Gold(I)-catalyzed intramolecular hydroamination of unactivated C=C bonds with alkyl ammonium salts†

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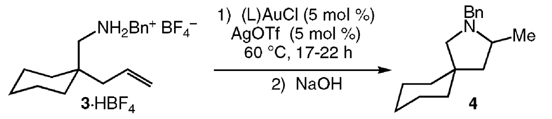
A mixture of (5)AuCl {5 = $PCy_2[2\text{-}(2,6\text{-}C_6H_3(OMe)_2)C_6H_4]$} and AgOTf catalyzes the intramolecular hydroamination of unactivated C=C bonds with primary and secondary ammonium salts.

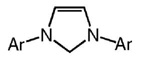
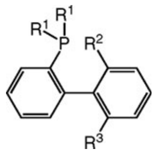
The transition metal-catalyzed addition of the N–H bond of an amine or carboxamide derivative across a C–C multiple bond (hydroamination) has attracted considerable attention as an atom economical and potentially expedient route to nitrogen heterocycles.[1] The hydroamination of unactivated C=C bonds with alkylamines represents one of the most challenging permutations of this transformation. Although complexes of rare earth,[2] alkali,[3] alkaline earth,[4] and group 4[5] metals catalyze the intramolecular hydroamination of unactivated C=C bonds with alkyl amines, the synthetic utility of these procedures is compromised by the excessive oxophilicity and/or basicity of the catalysts. Conversely, the hydroamination of unactivated C=C bonds with alkylamines catalyzed by late transition metal complexes, which holds promise owing to the low oxophilicity of these complexes, has been realized in only two cases. We have shown that mixtures of $[PtCl_2(H_2C{=}CH_2)]_2$ and PPh_3 catalyze the intramolecular hydroamination of alkenes with secondary alkylamines,[6] while Liu and Hartwig have recently reported that mixtures of $[Rh(COD)_2]BF_4$ and $PCy_2[2\text{-}(2\text{-}C_6H_4NMe_2)C_6H_4]$ catalyze the hydroamination of alkenes with both primary and secondary alkylamines.[7–9]‡

Concurrent with the recent proliferation of gold(I)-catalyzed organic transformations[10,11] has been the development of a number of gold(I)-catalyzed protocols for the hydroamination of unactivated C=C bonds with carboxamide derivatives[12] and sulfonamides.[13] However, extension of gold(I)-catalyzed alkene hydroamination to include alkylamines has not been demonstrated, presumably due to non-productive displacement of the alkene by the amine and/or inefficient protonolysis of Au–C bonds with the weakly acidic ammonium salt (pK_a = 10–11). Inspired by the efforts of Venanzi[8] and Trogler,[14] we considered that employment of alkylamines in their protonated form might ameliorate both of these problems, provided that a sufficient concentration of free amine would be available for nucleophilic attack. Indeed, here we report a gold(I)-catalyzed protocol for the intramolecular hydroamination of unactivated C=C bonds with primary and secondary alkyl ammonium salts.

We targeted the gold *N*-heterocyclic carbene complex (**1**)AuCl [**1** = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] and the *o*-biphenylphosphine complex (**2**)AuCl [**2** = $P(t\text{-}Bu)_2$*o*-biphenyl] as precatalysts for the intramolecular hydroamination of alkenes with alkylammonium salts owing to their effectiveness as precatalysts for the hydroamination of *N*-alkenyl carboxamide derivatives.[10,12] Initial experiments were disappointing, and reaction of benzyl 4-pentenyl ammonium salt **3**·HBF_4 with a catalytic mixture of either (**1**)AuCl or (**2**)AuCl and AgOTf (5 mol%) in dioxane at 60 °C for 22 h followed by basification formed pyrrolidine **4** in 3% and 11% yield, respectively (Table 1, entries 1 and 2). However, subsequent optimization of the conversion of **3**·HBF_4 to **4** catalyzed by (**2**)AuCl/AgOTf identified toluene as a markedly superior solvent for hydroamination (Table 1, entry 6). Optimization of the gold(I)-catalyzed conversion of **3**·HBF_4 to **4** in

Table 1 Ligand and solvent dependence of the gold(I)-catalyzed hydroamination of **3**·HBF_4



Entry	Ligand	Solvent	Yield[a] (%)
1	 Ar = 2,5-$C_6H_3(i\text{-}Pr)_2$ (**1**)	Dioxane	3
2	 R^1 = *t*-Bu, R^2 = R^3 = H (**2**)	Dioxane	11
3	**2**	MeOH	48
4	**2**	THF	15
5	**2**	EtOAc	37
6	**2**	Toluene	61
7	R^1 = Cy, R^2 = R^3 = H	Toluene	27
8	R^1 = *t*-Bu, R^2 = NMe_2, R^3 = H	Toluene	77
9	R^1 = Cy, R^2 = R^3 = OMe (**5**)	Toluene	99

[a] Determined by GC analysis of the crude reaction mixture after treatment with NaOH.

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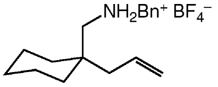
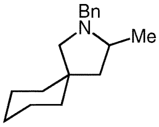
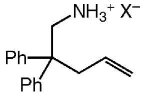
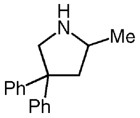
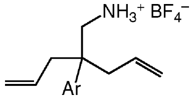
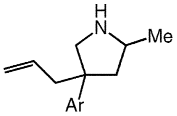
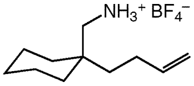
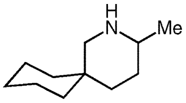
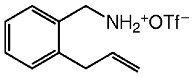
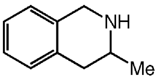
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and scans of NMR spectra. See DOI: 10.1039/b804081h

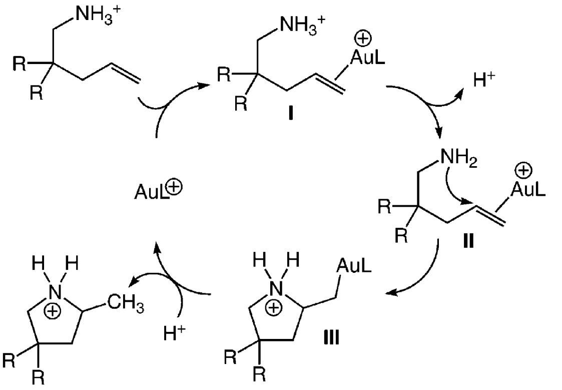
Table 2 Intramolecular hydroamination of alkenes with alkylammonium salts catalyzed by a 1 : 1 mixture of (**5**)AuCl and AgOTf (5 mol%) in toluene at 80 °C for 18–24 h

Entry	Alkene	Heterocycle	Yield[a] (%)
1	 **3**·HBF_4	 **4**	82
			
2	X = BF_4 (**6**·HBF_4)	**7**	94
3[b]	X = BF_4 (**6**·HBF_4)		93
4	X = OTf (**6**·OTf)		43[c]
5[d]	 **8**·HBF_4 (Ar = 4-$MeOC_6H_4$)	 **9**	93 (1.9 : 1)
			
6	R = H (**10**·HBF_4)	**11**	91
7	R = Bn (**12**·HBF_4)	**13**	21[c]
8[d]			45[c]

[a] Material of ≥ 95% purity isolated after basification of the reaction mixture with NaOH. [b] Ammonium salt generated *in situ* from free amine and $HBF_4 \cdot OEt_2$ (1 : 1) prior to catalyst introduction. [c] Yield determined by GC analysis of the basified reaction mixture. [d] Reaction run with 10% catalyst loading at 100 °C.

toluene as a function of phosphine identified $PCy_2\{2\text{-}[2,6\text{-}C_6H_3(OMe)_2]C_6H_4\}$ (**5**) as a highly effective supporting ligand (Table 1, entry 9). In a preparative scale reaction, treatment of **3**·HBF_4 with a catalytic 1 : 1 mixture of (**5**)AuCl and AgOTf in toluene at 80 °C for 17 h followed by treatment with NaOH led to isolation of **4** in 82% yield (Table 2, entry 1).§

Primary alkyl 4-pentenyl ammonium salts underwent intramolecular hydroamination more efficiently than did secondary alkyl salts. As an example, reaction of **6**·HBF_4 with (**5**)AuCl/AgOTf led to isolation of pyrrolidine **7** in 94% yield (Table 2, entry 2). Employment of preformed ammonium salt was not required for efficient hydroamination and sequential treatment of **6** with $HBF_4 \cdot OEt_2$ and (**5**)AuCl/AgOTf led to isolation of **7** in 93% yield (Table 2, entry 3). Conversely, the efficiency of hydroamination was sensitive to the nature of the ammonium counterion and gold(I)-catalyzed hydroamination of **6**·HOTf formed **7** in only 43% yield (Table 2, entry 4). The dienyl ammonium salt **8**·HBF_4 underwent intramolecular hydroamination to form pyrrolidine **9** in good yield with modest diastereoselectivity (Table 2, entry 5). Gold(I)-catalyzed hydroamination of 5-hexenyl ammonium salt **10**·HBF_4 led to isolation of piperidine **11** in 91% yield (Table 2, entry 6). Secondary and aromatic piperidine derivatives were also accessible *via* gold(I)-catalyzed hydroamination, albeit with significantly diminished efficiency (Table 2, entries 7 and 8). Internal alkenes failed to undergo hydroamination under these conditions.



Scheme 1

Stereochemical analysis of gold(I)-catalyzed hydrofunctionalization has consistently supported outer-sphere mechanisms for C–X bond formation.[13,15] As such, we envision a mechanism for the gold(I)-catalyzed hydroamination of alkyl alkenyl ammonium salts initiated by formation of a gold π-alkene complex **I** (Scheme 1). Deprotonation of the pendant ammonium salt followed by outer-sphere attack of the free amine on the complexed alkene of **II** would form the cationic pyrrolidine complex **III**. Protonolysis of the Au–C bond of **III** with HNR_3^+ would then release the protonated pyrrolidine.

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Notes and references

‡ Venanzi and co-workers reported the Pt-catalyzed intramolecular hydroamination of alkenyl amines under acidic conditions, but these transformations were prohibitively slow.[8] More recently, Ackermann *et al.* have demonstrated the intramolecular hydroamination of alkyl 4-pentenyl amines under Brønsted acid catalysis at 120–130 °C.[9]

§ Heating a solution of **3**·HBF_4 or a mixture of **3**·HBF_4 and either **5**, AgOTf, or (**5**)AuCl (15 mol%) in toluene at 80 °C for 17 h followed by basification with NaOH led to no detectable formation of **4**.

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