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Mild and Efficient Desymmetrization of Diynes via Hydroamination: Application to the Synthesis of (±)-Monomorine I

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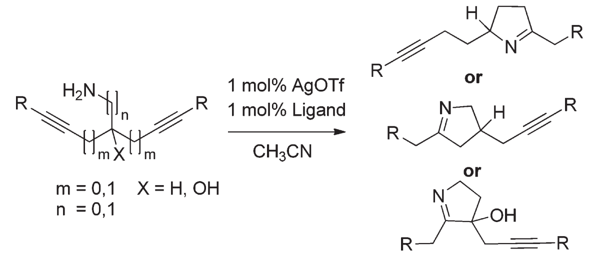
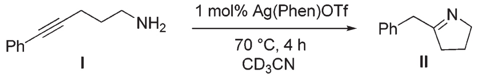


An efficient silver-catalyzed desymmetrization of amino diynes via hydroamination is reported. A variety of functionalized 1-pyrroline derivatives were synthesized in 73% to 88% isolated yields (>98% by ^{1}H NMR in some cases). The usefulness of this mild hydroamination method was further shown by the desymmetrization of unprotected *tert*-hydroxy diynes. Structures of two transition states have been studied computationally. An application of this method was demonstrated by a short and efficient synthesis of (±)-monomorine I.

Nitrogen-containing heterocycles are found among many biologically important compounds. Their synthesis via the intramolecular hydroamination of C−C multiple bonds, an atom economical process,[1,2] is a subject of great interest in synthetic organic chemistry. Metal-catalyzed intramolecular hydroamination/cyclization of aminoalkynes,[3−5] aminoalkenes,[6−9] aminoallenes,[10,11] and aminodienes[12,13] has been documented in numerous studies. The search for appropriate metal catalysts for these reactions has been the subject of extensive research, particularly for hydroamination of alkenes and alkynes.[1] The hydroamination of alkynes has been reported to proceed in the presence of various metals such as lithium,[14] group 4 metals,[15] nickel,[16] palladium,[17−19] platinum,[20] calcium,[21] copper,[22] gold,[23] and zinc.[24] Although good catalytic hydroamination conditions have been developed, many of the metals used are expensive, and the susceptibility of some of their complexes to moisture and oxygen constitutes a serious drawback in many cases.

SCHEME 1. Hydroamination of Aminoalkyne[3]



As part of an ongoing program directed toward the development of new methodologies for transition metal-catalyzed reactions in our laboratory,[25−28] we previously reported an efficient intramolecular hydroamination of aminoalkynes (Scheme 1) using catalytic amounts of a silver-(1,10-phenanthroline)OTf complex, Ag(phen)OTf, which is highly stable toward moisture and air, employs a metal having moderate cost, and is readily recyclable.[3]

Our earlier results suggested the utility of this reaction for desymmetrization of diynes via intramolecular hydroamination. Desymmetrization of many classes of compounds including alkynes[29−32] is an efficient strategy to generate useful

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SCHEME 2. Hydroamination of Diynes 1a−c

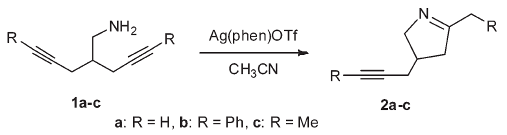


TABLE 1. Hydroamination of Diynes 1a−c

entry	substrate	R	catalyst	mol %	temp (°C)	time (h)	yield (%)
1	**1a**	H	AgOTf	10	25	1	< 5[a]
2	**1a**	H	Ag(Phen)OTf	10	25	< 5 min	> 98[a] (85)[b]
3	**1b**	Ph	Ag(Phen)OTf	10	25	4	> 90[a] (82)[b]
4	**1c**	Me	Ag(Phen)OTf	10	25	6	> 90[a]
5	**1c**	Me	Ag(Phen)OTf	10	50	2	88[b]
6	**1a**	H	Ag(Phen)OTf	2	25	< 5 min	> 98[a]
7	**1b**	Ph	Ag(Phen)OTf	2	50	1	> 90[a] (83)[b]
8	**1a**	H	Ag(Phen)OTf	0.5	25	1	> 98[a]

[a] Yields measured by ^{1}H NMR of the crude material. [b] Isolated yields.

SCHEME 3. Hydroamination of Diynes 3a−c

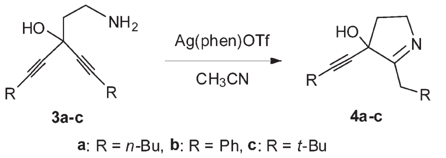
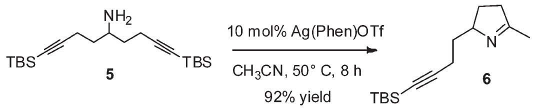


TABLE 2. Hydroamination of Diynes 3a−c

entry	substrate	R	catalyst	mol %	temp (°C)	time (h)	yield (%)[a]
1	**3a**	*n*Bu	Ag(Phen)OTf	5	50	2	85
2	**3a**	*n*Bu	Ag(Phen)OTf	2	50	3	87
3	**3a**	*n*Bu	Ag(Phen)OTf	2	rt	10	69
4	**3b**	Ph	Ag(Phen)OTf	5	rt	10	-
5	**3b**	Ph	Ag(Phen)OTf	2	50	5	73
6	**3c**	*t*Bu	Ag(Phen)OTf	5	50	8	80

[a] isolated yields.

SCHEME 4. Hydroamination of Diyne 5



building blocks in organic synthesis. Here we demonstrate the utility of this concept for the synthesis of a range of functionalized 1-pyrroline derivatives. In addition to the development of a diyne desymmetrization, we have also perfomed DFT studies of two possible transition states for this reaction.

As an initial class of substrates, we chose to study the aminodiynes **1a−c** (Scheme 2), which are easily accessible from commercially available starting materials by standard transformations.[33] The results of the hydroaminations of **1a−c** are summarized in Table 1.

A control reaction was performed with **1a**, using 10 mol % AgOTf without any ligand, but almost no reaction was observed (entry 1). This result suggests the requirement for a suitable ligand for the desired reaction in this system. The catalyst generated from AgOTf and 1,10-phenanthroline produced the cyclic imine **2a** as the sole detectable product (> 98% yield by ^{1}H NMR) from diyne **1a** at room temperature (entry 2). The same catalyst converted **1b** to **2b** (> 90% yield by ^{1}H NMR) at room temperature (entry 3). The diyne **1c** underwent cyclization slowly at room temperature to give **2c** with 10 mol % of Ag(phen)OTf (entry 4). However, an increase in temperature to 50 °C significantly shortened the reaction time (entry 5). Interestingly, lowering the amount of catalyst from 10 mol % to 2 mol % also produced the products **2a** and **2b** in over 90% yields (entries 6 and 7), whereas **1a** underwent cyclization to give **2a** with even 0.5 mol % catalyst for 1 h (entry 8).

After observing promising hydroamination results with diynes **1a−c**, we were interested in testing the compatibility of the reaction in the presence of a potentially interfering functional group. For this purpose, hydroxyaminodiynes **3a−c** were prepared from *β*-alanine by standard transformations.[17] This series of compounds also provide an altered substrate skeleton for generating 1-pyrrolines **4** (Scheme 3) having a modified substitution pattern compared to **2**.

After applying the previously utilized hydroamination conditions optimized for **1a−c**, we found that either an extension of the reaction time or an increase in reaction temperature is required to cyclize **3a−c**. The diyne **3a** was cyclized to **4a** with 5 mol % of Ag(phen)OTf at 50 °C for 2 h in 85% yield (entry 1, Table 2). A lower amount of catalyst of Ag(phen)OTf (2 mol %) also gave **4a** at 50 °C in essentially the same yield (entry 2). Lowering the reaction temperature to 25 °C reduced the reaction rate, but gave **4a** in moderate yield (entry 3). The phenyl-substituted diyne **3b** did not undergo hydroamination at room temperature but at 50 °C readily underwent cyclization with 5 mol % of Ag(phen)OTf for 5 h to give **4b** in 73% yield. Similarly, the diyne **3c** also gave **4c** at 50 °C in 80% yield with 5 mol % of catalyst (entry 5).

To examine another substrate skeleton, amino diyne **5** was synthesized (Scheme 4).[17] This substrate was also chosen to examine the effect of silylated alkyne groups. Furthermore, **5** could be employed as the starting point for a natural product synthesis (vide infra). The diyne **5** underwent cyclization with 5 mol % of Ag(phen)OTf for 8 h at 50 °C to give **6** in 92% yield. Interestingly, desilylation was observed only from the alkyne group that underwent the hydroamination.

To gain a better understanding of the silver-catalyzed hydroamination and to explore the effects of substituted phenanthroline ligands, we calculated the relevant transition structures at the B3LYP[34,35]/LanL2DZ[36,37] level of theory in analogy to our previous work.[28] We considered a simplified model, the hydroamination of acetylene with ethylamine catalyzed by a (2-methylphenathroline)silver complex (Figure 1). In this model, the two possible region isomeric transition structures *anti*-TS1 and *syn*-TS2 are possible. The energy difference between the two can serve as a measure of the regio- or stereochemical differentiation that a substituent, including chiral groups, on the ligand may have on the reaction. The two transition states were fully optimized

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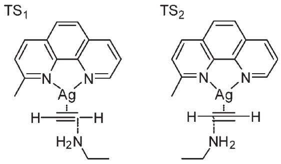


FIGURE 1. Representation of the Ag(I) 2-methyl, *o*-phenanthroline diastereomers for the acetylene amination transition state model.

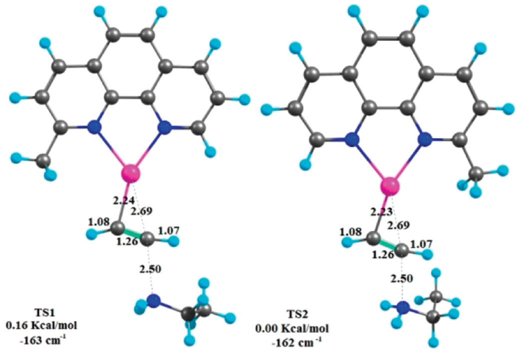


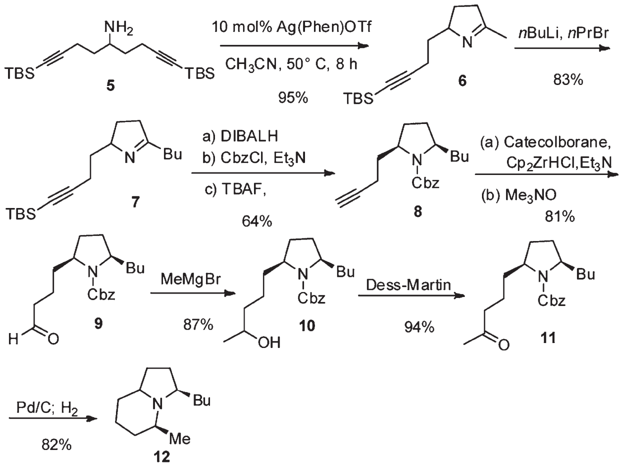
FIGURE 2. Optimized isomeric transition structures for the hydroamination model. Most important atomic distances are reported for TS1 and TS2 transition states.

without any constraints by using the Berny algorithm implemented in Gaussian03.[38]

The final structures with highlighted parameters are shown in Figure 2. Structurally, TS1 and TS2 are essentially identical and the calculated energy difference is much smaller than what can be considered significant at this level of theory. This weak differentiation indicates that 2-substituted phenanthrolines are unlikely to induce significant regio- or stereoselectivity. The coordinated carbon shows a Ag−C bond length of 2.24 Å, which is significantly shorter than that for the carbon undergoing nucleophilic attack (2.69 Å). The partial triple bond (1.26 Å) is longer in both transition states than in uncoordinated acetylene (1.20 Å). This indicates donation into the antibonding π^* orbital, thus weaking the backbonding from silver upon nucleophilic attack of the amine. Rehybridization of the alkyne has progressed significantly, but the N−C distance of 2.50 Å in the transition structures is quite long, indicating a relatively early transition state. These differences are again due to the changes from dicoordination to monocoordination of the alkyne to the silver.

The structural and energetic similarities between the two transition states suggest that a different approach needs to be explored in order to introduce stereoselectivity in future studies of the hydroamination reaction. These conclusions will also apply to potential chiral substitutents larger than methyl[26] as shown by two characteristics of the model ligand considered here: (1) the ligand is planar, and the silver preferentially coordinates in a square-planar fashion, leaving the triple bond open to attack from any direction; (2) substituents at C(2) of the phenanthroline ligand are not in the path of the nucleophile and thus are not sufficiently close to the prochiral alkyne substrate to impact the potential enantioselectivity of the reaction. Preliminary results of similar calculations extended to chiral phenanthroline derivatives and BOX-type ligands confirm that even with bulky substituents, an enantioselective desymmetrization is not readily achievable because of the silver square-planar coordination.

SCHEME 5. Synthesis of (±)-Monomorine



On the basis of the foregoing experimental results, we chose to demonstrate the utility of the desymmetrization reaction by performing a synthesis of the alkaloid (±)-monomorine I. (+)-Monomorine is an indolizidine alkaloid isolated from the cosmopolitan ant *Monomorium pharaoins* L.[39] Along with other indolizidine alkaloids,[40] both natural (+)-monomorine and nonnatural (−)-monomorine have been the target of many syntheses.[41−47] Particularly relevant to the present study were the syntheses reported by Bäckvall[47] and Toyooka,[43] who used ketone **11** as a key intermediate. Our route (Scheme 5) begins with the aforementioned cyclization of diyne **5**, which was synthesized from 4-bromo-1-butyne.[48]

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The resulting cyclic imine **6** was subjected to chain extension by lithiation[49] of the methyl group and subsequent reaction with *n*-propylbromide to give imine **7** in 83% yield. This imine was subjected to a one-pot conversion involving DIBAL reduction,[50] Cbz protection, and TBS removal[51] without purification of intermediates to give pyrrolidine **8** in 64% overall yield. The alkyne **8** was converted to aldehyde **9** in a one-pot, two-step transformation by employing Knochel's hydroboration procedure[52,53] and alkenylborane oxidation with Me_3NO[54] in 81% overall yield. The aldehyde **9** was then treated with MeMgBr to obtain the alcohol **10** in 87% yield, followed by oxidation with the Dess−Martin periodinane to give the previously employed ketone[43,47,55] **11** in 94% yield. A combination of hydrogenolysis and reductive amination of **11** with Pd/C and H_2 in ethanol gave (±)-monomorine **12** in 82% yield. The overall yield is 26% for 7 steps.

In conclusion, we have developed an efficient procedure for desymmetrization of diynes by means of the silver-catalyzed intramolecular hydroamination. This method shows reliability in producing functionalized 1-pyrroline derivatives in good to excellent yields. A key strategic feature of this reaction is that it converts a diyne into a product having two entirely different, orthogonal functional groups, each of which is independently capable of undergoing further diverse transformations. As such this reaction is amenable to the synthesis of a variety of useful intermediates and natural products as demonstrated by the synthesis of (±)-monomorine I. A remaining need is the development of an enantioselective version of this reaction.

Experimental Section

General Procedure (GP1) for the Hydroamination. To a solution of aminodiyne (1 mmol) in CH_3CN (4 mL) was added Ag(phen)OTf (0.1 mmol). The mixture was heated to 50 °C by use of an oil bath for 4 h in the absence of light. The reaction mixture was then cooled to 25 °C, passed through a column of silica gel, and eluted with EtOAc/hexanes (1/9). Solvent evaporation gave the 1-pyrroline as a clear oil.

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Supporting Information Available: Starting material preparation, characterization data for all new compounds, ^1H and ^{13}C spectra, and Cartesian coordinates and energies for the calculated transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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