Gold Catalysis

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Gold(I)-Catalyzed Enantioselective Synthesis of Pyrazolidines, Isoxazolidines, and Tetrahydrooxazines**

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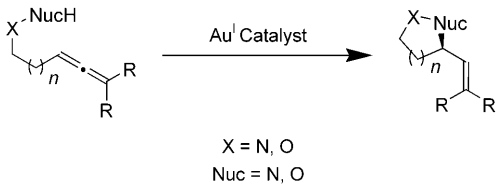
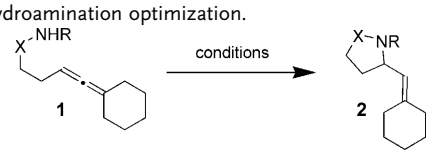
The field of gold(I)-catalyzed addition of heteroatom nucleophiles to allenes[1] has recently expanded to include enantioselective synthesis of heterocyclic products.[2,3] Despite the growth in this area of research and the biological relevance of heterocycles containing multiple heteroatoms, the asymmetric addition of hydrazine and hydroxylamine nucleophiles to allenes has not yet been reported.[4] In 2007, our group reported the enantioselective hydroamination of allenes catalyzed by gold(I)/bis(*p*-nitrobenzoate) complexes.[2a] We hypothesized that in addition to tosyl amines, gold(I)/bis(*p*-nitrobenzoate) complexes would perform as efficient catalysts for the enantioselective addition of hydroxylamines and hydrazines to allenes. The heterocycles formed from these reactions, vinyl isoxazolidines[5] and pyrazolidines,[6] appear frequently in biologically important molecules.[7] In addition, these heterocycles serve as precursors to unnatural amino acid derivatives such as 5-oxaproline[7,8] as well as chiral allylic alcohols and 1,3-diamines [Eq. (1)].



(1)

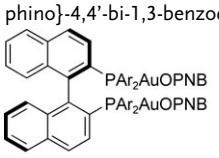
We began our studies with a mono-Boc-protected homoallenic hydrazine, easily synthesized in four steps from the homoallenic alcohol. Whereas unprotected amines are usually considered incompatible with cationic gold complexes, we hypothesized that the reduced Lewis basicity of the hydrazine would allow the use of an unprotected terminal amine. Indeed, upon treatment of **1a** with [(*R*)-xylyl-binap-(AuOPNB)$_2$] (**I**) in nitromethane at 50 °C the desired product **2a** was formed, although in modest yield and low enantioselectivity (Table 1, entry 1). By simply adding a second protecting group, both the yield and enantiomeric excess of **2b** were improved (Table 1, entry 2). This result led us to theorize that sterically differentiating the protecting groups would be necessary to additionally improve the enantioselectivity. Indeed, utilizing a mesitylenesulfonyl protecting group on the terminal nitrogen atom raised the observed enantioselectivity to 80% *ee* (Table 1, entry 3). A brief examination of chiral ligands revealed that (*R*)-DTBM-Segphos was optimal, yielding pyrazolidine **2c** in 97% *ee* (Table 1, entry 4). Similar to hydroamination with hydrazines, we found that although unprotected hydroxylamines were transformed into the isoxazolidines in excellent conversion (>92%), low enantioselectivity (10% *ee*) was observed (Table 1, entry 5). Upon treating N-Boc-protected hydroxylamine **1f** with catalyst **I** the isoxazolidine **2f** was formed in 93% yield and 93% *ee* (Table 1, entry 7). Other protecting

Table 1: Hydroamination optimization.

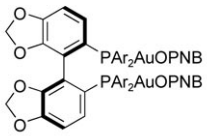


Entry	**1**; X	R	Cond.[a]	**2**; Yield[b] [%]	*ee*[c] [%]
1	**1a**; NBoc	H	A	**2a**; 46	5
2	**1b**; NBoc	Boc	A	**2b**; >98[d]	70
3	**1c**; NBoc	Mts	A	**2c**; >98[d]	80
4	**1c**; NBoc	Mts	A[e]	**2c**; 78	97
5	**1d**; O	H	B[f]	**2d**; 92	10
6	**1e**; O	Cbz	B	**2e**; 8[d]	–
7	**1f**; O	Boc	B	**2f**; 93	93

[a] Reaction Conditions: A = Catalyst **I** (5 mol%), 0.3 M in $MeNO_2$, 50 °C, 15 h; B = Catalyst **I** (3 mol%), 0.1 M in CH_2Cl_2, 23 °C, 24 h; [b] Yield of product isolated after column chromatography. [c] Determined by HPLC methods. [d] Conversion determined by ^{1}H NMR analysis. [e] Catalyst **II**. [f] 18 h. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Mts = 2-mesitylsulfonyl, binap = 2,2-bis(diphenylphosphanyl)-1,1-binaphthyl, DTBM-Segphos = 5,5'-bis{di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino}-4,4'-bi-1,3-benzodioxole.



Catalyst **I**
Ar = 3,5-xylyl
[(*R*)-xylyl-binap(AuOPNB)$_2$]



Catalyst **II**
Ar = 3,5-di-*tert*-butyl-4-methoxyphenyl
[(*R*)-DTBM-Segphos(AuOPNB)$_2$]

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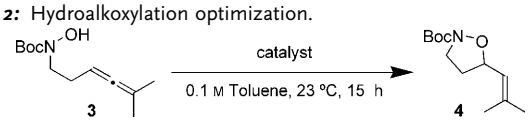
groups, such as Cbz, significantly reduced the conversion to 8% (Table 1, entry 6). Additionally, a polar, noncoordinating solvent such as nitromethane was effective, producing **2f** in 98% conversion and 87% *ee*. However, nonpolar solvents (benzene) and coordinating solvents (dioxane) completely eliminated catalyst activity.

Whereas gold(I)/bis(*p*-nitrobenzoate) complexes proved to be ineffective catalysts for the hydroalkoxylation of allenes (Table 2, entry 1), we hypothesized that employing a more noncoordinating counterion with a lower pK_a value would improve catalysis. Chiral silver sulfonate (*S*)-(**5**)Ag (**IV**) was synthesized in seven steps from (*S*)-binol (binol = 2,2-dihydroxy-1,1-binaphthyl).[9] Gratifyingly, upon treatment with 3 mol% [dppm$(AuCl)_2$] and 3 mol% **IV**, isoxazolidine **4** was formed in quantitative conversion and 65% *ee* (Table 2, entry 2). However, attempts to improve the enantioselectvity by matching the chiral counterion with chiral gold/binap complexes were unsuccessful (Table 2, entries 3 and 4). Both the matched and mismatched mixtures produced **4** with lower enantioselectivity (42% and 8% *ee*, respectively). Chiral silver phosphate (*S*)-TriPAg (**III**) proved to be the key to enhancing the enantioselectivity to 97% *ee* (Table 2, entry 5).

We next sought to test the substrate scope of our optimized hydroamination conditions (Table 3). Linear and cyclic alkyl substitutions were tolerated at the allene terminus in both the hydrazine and hydroxylamine hydroamination. For instance, methyl-substituted substrates cyclized with excellent enantioselectivity (Table 3, entries 1 and 4). Cyclohexyl-substituted allenes also reacted with high enantioselectivity (Table 3, entries 3 and 6). Cyclopentyl-substituted substrates **8** and **12** also provided pyrazolidine **9** and isoxazolidine **13** in good yield and slightly lower enantioselectivity (Table 3, entries 2 and 5). Furthermore, sterically challenging backbone substitutions were accommodated by heating gently (50°C) in a polar, noncoordinating solvent (nitromethane). Whereas substitution at the allenic position (Table 3, entry 8) gave enhanced enantioselectivity (99%) with modest yield (73%), the homoallenic position showed the reverse trend: modest enantioselectivity (63%) and excellent yield (94%).

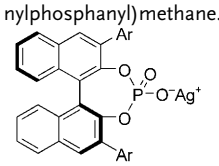
We also applied our hydroamination conditions to the formation of six-membered ring tetrahydrooxazine heterocycles. Gentle heating in a polar noncoordinating solvent was required to produce tetrahydrooxazines in good yield (63–85%). Substrates with backbone substitutions (Table 3, entries 10 and 11) have higher yield than those without substitutions, presumably the result of a Thorpe–Ingold effect. Also, both linear and cyclic alkyl substitutions were tolerated at the allene terminus, providing the heterocycles with 89% *ee* in all cases.

Table 2: Hydroalkoxylation optimization.

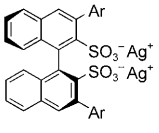


Entry	Catalyst[a]	Yield [%][b]	*ee* [%][c]
1	**I**	0	–
2	3 mol% [dppm$(AuCl)_2$] 3 mol% **IV**	98[d]	65
3	3 mol% [(*R*)-binap$(AuCl)_2$] 3 mol% **IV**	98[d]	8
4	3 mol% [(*S*)-binap$(AuCl)_2$] 3 mol% **IV**	98	42
5	3 mol% [dppm$(AuCl)_2$] 6 mol% **III**	98	98

[a] Reaction Conditions: 0.1 M in toluene, 23°C, 15 h; [b] Yield of product isolated after column chromatography. [c] Determined by HPLC methods. [d] Conversion determined by ^{1}H NMR analysis. dppm = bis(diphenylphosphanyl)methane.



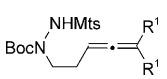
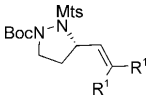
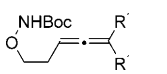
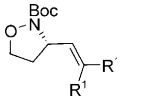
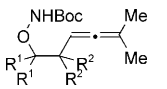
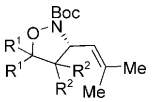
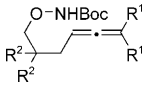
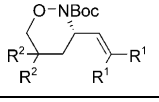
(*S*)-TriPAg (**III**)
Ar = 2,4,6-triisopropylphenyl



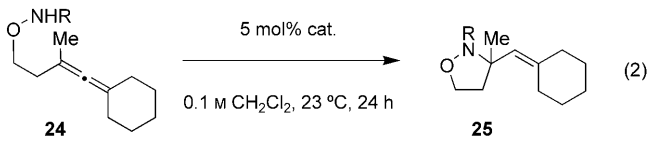
(*S*)-(**5**) Ag (**IV**)
Ar = 3,5-ditrifluoromethylphenyl

The advantage of the increased nucleophilicity of hydroxylamines was demonstrated in the cyclization onto tetrasubstituted allenes. Nucleophilic additions to tetrasubstituted allenes is challenging; only a handful of substrates have been reported.[4a,10] Whereas the use of a protecting group is normally beneficial to enantioselectivity (vide supra), in the case of addition to sterically encumbered substrates such protecting groups are detrimental to both the observed enantioselectivity and conversion [Eq. (2)]. Unprotected hydroxylamines, however, when treated with the same

Table 3: Hydrazine and hydroxylamine hydroamination scope.

Entry	Substrate		R^1	R^2	Cond.[a]	Product		Yield [%][b]	*ee* [%][c]
1		**6**	Me	–	A		**7**	98	99
2		**8**	-$(CH_2)_4$-	–	A		**9**	90	83
3		**1c**	-$(CH_2)_5$-	–	A		**2c**	75	97
4		**10**	Me	–	B		**11**	91	98
5		**12**	-$(CH_2)_4$-	–	B		**13**	98	91
6		**1f**	-$(CH_2)_5$-	–	B		**2f**	93	93
7		**14**	Me	H	C		**15**	94	63
8		**16**	H	Me	C		**17**	73	99
9		**18**	-$(CH_2)_5$-	H	D[d]		**19**	63	89
10		**20**	-$(CH_2)_5$-	Me	D		**21**	85	89
11		**22**	Me	Me	D		**23**	79	89

[a] Reaction Conditions: A = [(*R*)-DTBM-Segphos$(AuOPNB)_2$] (5 mol%), 0.3 M in $MeNO_2$, 50°C, 15 h; B = **I** (3 mol%), 0.1 M in CH_2Cl_2, 23°C, 24 h; C = [(*R*)-DM-MeOBiPhep$(AuOPNB)_2$] (5 mol%), 0.1 M in $MeNO_2$, 50°C, 24 h; D = **I** (5 mol%), 0.3 M in $MeNO_2$, 50°C, 24 h. [b] Yield of the product isolated after column chromatography. [c] Determined by HPLC methods. [d] 36 h, 65°C. DM-MeOBiPhep = 2,2′-bis[di(3,5-xylyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl.



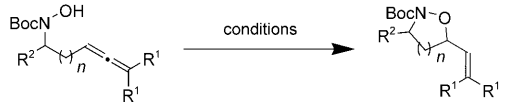
(2)

[(*R*)-xylyl-binap(AuOPNB)$_2$] (I)	**25a** R = Boc	50% conv; 17% *ee*
	25b R = H	>98% conv; 32% *ee*
[(*R*)-MeOBiPhep(AuOPNB)$_2$]	**25c** R = H	80% yield; 49% *ee*

catalyst produce the desired product in quantitative conversion and 32% *ee*. Modifying the catalyst ligand to (*R*)-MeOBiPhep additionally improved the enantioselectivity to 49%.

We were pleased to find that chiral silver salts used with gold(I) complexes catalyze the hydroalkoxylation of N-linked hydroxylamines with good to excellent enantioselectivity. Both cyclic and linear alkyl substitutions at the allene terminus were well tolerated, yielding the corresponding isomeric vinyl-isoxazolidines in good yield and high enantiomeric excess (Table 4, entries 1 and 2). Formation of oxazines

Table 4: Hydroxylamine hydroalkoxylation scope.



Entry	Substr.	*n*	R^1; R^2	Cond.[a]	Prod.	Yield [%][b]	*ee* [%][c]
1	**26**	1	Me; H	A	**27**	98	98
2	**3**	1	-$(CH_2)_5$-; H	A	**4**	75	99
3	**28**	1	Me; Me	A	**29**	99[d]	40/97
4	**30**	2	Me; H	A[e]	**31**	66	50
5	**30**	2	Me; H	B	**31**	94	87
6	**30**	2	Me; H	C	**31**	36	45

[a] Reaction Conditions: A = [dppm(AuCl)$_2$] (3 mol%), **III** (6 mol%), 0.1 M in toluene, 23 °C, 18 h; B = [(*S*,*S*)-dipamp(AuCl)$_2$] (3 mol%), **III** (6 mol%), 0.1 M in toluene, 23 °C, 18 h; C = [(*S*,*S*)-dipamp(AuCl)$_2$] (3 mol%), (*R*)-AgTriP (6 mol%), 0.1 M in toluene, 23 °C, 18 h. [b] Yield of product isolated after column chromatography. [c] Determined by HPLC methods. [d] 5:1 d.r. [e] 60 h. dipamp = 1.

proved to be more challenging, with the gold(I)-catalyzed reaction affording **31** in modest yield and 50% *ee* (Table 4, entry 4).[11] However, both the yield and enantioselectivity were greatly improved by combining a chiral ligand with the chiral silver salt (Table 4, entry 5). Additionally, whereas good diasteroselectivity was observed for substituted substrates (Table 4, entry 3), the corresponding enantioselectivities favor the minor diasteromer.

In conclusion, we have developed a series of enantioselective gold(I)-catalyzed hydroaminations and hydroalkoxylations of allenes with hydroxylamines and hydrazines. Whereas chiral biarylphosphinegold(I) complexes[12] are suitable catalysts for the enantioselective addition of nitrogen nucleophiles to allenes, the addition of oxygen nucleophiles requires the use of chiral anions. These complementary methods allow rapid access to chiral vinyl isoxolidines, oxazines, and differentially protected pyrazolidines.[13,14] Studies on the mechanism of enantioinduction in these transformations are ongoing in our laboratories.

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Keywords: asymmetric catalysis · gold · heterocycles · hydroamination · pyrazolidines

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[10] For a single example of an intermolecular gold(I)-catalyzed addition of methyl carbamate to tetramethyl allene (61% yield), see: a) R. E. Kinder, Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 3157 – 3159; For a single example of an intermolecular gold(I)-catalyzed addition of indole to tetramethyl allene (56% yield), see: b) K. Toups, G. Liu, R. A. Widenhoefer, *J. Organomet. Chem.* **2009**, *694*, 571 – 575.

[11] Use of 3 mol% [dppm$(AuCl)_2$], 6 mol% (*S*)-Ag(**5**), 0.1M in toluene, 23°C, 18 h gave oxazine **27** in 60% yield and 34% *ee*.

[12] a) F. Kleinbeck, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 9178 – 9179; b) Z. Zhang, S. D. Lee, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 5372 – 5373; c) M. Uemura, I. D. G. Watson, M. Katsukawa, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 3464 – 3465; d) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2056 – 2057; e) C.-M. Chao, M. R. Vitale, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319 – 1323.

[13] The absolute configuration of **11** was assigned by oxidative cleavage, Boc removal, and Cbz protection to (*S*)-methyl-2-benzyloxycarbonyl-3-isoxazolidinecarboxylate (see the Supporting Information). The absolute configurations of the remaining hydroamination products were assigned by analogy to **11**.

[14] For a representative procedure to cleave the N–O bond, see: A. Vasella, R. Voeffray, J. Pless, R. Hugenin, *Helv. Chim. Acta* **1983**, *66*, 1241 – 1252.

