Hydroamination

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Silver-Catalyzed Hydroamination of Siloxy Alkynes**

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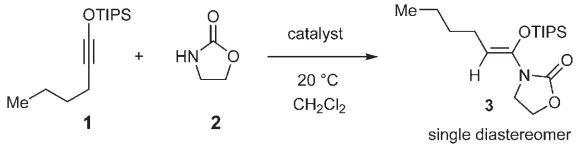
Transition-metal-catalyzed hydroamination of alkynes has emerged as a valuable method for C–N bond formation.[1] While significant progress in this area has been made,[2] several important limitations remain to be addressed. The majority of the previously developed catalytic processes employ highly nucleophilic primary amines that afford the corresponding imines as a result of tautomerization of the initially produced enamides.[3–5] We describe herein the first example of hydroamination of electron-rich alkynes by using a silver-based catalyst that enables *syn*-selective addition of secondary amides and carbamates to furnish the corresponding silyl ketene aminals with high efficiency and excellent diastereoselectivity. Our mechanistic studies demonstrate that the reaction proceeds by a fast and reversible silver–alkyne complexation, followed by a rate-determining C–N bond-forming step, which provides an important mechanistic platform for further development of d^{10} catalysts for alkyne and alkene hydroamination.

During our continuing investigation of the development of new catalytic C–C and C–X bond-forming reactions with electron-rich alkynes,[6] we discovered that treatment of siloxy alkyne **1** (TIPS = $i\text{Pr}_3\text{Si}$) with carbamate **2** in the presence of either a silver- or a gold-based catalyst resulted in the formation of silyl ketene aminal **3** (Table 1). Initial investigations revealed that the use of AgNTf_2 ($\text{Tf} = \text{CF}_3\text{SO}_2$) proved to be superior to that of AuCl and AuCl_3 (Table 1, entries 1–3).[7] This finding is especially noteworthy as silver-based catalysts have not been used extensively for the hydroamination of alkynes and alkenes.[8] The hydroamination product, **3**, was obtained in 86 % yield after 30 min at room temperature by using only 1 mol % of AgNTf_2 (Table 1, entry 4). The catalyst loading could be further decreased to 0.3 mol % without significant loss of efficiency (Table 1, entry 5). Furthermore, subjecting the reactants to HNTf_2 (5 mol %) produced only a trace of enol silane **3**, which ruled out a possible involvement of the conjugate Brønsted acid in the alkyne activation (Table 1, entry 6). Interestingly, PdCl_2 and PtCl_2 proved to be much less effective at catalyzing this reaction (Table 1, entries 7 and 8).

Table 1: Hydroamination of siloxy alkynes: catalyst evaluation.



Entry	Catalyst	Catalyst loading	Reaction time	Yield [%][a]
1	AuCl	5 mol %	1.5 h	51
2	AuCl_3	5 mol %	30 min	75
3	AgNTf_2	5 mol %	30 min	91 (82[b])
4	**AgNTf_2**	**1 mol %**	**30 min**	**95 (86[b])**
5	AgNTf_2	0.3 mol %	2 h	81
6	HNTf_2	5 mol %	3 h	< 5
7	PdCl_2	5 mol %	3 h	< 5[c]
8	PtCl_2	5 mol %	3 h	40[c]

[a] Determined by NMR integration with respect to an internal standard. [b] Yield of isolated product (reaction giving best yield highlighted in bold). [c] The reaction was conducted in toluene at 80 °C.

Having established a standard reaction protocol, we examined the scope of this catalytic process. The reaction of either 5- or 4-substituted oxazolidinones, **4** and **6**, with siloxy alkyne **1** afforded the desired products, **5** and **7**, respectively (Table 2, entries 1 and 2). Hydroamination of **1** with secondary amide **8** afforded silyl ketene aminal **9** with good efficiency (Table 2, entry 3), thus demonstrating that the

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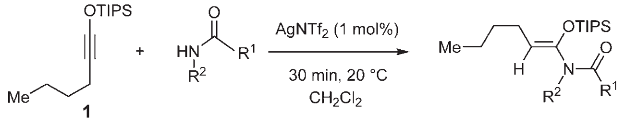
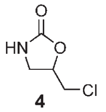
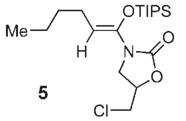
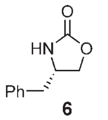
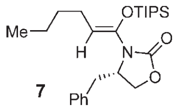
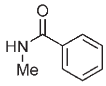
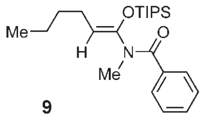
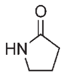
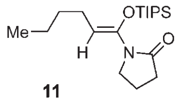
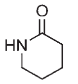
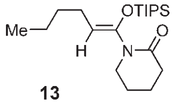
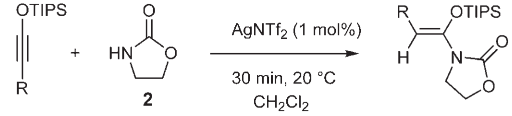
Table 2: Ag-catalyzed hydroamination: nucleophile scope.[a]

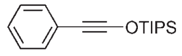
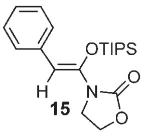
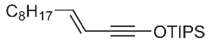
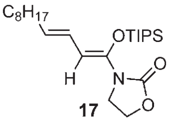
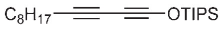
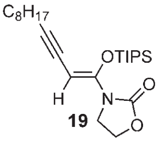
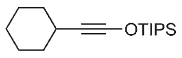
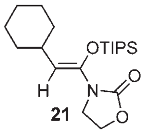
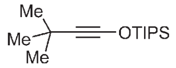
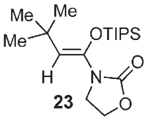


Entry	Nucleophile	Product	Yield [%][b]
1	 **4**	 **5**	72
2	 **6**	 **7**	86
3	 **8**	 **9**	71
4	 **10**	 **11**	80
5	 **12**	 **13**	86

[a] General reaction protocol: siloxy alkyne (0.40 mmol) and amide (0.36 mmol) were dissolved in CH_2Cl_2 (5 mL) and treated with $AgNTf_2$ (0.0036 mmol) at 20 °C. The resulting solution was stirred for 30 min, then treated with one drop of Et_3N. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel. [b] Yield of isolated spectroscopically pure products that were fully characterized by NMR and IR spectroscopies and mass spectrometry.

Table 3: Ag-catalyzed hydroamination: alkyne scope.



Entry	Alkyne	Product	Yield [%][a]
1	 **14**	 **15**	86
2	 **16**	 **17**	81
3	 **18**	 **19**	76
4	 **20**	 **21**	73
5	 **22**	 **23**	45

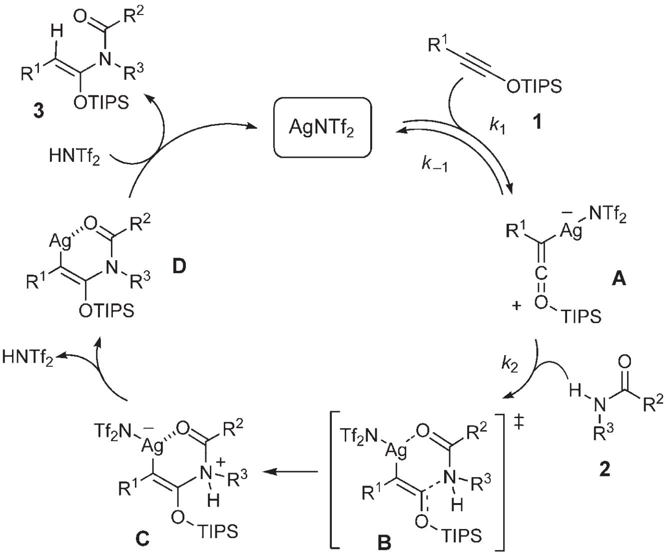
[a] Refers to yields of isolated spectroscopically pure products that were fully characterized by NMR and IR spectroscopies and mass spectrometry.

reaction is not limited to the use of cyclic carbamates. Furthermore, lactams **10** and **12** were used to produce the corresponding enol silanes, **11** and **13** (Table 2, entries 4 and 5), thus illustrating the ability of this method to produce silyl ketene aminals that would not be available by using conventional silylation methods due to the problems associated with chemoselective generation of the required enols or enolates.

We next examined the scope of siloxy alkyne substitution (Table 3). Subjecting arene- or alkene-conjugated alkynes, **14** and **16**, to the standard reaction conditions with carbamate **2** afforded the corresponding ketene aminals, **15** and **17**, respectively (Table 3, entries 1 and 2). Hydroamination of diyne **18** proceeded to give enyne **19** with complete chemo- and diastereoselectivity (Table 3, entry 3). Other alkyl-substituted alkynes, **20** and **22**, gave the expected hydroamination products, **21** and **23** (Table 3, entries 4 and 5). The lower efficiency of the reaction in entry 5 of Table 3 is attributed to the significant increase in the steric bulk in direct proximity to the reaction site. While the current protocol is highly effective for hydroamination of a wide range of siloxy alkynes, ynamides and simple internal alkynes proved to be unreactive under its conditions.

To gain further insight into the mechanism of the Ag-catalyzed hydroamination and the nature of the observed high *syn* selectivity, we carried out a series of kinetic studies of the reaction of alkyne **1** with carbamate **2** in the presence of $AgNTf_2$ at −20 °C. We found that the reaction was first-order with respect to both carbamate **2** and the silver catalyst, and zero-order with respect to alkyne **1**, thus providing the empirical rate law: $r = k_{obs}[AgNTf_2][\mathbf{2}]$, in which $k_{obs} = 1.52 \times 10^{-2}\,M^{-1}\,s^{-1}$.[9] Furthermore, using deuterated oxazolidinone **2**, we found no primary deuterium isotope effect ($k_H/k_D = 1.03$).

We propose that the reaction begins with a fast and reversible complexation between **1** and $AgNTf_2$ to give silver–alkyne complex **A** (Scheme 1), which is supported by our previous stoichiometric studies.[6b] At high concentrations of alkyne, the catalyst is saturated with the alkyne and the equilibrium favors intermediate **A**, which explains why the reaction is zero-order with respect to the alkyne. The alkyne activation is followed by the rate-determining step, which entails the addition of the carbamate **2** to the silver–alkyne complex **A**. We believe that this reaction proceeds via a six-membered chelated transition state, **B**, which explains the high *syn* selectivity of the hydroamination process.[10] Subsequent release of the proton from intermediate **C**, followed by protodemetallation of the alkenyl–silver compound **D** affords the observed product, **3**, and regenerates the silver catalyst. The proposed rate-determining step is fully consistent with the absence of any primary deuterium isotope effect.



Scheme 1. Proposed catalytic cycle for the silver-catalyzed hydroamination of siloxy alkynes.

In summary, our study demonstrates for the first time the ability of a silver-based catalyst to promote a *syn*-selective hydroamination of electron-rich alkynes with either secondary amides or carbamates. This process represents an efficient method for the synthesis of a range of synthetically useful silyl ketene aminals and provides an important mechanistic platform for further development of hydroamination reactions with late-transition-metal catalysts.[11]

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