Palladium-Mediated Intramolecular Buchwald–Hartwig α-Arylation of β-Amino Esters: Synthesis of Functionalized Tetrahydroisoquinolines

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Received 7 April 2011

Dedicated to Professor A. Srikrishna

Abstract: A concise and efficient three-step strategy for the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines based on an intramolecular Buchwald–Hartwig α-arylation of β-amino esters is described. The synthesis presented is operationally simple and is amenable for the synthesis of a number of analogues.

Key words: palladium catalysis, α-arylation, tetrahydroisoquinolines, natural products

Transition-metal catalysis is a powerful tool that permits C–C bond-forming reactions most efficiently. In this context, palladium turns out to be one of the most used metals suitable for oxidations, reductions, and many efficient cross-coupling reactions. Some important classical palladium-mediated cross-coupling reactions are the Heck,[1] Stille,[2] Suzuki,[3] Sonogashira,[4] and Buchwald–Hartwig[5] couplings; while in recent years, C–H activation reactions via organopalladium intermediates have became popular in organic synthesis.[6,7] One useful reaction mediated by palladium is the α-arylation of carbonyl compounds developed by Buchwald and Hartwig. A useful application of this reaction includes the synthesis of N-heterocycles involving intramolecular arylation of α-haloaniline-based carbonyl compounds.[8] In this context, Hartwig et al. reported the synthesis of a δ-lactam using Pd-mediated intramolecualr α-arylation, albeit in poor yield. Later the research group of Honda improved the strategy, by incorporating an α-aryl group onto the amide, thereby increasing the acidity of α-hydrogen atom. Highlighting the importance of transition-metal catalysis, as an alternative to the Pictet–Spengler reaction for the synthesis of tetrahydroisoquinoline, Buchwald et al. disclosed the Pd-catalyzed α-arylation of esters, wherein the ester functionality resides on a carbon α-to the nitrogen atom.[9] Herein we report a concise, practical, and efficient strategy for the synthesis of tetrahydroisoquinolines based on a hitherto unexplored intramolecular Buchwald–Hartwig α-arylation of (*N*-2-bromobenzyl)-β-amino esters, in which the ester functionality is located on the carbon β-to the nitrogen atom.

The 1,2,3,4-tetrahydroisoquinoline moiety is a ubiquitous structural unit present in a number of isoquinoline alkaloid natural products,[10] which exhibit biological properties such as antitumor,[11] antimicrobial,[11,12] anti-inflamatory,[13] anti-HIV,[14] and analgesic[15] activities. Representative examples of such structures are cherylline, latifine,[16,17] canadine,[18] stepharinine, pronuciferine,[19] erythrocarine,[20] and 6,6a-dihydrodemethoxygaudiscine[21] (Figure 1).

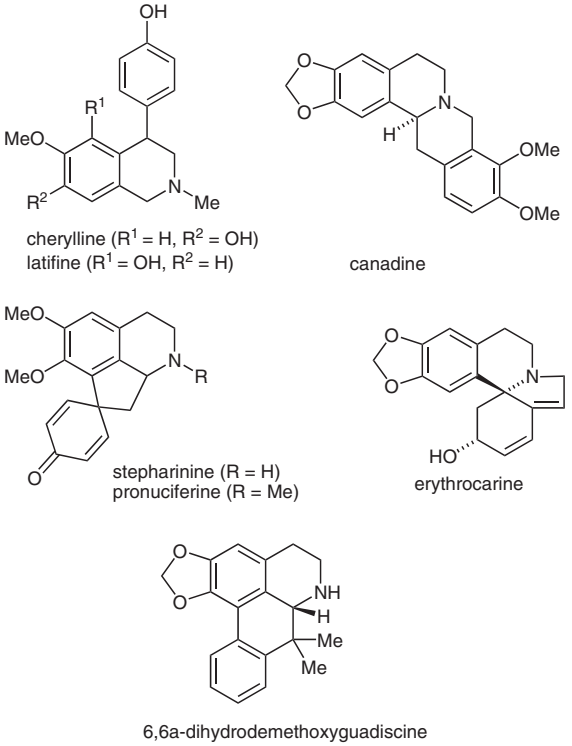
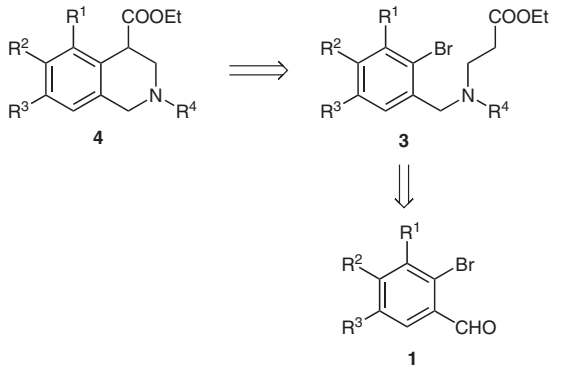


Figure 1 Representative examples of naturally occurring isoquinoline alkaloid natural products

Our approach to the synthesis of substituted 1,2,3,4-tetrahydroisoquinolines **4** is based on an intramolecular Pd-mediated α-arylation of an ester-enolate, derived from **3**, as the key transformation. The required precursors **3** could be obtained from the readily available *ortho*-bromobenzaldehydes **1** by a reductive amination followed by an intermolecular aza-Michael reaction (Scheme 1).

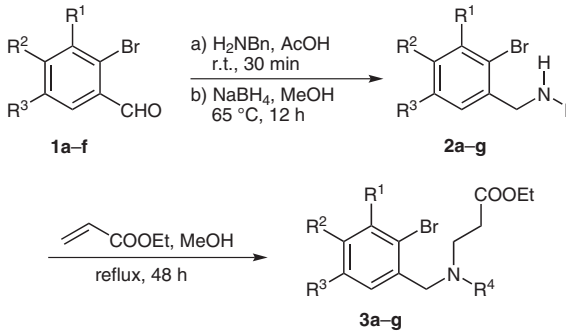
Accordingly, treatment of 2-bromobenzaldehydes **1a–f**[22] with benzylamine in refluxing methanol in the presence of a catalytic amount of acetic acid followed by addition of sodium borohydride, led to the secondary amines **2a–g** in

SYNLETT 2011, No. 12, pp 1756–1760
Advanced online publication: 05.07.2011
DOI: 10.1055/s-0030-1260934; Art ID: D10811ST



Scheme 1 Retrosynthesis for 1,2,3,4-tetrahydroisoquinolines

very good (74–94%) yields.[5g] Reaction of the amines **2a–g** with ethyl acrylate in refluxing methanol furnished the *N*-benzyl esters **3a–g** in excellent (86–95%) yields[23] (Scheme 2, Table 1).

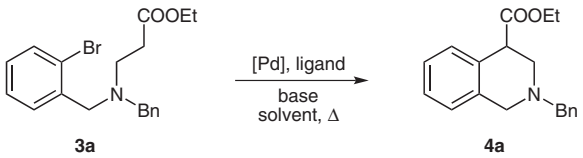


Scheme 2 Synthesis of amino esters **3a–g** via secondary amines **2a–g** using bromobenzaldehydes **1a–f**

Table 1 Synthesis of Amino Esters **3a–g** via Secondary Amines **2a–g**

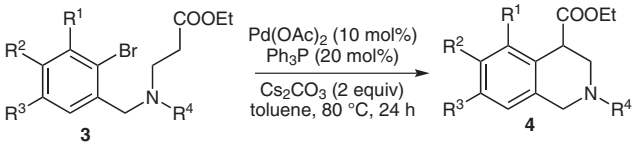
Aldehyde **1**	R^1	R^2	R^3	R^4	Yield of **2** (%)	Yield of **3** (%)
1a	H	H	H	Bn	**2a** 94	**3a** 88
1b	H	OMe	OMe	Bn	**2b** 91	**3b** 95
1c	OMe	OMe	OMe	Bn	**2c** 91	**3c** 92
1d	H	H	OMe	Bn	**2d** 93	**3d** 86
1e	H	OCH_2	OCH_2	Bn	**2e** 93	**3e** 93
1f	H	H	OBn	Bn	**2f** 74	**3f** 90
1g	H	H	H	4-$MeC_6H_4CH_2$	**2g** 87	**3g** 84

With the bromo esters **3a–g** in hand, the key Buchwald–Hartwig α-arylation of the ester **3a** was performed under various conditions, and the results are summarized in Table 2. Reaction of the ester **3a** under standard Buchwald conditions with $Pd(dba)_2$ (5 mol%), *N*-[2′-(dicyclohexylphosphino)-1,1′-biphenyl-2-yl]-*N*,*N*-dimethylamine ligand (10 mol%), and either with NaHMDS (4 equiv) or with KO*t*-Bu (4 equiv) as base in THF failed to furnish the product, and starting material was recovered (entries 1 and 2, Table 2). A similar outcome was observed on changing the ligand to Ph_3P (10 mol% or 20 mol%), solvent to DMF at 80 °C, or increasing reaction time (24 h) or quantity of the bases KO*t*-Bu (4 equiv) and Cs_2CO_3 (2 equiv; entries 3–5, Table 2). Change of solvent to toluene and performing the reaction under microwave irradiation at 70 °C for one hour also failed to produce the product (entry 6, Table 2). Interestingly, an increase in temperature from 70 °C to 110 °C and longer reaction time (3 h) led to formation of the expected product **4a** in moderate 40% yield (entry 7, Table 2, Scheme 3). Changing the base from Cs_2CO_3 to K_2CO_3 and performing the reaction in toluene at 70 °C for 24 hours did not yield any product (entry 8, Table 2); while performing the reaction at higher temperature 110 °C and longer reaction time (48 h), gave the product **4a** in moderate yield 43% (entry 9, Table 2). Interestingly, the reaction with K_3PO_4 as the base in hot toluene afforded the product **4a** in 35% yield along with acid resulting from the hydrolysis of the ester (entry 10, Table 2). Employing $Pd(OAc)_2$/BINAP as catalyst in combination with KO*t*-Bu in anhydrous toluene or $Pd(OAc)_2/Ph_3P$ with KO*t*-Bu/NaHMDS in anhydrous THF were unsuccessful and produced the acid resulting from saponification of the ester (entries 11–13, Table 2). It is not clear how the acid was generated under the reaction conditions, although it is unlikely to form during neutral workup. An improved yield of 61% of the product **4a** was observed when the reaction was performed with Cs_2CO_3 as base in toluene at 120 °C (entry 14, Table 2). Finally, increase of catalyst [$Pd(OAc)_2$] loading from 5 mol% to 10 mol% and that of ligand (Ph_3P) from 10 mol% to 20 mol% smoothly furnished the α-arylated product **4a** in very good yield 82% (entry 15, Table 2). Furthermore, use of $Pd[PPh_3]_4$ (10 mol%) under similar conditions without using the phosphine ligand afforded the product **4a** in good yield 68% (entry 16, Table 2).



Scheme 3

After optimizing the reaction conditions, the generality of the reaction was established by transforming the esters **3a–g** into the tetrahydroisoquinolines **4a–g**, and the results are summarized in Table 3 (Scheme 4).[24]



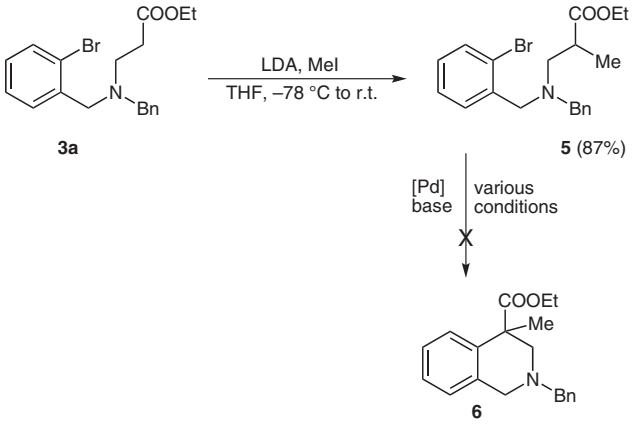
Scheme 4

Table 2 Optimization of Reaction Conditions for the Synthesis of 1,2,3,4-Tetrahydroisoquinolines

Entry[a]	Pd (mol%)	Ligand (mol%)	Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield of **4a** (%)[b]
1	$Pd(dba)_2$ (5)	L[c] (10)	THF	NaHMDS (4)	65	12	0
2	$Pd(dba)_2$ (5)	L[c] (10)	THF	*t*-KOBu (4)	65	12	0
3	$Pd(dba)_2$ (5)	Ph_3P (10)	DMF	*t*-KOBu (4)	80	24	0
4	$Pd(dba)_2$ (5)	Ph_3P (10)	DMF	Cs_2CO_3 (2)	80	24	0
5	$Pd(dba)_2$ (5)	Ph_3P (20)	DMF	Cs_2CO_3 (2)	80	24	0
6	$Pd(OAc)_2$ (5)	Ph_3P (10)	toluene	Cs_2CO_3 (3)	70 (MW)	1	0
7	$Pd(OAc)_2$ (5)	Ph_3P (10)	toluene	Cs_2CO_3 (3)	110 (MW)	3	40
8	$Pd(OAc)_2$ (5)	Ph_3P_3 (10)	toluene	K_2CO_3 (4)	70	24	0
9	$Pd(OAc)_2$ (5)	Ph_3P (10)	toluene	K_2CO_3 (4)	110	48	43
10	$Pd(OAc)_2$ (5)	Ph_3P (20)	toluene	K_3PO_4 (2)	80	24	35[d]
11	$Pd(OAc)_2$ (5)	BINAP (10)	toluene	*t*-KOBu (3)	120	24	[d]
12	$Pd(OAc)_2$ (5)	Ph_3P (10)	THF	*t*-KOBu (4)	65	24	[d]
13	$Pd(OAc)_2$ (5)	Ph_3P (10)	THF	NaHMDS (4)	65	24	[d]
14	$Pd(OAc)_2$ (5)	Ph_3P (10)	toluene	Cs_2CO_3 (2)	120	32	61
15	$Pd(OAc)_2$ (10)	Ph_3P (20)	toluene	Cs_2CO_3 (2)	80	24	82
16	$Pd[PPh_3]_4$ (10)	no ligand	toluene	Cs_2CO_3 (2)	80	24	68

[a] Unless otherwise noted all the reactions were carried out under anhydrous and inert atmospheric conditions.
[b] Isolated yields of chromatographically pure products.
[c] *N*-[2′-(Dicyclohexylphosphino)-1,1′-biphenyl-2-yl]-*N*,*N*-dimethylamine was used as a ligand.
[d] Corresponding acid resulting from the hydrolysis of the ester is isolated.

In order to check the scope and limitation of the method, the reactivity of the secondary ester **5**, which would produce a tetrahydroisoquinoline possessing a quaternary carbon, was investigated. Thus, LDA-mediated methylation of the bromo ester **3**, at –78 °C gave the methylated product **5** in 87% yield. However, Pd-catalyzed α-arylation under various conditions failed to furnish the cyclized product **6** (Scheme 5).



Scheme 5

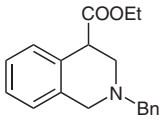
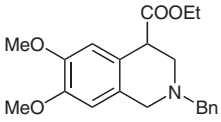
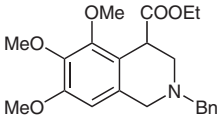
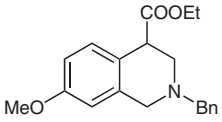
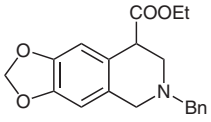
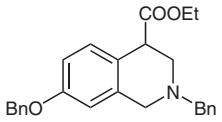
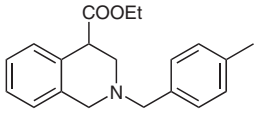
In summary, we have developed a short and efficient three-step strategy for the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines based on an intramolecular Buchwald–Hartwig α-arylation of β-amino esters. The strategy is very efficient and amenable for the synthesis of a number of analogues. Further investigations on the application of the current strategy for the construction of quaternary carbon center, synthesis of pharmaceutically interesting compounds, and for the total synthesis of isoquinoline alkaloid natural products are in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support by the Department of Science and Technology [(DST), CHE/2010-11/006/DST/GSN], New Delhi, and Indian Institute of Technology (IIT), Hyderabad, is gratefully acknowledged. We thank Prof. K. R. Prasad for his valuable suggestions. A.G.K. and J.K. thank CSIR, New Delhi, for the award of research fellowship.

Table 3 Synthesis of Tetrahydroisoquinolines **4a–g** by Buchwald–Hartwig α-Arylation of Amino Bromo Esters **3a–g**

Entry	Bromo ester **3a–g**	Cyclized product **4a–g**	Yield of **4a–g** (%)
1	**3a**	 **4a**	82
2	**3b**	 **4b**	79
3	**3c**	 **4c**	85[a]
4	**3d**	 **4d**	87
5	**3e**	 **4e**	70
6	**3f**	 **4f**	80
7	**3g**	 **4g**	74

[a] Yield based on the starting material consumed (81% conversion).

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(25) **General Procedure for Buchwald–Hartwig Cyclization: The following Procedure for 4a is Representative**
In an oven-dried Schlenk tube under nitrogen atmosphere were taken $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), and Cs_2CO_3 (2 mmol) in toluene (ca. 1.5 mL), and the mixture was stirred for 5 min. To this mixture was added ester **3a** (1 mmol) in toluene (ca. 3.0 mL), and the reaction mixture was stirred for 24 h at 80 °C. Progress of the reaction was monitored by TLC, and, after the reaction is complete, it was quenched by addition of aq NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel using PE–EtOAc as eluent furnished the product **4a** in 82% yield.

Representative Analytical Data

Compound **4a**: IR: 3027, 2982, 1732, 1684, 1452, 1242, 1166, 1034, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.10 (m, 8 H, ArH), 7.06–6.98 (m, 1 H, ArH), 4.20–4.10 (m, 2 H, OCH_2CH_3), 3.85 (dd, 1 H, *J* = 5.2, 5.2 Hz, 4′-H), 3.80 [d, 1 H, *J* = 14.9 Hz, NCH_2 (a,b)], 3.74 [d, 1 H, *J* = 13.2 Hz, NCH_2 (a′,b′)], 3.65 [d, 1 H, *J* = 13.2 Hz, NCH_2 (a′,b′)], 3.59 [d, 1 H, *J* = 14.9 Hz, NCH_2(a,b)], 3.18 (dd, *J* = 11.5, 5.6 Hz, 1 H, $NCH_{2a}CHCOOEt$), 2.85 (dd, *J* = 11.5, 4.8 Hz, 1 H, $NCH_{2b}CHCOOEt$), 1.23 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.25 (s, OC=O), 138.13 (s, ArC), 135.19 (s, ArC), 131.58 (s, ArC), 129.31 (d, ArC), 129.05 (d, 2 C, ArC), 128.32 (d, 2 C, ArC), 127.25 (d, ArC),126.92 (d, ArC), 126.75 (d, ArC), 126.31 (d, ArC), 62.31 (t, NCH_2), 60.95 (t, OCH_2CH_3), 56.11 (t, NCH_2), 52.95 (t, C-3′), 45.46 (d, C-4′), 14.22 (q, OCH_2CH_3) ppm.

Compound **4b**: 79% yield. IR: 2931, 2828, 1729, 1610, 1514, 1455, 1252, 1134, 1031, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.24 (m, 5 H, ArH), 6.74 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 4.26–4.06 (m, 2 H, OCH_2CH_3), 3.85 (s, 3 H, $ArOCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 3.78 (dd, 1 H, *J* = 5.0, 5.0 Hz, 4′-H), 3.74 [d, 1 H, *J* = 13.1 Hz, NCH_2(a′,b′)], 3.67 [d, 1 H, *J* = 14.5 Hz, NCH_2(a,b)], 3.65 [d, 1 H, *J* = 13.1 Hz, NCH_2(a′,b′)], 3.52 [d, 1 H, *J* = 14.5 Hz, NCH_2(a,b)], 3.17 (dd, 1 H, *J* = 11.4, 5.5 Hz, $NCH_{2a}CHCOOEt$), 2.85 (dd, 1 H, *J* = 11.4, 4.8 Hz, $NCH_{2b}CHCOOEt$), 1.22 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (s, OC=O), 148.1 (s, ArC), 147.48 (s, ArC), 138.10 (s, ArC), 129.05 (d, 2 C, ArC), 128.29 (d, 2 C, ArC), 127.36 (s, ArC), 127.22 (d, ArC), 123.27 (s, ArC), 111.82 (d, ArC), 109.22 (d, ArC), 62.23 (t, NCH_2), 60.87 (t, OCH_2CH_3), 55.92 (q, $ArOCH_3$), 55.83 (q, $ArOCH_3$), 55.66 (t, NCH_2), 52.98 (t, C-3′), 44.91 (d, C-4′), 14.24 (q, OCH_2CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{21}H_{25}NNaO_4]^+$ = [M + Na]$^+$: 378.1676; found: 378.1685.

Compound **4c**: 85% based on the recovery of 19% of starting material. IR: 2938, 2834, 1732, 1598, 1458, 1238, 1118, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 5 H, ArH), 6.35 (s, 1 H, ArH), 4.25–4.00 (m, 2 H, OCH_2CH_3), 3.87 (s, 3 H, $ArOCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 3.81 (s, 3 H, $ArOCH_3$), 3.80–3.67 (m, 1 H, 4′-H), 3.74 [d, 1 H, *J* = 14.8 Hz, NCH_2(a,b)], 3.72 [d, 1 H, *J* = 13.2 Hz, NCH_2(a′,b′)], 3.70 [d, 1 H, *J* = 14.8 Hz, NCH_2(a,b)], 3.60 [d, 1 H, *J* = 13.2 Hz, NCH_2(a′,b′)], 3.08 (dd, 1 H, *J* = 11.5, 5.1 Hz, $NCH_{2a}CHCOOEt$), 2.81 (dd, 1 H, *J* = 11.5, 5.1 Hz, $NCH_{2b}CHCOOEt$), 1.20 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.86 (s, OC=O), 152.79 (s, ArC), 151.54 (s, ArC), 140.05 (s, ArC), 138.05 (s, ArC), 130.75 (s, ArC), 128. 94 (d, ArC), 128.59 (s, ArC), 128.30 (d, ArC), 127.22 (d, ArC), 118.36 (s, ArC), 104.82 (d, ArC), 61.98 (t, NCH_2), 60.71 (q, $ArOCH_3$), 60.69 (t, NCH_2), 60.33 (q, $ArOCH_3$), 55.90 (t, 2 C, OCH_2CH_3 and OCH_3), 53.48 (t, $NCH_2CHCOOEt$), 41.27 (d, $NCH_2CHCOOEt$), 14.23 (q, OCH_2CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{27}NNaO_4]^+$ = [M + Na]$^+$: 408.1781; found: 408.1787.