has been assigned using a 1-D NOE experiment. Selective irradiation of the vinylic proton effected the enhancement of the signals of C_5–H (11%; Fig. 2a). Irradiation of C_3–H effected the enhancement of *ortho*-anisyl proton (9%) and *ortho*-phenyl proton (15%). There is no enhancement of vinylic proton (Fig. 2b). This observation confirmed that the vinylic proton is *cis* to C_5–H, thus compound **5d** is *Z* configured.[14] A possible pathway of the Pd-catalyzed intramolecular carbocylization is shown in Scheme 5.

In summary, we have developed a new and efficient two-step protocol for the synthesis of tetrahydroisoquinolines. The first step

Table 4
Synthesis of tetrahydroisoquinoline derivatives **(5a–l)**

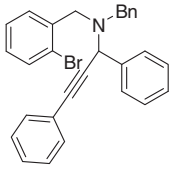
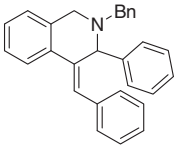
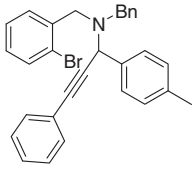
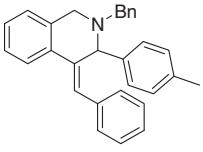
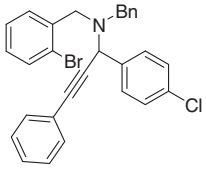
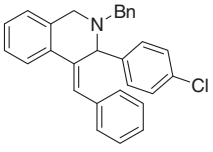
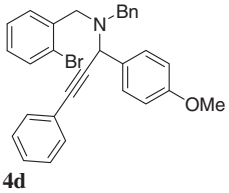
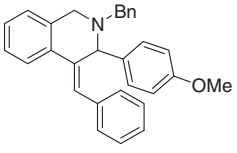
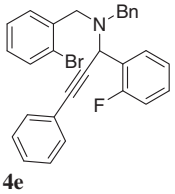
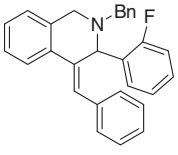
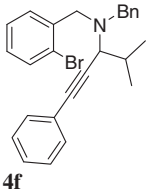
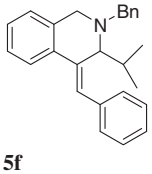
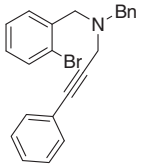
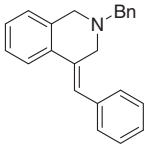
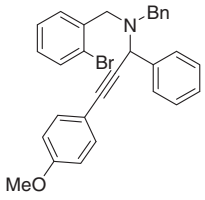
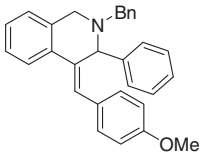
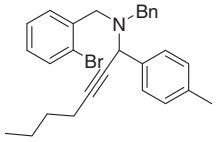
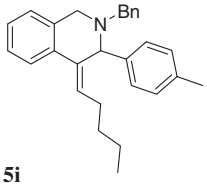
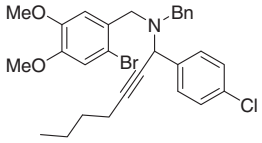
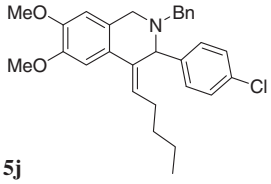
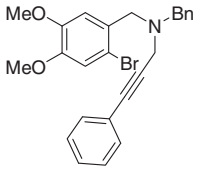
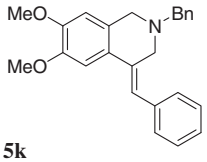
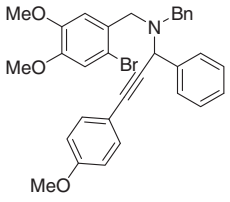
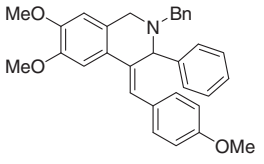
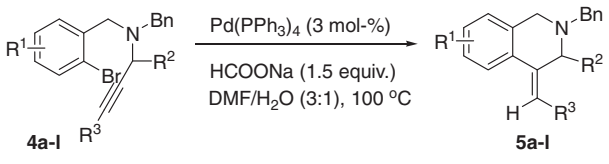
Entry	Substrate (4)	Product (5)	Yield[a,b] (%)
1	 **4a**	 **5a**	76
2	 **4b**	 **5b**	78
3	 **4c**	 **5c**	75
4	 **4d**	 **5d**	73
5	 **4e**	 **5e**	76
6	 **4f**	 **5f**	79

Table 4 (*continued*)

Entry	Substrate (4)	Product (5)	Yield[a,b] (%)
7	 **4g**	 **5g**	70
8	 **4h**	 **5h**	77
9	 **4i**	 **5i**	70
10	 **4j**	 **5j**	71
11	 **4k**	 **5k**	68
12	 **4l**	 **5l**	76

[a] Isolated yields.
[b] All the compounds were characterized by IR, ^{1}H and ^{13}C NMR and mass spectroscopic techniques.



Scheme 4. Synthesis of tetrahydroisoquinoline derivatives.

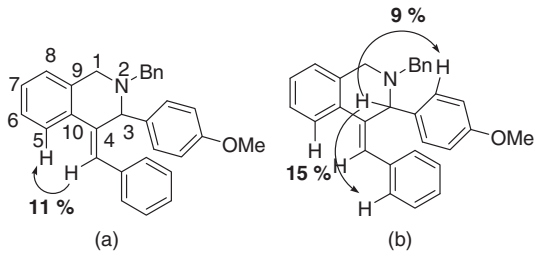
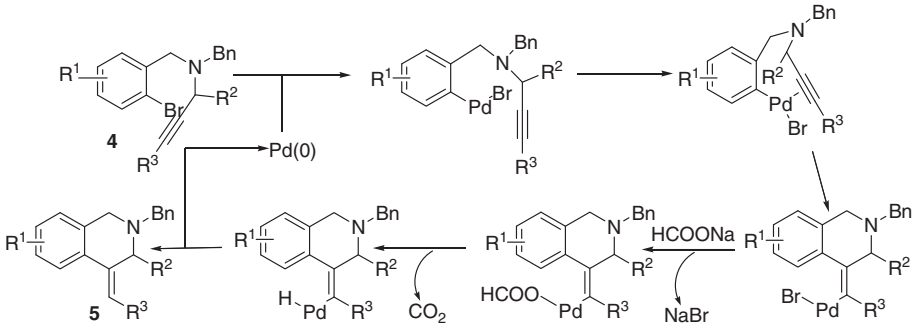


Figure 2. 1-D NOE enhancement of compound **5d**.

is a CuI-catalyzed three-component coupling of an aldehyde, an alkyne and an amine leading to propargylamines, which are the key intermediates for the regio- and stereoselective Pd-catalyzed intramolecular acetylene hydroarylation that generates the tetrahydroisoquinolines. The scope of this reaction and its application for the bioactive compounds is currently under investigation in our laboratory.



Scheme 5. A possible pathway for the formation of product **5**.

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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.2011.01.127.

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11. *General procedure for the synthesis of propargylamine* (**4**): A mixture of CuI (15 mol %), amine (0.50 mmol), aldehyde (0.55 mmol) and phenylacetylene (0.75 mmol) in toluene (3 mL) was heated at 100 °C for 3 h. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. After removal of the solvent, the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent, affording compound in good yield (shown in Table 2).
12. *Spectral data of compound* (**4d**): *N*-(2-bromobenzyl)-*N*-benzyl-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine; yellow oil; R_f 0.80 (5% AcOEt/petroleum ether); IR (KBr): 1020, 1242, 1593, 2363, 2928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.63 (d, J = 13.75 Hz, 1H, $-CH_2$-Ar), 3.72 (d, J = 14.50 Hz, 1H, $-CH_2$-Ar), 3.81 (s, 3H, $-OCH_3$), 3.82 (d, J = 13.75 Hz, 1H, $-CH_2$-Ar), 4.00 (d, J = 14.55 Hz, 1H, $-CH_2$-Ar), 4.92 (s, 1H, $-CH$), 6.92 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.10 (t, J = 7.65 Hz, 1H, Ar-*H*), 7.26 (t, J = 7.65 Hz, 1H, Ar-*H*), 7.31–7.35 (m, 3H, Ar-*H*), 7.40–7.42 (m, 3H, Ar-*H*), 7.46 (d, J = 7.65 Hz, 2H, Ar-*H*), 7.52 (d, J = 7.65 Hz, 1H, Ar-*H*), 7.66–7.69 (m, 5H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.9, 55.0, 55.4, 55.9, 85.1, 88.7, 113.6, 123.4, 124.8, 127.2, 127.5, 128.4, 128.5, 129.1, 129.6, 130.8, 131.1, 132.1, 132.8, 138.7, 139.4, 159.1; MS (EI): m/z 496.58 $[M+H]^+$; Anal. Calcd for $C_{30}H_{26}BrNO$: C, 72.58; H, 5.28; N, 2.82. Found: C, 72.62; H, 5.26; N, 2.85.
13. *General procedure for the synthesis of compound* (**5**): $Pd(PPh_3)_4$ (3 mol %) and HCOONa (1.5 equiv) were added into a two-neck round bottom flask. The flask was evacuated and flushed with nitrogen. Propargylamine (0.4 mmol) dissolved in DMF (4.5 ml) was added, followed by distilled water (1.5 ml). The flask was heated to 100 °C in an oil bath for 3 h under N_2 atmosphere. Upon completion of the reaction the mixture was diluted with CH_2Cl_2. The organic phase was washed several times with brine, dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The crude product was chromatographed (petroleum ether/ethyl acetate as eluent) and its appropriate yield is shown in Table 4.
14. *Spectral data of compound* (**5d**): (*Z*)-2-benzyl-4-benzylidene-1,2,3,4-tetrahydro-3-(4-methoxyphenyl)isoquinoline; yellow oil; R_f 0.71 (5% AcOEt/petroleum ether); IR (KBr): 1024, 1237, 1564, 1645, 2369, 2938 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.54 (d, J = 13.75 Hz, 1H, $-CH_2$-Ar), 3.60 (d, J = 14.50 Hz, 1H, $-CH_2$-Ar), 3.73 (d, J = 13.75 Hz, 1H, $-CH_2$-Ar), 3.77 (s, 3H $-OCH_3$), 3.84 (d, J = 14.55 Hz, 1H, $-CH_2$-Ar), 4.98 (s, 1H, $-CH$), 6.83 (d, J = 8.4 Hz, 2H, Ar-*H*), 6.89 (d, J = 7.65 Hz, 1H, Ar-*H*), 7.12–7.14 (m, 5H, Ar-*H*), 7.16–7.22 (m, 6H, Ar-*H*), 7.29 (t, J = 7.85 Hz, 1H, Ar-*H*), 7.37 (d, J = 9.15 Hz, 2H, Ar-*H*), 7.45 (s, 1H, $=CH$), 7.83 (d, J = 7.65 Hz, 1H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.6, 55.2, 58.2, 60.9, 113.8, 124.2, 126.7, 126.8, 126.9, 127.1, 127.8, 128.0, 128.3, 128.6, 128.7, 129.0, 129.6, 132.4, 132.9, 133.8, 134.3, 137.0, 139.2, 158.7, 163.1; MS (EI): m/z 418.60 $[M+H]^+$; Anal. Calcd for $C_{30}H_{27}NO$: C, 86.30; H, 6.52; N, 3.35. Found: C, 86.33; H, 6.55; N, 3.33.