Gold Catalysis

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Regio- and Enantioselective Hydroamination of Dienes by Gold(I)/Menthol Cooperative Catalysis**

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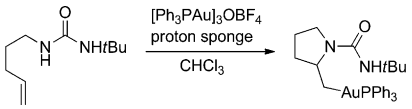
Gold(I)-mediated hydroamination reactions have emerged as attractive methods for the formation N-containing heterocycles.[1,2] While significant progress has been made in the asymmetric hydroamination of allenes, enantioselective gold-catalyzed hydroamination of simple alkenes and dienes has been limited to reactions in which urea is employed as a nucleophile.[3] Furthermore, as simple Brønsted acids are also known to be effective catalysts for alkene hydroamination[4] and gold(I) triflates are often employed in olefin activation,[5] the role of gold in these reactions is unclear. In 2009, we found that, in presence of stoichiometric amounts of base, alkyl-gold(I) complexes could be formed by gold-promoted addition of nitrogen nucleophiles to unactivated alkenes [Eq. (1)].[6,7] This result led us to posit that generation of an

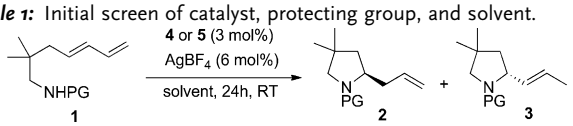


(1)

acidic species was important for catalytic turnover in the reported alkene hydroamination reactions. Moreover, Tilley et al. proposed that the catalyst in the related platinum-catalyzed reaction is a platinum sulfonamide complex derived from coordination of the Lewis-acidic metal to the relatively acidic sulfonamide nucleophile.[8] On the basis of these reports, we envisioned that simple alcohols might serve an analogous role in Lewis acid activated Brønsted acid catalyzed[9,10] processes with gold(I) complexes playing the role of the Lewis acid. Herein, we report the application of this hypothesis to the development of an enantioselective hydroamination of 1,3-dienes.[11]

Our initial studies focused on the reaction of diene **1** with catalytic amounts cationic gold(I) complexes (see the Supporting Information for a complete list). While attempts to catalyze the reaction with triphenylphosphinegold(I) did not produce appreciable amounts of pyrrolidine (Table 1, entry 1), we were pleased to find that the combination of (*R*)-DTBM-SEGPHOS(AuCl)$_2$ (**5**) and $AgBF_4$ in dichloromethane gave pyrrolidine **2** exclusively in 5% conversion after 24 hours (entry 2). After examining a variety of protecting groups on the nitrogen atom, we found that the Mbs-protected (Mbs = *p*-methoxy benzenesulfonyl) amine gave a small enhancement in reactivity (entry 3). Having established reaction conditions for productive hydroamination, we envisioned that addition of a potential Brønsted acid would enhance the reactivity of the catalyst system. Accordingly, when the solvent was switched to MeOH (entry 4), we saw dramatic increases in the reaction rate. Additionally, both products **2** and **3** were observed, with the major product **3** formed in 92% enantioselectivity (entry 5) when *i*PrOH was employed as solvent. The pronounced rate acceleration and change in product distribution suggested that alcohols are important for controlling the regioselectivity and rate of reaction.

Table 1: Initial screen of catalyst, protecting group, and solvent.



Entry	1	PG	Cat.	Solvent	Conv. [%][a]	2/3	*ee* [%] 2	*ee* [%] 3[c]
1	**1a**	Ts	**4**	CH_2Cl_2	trace	–	–	–
2	**1a**	Ts	**5**	CH_2Cl_2	5	1:0	–	–
3	**1b**	Mbs	**5**	CH_2Cl_2	18	1:0	35	–
4	**1b**	Mbs	**5**	MeOH	81	1:0.5[b]	2	84
5	**1b**	Mbs	**5**	*i*PrOH	>99	1:1.2[b]	11[d]	92

[a] Conversion was determined by ^{1}H NMR spectroscopy and HPLC analysis. [b] A very small amount of (*Z*)-**3b** was included (1–3%). [c] The *ee* value corresponds to that of the *E* isomer. [d] 11% *ee* was observed for the *S* enantiomer. (*R*)-DTBM-SEGPHOS = (*R*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, PG = protecting group, Ts = 4-toluenesulfonyl.

Thus, we examined the effect that a range of achiral and chiral alcohols additives had on the catalytic reaction in CH_2Cl_2 (Table 2). In particular, we hypothesized that a chiral alcohol may "match" the chiral information enforced by **5** and lead to higher levels of selectivity. Gratifyingly, we found that (−)-menthol provided the desired products in quantitative conversion and a 1:9 ratio of **2b** to **3b** with excellent enantioselectivity (95% *ee*) for the major product (entry 6). Furthermore, the amount of (−)-menthol used could be reduced to 2.0 equivalents without significantly impacting the regio- or enantioselectivity (entry 7).

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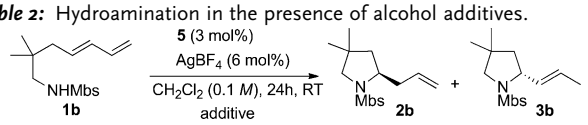
Table 2: Hydroamination in the presence of alcohol additives.

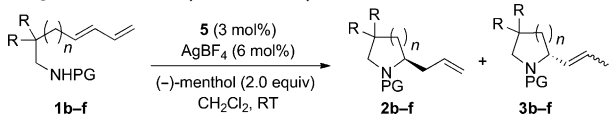


Entry	Additive	Equiv	Conv. [%][a]	**2**/**3**[b]	*ee* [%][c]
1	*t*BuOH	10	94	1:0.6	91
2	cyclohexanol	10	97	1:1.5	97
3	(*R*)-methyl lactate	10	40	1:0.3	–
4	(*R*)-1-phenethyl alcohol	10	46	1:1.2	90
5	(+)-menthol	10	94	1:1.9	94
6	(−)-menthol	10	>99	1:9.0	95
7	(−)-menthol	2	95	1:6.3	95

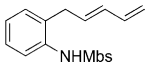
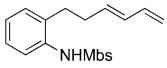
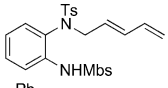
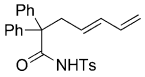
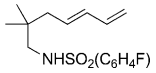
[a] Conversion was determined by ^{1}H NMR spectroscopy and HPLC analysis. [b] A very small amount of (*Z*)-**3b** was included (1–3%). [c] The *ee* value corresponds to that of (*E*)-**3b**. See the Supporting Information for *ee* values of **2b**.

With these results in hand, we were able to perform the cyclization of a variety of 1,3-dienes at ambient temperature in good yield and enantioselectivity for the major product (Table 3). Although the *gem*-dimethyl group in the backbone of the substrate was not required for good selectivity, the reaction was significantly slower without the substitution (entry 2) By incorporating N-protected piperidine into the backbone, the spiro-bicyclic product **3e** could be formed in excellent yield, regioselectivity, and with 89% *ee* (entry 4).

Table 3: Substrate scope of diene hydroamination.



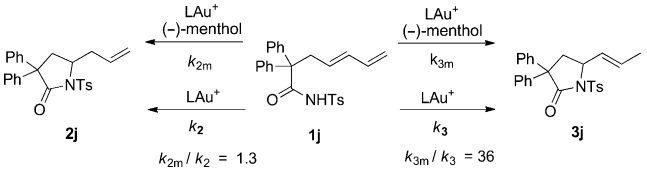
Entry	**1**	*n*	R	*t* [h]	Yield [%][a] (**2**/**3**[b])	*ee* [%][c]
1[d]	**1b**	1	Me	24	95 (1:6.3)	95
2[d]	**1c**	1	H	144	91 (1:6.1)	85
3[d]	**1d**	1	Ph	24	93 (1:3.5)	84
4[d]	**1e**	1		24	99 (1:5.0)	89
5[d]	**1f**	2	Me	–	n.r.	–

Entry		Substrate	*t* [h]	Yield [%][a] (**2**/(*Z*)-**3**/(*E*)-**3**)	*ee* [%][c]
6	**1g**		72	80 (1:0.5:7.5)	97
7	**1h**		72	77 (1:3.9:8.2)	97
8	**1i**		168	42 (1:1.2:2.0)	98
9	**1j**		6	99 (1:0.03:1.5)	94
10	**1k**		24	67 (1:<0.1:7.5)	91

[a] Based on the combined yield of isolated **2** and **3**. [b] A very small amount of (*Z*)-**3** was included (1–3%). [c] The *ee* value corresponds to that of (*E*)-**3**. See the Supporting Information for *ee* values of **2b–k**. [d] The protecting group (PG) is Mbs. n.r. = no reaction.

While hydroamination of dienes to form the six-membered ring remains difficult for the standard substrate (entry 5), incorporation of aryl groups into the backbone allow the transformation to be performed in modest to good yield (entry 7–8). Additionally, endocyclic amides could be prepared readily with modest regioselectivity and excellent enantioselectivity for the vinyl-substituted product (entry 9). The absolute configurations of the products were determined by analogy from the crystal structure of the product **3k** (see the Supporting Information).

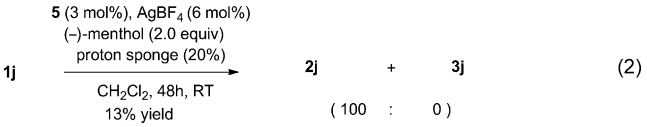
To investigate the mechanism of the hydroamination and to determine the role of gold and menthol, we monitored the reaction by ^{1}H NMR spectroscopy. For this purpose, we chose substrate **1j**, as its reaction is significantly faster than any other substrate and thus suitable for studies by point kinetics. We examined the reaction of **1j** under two reaction conditions: 1) with 2.0 equivalents of (−)-menthol as an additive and 2) with no additives (Scheme 1). As two products can be



Scheme 1. Relative rate enhancement by (−)-menthol for formation of **2j** and **3j** under two different reaction conditions.

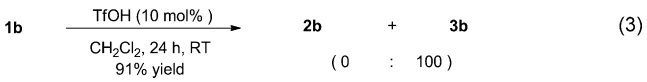
formed from **1j**, the overall rate constant for the reaction is equal to the sum of the rate constants for the formation of each product and the ratio of rate constants for each product, k_3/k_2, is directly proportional to the concentration of **2j** and **3j** at all times. Interestingly, we found that (−)-menthol had almost no effect on the rate of formation of **2j**, but increased the rate of formation of **3j** by 36-fold.[12] To ensure that the rate acceleration observed was not due to interconversion of the two products to a thermodynamic distribution, we isolated an authentic sample of **2j** and resubjected it to 3 mol% **5**, 6 mol% $AgBF_4$, and 2.0 equivalents of (−)-menthol overnight at room temperature. Indeed, no equilibration to **3j** was observed after 18 hours.

In addition, when 20% proton sponge is added to the reaction of **1j** with **5** and (−)-menthol, none of the vinyl product **3j** is formed [Eq. (2)] and the rate of overall reaction



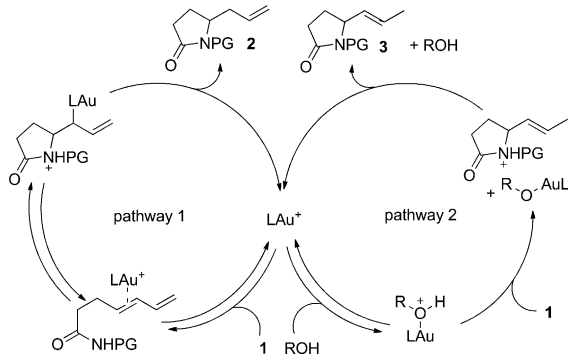
(2)

is significantly reduced. However, if a related but acid-stable substrate (**1b**) is treated with 10 mol% TfOH in the absence of gold(I), the allylic product **3b** is formed exclusively [Eq. (3); Tf = trifluorosulfonyl]. Finally, mass spectrometry of a solution of **5** and (−)-menthol show peaks at $m/z = 1727$ (singly charged ion) and 864 (doubly charged ion), which



correspond to a 1:1 complex of (*R*)-[DTBM-SEGPHO-S(Au)$_2$]$^{2+}$ and (−)-menthol (see the Supporting Information).

These experiments lead us to believe that **2j** and **3j** are being formed predominantly through two different mechanisms: pathway 1 involves traditional coordination, nucleophilic addition, and proto-demetalation by gold similar to what has been previously observed for allenes;[13] pathway 2 proceeds through an Brønsted acid catalyzed pathway in which **5** acts as a Lewis acid by binding to menthol, thus increasing its Brønsted acidity (Scheme 2). In pathway 1, coordination of the gold catalyst to the diene enables intramolecular addition, and proto-demetalation[14] frees the gold catalyst. In pathway 2, gold coordinates to menthol and generates a Bronsted acidic species that then allows diene protonation and cyclization of the nucleophile. When a base such as a proton sponge is added, catalysis through the acid-mediated pathway 2 is inhibited; however, pathway 1 is still operative, albeit at a diminished rate. Exclusive formation of **3j** by Brønsted acid catalysis with TfOH is also consistent with our mechanistic proposal.



Scheme 2. Two mechanisms, pathway 1 and pathway 2, are proposed to account for formation of **2** and **3**, respectively.

In conclusion, we report the first examples of Lewis acid activated Brønsted acidity in gold(I) catalysis. This novel catalyst system was applied to the formation of pyrrolidine and piperidine adducts through a phosphinegold(I)/menthol-catalyzed enantioselective diene hydroamination. The regioselectivity and enantioselectivity of the reaction can be controlled by the addition of menthol as a cocatalyst, which we believe acts as a Brønsted acid when coordinated to the gold catalyst and results in the formation of vinyl-substituted products (**3**). Thus, the 1,3-diene scaffold has access to both mechanistic pathways involved for gold(I)-catalyzed hydroamination, depending upon the presence of a potential Brønsted acid, such as an alcohol. Detailed kinetic studies of this reaction and application of Lewis acid activated Brønsted acidity by gold(I) to other reactions are ongoing and will be reported in due course.[15]

Experimental Section

General procedure for gold(I)-catalyzed hydroamination: A mixture of $AgBF_4$ (0.58 mg, 3.0 μmol) and the phosphine gold(I) chloride complex (1.5 μmol) was suspended in 400 μL of solvent in a sealed vial, and sonicated or stirred magnetically for 15 min at room temperature. The resulting suspension was filtered through a glass-microfiber plug directly into a solution of substrate (0.05 mmol) in 100 μL of same solvent. The mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of one drop of triethylamine and the conversion was determined by 1H NMR spectroscopy or HPLC analysis of the crude reaction mixture after filtration though a short silica gel column. Reported yields reflect yields of mixtures of olefin regioisomers that were isolated after chromatography on silica gel.

Full experimental details including preparation of the diene substrates, determination of enantioselectivity and HPLC data, kinetic studies, and mass spectrometry data are provided in the Supporting Information.

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