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Stereo- and Regioselective Gold-Catalyzed Hydroamination of Internal Alkynes with Dialkylamines

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Abstract: We report the use of a P,N-ligand to support a gold complex as a state-of-the-art precatalyst for the stereoselective hydroamination of internal aryl alkynes with dialkylamines to afford *E*-enamine products. Substrates featuring a diverse range of functional groups on both the amine (ether, sulfide, *N*-Boc amine, fluoro, nitrile, nitro, alcohol, *N*-heterocycles, amide, ester, and carboxylic acid) and alkyne (ether, *N*-heterocycles, *N*-phthalimide amines, and silyl ethers) are accommodated with synthetically useful regioselectivity.

The intermolecular hydroamination of internal alkynes with basic dialkylamines represents an appealing method for the synthesis of functionalized enamine intermediates that are poised for further synthetic manipulations.[1,2] However, the lack of general methods for promoting these transformations has rendered this strategy underutilized in synthesis. Although significant contributions involving group 4 based catalysts have been made for the addition of primary alkylamines to alkynes,[3,4] these catalysts exhibit characteristically poor performance for dialkylamine and internal alkyne pairings.[4]

The most effective catalyst for the addition of dialkylamines to internal alkynes is a cationic gold complex featuring a CAAC ancillary ligand (CAAC = cyclic(alkyl)(amino)carbene).[5] However, this catalyst has only been reported for the addition of a limited number of dialkylamine and alkyne partners that do not possess any other functional groups. Moreover, only a single example of an unsymmetrically substituted alkyne was reported, wherein negligible regioselectivity was observed. In this regard, the stereoselective addition of dialkylamines to a range of internal alkynes featuring a diverse substrate scope and with controlled regioselectivity represents an unmet challenge in hydroamination catalysis. Such challenges must be addressed in order to enable the application of alkyne hydroamination with dialkylamines in more complex synthesis.

We report herein on the use of a P,N-ligand (**L6**, Mor-DalPhos) to support the gold complex **1** as a highly effective precatalyst for the stereo- and regioselective hydroamination of internal aryl alkynes with dialkylamines containing a diverse range of functional groups. Also presented are the results of preliminary stoichiometric reactivity studies directed toward providing insight into the nature of the catalytically active gold species.

We initiated our studies by evaluating a series of P,N-substituted phenylene ligands developed in our laboratory,[6] as well as other ligand motifs that have been employed successfully in gold-mediated hydroamination reactions, for the hydroamination of diphenylacetylene with morpholine employing 5 mol % [Au(SMe$_2$)Cl], 5 mol % LiB(C$_6$F$_5$)$_4$•2.5OEt$_2$, and 6 mol % ligand at 110 °C in 1,4-dioxane for 1 h (Figure 1). Although P,N-ligands with Ph, Cy, or *t*Bu substituted phosphines provided modest

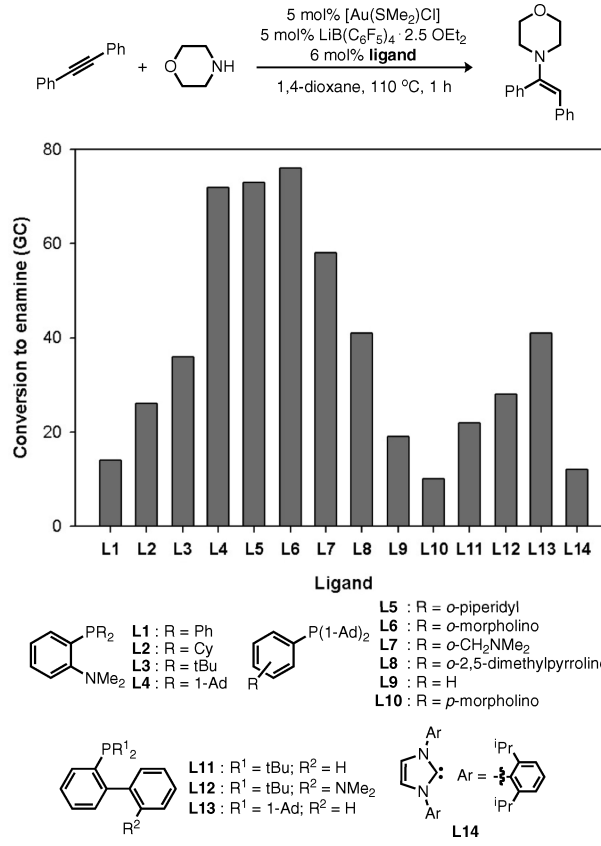

Figure 1. Ligand screen for the Au-catalyzed hydroamination of diphenylacetylene with morpholine (conversions determined by GC).

conversions, those featuring a bulky, electron-rich di(1-adamantyl)phosphinyl ((1-Ad)$_2$P−) group and an *ortho*-dialkylamino donor (**L4**, **L5**, or **L6**) provided the highest yields of the desired enamine product (68−76%).[7] Replacement of the *ortho*-amine for a benzylic amine (**L7**), lowering the basicity of the nitrogen (**L8**), removing the pendent nitrogen moiety (**L9**), or positioning the nitrogen donor in the *para*-position (**L10**) were all deleterious to catalyst activity. In combination, these results suggest that the *ortho*-amine fragment in **L4**, **L5**, and **L6** may play a direct role in the observed hydroamination catalysis.[8] Alternatively, using the ligand *t*Bu-JohnPhos (**L11**), *t*Bu-DavePhos (**L12**), Ad-JohnPhos (**L13**), or IPr (**L14**) gave comparatively poor results (<40% conv). The test reaction proved to be highly sensitive to the nature of the chloride-abstracting metal salt, whereby AgB(C$_6$F$_5$)$_4$ provided superior conversions versus more commonly used activators in Au-catalysis, such as triflate and triflimide salts.[9] The coordination complex [(**L6**)AuCl] (**1**) was prepared using established methods (eq 1) and was used as a catalyst precursor for all subsequent hydroamination reactions.[9] Monitoring the initial reaction kinetics for the test

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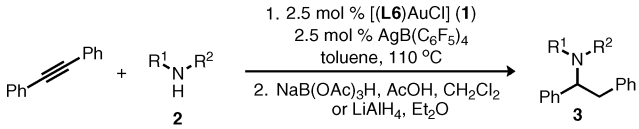
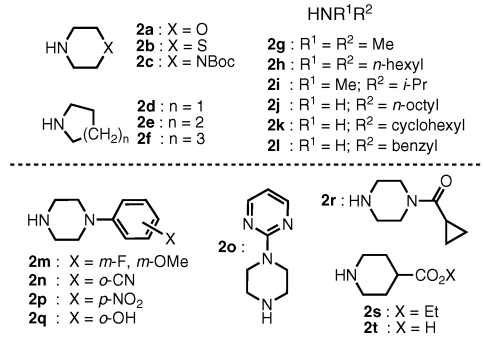
Table 1. Gold-Catalyzed Hydroamination of Diphenylacetylene with Primary and Secondary Alkylamines[a]

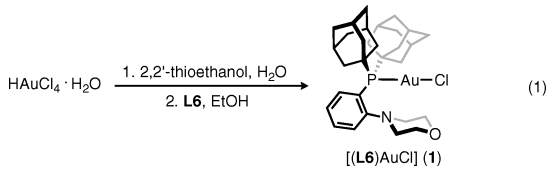


entry	amine	yield[b]	entry	amine	yield[b]
1	**2a**	86	11	**2k**	72[e]
2[c]	**2b**	80	12	**2l**	75
3	**2c**	92	13	**2m**	84
4	**2d**	90	14[c,f]	**2n**	90
5[c]	**2e**	80	15[c,f]	**2o**	85
6	**2f**	91	16	**2p**	91
7[d]	**2g**	90[e]	17	**2q**	86
8	**2h**	80	18[c,f]	**2r**	93
9	**2i**	83	19	**2s**	76
10	**2j**	84[e]	20[c,g]	**2t**	80[h]



[a] Conditions. alkyne/amine/**1**/$AgB(C_6F_5)_4$ = 1:1.1:0.025:0.025 (0.8 mmol of alkyne) in 0.8 mL of toluene at 110 °C for 16 h; <5% of the *Z*-enamine product was observed prior to reduction (^{1}H NMR and NOE experiments). [b] Isolated yield of reduction product. [c] 5 mol % **1** and 5 mol % $AgB(C_6F_5)_4$ used. [d] In THF/1,4-dioxane (3:2) at 90 °C for 16 h. [e] GC yield of *E*-enamine relative to dodecane as an internal standard. [f] Reaction time = 24 h. [g] In 1,4-dioxane ([alkyne] = 0.5 mM). [h] Isolated as the enamine hydrolysis product.[9]

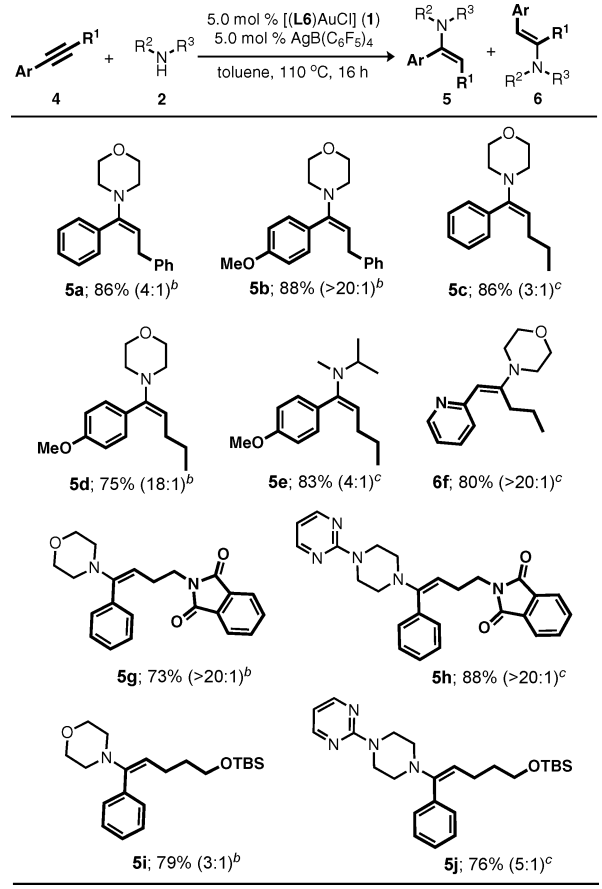
reaction using preformed complexes [(**L6**)AuCl] (**1**), [(**L13**)AuCl], and [(**L14**)AuCl] in the presence of $AgB(C_6F_5)_4$ demonstrated that the discrepancy between the performance of these ligands, under the test conditions selected, is a consequence of the higher initial rates of reaction that are achieved when using **1**, rather than differences in the catalyst lifetime (see Figure S4).[9]



(1)

The scope of the hydroamination of diphenylacetylene with a diversity of functionalized dialkylamines, as well as primary alkylamines, using catalytic mixtures of **1** and $AgB(C_6F_4)_5$ was explored (Table 1).[10] The addition of cyclic secondary alkylamines containing ether, sulfide, or N-Boc linkages (entries 1−3), as well as those based on five-, six-, and seven-membered rings (entries 4−6), proceeded stereoselectively in excellent yields. Acyclic primary and secondary alkylamines, in particular dimethylamine, were also suitable substrates for the addition to diphenylacetylene (entries 7−12); however, attempts to use more bulky dialkylamines such as $(i\text{Pr})_2$NH proved unsuccessful.

Table 2. Gold-Catalyzed Hydroamination of Unsymmetrical Internal Aryl Alkynes with Dialkylamines[a]

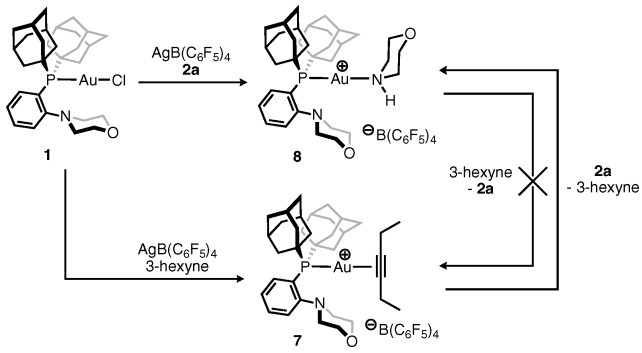


[a] Conditions: alkyne/amine/**1**/$AgB(C_6F_5)_4$ = 1:1.1:0.05:0.05 (0.8 mmol of alkyne) in 0.8 mL of toluene at 110 °C for 16 h; major regioisomer is shown with the ratio of regioisomers in parentheses. In all cases <5% of the *Z*-enamine of the major product was observed (^{1}H NMR and NOE experiments) and the stereochemistry of the minor regioisomer was not determined. [b] Isolated yield of combined enamine reduction products; regiochemistry determined by ^{1}H NMR relative to 1,3,5-trimethoxybenzene prior to reduction. [c] ^{1}H NMR yield of enamine relative to 1,3,5-trimethoxybenzene. TBS = *tert*-butyldimethylsilyl.

Given the ubiquity of 1-arylpiperazines in pharmaceuticals,[11] the development of efficient methods for their incorporation into organic molecules is of significant interest. The hydroamination of diphenylacetylene with 1-arylpiperazines featuring halide, ether, nitrile, nitro, hydroxy, and cyclopropylamide functional groups, as well as a 2,6-pyrimidyl substituted piperazine, proceeded with excellent isolated yields (entries 13−18). Notably, dialkylamine substrates containing alcohol or carboxylic acid groups were readily added to diphenylacetylene without observable side products arising from hydrophenoxylation or hydrocarboxylation (entries 17 and 20).[12]

The hydroamination of unsymmetrically substituted internal aryl acetylenes with dialkylamines proceeded in good to excellent yields with moderate to excellent regioselectivity and complete stereoselectivity (Table 2).[10] Using the aryl-benzyl alkyne **4a**, a 4:1 mixture of *E*-enamine products **5a**:**6a** was isolated as the corresponding amines in an 86% combined yield. The regiochemistry could be improved by substitution of the phenyl ring with electron-donating groups; for instance, *p*-OMe substitution of the aryl ring promoted the exclusive formation of **5b**.[13] This trend was further exploited in the hydroamination of aryl-alkyl

Scheme 1. Stoichiometric Reactions of **1**/$AgBC(_6F_5)_4$ Mixtures with Morpholine and 3-Hexyne



alkynes. Using the parent phenyl substrate **4c**, *E*-enamine products **5c** and **6c** were observed in a 3:1 ratio; however, *p*-OMe substitution resulted in a change in regiochemistry to favor **5d** in a 75% yield with an 18:1 ratio.[13] When employing the acyclic amine **2i** in the hydroamination of this alkyne, the enamine products **5e** and **6e** were formed with 4:1 regioselectivity. The use of an electron-deficient pyridyl-substituted alkyne proceeded with complete regioselectivity affording **6f** in 80% yield. Though it is well-known that 2-alkynylpyridines can be suitable Michael acceptors, in the absence of catalytic mixtures of **1**/$AgB(C_6F_5)_4$ negligible consumption of the reactants was observed. These results suggest that the electronic characteristics of the alkyne significantly guide the regioselectivity of this catalysis. Furthermore, the hydroamination of alkynes possessing a phthalimide-protected amine or a silyl-protected alcohol with amine substrates **2a** or **2o** proceeded regioselectively in good yields.

In order to gain insight into the reaction mechanism of the Au-catalyzed alkyne hydroamination with dialkylamines, some preliminary stoichiometric experiments were conducted (Scheme 1). The reaction of crystallographically characterized **1**[9] and $AgB(C_6F_5)_4$ (1:1) in the presence of 3-hexyne (1 equiv) produced the cationic alkyne complex $[(\mathbf{L6})Au(3\text{-hexyne})]^+B(C_6F_5)_4^-$ (**7**).[14] Upon treatment of **7** with 1 equiv of **2a**, the alkyne was readily displaced to form the isolable and crystallographically characterized morpholine adduct $[(\mathbf{L6})Au(\mathbf{2a})]^+B(C_6F_5)_4^-$ (**8**).[9] Notably, treatment of **8** with excess alkyne did not regenerate **7**, which may suggest the intermediacy of **8** in catalysis (Scheme 1).[15] Indeed, using **8** as a precatalyst afforded comparable activity to that of **1**/$AgB(C_6F_5)_4$ mixtures for the hydroamination of diphenylacetylene with **2a**.

Collectively, these stoichiometric observations, coupled with the observed stereo- and regioselectivity, are most consistent with an alkyne insertion mechanism.[14b,16] A plausible inner-sphere mechanism might involve associative coordination of the alkyne to **8** concomitant with proton transfer followed by insertion of the alkyne to generate a vinyl-gold intermediate.[17] Subsequent stereoselective protodeauration would liberate the *E*-enamine product and, when in the presence of excess **2a**, regenerate **8**. In light of the rate-accelerating effects achieved when employing a P,N-ligand such as **L6**, we envision that the pendant nitrogen donor may participate in catalysis by facilitating one or more mechanistically relevant proton-transfer steps.[18] Given the mechanistic complexities of Au-mediated transformations,[19] further experimentation is needed in order to elucidate the origin of high catalytic activity when employing **L6** and related ligands.

In summary, we have identified a gold precatalyst (**1**) featuring a P,N-ligand (**L6**) that has significantly extended the substrate scope and synthetic utility of alkyne hydroamination. This precatalyst represents the only system documented for the stereoselective addition of a range of functionalized dialkylamines to internal alkynes. The hydroamination of unsymmetrical internal aryl acetylenes with dialkylamines has been achieved with synthetically useful regioselectivities. Studies aimed at further expanding the scope of the reaction and elucidating the mechanism, in particular the rate-enhancing role of the P,N-ligand architecture, will be the subject of future reports.

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Supporting Information Available: Full experimental details and characterization data, including crystallographic data in CIF format for **1** and **8**. The material is available free of charge via the Internet at http://pubs.acs.org.

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