Intramolecular Hydroamination of Aminoalkynes with Silver–Phenanthroline Catalysts
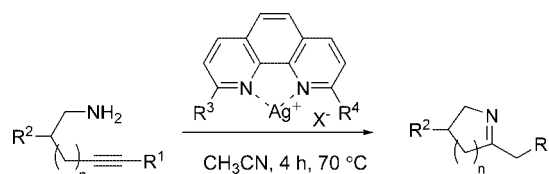
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ABSTRACT

Intramolecular hydroamination of several aminoalkynes catalyzed by silver–phenanthroline complexes is reported. This catalyst system complements previous protocols by employing air- and moisture-stable complexes without compromising activity or reaction control. Some of the hydroamination products are subject to a useful aerobic oxidation. Silver–phenanthroline complexes have successfully demonstrated efficacy in the desymmetrization of a prochiral diyne.

Nitrogen heterocycles are important because of their presence in a variety of biologically relevant compounds.[1] Therefore, the synthesis of these heterocycles is of paramount interest. Among the more versatile means for incorporation of nitrogen into organic compounds is the metal-catalyzed hydroamination reaction,[2–4] with *N*-heterocycles arising from intramolecular hydroamination of a carbon–carbon double or triple bond by a tethered amine or amine derivative. The search for appropriate metal catalysts and corresponding ligand systems for these reactions has been the subject of extensive research.[2–7] The hydroamination of alkynes has been reported as both an intra- and intermolecular[4] reaction

proceeding in the presence of various metals, including lanthanides,[5] transition metals,[6] and some alkaline earth metals.[7] The use of late transition metals as catalysts is thought to facilitate the attack of nitrogen nucleophiles onto unsaturated carbon moieties through activation of the double or triple bond such that the electron-rich alkene or alkyne is transformed into an electrophile.[3a] As a clear indication of their utility, alkyne hydroaminations have been employed as key steps in total syntheses of a number of natural products.[8]

Previous processes for the catalytic hydroamination are often limited by use of air- or moisture-sensitive catalysts or the prohibitive cost of metal complexes. Despite the relatively low cost of silver compared to more precious

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metals, silver-catalyzed hydroaminations have not been as extensively studied.[9] Many types of supporting ligands may be used in these reactions, and although 1,10-phenanthrolines have broad utility,[10] their use in hydroaminations has not been demonstrated.[11] This fact, as well as our previous development of methods for the synthesis of functionalized phenanthrolines,[12] has prompted us to investigate the use of this ligand class in these reactions. We wish to report the results of these studies whereby silver−1,10-phenanthroline complexes function as efficient and recyclable catalysts for the intramolecular hydroamination of aminoalkynes.

The efficacy of the parent 1,10-phenanthroline as a ligand in the hydroamination of 5-phenyl-4-pentyn-1-amine (**1a**) was initially tested in a brief qualitative screening of several metal catalyst candidates, including Ni, Yb, Sm, Ti, Cu, Au, and Ag. These preliminary experiments found that there was a metal dependence of whether the imine **2a** or the isomeric enamine **3a** was obtained as the major product (Scheme 1).

Scheme 1. Initial Metal-Catalyzed Hydroamination Screening
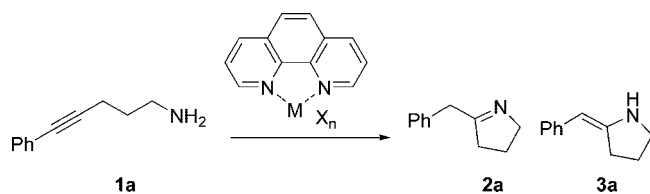
This initial screening found that both Ag and Pd favored formation of **2a**, whereas Yb, Sm, and Ni preferentially gave tautomeric enamine **3a** (data not shown). For purposes of this study, we chose to focus on the use of those metals that led to selective formation of cyclic imines as highly versatile products.

With this knowledge, we attempted a more quantitative screening of selected metal catalysts in the hydroamination of **1a** (Table 1). The advantage of silver−phenanthroline

Table 1. Screening of Metal−Phenanthroline Complexes

entry	catalyst	mol %	time (h)	temp (°C)	% yield[a]
1	AgOTf	10	4	70	55
2	Ag(phen)OTf	10	4	70	95
3	Ag(phen)OTf	4	4	70	82
4[b]	Ag(phen)OTf	4	4	70	84
5	Ag(phen)OTf	1	4	70	71
6	Pd(acac)$_2$	10		100	0[d]
7	Pd(phen)(acac)$_2$[c]	15	6	100	69
8	NaAuCl$_4$	10	4	25	46
9	Au(phen)Cl$_2$NO$_3$	10	4	25	59

[a] Yields were calculated from ^{1}H NMR spectra using mesitylene as an internal standard. [b] Result from catalyst that was collected by filtration after reaction in entry 3, washed with CH$_2$Cl$_2$, and reused. [c] Reactions run in d_6-dimethyl-sulfoxide. [d] In the absence of supporting ligand, Pd(acac)$_2$ formed Pd black and did not catalyze the cyclization.

(phen) complexes over the naked silver salt was demonstrated with the increase in yield of **2a** (entry 1 vs entry 2, Table 1). In palladium-catalyzed reactions, the benefit of phenanthroline was seen in its ability to stabilize the metal in the reaction mixture (entry 6 vs entry 7, Table 1). Au(phen)Cl$_2$NO$_3$ provided good reactivity in the intramolecular hydroamination (reactions proceeded at 25 °C), but the yield of **2a** was lower than for the other two metals studied (entries 8 and 9). Enamine **3a** was not observed in any of the reactions in Table 1.

Overall, silver complexes provided **2a** in higher yields than either palladium or gold. There were also other benefits to the Ag(phen)-based catalysts that led us to choose silver as the catalyst for further studies. The reactions run in acetonitrile using phenanthroline complexes were heterogeneous at 25 °C but became homogeneous above 35 °C. After the reaction mixture was cooled, the phenanthroline complex could be recovered by filtration, whereas AgOTf could not be recycled as readily because of its solubility at 25 °C. No loss of activity was observed in a second run (entry 4, Table 1), and Ag(phen)OTf was also active using a catalyst loading as low as one mole percent (entry 5, Table 1), but the rate was too slow for the reaction to go to completion under the normal conditions. In addition to its recyclability, the silver−phenanthroline complex was air- and moisture-stable

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for at least 6 months after preparation,[13] a benefit over other catalysts for which strict anhydrous and anaerobic conditions are necessary.

Complexes of silver−1,10-phenanthroline and silver−2,9-dimethyl-1,10-phenanthroline (neocuproine, dmp) were synthesized by reaction of the ligands with silver triflate, and these catalysts were studied in the hydroamination of a series of primary aminoalkynes (Table 2). These reactions were

Table 2. Silver-Catalyzed Hydroamination of Aminoalkynes

entry	substrate	R′	time (h)	product	% yield[a]
1	**1a**	H	4	**2a**	95 (87)
2	**1a**	CH₃	6	**2a**	95
3	**1b**	H	6	**2b**	77 (70)
4	**1c**	CH₃	4	**2c**	95
5	**1d**	CH₃	5	**2d**	78
6	**1e**	CH₃	10	**2e**	90

[a] Yields were calculated from ¹H NMR spectra using mesitylene as an internal standard. Isolated yields shown in parentheses where applicable.

carefully monitored to minimize reaction times. A catalyst loading of 10 mol % was standardized, despite the demonstration of the potential for lower loadings, because this loading allowed for the complete conversion of starting material within a reasonable reaction time. Replacement of phenanthroline with neocuproine showed no effect on activity, thus demonstrating tolerance for substitution at the 2 and 9 positions of the phenanthroline scaffold.

In general, 5-aminopentyne derivatives cyclized more efficiently than their 6-aminohexyne counterparts (entries 1, 2, and 4 as compared to entries 3 and 5, Table 2). The catalysts were effective in the cyclization of terminal and disubstituted alkynes, including an unactivated methyl substituted alkyne (entry 6). Because of its volatility, 2-methyl-1-pyrroline (**2c**) was isolated as its N-methyl pyrrolinium derivative by reaction with iodomethane in acetonitrile.
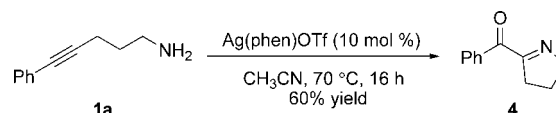
In addition to the desired imine product **2a**, a useful product of oxidation, 2-benzoyl-1-pyrroline (**4**), could be

obtained when the reaction times were extended (Scheme 2).[14] Although this oxidation occurred readily for the

Scheme 2. Hydroamination and Facile Benzylic Oxidation

2-benzylpyrroline **2a**, it was not observed for the corresponding 2-benzyltetrahydropyridine **2b** or for the non-benzyl substituted products **2c**−**e**. In previous work, imines similar to **2a** have been formed under Ag-catalyzed conditions, but detection of compounds analogous to **4** were not discussed.[9e]

Hydroamination of the alkynes above leads to imine products that lack chirality. To demonstrate that such reactions could potentially generate chiral products,[15] we have done a preliminary study of a desymmetrization of a prochiral diyne **5**, using an achiral catalyst prior to future efforts to develop appropriate chiral catalysts. The substrate **5** was synthesized as shown in Scheme 3. Under the

Scheme 3. Synthesis of Prochiral Diyne **5**
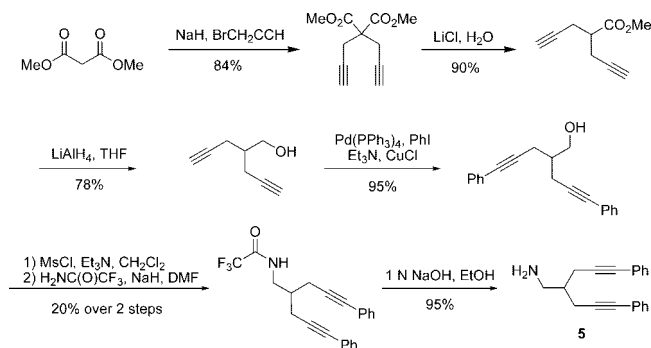
conditions optimized for the simple aminoalkynes, **5** was cyclized to form the racemic but desymmetrized cyclic imine **6**. Interestingly, it was found that the prochiral diyne underwent cyclization under much milder conditions than the previous alkynes. When Ag(phen)OTf and Ag(dmp)OTf complexes were used to catalyze this reaction, a temperature

(13) The catalyst was stored at 25 °C in the dark with no precautions to avoid exposure to air.

(14) Although the hydroamination reactions were initially set up under argon, no rigorous measures were taken to exclude adventitious oxygen during the long reaction times. For a similar oxidation of a benzylic imine, see: Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. J. Org. Chem. **2007**, 72, 4886. For comparison of spectroscopic data of **4**, see: Schieberle, P. J. Agric. Food Chem. **1995**, 43, 2442. In a similar Pd-catalyzed reaction, a byproduct of identical molecular weight was also observed; however, it was thought to be PhCC(CH₂)₃NO. Richmond, M. K.; Scott, S. L.; Yap, G. P. A.; Alper, H. Organometallics **2002**, 21, 3395.

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of 35 °C was found to be adequate for formation of imine **6** (Table 3). Reactions using these catalysts in d_6-DMSO allowed for shorter reaction times when compared to those in d_3-acetonitrile.
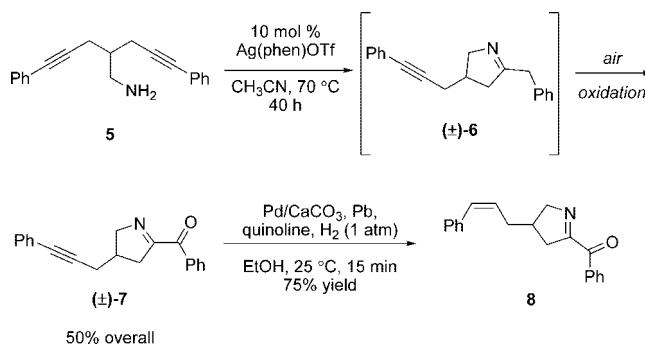
Table 3. Desymmetrization of Prochiral Diyne **5**

catalyst[a]	solvent	temp (°C)	time (h)	% yield[b]
Ag(phen)OTf	CD$_3$CN	70	4	72
Ag(phen)OTf	CD$_3$CN	35	2	67 (48)
Ag(dmp)OTf	CD$_3$CN	35	4	67
Ag(dmp)OTf	(CD$_3$)$_2$SO	35	2	67

[a] phen = 1,10-phenanthroline; dmp = 2,9-dimethyl-1,10-phenanthroline. [b] Yields were calculated from ^{1}H NMR spectra using mesitylene as an internal standard. Isolated yields shown in parentheses where applicable.

A consequence of the initial formation of an imine **6** is the differentiation of the identical alkynes in diyne **5**.[16] Fundamentally distinct reactions are applicable to the now different functional groups in imine **6**. As was the case with pyrroline **2a**, extended heating of the reaction mixture results in the conversion of pyrroline **6** to the corresponding α-ketoimine **7** (Scheme 4). This facile oxidation allows for complex functionality to be obtained in one step. In turn, the remaining alkyne can be employed in reactions typical of this group, such as Lindlar hydrogenation to give *cis*-alkene **8** (Scheme 4).

In conclusion, silver−phenanthroline complexes have been shown to be effective catalysts for the intramolecular hydroamination of a variety of primary aminoalkynes. In addition to being air- and moisture-stable, the complexes are readily recyclable. These complexes provide the field of

Scheme 4. Further Elaboration of Diyne **5**

catalytic alkyne hydroamination with an alternative to sensitive or cost-prohibitive catalysts. Studies of secondary amines in these reactions and of the enantioselective desymmetrization of prochiral diynes and related dienes by employing chiral ligand complexes are currently underway and will be reported in due course.

Supporting Information Available: Experimental details for all reactions and characterization data for compounds **2a−e** and **4−8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801458G