ORGANIC LETTERS

2007
Vol. 9, No. 15
2887−2889

Gold(I)-Catalyzed Enantioselective Hydroamination of *N*-Allenyl Carbamates

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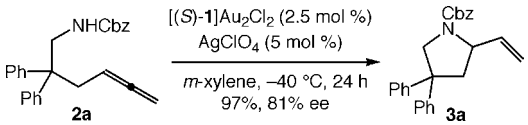
Received May 13, 2007

ABSTRACT



Treatment of the *N*-4,5-hexadienyl carbamate 2a with a catalytic 1:2 mixture of [(*S*)-1]Au_2Cl_2 [(*S*)-1 = (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP] and $AgClO_4$ in *m*-xylene at –40 °C for 24 h led to isolation of 2-vinylpyrrolidine 3a in 97% yield with 81% ee. Gold(I)-catalyzed enantioselective hydroamination was effective for a number of carbamate groups and tolerated terminal disubstitutution of the allenyl moiety.

Transition-metal-catalyzed addition of the N−H bond of an amine or carboxamide derivative across a C−C multiple bond (hydroamination) is a transformation with potential application to target-oriented synthesis, pharmaceutical development, and large-scale alkene functionalization.[1] Although considerable progress has been made in the area of catalytic hydroamination, effective enantioselective processes remain scarce.[2] Rare earth and group 4 complexes catalyze the enantioselective hydroamination of alkenes, but asymmetric induction is typically modest, and the synthetic utility of these systems is compromised by the excessive oxophilicity of the catalysts.[3] In comparison, enantioselective hydroamination catalyzed by late transition-metal complexes typically suffers from limited scope, modest selectivity, and/or high catalyst loading.[4]

As part of our ongoing efforts directed toward the development of new methods for catalytic alkene hydrofunctionalization,[5] we recently reported the intramolecular *exo*-hydroamination of *N*-allenyl carbamates catalyzed by a 1:1 mixture of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl and AgOTf[6] and the enantioselective, intramolecular hydroalkoxylation[7] and hydroarylation[8] of allenes catalyzed by a 1:2 mixture of the

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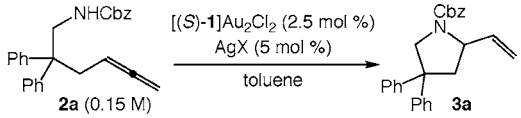
10.1021/ol071108n CCC: $37.00
Published on Web 06/27/2007

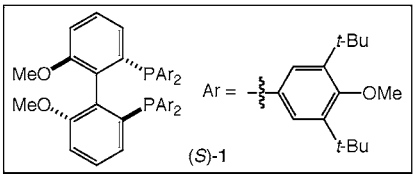
bis(gold) phosphine complex [(*S*)-**1**]Au_2Cl_2 and either AgOTs or $AgBF_4$, respectively.[9] On the basis of these results, we began working toward a protocol for the enantioselective hydroamination of *N*-allenyl carbamates. During the course of these studies, Toste and co-workers reported the enantioselective hydroamination of *N*-allenyl sulfonamides catalyzed by bis(gold) complexes such as (*R*)-xylyl-BINAP-$(AuOPNB)_2$ [OPNB = *p*-nitrobenzoate].[10,11] Although enantioselectivities of up to 99% ee were realized with this system, effective hydroamination was restricted to *N*-allenyl sulfonamides that possessed a terminally disubstituted allenyl moiety. The authors also noted that *N*-allenyl carbamates failed to undergo hydroamination under these conditions. We found this latter limitation peculiar as preliminary results from our laboratory pointed to the high activity of [(*S*)-**1**]-Au_2Cl_2 as a precatalyst for the hydroamination of *N*-allenyl carbamates. Here we provide an account of our results in this area.

Our approach to the development of a catalyst system for the enantioselective hydroamination of *N*-allenyl carbamates targeted the systems optimized for the enantioselective hydroalkoxylation and hydroarylation of allenes.[7,8] Unfortunately, treatment of *N*-4,5-hexadienyl carbamate **2a** with a catalytic 1:2 mixture of [(*S*)-**1**]Au_2Cl_2 and either AgOTs or $AgBF_4$ required >6 days to reach completion to form pyrrolidine **3a** with ≤58% ee (Table 1, entries 1 and 2). However, subsequent optimization revealed a pronounced effect of the silver source on the rate of hydroamination (Table 1). For example, reaction of **2a** with a catalytic 1:2 mixture of [(*S*)-**1**]Au_2Cl_2 and $AgClO_4$ was complete within 10 min at room temperature to form **3a** as the exclusive product with 66% ee (Table 1, entry 8). This represents a 1000-fold increase in reaction rate relative to cyclization employing AgOTs with no deterioration in enantioselectivity. The high activity of the [(*S*)-**1**]$Au_2Cl_2/AgClO_4$ catalyst system allowed the reactions to be conducted at low temperature, which led to a marked increase in enantioselectivity (Table 1, entries 9 and 10). Subsequent optimization with respect to solvent revealed that substitution of *m*-xylene for toluene produced a modest but reproducible increase in enantioselectivity (Table 1, entry 11). In a preparative-scale experiment, reaction of **2a** with a catalytic mixture of [(*S*)-**1**]Au_2Cl_2 and $AgClO_4$ in *m*-xylene at −40 °C for 24 h led to isolation of **3a** in 97% yield with 81% ee (Table 2, entry 1).[12]

Table 1. Effect of Silver Source and Temperature on the Enantioselective Hydroamination of **2a** Catalyzed by [(*S*)-**1**]Au_2Cl_2



entry	X	temp (°C)	time (h)	convn (%)	ee (%)
1	OTs	23	160	100	58
2	BF_4	23	144	55	51
3	PF_6	23	4.0	100	65
4	OTf	23	2.0	100	58
5	NTf_2	23	1.0	100	43
6	SbF_6	23	1.0	100	58
7	AsF_6	23	0.17	100	65
8	ClO_4	23	0.17	100	66
9	ClO_4	−20	13.5	94	76
10[a]	ClO_4	−40	24	100	80
11[b]	ClO_4	−40	24	100	81



[a] [**2a**] = 0.30 M. [b] [**2a**] = 0.30 M in *m*-xylene.

Enantioselective hydroamination catalyzed by [(*S*)-**1**]-$Au_2Cl_2/AgClO_4$ was effective for a number of carbamate (**2b**−**d**) and carboxamide nucleophiles (**2e**), forming the corresponding pyrrolidines **3b**−**e** with 73−84% ee (Table 2, entries 2−5).[13] Likewise, *N*-allenyl carbamates that possessed a terminally disubstituted allenyl moiety (**4**−**6**) underwent gold(I)-catalyzed enantioselective hydroamination to form the corresponding pyrrolidines **7**−**9** in good yield with 76−91% ee (Table 2, entries 6−8). In contrast, gold-(I)-catalyzed conversion of *N*-(4,5-undecadienyl)carbamate **10** to 2-(1-hepteny)pyrrolidine **11** occurred with high diastereoselectivity but with negligible enantioselectivity (Table 2, entry 9), which pointed to predominant substrate control of stereoinduction. Substrate contol of stereoinduction was also observed for the hydroarylation of axially chiral 2-allenyl indoles catalyzed by [(*S*)-**1**]$Au_2Cl_2/AgBF_4$.[8] In contrast, stereoinduction in the hydroalkoxylation of axially chiral γ-hydroxyallenes catalyzed by [(*S*)-**1**]Au_2Cl_2/AgOTs was, to an overwhelming extent, controlled by the catalyst.[7] The

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(11) For additional examples of enantioselective transformations catalyzed by chiral bis(gold) complexes of the form $(P-P)Au_2X_2$ (P−P = bidentate phosphine; X = anionic ligand or counterion), see: (a) Munoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (b) González-Arellano, C.; Corma, A.; Iglesias, M.; Sanchez, F. *Chem. Commun.* **2005**, 3451. (c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002.

(12) Treatment of **2a** (0.30 M) with either [(*S*)-**1**]Au_2Cl_2 (2.5 mol %) or a mixture of (*S*)-**1** (2.5 mol %) and $AgClO_4$ (5 mol %) in *m*-xylene at rt for 24 h led to no consumption of **2a**.

(13) *N*-Allenyl sulfonamides failed to undergo efficient enantioselective hydroamination under these conditions. For example, reaction of *N*-(2,2-diphenyl-4,5-hexadienyl)-*p*-toluenesulfonamide (0.30 M) with a catalytic mixture of [(*S*)-**1**]Au_2Cl_2 (2.5 mol %) and $AgClO_4$ (5 mol %) at −20 °C for 48 h led to 66% conversion to form 4,4-diphenyl-1-*p*-toluenesulfonyl-2-vinylpyrrolidine with 8% ee.

Table 2. Enantioselective Hydroamination of *N*-Allenyl Carbamates and Carboxamides (0.30 M) Catalyzed by a Mixture of [(*S*)-**1**]Au_2Cl_2 (2.5 mol %) and $AgClO_4$ (5 mol %) in *m*-Xylene

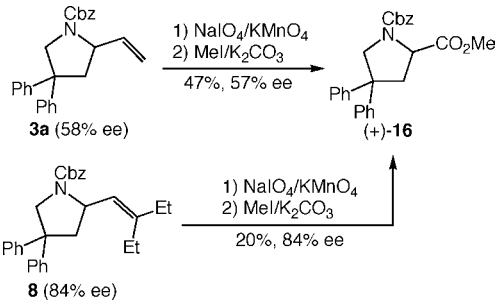
entry	allene	pyrrolidine	condn[a]	yield (%)	ee (%)
1	**2a** (R = Cbz)	**3a**	A	97	81
2	**2b** (R = Troc)	**3b**	B	61	83
3	**2c** (R = Fmoc)	**3c**	B	82	73
4	**2d** (R = CO_2Me)	**3d**	C	92	77
5	**2e** (R = COMe)	**3e**	D	97	84
6	**4** (R = Me)	**7**	B	80	80
7	**5** (R = Et)	**8**	E	83	91
8	**6**	**9**	F	91	76
9	**10** (R = *n*-pentyl)	**11**	G	86	6
10	**12**	**14**	A	98	50
11	**13**	(*S*)-**15**	G	99	34

[a] Conditions: A = −40 °C, 24 h; B = −20 °C, 48 h; C = −40 °C, 24 h followed by −20 °C, 24 h; D = −20 °C, 48 h followed by rt, 24 h; E = 0 °C, 24 h followed by rt, 24 h; F = 0 °C, 24 h; G = −20 °C, 24 h.

enantioselectivity of hydroamination was sensitive to the nature of the groups at the C2 position of the 4,5-hexadienyl chain. For example, gold(I)-catalyzed hydroamination of the cyclohexyl-substituted *N*-allenyl carbamate **12** or the unsubstituted derivative **13** led to formation of pyrrolidines **14** and (*S*)-**15**,[14] respectively, in excellent yield but with ≤50% ee (Table 2, entries 10 and 11).

It is worth noting that the sense of absolute stereoinduction in the conversion of **13** to (*S*)-**15** catalyzed by [(*S*)-**1**]Au_2Cl_2 (Table 2, entry 11) is opposite that observed for the enantioselective hydroalkoxylation of γ-hydroxy allenes catalyzed by [(*S*)-**1**]Au_2Cl_2/AgOTs and for the enantioselective hydroamination of *N*-allenyl sulfonamides catalyzed by (*R*)-xylyl-BINAP(AuOPNB)$_2$.[7,10] The substrates in these latter examples differ from **13** both in the nature of the nucleophile and in the degree of substitution at the terminal allenyl carbon atom. The possibility that the absolute configuration of the pyrrolidines formed in the gold(I)-catalyzed hydroamination of *N*-allenyl carbamates was affected by the presence or absence of substitution at the terminal allenyl carbon atom was firmly ruled out by the following experiments. Pyrrolidines **3a** and **8** were converted separately to the 2-methoxycarbonylpyrrolidine (+)-**16** via oxidative cleavage of the C=C bond followed by esterification (Scheme 1). Pyrrolidine (+)-**16** generated

Scheme 1



from **3a** and (+)-**16** generated from **8** possessed the same absolute configuration as determined by chiral HPLC analysis.[15]

In summary, we have developed a gold(I)-catalyzed protocol for the enantioselective hydroamination of *N*-allenyl carbamates. The protocol was effective for a number of carbamate and carboxamide nucleophiles and tolerated disubstitution at the terminal allenyl carbon atom. Conversely, enantioselective hydroamination was sensitive to substitution on the alkyl chain that tethered the carbamate group to the allenyl moiety. We continue to work toward the identification of more selective and more general catalysts for enantioselective hydroamination and toward an understanding of the mechanisms of stereoinduction in this process and in related hydrofunctionalization processes.

Acknowledgment is made to the NSF (CHE-0304994 and CHE-0555425) and Johnson & Johnson for support of this research. We thank Dr. Rudolf Schmid (Hoffmann-La Roche) for a gift of (*S*)-**1**.

Supporting Information Available: Experimental procedures and scans of chiral HPLC traces and NMR spectra for pyrrolidines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071108N

(14) (a) An authentic sample of (*S*)-**15** (98% ee) was prepared from commercially available *Z*-L-prolinol in two steps employing published procedures.[14b,c] (b) Takeuchi, T.; Yamada, A.; Suzuki, T.; Koizumi, T. *Tetrahedron* **1996**, *52*, 225. (c) Seijas, J. A.; Vázquez-Tato, P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruíz, M. *Tetrahedron* **1992**, *48*, 1637.

(15) A solution of (+)-**16** (~13 mM, 84% ee) in hexane/CH_2Cl_2 [1:1 (v/v)] in a 10 cm cell displayed an optical rotation of +0.41.