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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1451–1453

Copper-catalyzed allylic hydroxyamination and amination of alkenes with Boc-hydroxylamine

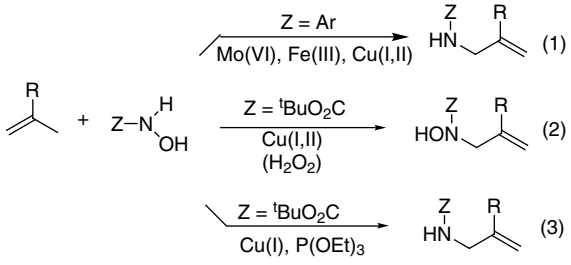
Biswajit Kalita and Kenneth M. Nicholas*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA

Received 15 December 2004; revised 27 December 2004; accepted 7 January 2005
Available online 22 January 2005

Abstract—Olefins react regioselectively with Boc-NHOH in the presence of Cu(I,II) salts to produce allyl-N(OH)(Boc) derivatives, apparently via the intermediacy of Boc-N=O; yields and rates are dramatically improved by the addition of H_2O_2. The corresponding allylamine derivatives, allyl-NH(Boc), are formed selectively from Boc-NHOH/olefin with CuBr/P(OEt)$_3$.

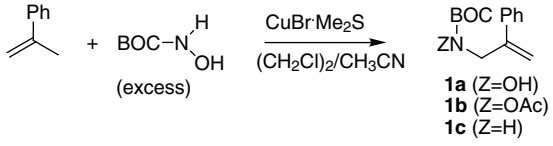
The direct *N*-functionalization of unsaturated hydrocarbons is an attractive, but underdeveloped synthetic methodology.[1] Additions to C–C unsaturation such as hydroxyamination,[2] aziridination[3] and, most recently, hydroamination,[4] have received the most attention. Allylic *N*-functionalization reactions have also been emerging, which employ S/Se-imido reagents,[5] azo-derivatives,[6] nitro-aryls[7] and hydroxylamines[8–10] as nitrogen sources. Our prior contributions in the latter area have included the development of Mo(VI)-,[8] Fe(II/III)-[9] and Cu(I/II)-[10] catalyzed allylic aminations of olefins by aryl hydroxylamines (Scheme 1), all of which proceed with excellent ene reaction-like regioselectivity[11] (i.e., with C=C transposition). In search of a convenient reagent to access primary allyl amines we have now examined copper-catalyzed reactions of olefins with the readily available[12] and deprotectable[13] Boc-NHOH (Boc = ^{t}BuO$_2$C–). Presented here is the unexpected outcome of such reactions: (1) that *N*-Boc-*N*-hydroxy-*N*-allyl amines are the major products (Scheme 1); and (2) that Boc-*N*-allyl amines are formed selectively in the presence of suitable ligands (Scheme 1).



Scheme 1.

Initial reactivity studies were conducted between α-methyl styrene (AMS, R = Ph) and Boc-NHOH with various Cu(I) and Cu(II) salts (10 mol%) in 1,2-dichloroethane/acetonitrile (2:1) at reflux. Several of the salts catalyzed the slow consumption of the hydroxylamine,[14] with CuBr·Me$_2$S showing the highest activity and product selectivity (by TLC). Employing a 3:1 Boc-NHOH/AMS ratio and the latter catalyst, two products were isolated (Scheme 2) the Boc-N-OH allyl derivative **1a** (48%) and the known (Boc)$_2$NOH[15] (3%). The identity of **1a** was established spectroscopically and by conversion to the corresponding *O*-acetate (**1b**; Ac$_2$O/pyridine) and Boc-amine derivatives (**1c**; TiCl$_3$/MeOH).[16]

The formation of hydroxylamine **1a** contrasts with the corresponding Cu-catalyzed reactions of AMS with aryl hydroxylamines, which afford the reduced *N*-aryl-*N*-allyl amines (e.g., **1c**).[10] Since the present conversion



Scheme 2.

Keywords: Allylic amination; Hydroxyamination; Copper-catalyzed.
* Corresponding author. Tel.: +1 405 325 3696; fax: +1 405 325 4811; e-mail: knicholas@ou.edu

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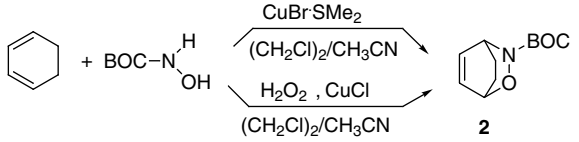
doi:10.1016/j.tetlet.2005.01.024

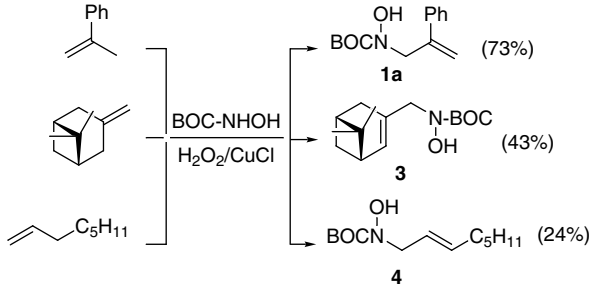


Scheme 3.

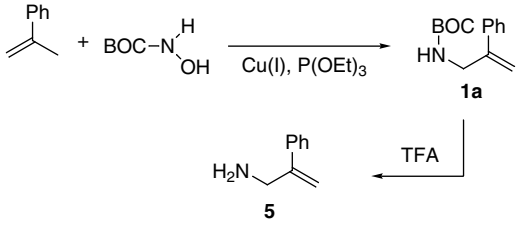
constitutes a net oxidation of the two reactants, it seemed possible that the oxidizing equivalents were derived from Cu-catalyzed disproportionation of Boc-NHOH,[17] with the intermediate Boc-NO undergoing an ene reaction with the olefin. Support for this notion was provided by the finding that when Boc-NHOH and 1,3-cyclohexadiene were heated together with 10 mol% $CuBr{\cdot}Me_2S$, the Diels–Alder adduct **2** derived from Boc-NO (65 h, 41%) was isolated (Scheme 3).[12c,18]

Accordingly, a dramatic improvement in the facility and the efficiency of both the Diels–Alder reaction (quantitative) and the AMS hydroxamination (73% of **1a**) could be achieved if these reactions were conducted using a stoichiometric oxidant, for example, 30% H_2O_2, for the Boc-NHOH (Schemes 3 and 4), proceeding at 20 °C within a few hours with CuCl as the catalyst.[19] Under these conditions, reactions of Boc-NHOH/H_2O_2 with β-pinene and 1-octene also afforded moderate yields of the corresponding *N*-hydroxallyl amine derivatives **3** (43%) and **4** (24%), displaying the regioselectivity typical of ene-type reactions.[11] Although [2 + 4]-cycloadditions of transient Boc-NO are well established, the CuCl–H_2O_2 system offers the most economical method for generating this species.[12c,18,20,21] Furthermore, the novel function of Boc-NO as an enophile,[20a] illustrated by these examples, is firmly established here.

Since it was apparent that Cu(I)X salts were ineffective at reducing Boc-*N*-hydroxy amines to the desirable Boc-*N*-allyl amines directly, we investigated the effects of added ligands which could enhance the Cu(I) reduction potential. Indeed, among several representative N- and P-based ligands surveyed,[22] the reaction between Boc-NHOH and AMS in the presence of CuBr/$P(OEt)_3$ (10 mol%:100 mol%; 85 °C) afforded the allyl amine derivative **5** as the major product (37%). Similarly, amination of β-pinene afforded the corresponding Boc-*N*-pinyl amine regioselectively in modest yield (13%). Control experiments, involving heating N-hydroxy derivative **1a** and $P(OEt)_3$, with and without CuBr,



Scheme 4.

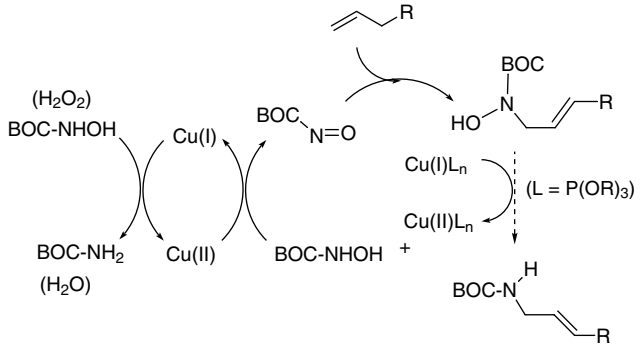


Scheme 5.

established that both CuX and the phosphite are required for the reduction. The Boc-*N*-allyl amines are convenient precursors to primary allyl amines by efficient removal of the Boc group under standard conditions, for example, **1a** → **5** (TFA/CH_2Cl_2, 68%; Scheme 5).

As to the origin of the differing outcomes of the Cu-catalyzed Boc-NHOH and Ar-NHOH reactions with olefins, we found that the CuBr-promoted reaction of AMS with MeO_2C–NHOH also gives the corresponding *N*-hydroxy allyl derivative as the main product. This suggests that the uniqueness of RO_2C–NHOH as aminating agents is electronic (rather than steric) in origin and that Cu(I)-catalysts modified with donor ligands are needed to convert the intermediate Boc-*N*-hydroxy allylamine to the corresponding Boc-allylamine. A possible catalytic pathway is outlined in Scheme 6, beginning with Cu-induced disproportionation of Boc-NHOH (or Cu(I) oxidation if H_2O_2 is present). The resulting Boc-NO (free or coordinated) can undergo an ene-reaction with the olefin to give the N-Boc allyl hydroxylamine. In the presence of $P(OEt)_3$ the $Cu(I)L_n$ complex formed can reduce the hydroxylamine to the allylamine (regenerating Cu(II) for catalytic recycle). Mechanistic details not withstanding, the combination of efficient hydroxyamination by Cu(I)/H_2O_2 with subsequent reduction or the direct amination with Boc-NHOH catalyzed by Cu(I)/$P(OR)_3$ provides convenient access to the synthetically valuable Boc-and primary allyl amines.

Experimental procedures and characterizational data for all new compounds (IR, NMR, MS) are provided in the Supplementary data that is available online with the paper in ScienceDirect.



Scheme 6.

Acknowledgements

We thank the National Science Foundation for support of this project.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.024.

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19. To a solution of Boc-NHOH (0.025 g, 0.19 mmol) in 1,2-dichloroethane was added AMS (0.56 mmol) and CuCl (15 mol%) followed by addition of 30% H_2O_2 (5 equiv). After stirring 7 h at 20 °C, TLC analysis indicated consumption of the Boc-NHOH. Petroleum ether (2 mL) and CH_2Cl_2 (8 mL) were added and the mixture was filtered. The filtrate was washed with water, dried over $MgSO_4$ and rotary evaporated. The residue was purified by preparative TLC (silica, 1:6 ethyl acetate/pet ether) to give the product **1a** (73%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H, $(CH_3)_3$), 4.52 (s, 2H, $-CH_2$), 5.29 (d, $J = 1.2$ Hz, 1H, –CH), 5.47 (s, 1H, –CH), 6.77 (br s, 1H, –OH), 7.28–7.45 (m, 5H, arom.). ^{13}C (75 MHz, $CDCl_3$) δ 28.3, 54.1, 82.1, 114.9, 126.4, 127.1, 128.4, 138.9, 142.9, 156.5. IR ($CHCl_3$, cm^{-1}) 1164, 1250, 1368, 1696, 2979, 3328. HRMS calcd for $C_{19}H_{27}NO_5Na$: 272.1263, found: 272.1249.
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