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Palladium-Catalyzed *N*-Arylations of 1,4,7-Triazacyclononanes

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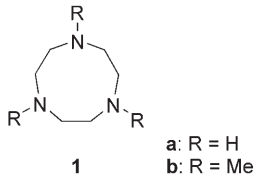
Abstract: Various 1,4,7-triazacyclononanes have been *N*-arylated by palladium catalysis. Using optimized Buchwald–Hartwig protocols the corresponding products have been obtained in high yields.

Keywords: *N*-arylations; Buchwald–Hartwig couplings; palladium catalysis; 1,4,7-triazacyclononanes

Over the last two decades 1,4,7-triazacyclononanes (TACNs, **1**) have extensively been used in various fields of chemistry. For example, Wieghardt and others applied TACNs such as **1a** or Me_3TACN (**1b**) as chelating ligands in bioinorganic chemistry.[1] Work by Hage from Unilever demonstrated the applicability of TACNs in industrial bleaching processes.[2] Based on the latter work, various oxidative transformations with TACN-bearing catalysts have been investigated.[3] In continuation of our studies of functionalized TACNs and their use in oxidation reactions,[4] we now focused our attention on the synthesis of *N*-arylated TACN derivatives **2**. This modification of the donor sites of the triazaheterocycle was expected to be useful for a fine-tuning of the steric and electronic properties of the compound, which could eventually have important implications in catalytic applications.[5]



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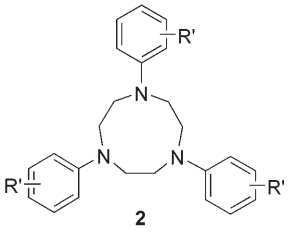
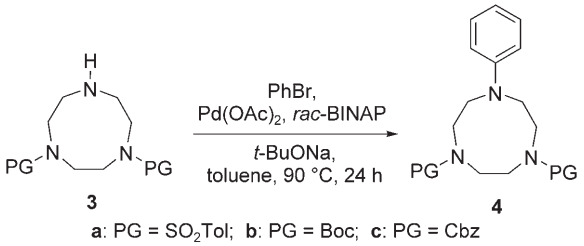


2

The study was initiated by investigating the monoarylation of ditosyl-protected TACN **3a** with phenyl bromide. Following Buchwald's original protocol using a catalyst comprising a mixture of $Pd(OAc)_2$ and racemic BINAP (8 mol% each) in the presence of sodium *tert*-butoxide,[6] the arylation of **3a** proceeded well leading to the quantitative formation of **4a** after 24 h (Scheme 1). In analogy, di(Boc)-TACN **3b** and di(Cbz)-TACN **3c** were coupled with phenyl bromide to give monoarylated **4b** and **4c** in 85 and 70% yields, respectively.



3 **4**

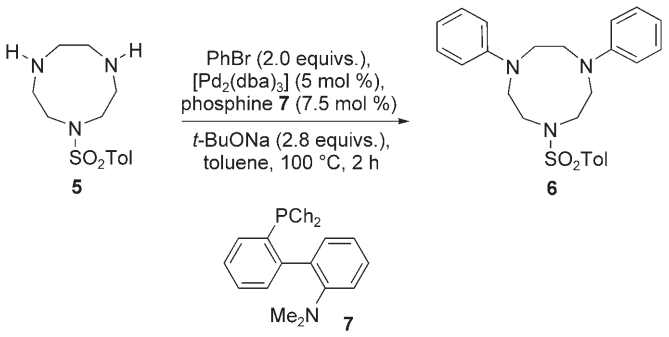
a: PG = SO_2Tol; **b**: PG = Boc; **c**: PG = Cbz

Conditions for the coupling:
3a→**4a**: PhBr (2.1 equivs.), $Pd(OAc)_2$ (8 mol %), *rac*-BINAP (8 mol %), *t*-BuONa (2.1 equivs.)
3b,**c**→**4b**,**c**: PhBr (2.8 equivs.), $Pd(OAc)_2$ (16 mol %), *rac*-BINAP (16 mol %), *t*-BuONa (2.8 equivs.)

Scheme 1. Monoarylation of diprotected TACN derivatives.

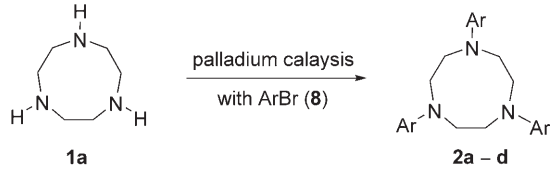
To our surprise, monotosylated TACN **5** did not couple to give **6** under these conditions. Presumably, the triazaheterocycle coordinated too tightly to the metal catalyst leading to its deactivation. In an attempt to enhance the catalyst activity, the palladium source was changed {from $Pd(OAc)_2$ to $[Pd_2(dba)_3]$; dba = dibenzylideneacetone} and the effect of other ligands such as Ph_3P, DPPF [1,1′-bis(diphenylphosphino)ferrocene], and *n*-Bu_3P was screened. Finally, the best result was achieved with a palladium catalyst {derived from $[Pd_2(dba)_3]$} bearing phosphine **7** as ligand, which allowed us to prepare diarylated TACN **6** in 70% yield (Scheme 2).[7,8]

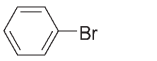
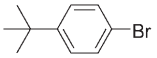
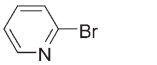
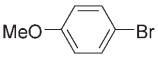
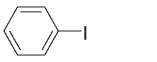
Analogous conditions were applicable for triple *N*-arylations of TACN **1a** with various aryl bromides **8** (Table 1, entries 1–4). Use of a catalyst comprising 3 mol% of $[Pd_2(dba)_3]$ and 7 mol% of phosphine **7** in the presence of 4.2 equivalents of sodium *tert*-butoxide in toluene at 100 °C led to the formation of triary-



Scheme 2. Diarylation of diprotected TACN derivative **5**.

Table 1. Palladium-catalyzed *N*-Arylation of TACN **1a**.[a]



Entry	ArBr		Product	Yield [%]
1		**8a**	**2a**	71
2		**8b**	**2b**	73
3		**8c**	**2c**	52
4		**8d**	**2d**	45
5		**9a**	**2a**	26

[a] *Reaction conditions:* ArX (3 equivs.), $[Pd_2(dba)_3]$ (3 mol%), phosphine **7** (7 mol%), *t*-BuONa (4.2 equivs.), toluene, 100°C, 2–24 h.

lated TACNs **2** in up to 73% yield. The attempt to apply iodobenzene (**9a**) in the synthesis of **2a** led to a low yield (26%) of the triarylated product (Table 1, entry 5).

In summary, we have developed a protocol for the synthesis of *N*-arylated TACNs. Until now, compounds of this type have only scarcely been described,[5] and we expect to see more applications of such *N*-arylated TACNs after the appearance of this report.

Experimental Section

Representative Procedure (RP 1) for the Triple Arylation of TACN 1a; Synthesis of Triarylated TACN 2a

In a Schlenk tube flushed with argon were successively added $[Pd_2(dba)_3]$ (46 mg, 0.05 mmol), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (**7**, 60 mg, 0.15 mmol), bromobenzene (1.5 mmol, 239 mg, 150 μL), TACN **1a** (65 mg, 0.5 mmol) and sodium *tert*-butylate (202 mg, 2.1 mmol). After the addition of toluene (4 mL) the reaction mixture was heated at 100°C for 1 day. The mixture was then allowed to cool to room temperature and diluted with ethyl acetate (10 mL). After filtration through Celite, the solvents of the filtrate were evaporated (rotary evaporator). The remaining mixture was separated by column chromatography (silica gel; EtOAc:pentane = 1:10) affording triarylated TACN **2a**; yield: 127 mg (71%).

Acknowledgements

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