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Pd-catalyzed amination as an alternative to nucleophilic aromatic substitution for the synthesis of *N*-alkyltacrine and analogues

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Abstract

A reliable Pd-catalyzed amination protocol is described for the synthesis of *N*-alkyltacrine and analogues. The Josiphos ligand CyPFrBu was found to provide optimum yields: 16 examples are given. Compared to the typical high-temperature nucleophilic aromatic substitution (NAS) routes, Pd-catalyzed aminations proceed at significantly lower reaction temperatures, and enable the synthesis of otherwise inaccessible products.

Intriguingly, acetylcholinesterase (AChE) inhibitors have found use both as memory-enhancing therapeutic drugs for Alzheimer's disease, and as insecticides.¹ Tacrine **1** was the first drug approved by the FDA to treat Alzheimer's memory loss, and since the initial report of enhanced AChE inhibition potency and selectivity of tacrine dimer **4a**,² a variety of tacrine and tacrine analogue dimers have been synthesized in search of further improvements.^{3,4} Although *bis*(7)-tacrine **4a** and its longer tether homologues *bis*(8)- to *bis*(10)-tacrine were first prepared by alkylation of the exocyclic amine of tacrine **1**,² this method proved unsatisfactory for the synthesis of short-tether homologues, due to the intervention of cyclization and elimination pathways.^{3a} A high-temperature nucleophilic aromatic substitution route was thus devised by reacting **2** with diamines (e.g. **3a**) in refluxing 1-pentanol (bp 138 °C).^{3a}

This amination protocol afforded the complete series of *bis*(2)- to *bis*(10)-tacrine in good yields, and in the last 10 years has been widely used to prepare tacrine heterodimers, as well as homo- and heterodimers of tacrine analogues.^{3,4} Until now it has not been necessary to explore other possible amination protocols.

However, in our search for inhibitors with high selectivity for AChE of the malaria mosquito (*Anopheles gambiae*),⁵ we found that the standard protocol could not dimerize 12-chloro-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline **5**, even when the 1-pentanol solvent was replaced by the even higher boiling (bp 195 °C) 1-octanol (Scheme 2). The use of excess amine to afford monomer **7a** was also unsuccessful.

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Supplementary Data

Supplementary data associated with this article (tabulated analytical data for synthesized compounds) can be found, in the online version, at doi: XXXXXX.

Given the widespread success of Buchwald-Hartwig protocols to effect amination of aryl halides,⁶ our attention turned to Pd-catalysis. Although Pd-catalyzed amination has been applied to several different classes of heteroaryl chlorides,⁷ including 4-haloquinolines,^{7d} to our knowledge there is only one published account of its application to the synthesis of an *N*-alkyltacrine and or analogue. Butini and co-workers reported the use of 2 mol% Pd(OAc)₂ and 2 mol % BINAP to couple **2** and 1,4-diaminobutane, affording **8b** in 40% yield (Scheme 3).^{7j}

Herein we report optimized conditions for the synthesis of *N*-alkyltacrines and analogues via Pd-catalyzed amination.

The reaction of 9-chloro-1,2,3,4-tetrahydroacridine **2** and *n*-heptylamine **3c** was initially used to screen for suitable reaction conditions. We selected DPEPhos,^{7d} RBINAP,^{7d,j} and CyPFrBu^{7b,f} as ligands since they had been previously used in Pd-catalyzed amination of heteroaryl chlorides (Table 1).

DPEphos was reported to be an effective ligand for the cross-coupling of 4-chloroquinoline with α -branched 1° amines,^{7d} and we successfully repeated several of the published aminations of this heteroaryl chloride (data not shown). However we found that this ligand is not very effective for Pd(OAc)₂-catalyzed coupling of **2** and heptylamine **3c** (Table 1, entries 1,2). Interestingly, when KO*t*-Bu was used as base, a 95% yield of reduced product **9** was obtained (Table 1, entry 1). When NaO*t*-Bu was used as base, the desired product **8c** was obtained in 41% yield, albeit at high catalyst/ligand loading (Table 1, entry 2). Use of R-BINAP as ligand (Table 1, entry 3) allowed lower catalyst loadings (1% Pd, 2% ligand) but provided **8c** in only 47% yield; note this yield is similar to that obtained by Butini and co-workers for **8b** (Scheme 3).^{7j} The best results were obtained with the Josiphos ligand CyPFrBu (87%, Table 1, entry 4). Hartwig and coworkers have shown that CyPFrBu functions well in Pd-catalyzed couplings of 1° amines with pyridin-2-yl, pyridin-4-yl, and quinolin-2-yl halides.^{7b,f} Reduction of Pd/ligand loadings below 1%/2% gave poor conversion even at longer reaction time (Table 1, cf. entries 4-6). In addition, a brief survey of toluene and dioxane suggested that DME is the best solvent for the CyPFrBu/NaO*t*-Bu system (Table 1, cf. entries 4, 7, 8).

Thus these optimized conditions were used to explore the generality of this Pd-catalyzed amination of **2** with various primary amines **3a-j** (Table 2).⁸ In general, moderate to good yields were obtained. Using 0.5 equiv of diamine **3a**, *bis*-(7)-tacrine **4a** can be obtained in 72% yield in 24 h, at lower temperature than the NAS procedure (cf. Table 2, entry 1 and Scheme 1). Reaction of **2** with 5.0 equiv of diamine **3a** gave a mixture of the intended amino-terminated tacrine monomer **8a** (78%) and tacrine dimer **4a** (17%, Table 2, entry 2). Thus the Pd-catalyzed amination route to **8a** affords a yield comparable to that of the published NAS route (71%).^{3d} Reactions with Butini's substrate 1,4-diaminobutane **3b** were also investigated. Using 1.05 equiv of **3b**, the desired product **8b** was obtained in 58% yield, and the dimer **4b** was isolated in 12% yield (Table 2 entry 3). Thus higher yields are again obtained with the CyPFrBu ligand relative to BINAP, at lower Pd loading (c.f. Table 2, entry 3 and Scheme 3). Furthermore, increasing the amount of **3b** to 5 equivalents gave the desired product **8b** in 76% yield (Table 2 entry 4). For mono-1° amines, use of 1.05 equiv of amine was generally successful, including 1° amines that are α -branched (Table 2, entries 6-7), and those containing polar functional groups (Table 2, entries 6, 10, 11). Interestingly, in some of these cases (Table 2, entries 6, 9, 10) a significant amount of tetrahydroacridine **9** was isolated; we believe this byproduct likely originates from β -hydride elimination.⁹⁻¹⁰ In particular, the low yield of **8g** relative to **8h** thus appears to be due to significant incursion of the β -hydride elimination pathway (Table 2, cf entries 9, 10). It is not clear whether coordination of the proximal pendant hydroxyl group in **3g** contributes towards this side

reaction, but we note that it is less problematic in the methyl ether analogue **3i** (Table 2, cf. entries 9,11). Note that no byproduct **9** was observed when the amine substrate did not have a β -hydrogen, such as *m*-methyl aniline **3e** (Table 2, entry 7). Reaction with the functionalized α,ω -diamine **3j** was most challenging, but with higher catalyst/ligand loading (4% Pd, 8% CyPFtBu) the desired dimer **4j** was obtained in 46% yield, significantly higher than the published two-step NAS route (11% overall).^{4b} Finally, we did explore the use of R-BINAP as ligand in cases where yields with CyPFtBu as ligand were lower than 50% (**3g**, **3j**); however, even at higher catalyst loading, R-BINAP did not afford higher yields (data not shown).

We then explored the reaction generality with regard to the heteroaryl chloride partner by carrying out reactions with the bulkier substrate **5** (Table 3). Although this substrate proved resistant to traditional NAS conditions (Scheme 2), as hoped, reaction with amines **3a,c,d** under the optimized conditions was successful (Table 3).

Important to note here is that reaction of **5** with 0.5 equiv diamine **3a** gave the dimer product **6a** in 62% yield after 24 hours at 100 °C; under traditional NAS conditions no trace of this product was found after refluxing in 1-octanol at 190 °C for 3 days (cf. Table 3, entry 1 and Scheme 2). Reaction of **5** with 5 equiv of diamine **3a** gave the intended amino-terminated monomer **7a** in 45% yield, and the unintended dimer **6a** in 11% yield. Reaction with unbranched 1° amine **3c** gave the desired product in 95% yield (Table 3, entry 3). Reaction with the α -branched amine **3d** was more challenging, providing only an 18% yield of **7d** (Table 3, Entry 4). A trace amount of byproduct **10** was found in this case, but mass balance was provided by recovered starting material **5**. Thus when the catalyst loading was increased (4% Pd, 8% ligand), the yield of **7d** increased to 50% (Table 3, entry 5).

In conclusion, we have developed a mild and convenient alternative to the synthesis of *N*-alkyltacrines and analogues via Pd-catalyzed amination. By using 2 mol% CyPFtBu as ligand and 1 mol% Pd(OAc)₂ as catalyst, unbranched, α -branched, and functionalized primary amines can be successfully coupled with sterically encumbered heteroaryl chlorides **2** and **5** (a total of 16 examples). In some cases (highly functionalized amines **3d**, **3j**) higher catalyst loadings are required. However, compared to the classical high-temperature NAS route, the Pd-catalyzed amination protocol offers milder reaction conditions (c.f. Schemes 1-2 and Table 1-3), and wider substrate scope.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. Representative procedure: Pd-catalyzed amination of 5 to *N*-alkyltacrines analogue 7c: Pd(OAc)₂ (0.86 mg, 0.0038 mmol) and CyPFtBu (4.26 mg, 0.0077 mmol) were dissolved in anhydrous DME (0.5 mL). The solution was stirred at room temperature under N₂ for 10 min. To the solution were added substrate 5 (100 mg, 0.38 mmol), amine 3c (0.06 mL, 0.40 mmol), NaOtBu (93 mg, 0.95 mmol) and anhydrous DME (0.5 mL). The solution was stirred at 100 °C for 4 h until substrate 5 was totally consumed as judged by TLC. The solution was cooled to the room temperature and evaporated under the vacuum. The crude product was purified by column chromatography to give pure 7c (124 mg, 95%).
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Scheme 1.
Synthesis of **4a** by nucleophilic aromatic substitution

Scheme 2.

Attempted conversion of 12-chloro-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline **5** to **6a** (x = 0.5) or **7a** (x = 3)

Scheme 3.
Synthesis of **8b** by Pd-catalyzed amination.

Table 1

Optimization of Pd-catalyzed amination of 9-chloro-1,2,3,4-tetrahydroacridine **2** by *n*-heptylamine **3c**

$\text{2} + \text{H}_2\text{N}-(\text{CH}_2)_6\text{CH}_3 \xrightarrow[\text{Solvent, T } ^\circ\text{C, t}]{\text{x mol\% Pd(OAc)}_2, \text{ y mol\% Ligand, 2.5 equiv Base}} \text{8c}$

3c (1.05 equiv)

$\text{8c} + \text{9}$

Entry	Ligand	x	y	Base	Solvent	T/°C	t/h	Yield ^a /%
1	DPEphos	4	8	KOtBu	1,4-dioxane	85	24	<5% (95% 9)
2	DPEphos	4	8	NaOtBu	1,4-dioxane	85	12	41
3	R-BINAP	1	2	NaOtBu	DME	100	24	47
4	CyPFtBu	1	2	NaOtBu	DME	100	4	87
5	CyPFtBu	0.5	1	NaOtBu	DME	100	20	51
6	CyPFtBu	0.1	0.2	NaOtBu	DME	100	40	20
7	CyPFtBu	1	2	NaOtBu	toluene	100	20	40
8	CyPFtBu	1	2	NaOtBu	1,4-dioxane	100	20	25

^aYield of isolated **8c** after chromatography.

Table 2

Pd-catalyzed amination of 9-chloro-1,2,3,4-tetrahydroacridine **2** and amines **3a-j** under the optimized conditions

$ \begin{array}{c} \text{2} \\ + \\ \text{3a (0.5 or 5 equiv)} \\ \text{3b (1.05 or 5 equiv)} \\ \text{3j (0.5 equiv)} \\ \text{or} \\ \text{H}_2\text{N}-\text{R} \\ \text{3c-j (1.05 equiv)} \end{array} \xrightarrow[\text{t}]{\begin{array}{c} 1 \text{ mol\% Pd(OAc)}_2, \\ 2 \text{ mol\% CyPFtBu}, \\ 2.5 \text{ equiv NaOtBu}, \\ \text{DME, } 100^\circ\text{C} \end{array}} \begin{array}{c} \text{4a,b,j or} \\ \text{8a-i} \\ + \text{ 9} \end{array} $				
Entry	Amine ^a	t/h	Product(s)	Yield ^b /%
1 ^c		24	4a	72 ^d
			8a	11
2 ^e		24	4a	17
			8a	78 ^c
			4b	12
3		24	8b	58
			4b	21
4 ^e		24	8b	76
5		4	8c	87 ^d
6		18	8d	70
			9	17
7		1	8e	92 ^f
8		3.5	8f	86 ^d
9		24	8g	35
			9	63

Entry	Amine ^a	t/h	Product(s)	Yield ^b /%
10		24	8h	68
			9	26
11		5	8i	60 ^d
12 ^{c,g}		40	4j	46

^a 1.05 equiv of amine unless otherwise specified.

^b Yield of isolated product after chromatography.

^c The amount of diamine used was 0.5 equiv.

^d A trace amount of byproduct **9** was detected by TLC.

^e The amount of diamine used was 5.0 equiv.

^f No byproduct **9** visible by TLC.

^g 4% Pd, 8% ligand.

Table 3

Pd-catalyzed amination of 12-chloro-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline **5** and amines **3a,c, d** under the optimized conditions

Entry	Amine	t/h	Product	Yield ^{a,b} /%
1 ^c		24	6a	62
			7a	16
2 ^d		24	6a	11
			7a	45
3		4	7c	95
4		18	7d	18 ^e
5 ^f		18	7d	50 ^e

^aYield of isolated product after chromatography.

^bTrace amounts of byproduct **10** was found on the TLC in all cases.

^c0.5 equiv of **3a** was used.

^dThe amount of diamine **3a** used was 5.0 equiv.

^eQuantitative recovery of remaining starting material.

^f4% Pd, 8% ligand.