DOI: 10.1002/adsc.201600410
Advanced Synthesis & Catalysis

Rhodium-Catalyzed *N*-*tert*-Butoxycarbonyl (Boc) Amination by Directed C–H Bond Activation

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Received: April 18, 2016; Published online: ■■ ▮▮, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600410.

Abstract: *N*-*tert*-Butoxycarbonyl azide ($BocN_3$) was shown to be an efficient and economic source for the directed introduction of *N*-Boc protected amino groups into the thiophene and benzene nucleus. Yields for the amination of 2-pyridin-2-ylthiophenes (10 examples) were 52–88%. For the amination of the respective benzenes (10 examples) yields between 54% and 99% were recorded with an improved reactivity observed for substrates that bear an electron-withdrawing group. The reaction was applied to short total syntheses of the indoloquinoline alkaloids quindoline and cryptolepine. The facile removal of the Boc protecting group was the key to the success of the syntheses. The scope of the reaction was extended to a C(sp^3)–H bond amination and to the amination of 2-phenyloxazoline. For the amination of 2-pyridin-2-ylbenzene a kinetic deuterium isotope effect of 2.0 was determined.

Keywords: amination; C–H activation; heterocycles; homogeneous catalysis; rhodium

Over many decades, the *tert*-butoxycarbonyl (Boc) group has established itself as the most frequently used protecting group for amines and anilines.[1] Its lipophilicity, its stability under a broad variety of conditions and its facile removal have made it extremely popular among synthetic chemists. There are literally hundreds of total syntheses, in which the Boc group has served to protect a nitrogen atom through a number of steps. While the protecting group is normally attached to a preexisting amine or aniline, recent advances in C–H activation chemistry enable the introduction of an appropriately protected amino unit directly into an arene or alkane scaffold.[2,3] Recent work on aromatic C–H amination has revealed that it is possible to introduce protected amino groups by transition metal catalysis employing the respective azides as the nitrogen source.[4] These reactions have been typically performed with amino precursors bearing protecting groups, the further manipulation of which is inferior to the Boc group.

Some time ago, we described *tert*-butoxycarbonyl azide ($BocN_3$) as a favorable reagent for the iron-catalyzed imination of sulfides and sulfoxides.[5] Based on this experience we wondered whether the reagent would be equally suitable for the introduction of a Boc-protected amino group into arenes and alkanes by C–H activation chemistry thus avoiding the production of undesired by-products generated by other reagents.[3] In this manuscript we describe our preliminary work, which led to the discovery of a broadly applicable amination reaction employing a pyridinyl-type directing group and a rhodium catalyst to achieve the C–H activation step. To illustrate the superior properties of the Boc group for preparative purposes, the protocol was applied to the total synthesis of the *Cryptolepis* alkaloids quindoline and cryptolepine.[6]

From recent work on the oxidative cross-coupling of thiophenes,[7] we had a variety of pyridin-2-yl substituted thiophenes at hand, which was the reason why we started optimization reactions (Table 1; for a complete set of the reactions, see the Supporting Information) with 2-pyridin-2-ylthiophene (**1a**). We were pleased to note that unlike related ruthenium (entry 1) and iridium (entry 3) complexes, the rhodium complex $(Cp^*RhCl_2)_2$ (Cp^* = pentamethylcyclopentadienyl)[8] was a competent catalyst for the desired amination (entry 2). After a reaction time of 14 h, conversion was incomplete and attempts to increase the conversion by increasing the temperature (entry 4) were unsuccessful. A change of solvent from DCE to either a less polar (entry 5) or a more polar (entries 6, 7) medium turned out not to be beneficial. The addition of alkali salts (one equiv.) had a positive effect on the conversion with K_3PO_4 being superior to other potassium salts (entries 8–10). While an increase of the $BocN_3$ equivalents had no effect on the conver-

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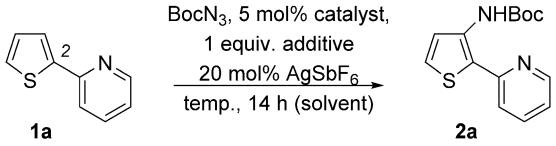
Table 1. Selected optimization conditions for the amination of 2-pyridin-2-ylthiophene (**1a**) with $BocN_3$.

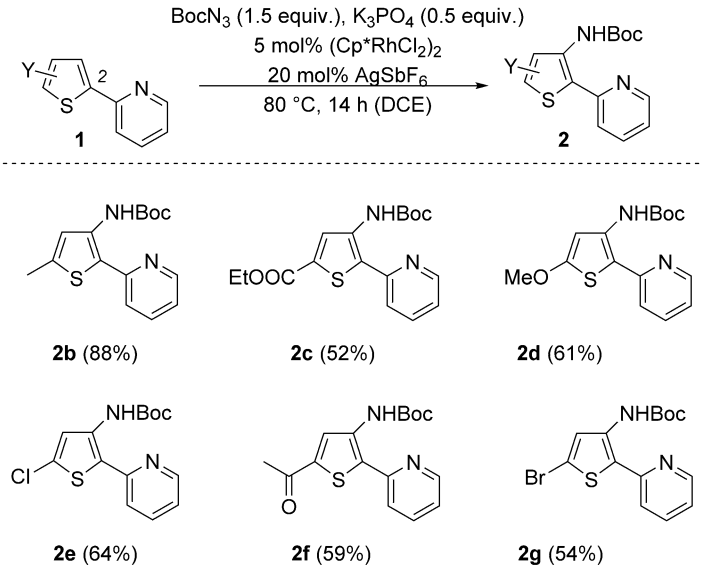


Entry	$BocN_3$ [equiv.]	Catalyst[a]	Additive	Temperature [°C]	Solvent	Conversion[b] [%]	Yield[b] [%]
1	1.5	$(pCyRuCl_2)_2$	–	80	DCE[c]	11	11
2	1.5	$(Cp^*RhCl_2)_2$	–	80	DCE	59	39
3	1.5	$(Cp^*IrCl_2)_2$	–	80	DCE	11	6
4	1.5	$(Cp^*RhCl_2)_2$	–	100	DCE	51	41
5	1.5	$(Cp^*RhCl_2)_2$	–	80	PhMe	5	5
6	1.5	$(Cp^*RhCl_2)_2$	–	80	DMA[d]	15	15
7	1.5	$(Cp^*RhCl_2)_2$	–	80	*t*-AmOH	12	11
8	1.5	$(Cp^*RhCl_2)_2$	K_2CO_3	80	DCE	60	44
9[e]	1.5	$(Cp^*RhCl_2)_2$	KOAc	80	DCE	59	40
10	1.5	$(Cp^*RhCl_2)_2$	K_3PO_4	80	DCE	75	65
11	3.0	$(Cp^*RhCl_2)_2$	K_3PO_4	80	DCE	70	63
12[e]	1.5	$(Cp^*RhCl_2)_2$	K_3PO_4	80	DCE	81	71 (81)[f]

[a] *Reaction conditions:* **1a** (1.0 equiv., $c = 0.1$ M), $t = 14$ h.
[b] Conversion and yield as determined by NMR analysis using 1,3,5-trimethoxybenzene as internal standard.
[c] 1,2-Dichloroethane.
[d] *N,N*-Dimethylacetamide.
[e] 0.5 equivalents of the additive were used.
[f] Yield of isolated product in brackets.

sion (entry 11), it was shown that the reaction could be promoted even with 0.5 equiv. K_3PO_4. In a preparative run on a larger scale, the conversion was further improved and product **2a** could be isolated in 81% yield.

Without any further modification, related thiophenes were subjected to the amination conditions (Scheme 1). Yields were good to moderate with a significant functional group tolerance for various thiophene substituents (alkoxycarbonyl, alkoxy, chloro, acyl, bromo). $BocN_3$, which is known to be a potential explosive, was employed in crude form without prior distillation.[9,10]



Scheme 1. Rhodium-catalyzed amination of various substituted 2-pyridin-2-ylthiophenes **1** with $BocN_3$.

Under identical conditions, 3-pyridin-2-ylthiophenes were subjected to the amination reaction. If the 2-position was available for C–H activation a facile amination was observed, which delivered the Boc-protected 2-aminothiophenes **3a** and **3b** in high yields (Figure 1). If the 2-position was blocked amination was directed to position C-4 and amination product **3c** was obtained in 55% yield.

When turning to benzenes as potential substrates we were pleased to note that they undergo the amination reaction even more readily than thiophenes. The reaction was highly chemoselective and side reactions were not notable. In all cases shown in Scheme 2, yields exceeded 75% if based on conversion. If lower yields of isolated product were recorded it was be-

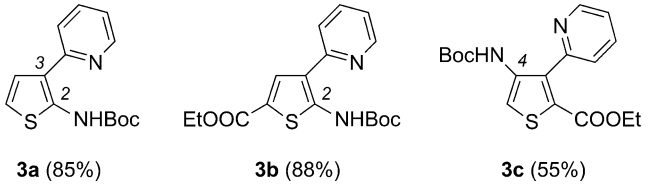


Figure 1. Products **3** obtained from the rhodium-catalyzed amination of 3-pyridin-2-ylthiophenes.

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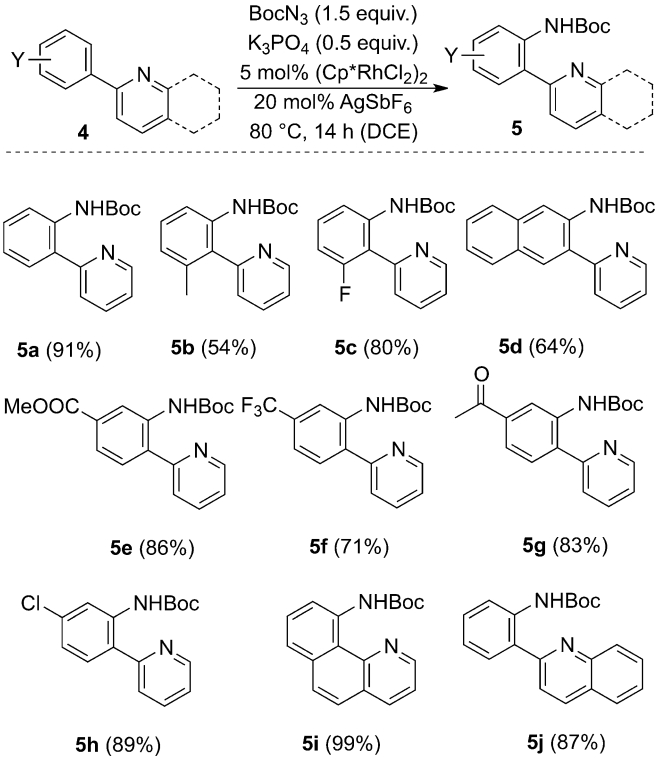


Scheme 2. Rhodium-catalyzed amination of various substituted pyridin-2-ylbenzenes **4** with $BocN_3$.

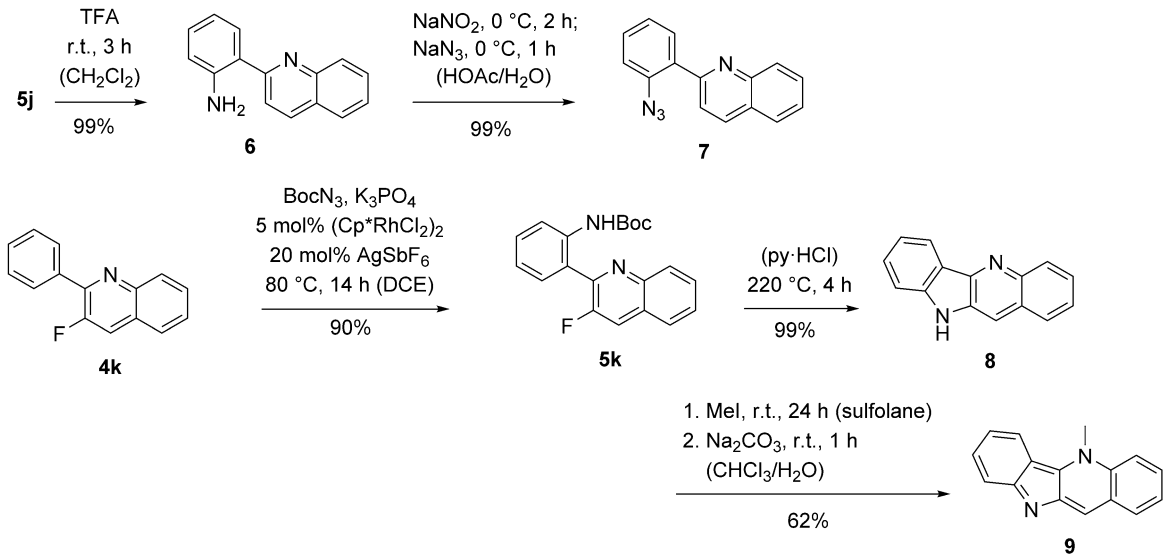
cause the reaction was not complete after 14 h. In the reaction of *ortho*-substituted pyridin-2-ylbenzenes **4b** and **4c**, for example, the substrates were recovered in yields of 31% and 20%.

Generally, there are two reactivity trends to be noted: (i) If the pyridine ring cannot adopt a synperiplanar position relative to the adjacent C–H bond, the conversion is lower. If the C–H bond is locked in the required planar arrangement (e.g., **4i**→**5i**) the yield is high. (ii) Electron-withdrawing groups facilitate the amination reaction while electron-donating groups retard it. This is in line with the observation that substituted benzenes react more readily than comparable thiophenes (e.g., **1c**→**2c** *vs.* **4e**→**5e** or **1f**→**2f** *vs.* **4g**→**5g**).

The fact that our protocol allows the introduction of an amino group in the phenyl *ortho*-position of 2-phenylquinolines invited an application to the synthesis of indoloquinoline alkaloids (Scheme 3). Compound **5j** was readily converted *via* amine **6** to azide **7**. Despite an encouraging literature precedent[11] it was, however, not possible to transform azide **7** successfully into an indoloquinoline.

As an alternative route, readily available 3-fluoro-2-phenylquinoline (**4k**)[12] was aminated to yield the *N*-Boc protected product **5k** in 90% yield based on conversion. This compound underwent a facile ring closure to quindoline (**8**) when heated in pyridinium hydrochloride.[13] Quindoline in turn was successfully converted into cryptolepine (**9**) following a reported procedure.[14]

For an extension of the directed *N*-Boc amination method, other substrates were explored. Notably, the method could be successfully applied to the functionalization of a C(sp^3)–H bond (Scheme 4). When 8-methylquinoline (**10**) was treated with $BocN_3$ under the conditions previously established for C(sp^2)–H amination a clean conversion into the respective *N*-Boc protected aminomethyl derivative **11** was observed. The product was obtained in 97% yield based on conversion. Moreover, it could be established that



Scheme 3. Synthesis of a potential precursor **7** to indoloquinoline alkaloids and total synthesis of quindoline (**8**) and cryptolepine (**9**).

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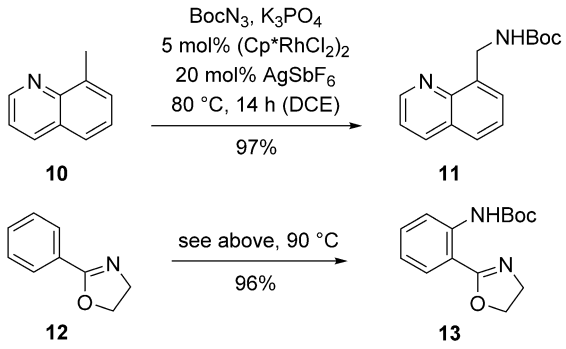
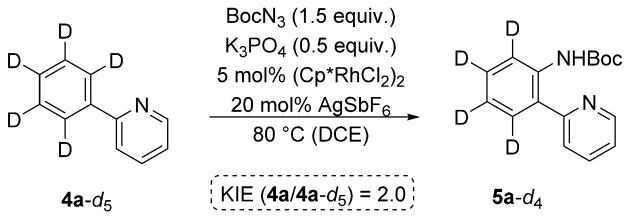


Scheme 4. Introduction of an *N*-Boc protected amino group into a C(sp^3)–H bond (**10**→**11**) and into the *ortho*-position of 2-phenyloxazoline (**12**) by rhodium-catalyzed amination.

other directing groups facilitate the amination reaction in the same fashion as the pyridin-2-yl group. 2-Phenyloxazoline (**12**) was transformed into the desired amination product **13**. No further optimization was required to enable the desired C–N bond formation, only the reaction temperature was increased to 90 °C.

Preliminary mechanistic work was performed with deuterated compound **4a**-d_5, which could be readily prepared from commercially available bromobenzene-d_5 (for the synthesis, see the Supporting Information). When subjected to the reaction conditions of the amination reaction, the respective deuterated analogue of product **5a**, compound **5a**-d_4, was observed. After appropriate calibration, initial rates could be determined for this reaction and for the analogous reaction of the undeuterated substrate **4a**→**5a**. The kinetic isotope effect (KIE) from these measurements was determined as $k_H/k_D = 2.0$ (Scheme 5). Intermolecular competition experiments in the same reaction vessel were found to be not suitable for KIE determination because an H/D scrambling was observed under the reaction conditions.

The preliminary data seem consistent with a rate-limiting C–H activation step which leads to a primary species **14** (Figure 2), to which $BocN_3$ adds in exchange for a weak ligand (L). The further course of the reaction can be interpreted – as suggested for



Scheme 5. Rhodium-catalyzed amination of deuterated substrate **4a**-d_5 that was employed to determine the kinetic isotope effect relative to **4a** in parallel experiments.

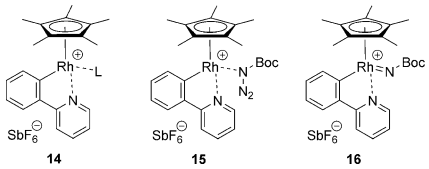


Figure 2. Putative intermediates **14** (L = ligand), **15**, and **16** in the rhodium-catalyzed amination reaction **4a**→**5a**.

other azides[4h,15] – by dediazotization of intermediate **15** and formation of an intermediate Rh(V) nitrene complex **16** which undergoes insertion into the Rh–C bond. The catalytic cycle is closed by protonation of this species by another substrate molecule, which leads to formation of compound **14** and liberation of the product.

In summary, a new method for the directed amination of aromatic and aliphatic C–H bonds has been developed. The readily available reagent $BocN_3$ was employed as the nitrogen source and allows for the immediate introduction of an *N*-Boc protected amino group. In contrast to other methods for the introduction of *N*-alkoxycarbonyl protected amino groups[3] the only by-product formed in this transformation is nitrogen. The reaction sets the stage for a versatile amination protocol as manifested by the successful total synthesis of two indoloquinoline alkaloids. Mechanistic studies suggest the involvement of the C–H activation in the rate-determining step but further experiments are required to provide a more detailed understanding of the reaction. In addition, an extension of the method and additional synthetic applications are currently being studied in our laboratory.

Experimental Section

General Procedure for Rhodium-Catalyzed C–H Amination with $BocN_3$

A 30-mL Schlenk vial with a screw cap was charged with thiophene **1a** (64.5 mg, 400 μmol, 1.0 equiv.) and K_3PO_4 (42.5 mg, 200 μmol, 0.5 equiv.) in air. The screw cap was tightly closed and the tube was evacuated and refilled with argon three times. Under a positive pressure of argon consecutively $[Cp^*RhCl_2]_2$ (12.4 mg, 20.0 μmol, 5 mol%), $AgSbF_6$ (27.5 mg, 80.0 μmol, 20 mol%) and a solution of $BocN_3$ (85.9 mg, 600 μmol, 1.5 equiv.) in 1,2-dichloroethane (DCE, 4 mL) were added. The resulting suspension was stirred at 80 °C for 14 h, cooled to room temperature and diluted with CH_2Cl_2 (10 mL). The suspension was filtered through a plug of Celite®, the plug was washed with additional CH_2Cl_2 (3×20 mL). The filtrate was concentrated under vacuum, loaded onto silica (1.5 g) and subjected to flash chromatography (pentane/Et_2O 100:3→100:5). The desired product **2a** was obtained as a colorless solid; yield: 89.7 mg (325 μmol, 81%); TLC: $R_f = 0.72$ (pentane/Et_2O 4:1) [UV]; mp 89–90 °C; IR (ATR): $\nu = 3221$ (br), 2977 (w),

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1719 (m), 1578 (s), 1475 (m), 781 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 1.55$ (s, 9H), 7.08 (ddd, $^3J = 7.5$, 5.0 Hz, $^4J = 1.1$ Hz, 1H), 7.23 (d, $^3J = 5.5$ Hz, 1H), 7.44 (*virt.* dt, $^3J = 8.1$ Hz, $^4J \approx {}^5J = 1.1$ Hz, 1H) 7.66 (*virt.* td, $^3J \approx 7.8$ Hz, $^4J = 1.8$ Hz, 1H), 7.94 (s, 1H), 8.55 (ddd, $^3J = 5.0$ Hz, $^4J = 1.8$ Hz, $^5J = 1.0$ Hz, 1H), 11.24 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$, 300 K): $\delta = 28.6$ (q), 80.3 (s), 117.8 (s), 120.2 (d), 120.3 (d), 123.1 (d), 124.7 (d), 137.1 (d), 139.3 (s), 148.1 (d), 153.1 (s), 154.4 (s); HR-MS (ESI): $m/z = 277.1003$, calcd. for $C_{14}H_{16}N_2O_2S$ $[M+H]^+$: 277.1005.

Acknowledgements

This project was supported by the Deutsche Forschungsgemeinschaft (Ba 1372-19/1), by the Elitenetzwerk Bayern (scholarship to J.W.), and by the TUM Graduate School. Dr. S. Breitenlechner is acknowledged for his help with the KIE measurements.

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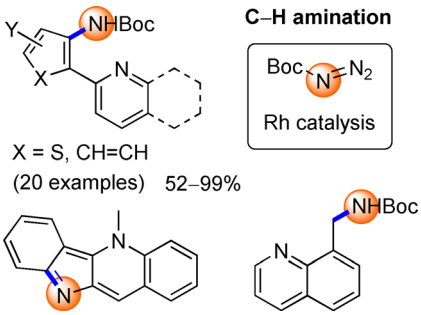

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