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Synthesis of Substituted Isoquinolines *via* Pd-Catalyzed Cross-Coupling Approaches

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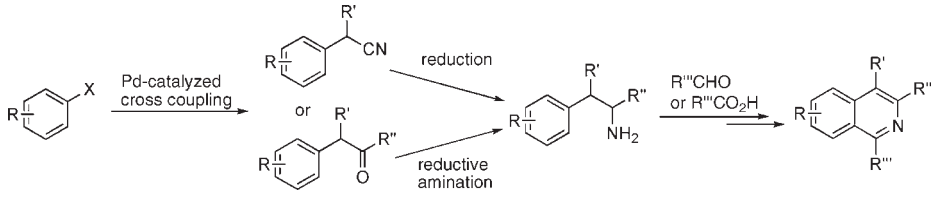
ABSTRACT



Palladium complexes incorporating ligands based on a 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantanyl scaffold were used to catalyze the arylation of ethyl cyanoacetate, malononitrile, and various ketones. The products from these reactions can be elaborated to substituted β-arylethylamines and used in microwave-assisted Pictet–Spengler reactions. The protocol developed is suitable for the synthesis of libraries of substituted isoquinolines.

A number of methods have been described in the chemical literature suitable for the synthesis of substituted isoquinolines (**1**).[1] Among these, approaches that utilize the Pictet–Spengler[2] or Bischler–Napieralski[3] reactions are among the most versatile and robust. Both these routes involve the derivatization of a β-arylethylamine (**2**) followed by cyclization and oxidation to give the isoquinoline ring system (shown retrosynthetically in Figure 1). We have previously described microwave-assisted variants of the Pictet–Spengler and Bischler–Napieralski reactions and used these protocols for the preparation of substituted isoquinoline libraries.[4] During the course of these studies, it became apparent that access to suitably functionalized β-arylethylamines was

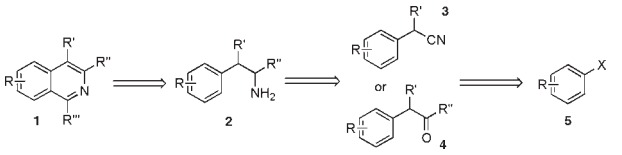


Figure 1. Retrosynthesis of isoquinolines.

key to synthesizing isoquinolines substituted at the 3- and 4-positions.

Compounds containing "active methylenes", such as ketones, aldehydes, esters, cyanoacetates, and malononitrile have been coupled with aryl halides using palladium catalysis.[5] We became interested in the products from these reactions as they represent useful synthons of the β-arylethylamines required in the Bischler–Napieralski and Pictet–Spengler reactions. For example, Pd-catalyzed arylation of a nitrile possessing an α-methylene with an aryl halide **5** provides compound **3** that can be reduced to the

(1) (a) Caille, F.; Buron, F.; Toth, E.; Suzenet, F. *Eur. J. Org. Chem.* **2011**, 2120–2127. (b) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051. (c) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042–8051. (d) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927–5931. (e) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719–723. (f) Sun, Q.; Kyle, D. J. *Comb. Chem. High Throughput Screening* **2002**, *5*, 75–81. (g) Yu, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 895–899.

(2) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036. (b) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521–2523.

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(5) (a) Schnyder, A.; Indolese, A. F.; Maetzke, T.; Wenger, J.; Blaser, H.-U. *Synlett* **2006**, 3167–3169. (b) Wang, X.; Guram, A.; Bunel, E.; Cao, G.-Q.; Allen, J. R.; Faul, M. M. *J. Org. Chem.* **2008**, *73*, 1643–1645. (c) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051–5053.

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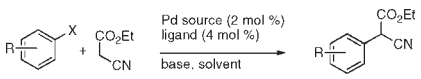
β-arylethylamine **2** (where R″ = H). Alternatively, Pd-catalyzed arylation of a ketone provides compounds of the general type **4** that can undergo reductive amination to supply **2** and elaborated to give the desired isoquinolines **1**. The present paper describes the use of palladium complexes incorporating ligands based on the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (PA) scaffold[6] in the arylation of cyanoacetates, malononitrile, and ketones along with the use of the compounds generated in the synthesis of substituted isoquinolines.

Initial efforts involved optimization of the reaction parameters (solvent, base, palladium source, and ligand) for the coupling between 3- and 4-iodoanisole and ethyl cyanoacetate. Screening (presented in Table 1) indicated that maximal yields were obtained when $Pd_2(dba)_3 \cdot CHCl_3$ was used as the palladium source and 1,3,5,7-tetramethyl-2,4,8-trioxa-6-*iso*-butyl-6-phosphaadamantane (PA-*i*Bu) was employed as the ligand. NaH proved to be the best base while reactions carried out in THF provided the highest yields. Finally, 3 equiv of the nucleophile for each equivalent of aryl halide was determined to be the optimal stoichiometric ratio.

Table 1. Optimization of Pd-Catalyzed Arylation of Ethyl Cyanoacetate[a]

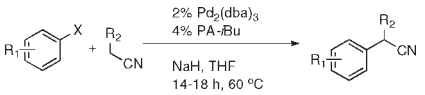


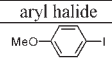
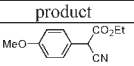
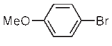
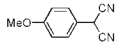
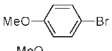
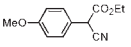
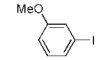
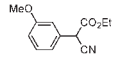
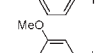
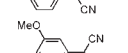
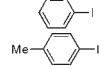
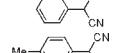
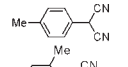
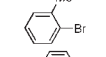
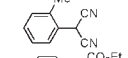
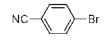
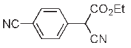
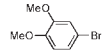
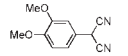
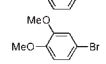
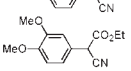
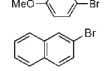
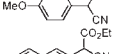
	aryl halide	Pd source	ligand	solvent	base	yield[d]
1	3-iodoanisole	$PdCl_2$	PA-*i*Bu	pyridine	NaH[b]	0%
2	3-iodoanisole	$PdCl_2$	PA-Ph	pyridine	NaH[b]	0%
3	4-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	KO^{t}Bu[b]	60%
4	3-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	NaH[c]	69%
5	4-iodoanisole	Pd_2dba_3	PA-Ph	THF	NaH[b]	50%
6	3-iodoanisole	Pd_2dba_3	PA-Ph	dioxane	NaH[c]	60%
7	3-iodoanisole	Pd_2dba_3	PA-Ph	DMSO	NaH[b]	0%
8	3-iodoanisole	Pd_2dba_3	PA-Ph	THF	KO^{t}Bu[b]	0%
9	4-iodoanisole	$PdCl_2$	PA-Ph	THF	NaH[b]	30%
10	3-iodoanisole	$Pd(OAc)_2$	PA-*i*Bu	pyridine	NaH[b]	40%
11	3-iodoanisole	$Pd(OAc)_2$	PA-*i*Bu	pyridine	NaH[b]	40%
12	4-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	NaH[c]	89%

[a] Reactions were carried out using 1.0 mmol of the iodoanisole and 3.0 mmol of ethyl cyanoacetate. [b] Reactions were carried out using 3 equiv of base and 1.25 equiv of ethyl cyanoacetate. [c] Reactions were carried out using 5.0 equiv of base and 3.0 equiv of ethyl cyanoacetate. [d] Isolated yields.

With the optimized reaction conditions in hand, a series of aryl halides were coupled with either ethyl cyanoacetate or malononitrile. The results are presented in Table 2. It should be noted that the synthetic plan to isoquinolines involves the reduction of these nitriles to β-arylethylamines followed by cyclization. As the planned Bischler–Napieralski and Pictet–Spengler reactions involve electrophilic aromatic substitution, many of the cross-couplings presented in Table 2 involve electron-rich aryl halides. As expected, the yields for the aryl iodides were uniformly better than those of the analogous bromides. In addition, it was noted that reactions with aryl bromide were generally slower. Overall yields ranged from good to moderate. Finally, we noted that reproducibility with respect to product yields became an issue if oxygen was not strictly excluded from the reaction. This is likely due to the propensity of the PA-*i*Bu ligand to undergo oxidation when dissolved in solvent.

Table 2. Pd-Catalyzed Arylation of Ethyl Cyanoacetate and Malononitrile[a]



entry	aryl halide	nucleophile	product	yield[b]
1				89
2				69
3				40
4				69
5				95
6				79
7				70
8				30
9				22
10				30
11				85
12				54

[a] Reactions were carried out using 1.0 mmol of the aryl halide and 3.0 mmol of the nucleophile. [b] Isolated yield.

Conditions for the reduction of the nitriles to β-arylethylamines were then examined (Figure 2). Ethyl 2-cyano-2-(3,4-dimethoxyphenyl)ethanoate (Table 2, entry 10) was used as our model substrate. Attempts at reduction using hydrogenation over Pd/C[7] resulted in numerous side products and incomplete reduction presumably due to catalyst poisoning. Hydrogenation using

(6) (a) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082–5086. (b) Adjabeng, G.; Brenstrum, T.; Wilson, J.; Frampton, C.; Robertson, A.; Hillhouse, J.; McNulty, J.; Capretta, A. *Org. Lett.* **2003**, *5*, 953–955. (c) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635–7639. (d) Gerristma, D.; Brenstrum, T.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 8319–8321. (e) Ohnmacht, S. A.; Brenstrum, T.; Bleicher, K. H.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 5661–5663.

(7) Maegawa, T.; Fujita, Y.; Sakurai, A.; Akashi, A.; Sato, M.; Oono, K.; Sajiki, H. *Chem. Pharm. Bull.* **2007**, *55*, 837–839.

Raney Ni[8] was met with limited success with ethyl 3-amino-2-(3,4-dimethoxyphenyl)propanoate (**7**) isolated in 12% yield. Given the moderate yields associated with the cross-coupling of electron-rich aryl halides and the issues surrounding the nitrile reduction, we felt that this approach would be unsuitable for the preparation of isoquinoline libraries.

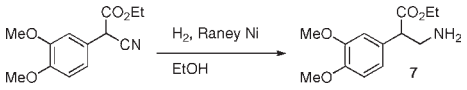


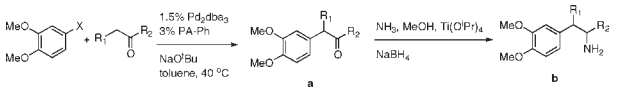
Figure 2. Reduction of ethyl 2-cyano-2-(3,4-dimethoxyphenyl)-ethanoate.

Our attention was then turned to the development of a protocol for the synthesis of β-arylethylamines *via* an α-ketone arylation/reductive amination sequence. We have previously described the use of the Pd/PA-Ph system for the effective α-ketone arylation of aryl halides.[6a] These conditions were applied to provide the ketones shown in Table 3 (compounds of the general type **a**).

A number of reductive amination conditions were screened.[9] Ultimately, we determined that the procedure described by Horiguchi and co-workers provided the best results.[10] Treatment of the ketone with methanolic ammonia in the presense of titanium isopropoxide followed by addition of $NaBH_4$ generated primary amines (Table 3, compound **b**) in very good yields. While $NaBH(OAc)_3$ and $NaBH_3(CN)$ were screened as reducing agents, it was found that $NaBH_4$ was far superior for these reaction conditions. It should also be noted that no attempt was made to separate the diastereomeric amines generated in the reaction. Rather, purification was carried out using reverse-phase preparative LC/MS with all fractions containing the correct mass for the product amine pooled together. Interestingly, the NMR of collected fractions showed the presense of a single species for entries 1b, 2b, and 3b while two diastereomers were clearly resolved for entry 4b. In all cases, the diagnostic signal for the newly installed hydrogen alpha to the amino group was clearly evident.

The β-arylethylamines thus produced could then be subjected to our previously developed microwave-assisted Pictet–Spengler/oxidation sequence. Treatment of the amine with 8 equiv of TFA in toluene was followed by microwave heating at 140 °C for 60 min. No attempts were made to separate or isolate the intermediate, diastereomeric tetrahydroisoquinolines. Rather, oxidation of the crude tetrahydroisoquinoline mixture to the corresponding isoquinoline derivatives involved dehydrogenation using Pd/C in refluxing toluene followed by purification. Application of the Pictet–Spengler/oxidation sequence was applied to the parallel synthesis of a small collection of isoquinolines (presented in Table 4). The yields presented are based on the amount of amine used as a starting material and are fairly consistent across the variety of substrates employed.

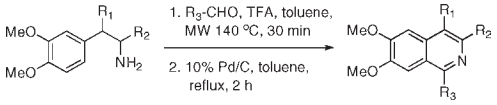
Table 3. Functionalized β-Arylethylamines *via* α-Ketone Arylation/Reductive Amination Reactions[a]



entry	R_1	R_2	% yield **a**[a]	% yield **b**[b]
1	CH_3	Ph	86	81
2	CH_3	*p*-Cl-C_6H_4	70	84
3	CH_3	CH_3CH_2	77	81
4	Ph	Ph	80	69

[a] Reactions were carried out using 1.0 mmol of the aryl halide and 1.1 mmol of the ketone. [b] Reactions were carried out using 1 mmol of the ketone, 1.2 mmol of methanolic ammonia (2 N), 1.5 mmol of Ti(*i*-OPr)$_4$, and 1.7 mmol of $NaBH_4$.

Table 4. Substituted Isoquinolines *via* a Microwave-Assisted Pictet–Spengler/Oxidation Reaction[a]



entry	R_1	R_2	R_3	yield[b]
1	CH_3	Ph	*p*-Cl-C_6H_4	55
2	CH_3	Ph	Ph	52
3	CH_3	Ph	*p*-CH_3-C_6H_4	45
4	CH_3	Ph	*p*-CH_3O-C_6H_4	40
5	CH_3	Ph	*p*-CN-C_6H_4	48
6	CH_3	Ph	*p*-F-C_6H_4	63
7	CH_3	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	56
8	CH_3	*p*-Cl-C_6H_4	Ph	49
9	CH_3	*p*-Cl-C_6H_4	*p*-CH_3-C_6H_4	50
10	CH_3	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	42
11	CH_3	*p*-Cl-C_6H_4	*p*-F-C_6H_4	60
12	CH_3	CH_3CH_2	*p*-Cl-C_6H_4	49
13	Ph	Ph	*p*-Cl-C_6H_4	43

[a] Reactions were carried out using 1.0 mmol of the amine and 1.2 mmol of the aldehyde. [b] Isolated yields.

Overall, the α-ketone arylation/reductive amination/microwave-assisted Pictet–Spengler/oxidation sequence developed has demonstrated itself to be a convenient method for the synthesis of small and moderate sized, substituted isoquinoline libraries.

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The method allows for the inclusion of aryl or alkyl substituents at the C3 and C4 positions in reasonable overall yields.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.