

Selective Cleavage of Cbz-Protected Amines

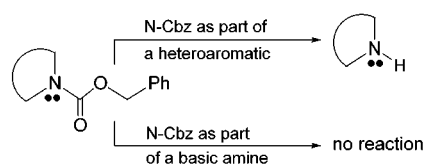
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ABSTRACT



Under conditions of catalytic Ni(0) and in most cases just over 1 equiv of $\text{Me}_2\text{NH}\cdot\text{BH}_3/\text{K}_2\text{CO}_3$ or Cs_2CO_3 , a Cbz-protected nitrogen, which is part of a heteroaromatic ring, can be chemosepecifically cleaved without affecting a Cbz group on an originally basic amine.

Among the myriad of protecting groups for nitrogen,¹ the Cbz moiety is regarded as one of the most useful in synthesis.² Installation of this residue follows from a standard protocol involving treatment of an amine with Cbz-Cl or the equivalent. The value of this blocking group lies in its susceptibility to removal under conditions that are orthogonal to those normally utilized to unmask alternative carbamate derivatives, in particular the BOC and Fmoc groups. Typical conditions include those associated with catalytic hydrogenation, strong acid, Na/NH_3 , and Lewis acids, although other less commonly employed methods exist as well.¹ None, to the best of our knowledge, offer opportunities for generally selective removal of a multiply Cbz-protected polyamine,³ thus necessitating use of at least two distinct protecting groups. In this Letter, we describe a novel set of conditions for the exclusive removal of a Cbz group attached to a nonbasic nitrogen contained within a heteroaromatic ring (Figure 1).

In the course of developing a highly functional group-tolerant method for reductions of aryl chlorides based on catalytic Ni(0), in combination with $\text{Me}_2\text{NH}\cdot\text{BH}_3$ and K_2CO_3 (1:1),⁴ it was observed in the case of Cbz-protected

7-chloroindole **1** that dechlorinated *and* deprotected indole was obtained if the reaction was allowed to proceed beyond the time required for initial chloride removal (Scheme 1). We surmised that the sequence leading to Cbz unraveling is akin to that which takes place with the analogous allyloxy-carbonyl unit.⁵ That is, with zerovalent palladium or in this case nickel as nucleophile, a π -allylmetal intermediate is likely that is subsequently trapped in situ (e.g., by hydride), along with release of the free amine (Scheme 2). Such a scenario does not distinguish between types of amines, however, and thus we were surprised to find that several Cbz derivatives of originally basic amines were untouched under otherwise identical conditions. This may be attributed to the availability of the nitrogen lone pair, which in the former substrate type is minimized as a result of its

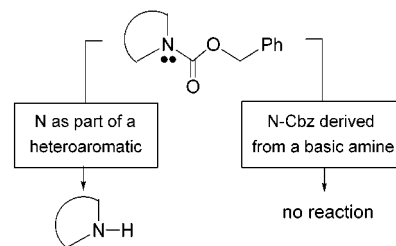


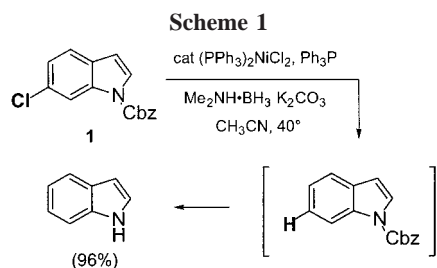
Figure 1.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

(2) Bergmann, M.; Zervas, L. *Ber.* **1932**, 65, 1192.

(3) Kohda, J.; Shinozuka, K.; Sawai, H. *Tetrahedron Lett.* **1995**, 36(31), 5575. Sakaitani, M.; Ohfuné, Y. *J. Org. Chem.* **1990**, 55, 870.

(4) (a) Lipshutz, B. H.; Tomioka, T.; Pfeiffer, S. S. *Tetrahedron Lett.* In press. (b) Lipshutz, B. H.; Tomioka, T.; Sato, K. *Synlett* **2001**, 970.



participation in aromaticity. In the latter, no such obligation allows for its influence to be felt by the carbonyloxy moiety, thus reducing electrophilicity at the aryl site. On the basis of these principles, it was to be expected that amines **2–5** are representative of cases that returned only starting material, including the highly electron-deficient Cbz-protected *p*-cyanoaniline **5** (Figure 2). On the other hand, a variety of *N*-heteroaromatic systems were very responsive, documenting the specificity associated with this process.⁶

Table 1 illustrates several examples of deprotections of nitrogen heterocycles, including pyrroles, pyrazoles, imidazoles, carbazoles, and purines. All substrates, many of which bear pendant functionality, reacted efficiently to afford high isolated yields of the corresponding N–H materials. Noteworthy cases include a trifluoromethylated pyrazole (entry 2) used in the preparation of modified ferrocenyl ligands as catalysts for asymmetric synthesis⁷ and a kinetin derivative (last entry), the parent system being known to cause rapid cell division in plants, while kinetin riboside is a known antitumor antiviral agent.⁸

Absent from this listing of successful educts are triazoles and tetrazoles, such as heteroaromatics **6** and **7** (Scheme 3). Much to our chagrin, all attempts to deprotect these compound types led to formation of a white precipitate assumed to involve complexed nickel.^{9a} When triazole **7** is mixed (1:1) with a substrate that reacts very efficiently in these reactions, such as *N*-Cbz-3-phenylimidazole (**8**), neither substrate shows any loss of the Cbz group (Scheme 3).^{9b}

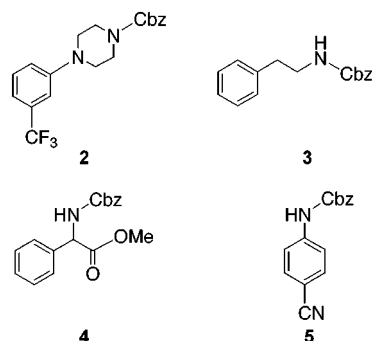
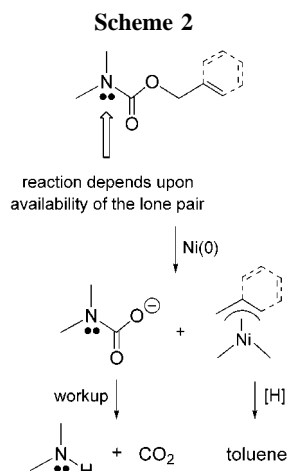


Figure 2.

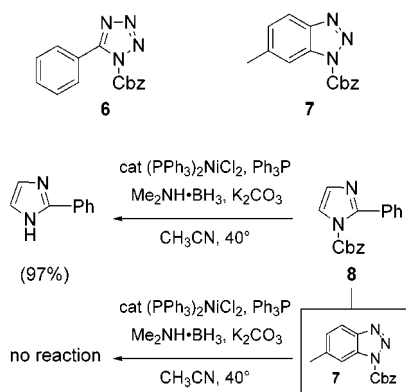
On the basis of these data, it was anticipated that substrates containing both heteroaromatic and non-heteroaromatic

Table 1. Cleavage of *N*-Cbz Carbamates Using Ni(0) Catalysis

starting material	Ph ₃ P & Ni (%)	Me ₂ NH·BH ₃ & base (eq)	time (h)	yield (%) ^a
	5	1.1 ^b	7	97
	3	1.2 ^b	8	94
	3	1.2 ^b	8	91
	5	2.1 ^b	24	96
	3	1.2 ^b	12	86
	3	1.1 ^b	23	82
	5	1.5 ^c	72	89
	5	1.4 ^c	6	88

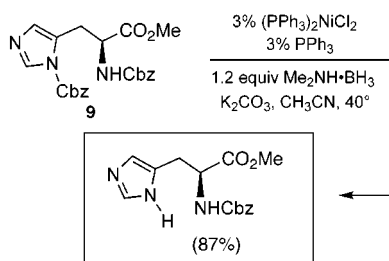
^a Isolated, chromatographically purified material. ^b K₂CO₃. ^c Cs₂CO₃.

Scheme 3



amines should undergo selective Cbz removal under the influence of a Ni(0) catalyst. Indeed, protected histidine methyl ester **9** could be converted to its mono-Cbz derivative in good yield (Scheme 4).

Scheme 4



Both K_2CO_3 and Cs_2CO_3 can be utilized for reagent generation with similar results. However, while formation of the standard red Ni(0) species is complete within 30 min at 40 °C when Cs_2CO_3 is employed, K_2CO_3 requires 3 h at 40 °C to form active nickel. It was also discovered that premixing of the reagents in the absence of substrate is necessary when a double bond or an aryl ketone is present in the molecule, which avoids possibilities for hydroboration or carbonyl reduction.^{4a}

Another important protecting group utilized with nitrogen-containing substrates is the allyloxy-carbonyl (Alloc) group developed by Corey.⁵ The synthesis of allyl carbamates is straightforward and easily achieved with allyl chloroformate

(7) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3223.

(8) Two control experiments were conducted with *N*-Cbz-3-phenylimidazole to verify the necessity of the nickel catalyst. The first reaction involved our standard conditions but without $Ni(PPh_3)_2Cl_2$ and PPh_3 , whereas the second reaction left out the $Ni(PPh_3)_2Cl_2$. Neither reaction produced more than 5% of the product amine by GC analysis after 24 h.

(9) Burckhardt, U.; Hintermann, L.; Schnyder, A.; Togni, A. *Organometallics* **1995**, *14*, 5415.

(10) Kaul, K.; Sabharwa, P. S. *Plant Physiol.* **1974**, *54*, 644.

(9) (a) Suzuki, H.; Ishiguro, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 83. (b) A white precipitate formed with 5 min, again suggesting complexation of Ni with **7**.

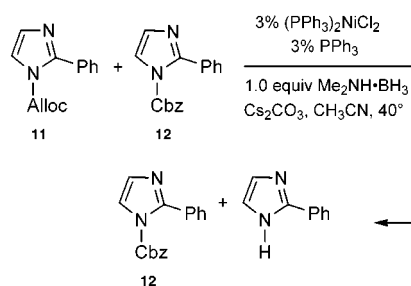
Table 2. Cleavage of *N*-Alloc Carbamate Using Ni(0) Catalysis

starting material	Ph_3P & Ni (%)	$Me_2NH \cdot BH_3$ & base (eq) ^a	time (min) ^b	yield (%)
	3	1.1	<10	96
	5	1.2	<30	100 ^c
	3	2.1	60	90
	3	1.2	<30	93

^a Cs_2CO_3 used for faster nickel reduction, all cases. ^b Based on pre-reduced Ni(0) followed by substrate addition. ^c By GC analysis.

and the amine of choice. However, removal of the Alloc group with Ni(0) has only been described employing toxic $Ni(CO)_4$.^{1,5} Applying our Ni(0)-catalyzed conditions to Alloc-protected substrates (Table 2) indicated that the rate of removal of this protecting group, independent of type of nitrogen, is rapid relative to cleavage of the corresponding Cbz derivatives (compare Tables 1 and 2, first entries).¹⁰ This has allowed for the selective removal of the Alloc moiety in **11** without affecting the Cbz in **12** (Scheme 5). Unlike

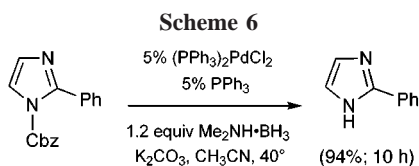
Scheme 5



circumstances involving the Cbz group, an Alloc-protected *N*-heteroaromatic cannot be selectively deprotected in the presence of an Alloc-protected basic amine.

By way of comparison of Ni(0) with Pd(0) for these deprotections, we have found that replacement of the nickel-(II) precursor with its palladium analogue, $(PPh_3)_2PdCl_2$, leads to essentially identical results with Cbz-protected heteroaromatics (Scheme 6; compare with Table 1, entry 1).

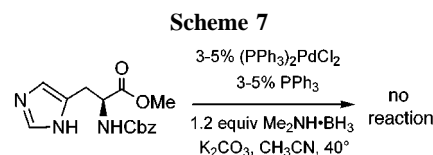
(10) Hydroboration of the alkene in the Alloc group was not observed in any of these cases.



Likewise, Pd(0) does not remove a Cbz moiety on a basic nitrogen (Scheme 7). Palladium(0)-catalyzed Alloc depro-

(11) For some representative examples, see: (a) Merzouk, A.; Guibe, F. *Tetrahedron Lett.* **1992**, 33, 477. (b) Sakaitani, M.; Kurokawa, N.; Ohfuné, Y. *Tetrahedron Lett.* **1986**, 27, 3753. (c) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, 47, 587.

(12) **Representative procedure.** (Table 1, entry 2) Into a flame-dried 10 mL round-bottomed flask equipped with a stir bar and septum were added Cbz-protected 3-methyl-5-(trifluoromethyl)pyrazole (284 mg, 1.0 mmol), $(\text{PPh}_3)_2\text{NiCl}_2$ (20 mg, 0.03 mmol, 3 mol %), PPh_3 (8 mg, 0.03 mmol), 98% borane–dimethylamine complex (71 mg, 1.2 mmol), and K_2CO_3 (166 mg, 1.2 mmol) under argon. Dry, deoxygenated acetonitrile (2 mL) was added via syringe, and the slurry was allowed to stir for 8 h at 40 °C. Upon completion, the mixture was cooled to room temperature and filtered through Celite, the filter cake being further washed with CH_2Cl_2 . The solvents were then removed on a rotary evaporator. The crude material was purified by column chromatography on silica gel (35% ethyl acetate in pet ether) to give 141 mg (94%) of the product.



tections, unlike those described herein using Ni(0), are well-documented.¹¹

In summary, it has been found that low valent nickel, in catalytic quantities and generated in situ with inexpensive reagents $(\text{PPh}_3)_2\text{NiCl}_2$, Ph_3P , $\text{Me}_2\text{NH}\cdot\text{BH}_3$, and K_2CO_3 or Cs_2CO_3 , can effect the selective unmasking of several Cbz-protected heteroaromatic amines.¹² Originally basic, non-heteroaromatic nitrogens derivatized with this blocking group are not susceptible to cleavage under these conditions. Taken together, these observations have the potential to significantly extend the scope of the widely utilized Cbz in synthesis.

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