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Primary Amides. A General Nitrogen Source for Catalytic Asymmetric Aminohydroxylation of Olefins

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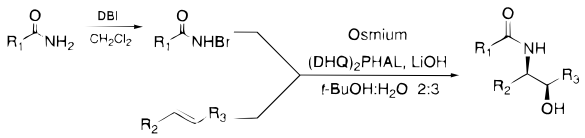
ABSTRACT



***N*-Bromo,*N*-lithio salts of primary carboxamides have been shown to be efficient nitrogen sources for catalytic asymmetric aminohydroxylation of olefins, behaving much like the parent *N*-bromoacetamide in these reactions. α-Chloro-*N*-bromoacetamide is a particularly interesting nitrogen source, as it is functionalized for further reaction, including easy deprotection by treatment with thiourea.**

The asymmetric aminohydroxylation (AA) provides a direct route to enantiomerically enriched vicinal amino alcohols, a moiety which is widespread throughout the modern pharmacopoeia.[1] The AA has been successfully performed with a variety of nitrogen sources, including sulfonamides,[2,3] carbamates,[4] and aminoheterocycles.[5] *N*-Bromoacetamide has also been demonstrated to act as a nitrogen source in the AA process,[6] but this is the only commercially available *N*-bromocarboxamide, and traditional methods to halogenate amides are limited in scope and facility.[7] Here we report the facile monobromination of a variety of primary amides and their subsequent use as nitrogen sources in the AA reaction.

Most *N*-halogenated oxidants used in the AA are prepared in situ by *N*-chlorination with *tert*-butyl hypochlorite in the presence of base;[8] however, primary carboxamides do not react under these conditions. Moreover, *N*-chloro, *N*-sodiocarboxamides are much more prone to undergo Hoffmann rearrangement[9] in the presence of base than their *N*-bromo, *N*-lithio counterparts. A largely unappreciated paper by Gottardi[10] reported dibromoisocyanuric acid (DBI) to be a

(1) *The Merck Index*, 12th ed.; Chapman & Hall: New York, 1996. Shaw, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 7, pp 397−429.

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(8) The exceptions are the three commercially available halogenated nitrogen salts, (*N*-chloro,*N*-sodio-*p*-toluenesulfonamide, *N*-chloro,*N*-sodiobenzene sulfonamide, and *N*-bromoacetamide), and the recently reported *N*-bromobenzamide (see: Song, C. E.; Oh, C. R.; Roh, E. J.; Lee, S.; Choi, J. H. *Tetrahedron Asymmetry* **1999**, *10*, 671−674).

(9) Wallis, E. S.; Lane, J. F. *Org. React.* **1967**, *3*, 267−306.

(10) Gottardi, W. *Monatsh. Chem.* **1975**, *106*, 611−623.

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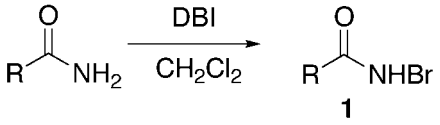
Scheme 1

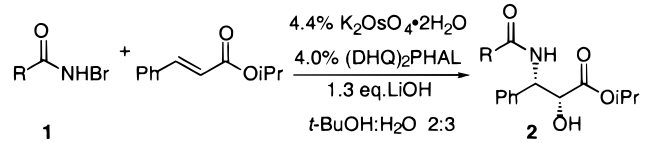


Scheme 1

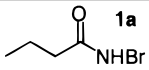
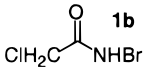
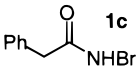
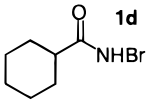
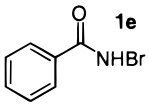
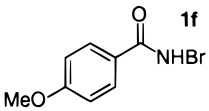
mild and highly effective brominating agent (Scheme 1). Using DBI[11] we were able to efficiently monobrominate a variety of carboxamides. The bromination typically proceeds in 90−99% conversion; filtration of the poorly soluble isocyanuric acid and a single recrystallization gives the *N*-bromocarboxamide in high purity.[12]

Addition of an *N*-bromocarboxamide **1** to a *tert*-butyl alcohol/water solution of the olefin, osmium, ligand, and base causes the lavender solution to turn deep green, consistent with the expected formation of a dioxo osmium(VI) monoazaglycolate species.[13] Upon completion of the reaction as monitored by TLC, workup affords the AA product **2** in isolated yields as high as 94%. All four stereo- and regioisomers are accessible by varying the ligand.[14] A variety of carboxamides were tested using isopropyl cinnamate as the olefin (Table 1).

Table 1. Asymmetric Aminohydroxylation of Isopropyl Cinnamate Using Various Amides as the Nitrogen Source



1 2

entry	bromoamide	T(°C)	conversion[a]	yield[b]	ee[c]	regioselectivity[a]
2a	 **1a**	4°C	96%	94%	95%	21 : 1
2b	 **1b**	10°C	86%	75%	95%	23 : 1
2c	 **1c**	4°C	81%	76%	93%	12 : 1
2d	 **1d**	4°C	84%	71%	80%	20 : 1
2e	 **1e**	4°C	50%	38%	77%	2.0 : 1
2f	 **1f**	0°C	70%	42%[d]	43%	2.5 : 1

[a] As determined by ^{1}H NMR spectroscopy of crude product. [b] Combined isolated yield of both regioisomers. [c] Major product. [d] Hoffmann rearrangement product interfered with isolation of product.

As nitrogen sources, aliphatic carboxamides were found to give the best results, with butyramide and acetamide showing greater than 95% conversion of isopropyl cinnamate to the corresponding β-hydroxyamide. Moderate steric hindrance does not have a marked effect on yield, although enantiomeric excess suffers slightly; e.g., see entry **2d**. Highly hindered carboxamides such as *tert*-butyl carboxamide and 1-adamantyl amide, however, give very low yields. Aromatic carboxamides are not as effective, showing a lower conversion, less regioselectivity, and lower levels of asymmetric induction.

Variation of the electronic nature of the carboxamides established a narrow window for successful asymmetric aminohydroxylation reactivity. Electron-deficient amides react more slowly, but as they are less likely to undergo Hoffmann rearrangement, higher temperatures can be used. Amides that are more electron-deficient than chloroacetamide give lower aminohydroxylation yields, and the diol becomes a major product, presumably because hydrolysis of the putative osmium imido intermediate is more rapid. Conversely, *N*-bromo, *N*-lithio species from electron-rich amides react faster but are also more sensitive to decomposition, so that lower temperatures are beneficial.

2-Chloroacetamide was used as a standard amide to explore the scope of the olefin component because it performs well and because its α-chloro substituent makes it very useful for subsequent derivitization reactions (see Table 2). Moreover, it is a useful amine-protecting group, being

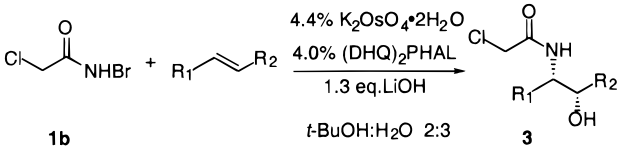
(11) Procedure: to a well-stirred solution of cyanuric acid (12.9 g, 100 mmol) and LiOH (8.4 g, 200 mmol) in water (1 L) is slowly added Br_2 (63.9 g, 400 mmol). After the bromine is dissolved, the solution is placed in the refrigerator overnight. The solution is then filtered, and the filtrate is dried in vacuo to yield DBI as a white powder. Taken from: *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: West Sussex, 1995; p 1560.

(12) Representative bromination: To a solution of chloroacetamide (4.34 g, 46.4 mmol) in DCM (300 mL) was added DBI (8.00 g, 1.2 equiv) and the suspension was refluxed in the dark for 5 h. The reaction mixture was filtered, and the precipitate was washed with CH_2Cl_2 (2 × 150 mL, or, in the case of poorly soluble *N*-bromoamides, with boiling EtOAc), and the solvent was removed under reduced pressure to afford the crude product as a white powder[10] (7.75 g, 97%), which by ^{1}H NMR analysis was shown to be 99% *N*-bromo chloroacetamide and 1% starting material. *N*-Bromoamides were stored under vacuum.

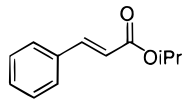
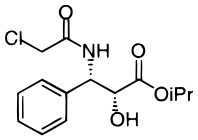
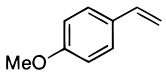
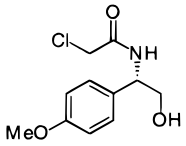
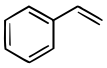
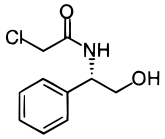
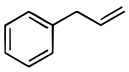
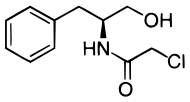
(13) Representative asymmetric aminohydroxylation [isopropyl (2*R*,3*S*)-3-(butyramido)-2-hydroxy-3-phenylpropanoate]: To a 500 mL round-bottom flask was added water (150 mL), in which was fully dissolved K_2OsO_4·$2H_2O$ (81 mg, 4.4 mmol) and LiOH·H_2O (273 mg, 1.3 equiv). The ligand, $(DHQ)_2PHAL$ (156 mg, 4.0 mmol), and isopropyl cinnamate (951 mg, 5.0 mmol) were dissolved in *t*-BuOH (100 mL), and the two solutions were combined and stirred until homogeneity was achieved. The solution was cooled to 4 °C. *N*-bromo butyramide (1.16 g, 1.40 equiv) was added in one portion. The reaction mixture was vigorously shaken until the pink solution turned a bright green. In some cases sonication was necessary. The reaction mixture was left to stir a constant temperature (4 °C). When the reaction had reached completion, Na_2SO_3 (1.0 g) was added and the solution was stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered, and the solvent removed under reduced pressure. Chromatography of the crude product on silica gel with 2% MeOH in CH_2Cl_2 afforded **2a** as a white powder (1.38 g., 94%, 21:1 regioisomeric ratio).

(14) In the case of 2-chloroacetamide as the N-source, and isopropyl cinnamate as olefin, when the $(DHQ)_2AQN$ ligand is used, the benzylic alcohol is favored over the benzylamine by a ratio of 3.2:1. For precedence see: Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507−2510. When the $(DHQD)_2PHAL$ ligand is used, the enantioselectivity was also 95%, with the (2*S*,3*R*) product predominating.

Table 2. Asymmetric Aminohydroxylation of Various Olefins Using α-Chloroacetamide as the Nitrogen Source



1b **3**

entry	olefin	product	yield[a]	ee[b]	regio-selectivity[c]
2b			75%	95%	23 : 1
3a			72%	97%	2.5 : 1
3b			77%	97%	1.3 : 1
3c			40%	50%	2.5 : 1

[a] Combined isolated yield of both regioisomers. [b] Major product. [c] As determined by ^{1}H NMR spectroscopy of crude product.

readily removed in the presence of 1 equiv of thiourea at reflux first in ethanol and then in water.[15]

Cinnamates were shown to give the highest regioselectivities (see entries **2a**−**f**), presumably due to the favorable aromatic interactions in the binding pocket.[16] Styrene and its derivatives also reacted well with excellent enantioselectivities, but poor to moderate regioselectivities (**3a**,**b**). Nonconjugated olefins gave inferior results compared to conjugated olefins (**3c**). Similar observations have been made for other versions of the AA process.[3,6]

We found the amount of base to be critical. Excess base is known to shut down the catalytic cycle entirely.[5a] On the other hand we also observed that insufficient base can significantly reduce catalytic turnover rates, leaving a very narrow window for optimal reactivity. Unexpectedly, we found that when the nonrecrystallized *N*-bromoamide containing several percent of the primary amide starting material is used, the reaction is more reliable,[17] especially when 2-chloroacetamide is used as the nitrogen source. The amount of primary amide impurity present should be kept below 5% if possible.

The diol byproducts, very similar in polarity to the desired hydroxyamides, are often challenging to remove chromatographically. A useful method to remove the diol is to simply treat the crude reaction product in a 4:1 (v:v) THF:water mixture with roughly 2 equiv of periodic acid (with respect to estimated diol content, monitor by TLC). This effects selective cleavage of the diol to the aldehydes which are then readily separated from the desired product.

In cases where solubility was an issue, for example with *N*-bromo-*p*-methoxybenzamide, we used 1-propanol in place of *tert*-butyl alcohol with no noticeable difference. Reactions were also carried out in acetonitrile/water and THF/water, but lower yields were observed.

The concentration of the reaction is of paramount importance. When the AA reaction was run under more dilute conditions, we observed higher regioselectivities, presumably due to the more selective first cycle being favored.[18] However, since decomposition of the *N*-bromo, *N*-lithio carboxamides is assumed to be concentration independent, too dilute conditions should favor Hoffman rearrangement—again a compromise is needed.

The reaction temperature employed depended on the electronic nature of the amide: for acetamides and benzamides with electron-withdrawing substituents the reaction was run at 12 °C, with electron-donating substituents it was run at 0 °C, otherwise it was run at 4 °C.

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Supporting Information Available: Full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Kolb, H. C.; Andresson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278−1291.

(17) Use of 10 mol % catalyst and ligand greatly increased both the reliability and the selectivity of the reaction. It also was noted that when the pH of the solution was above 9, or above 8 for electron-deficient amides, no reaction was observed.

(18) Chang, H.-T. Ph.D. Thesis, The Scripps Research Institute (US), 1996.