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Gold(I)-Catalyzed Stereoconvergent, Intermolecular Enantioselective Hydroamination of Allenes

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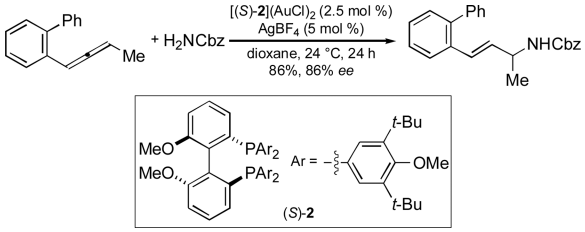
Abstract



A 1:2 mixture of [(*S*)-**2**](AuCl)$_2$ [(*S*)-**2** = (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP] and $AgBF_4$ catalyzes the stereoconvergent, intermolecular enantioselective hydroamination of chiral, racemic 1,3-disubstituted allenes with *N*-unsubstituted carbamates to form *N*-allylic carbamates in good yield, with high regio- and diastereoselectivity, and up to 92% *ee*.

Keywords

asymmetric synthesis; allenes; amination; Au; stereoselective catalysis

The intermolecular, enantioselective addition of the N–H bond of an amine or carboxamide derivative across a C–C multiple bond (hydroamination) represents an attractive, atom-economical approach to the synthesis of chiral, non-racemic amines and amine derivatives.[1] Within this family of transformations, the intermolecular enantioselective hydroamination (EHA) of allenes is of interest as a potentially expedient route to enantiomerically enriched α-chiral allylic amines, which are important chiral building blocks utilized in the synthesis of complex nitrogen-containing molecules.[2] However, despite considerable effort in this area,[1] effective intermolecular EHA processes are scarce,[3] and the intermolecular EHA of allenes remains unknown.[4]

One of the challenges associated with the intermolecular EHA of allenes is the regioselectivity of extant hydroamination catalysts, which form predominantly achiral products from electronically unbiased monosubstituted allenes.[4,5] To circumvent this regiochemical bias, we envisioned the stereoconvergent, intermolecular EHA of chiral, racemic 1,3-disubstutited allenes catalyzed by chiral bis(gold) phosphine complexes. This approach builds upon our previous efforts in the area of gold-catalyzed allene hydroamination.[6,7] In particular, we have shown that achiral gold(I) NHC complexes catalyze the regio- and diastereoselective hydroamination of chiral 1,3-disubstituted allenes with carbamates, which was superimposed on rapid allene racemization.[6] Furthermore,

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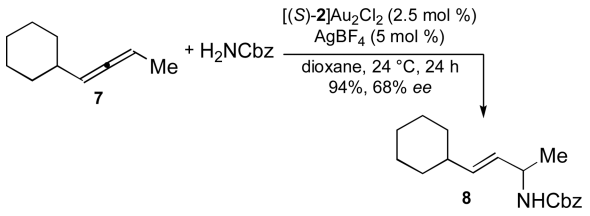
both we[7] and Toste[8] have demonstrated the enantioselective intramolecular hydroamination of allenes catalyzed by chiral bis(gold) phosphine complexes.[9] Herein we describe the stereoconvergent, enantioselective, intermolecular hydroamination of chiral, racemic 1,3-disubstituted allenes with carbamates catalyzed by chiral bis(gold) phosphine complexes.[10]

Initial experiments directed toward the intermolecular EHA of allenes were only modestly encouraging and reaction of benzyl carbamate (0.72 M) with 1-phenyl-1,2-butadiene (**1**; 1 equiv) catalyzed by a 1:2 mixture of [(*R*)-**2**]$(AuCl)_2$ [(*R*)-**2** = (*R*)-DTBM-MeOBIPHEP] and AgOTf in dioxane at 24 °C for 24 h led to isolation of *N*-allylic carbamate (*R*)-**3a** in 35% yield as a single diastereomer (≥25:1) with 50% *ee* (Table 1, entry 1).[11,12] Substitution of ligand (*R*)-**2** with the SEGPHOS ligand (*R*)-**4** led to deterioration in both the yield and enantioselectivity of hydroamination (Table 1, entry 2). Conversely, optimization with respect to silver salt revealed that substitution of $AgBF_4$ for AgOTf led to marked improvement in both yield and enantioselectivity of gold-catalyzed allene hydroamination (Table 1, entry 7). The reaction yield was further improved through employment of a slight excess of allene relative to benzyl carbamate and, in an optimized procedure, treatment of benzyl carbamate (0.72 M) with **1** (1.5 equiv) and a catalytic 1:2 mixture of [(*S*)-**2**]$(AuCl)_2$ and $AgBF_4$ in dioxane at 24 °C led to isolation of (*S*)-**3a** in 89% yield with 72% *ee* (Table 1, entry 10). A single recrystallization from warm hexanes increased the enantiopurity of (*S*)-**3a** to 96% *ee*.

In addition to benzyl carbamate, methyl carbamate, 9-fluorenylmethyl carbamate, and trichloroethyl carbamate underwent gold-catalyzed reaction with **1** to form *N*-allylic carbamates **3b**-**3d** with enantiopurities comparable to that of **3a** (Table 2, entries 1–3).[13] Likewise, gold-catalyzed intermolecular EHA was effective for a number of 1-aryl-1,2-butadienes (Table 2, entries 4–13). For example, gold(I)-catalyzed reaction of benzyl carbamate with *p*-substituted 1-aryl-1,2-butadienes **5a**-**5d** led to isolation of *N*-allylic carbamates **6a**-**6d** in 82–99% yield with 60–76% *ee*, albeit without a clear relationship between arene electron donicity and enantioselectivity (Table 2, entries 4–7). Also worth noting is that the enantiopurity of **6d** increased from 69% *ee* to 99% *ee* after a single recrystallization from warm hexanes (Table 2, entry 7). In comparison, gold-catalyzed hydroamination of the more sterically hindered *o*-substituted 1-aryl-1,2-butadienes **5e**-**5h** formed *N*-allylic carbamates **6e**-**6h** with 80–86% *ee* (Table 2, entries 8–11). Gold(I)-catalyzed intermolecular hydroamination of the more sterically hindered *o,o*-disubstituted 1-aryl-1,2-butadiene **5i** occurred with even higher enantioselectivity (92% *ee*) but with diminished yield (Table 2, entry 12). Gold-catalyzed intermolecular EHA was not restricted to 1-aryl-1,2-butadienes and gold-catalyzed reaction of 1,3-dialkyl substituted allene **7** with benzyl carbamate led to isolation of *N*-allylic carbamate **8** in 94% yield with 68% *ee* (eq 1). Conversely, gold-catalyzed intermolecular EHA was not effective for 1,3-disubstituted allenes lacking a methyl substituent.[14]



eq 1

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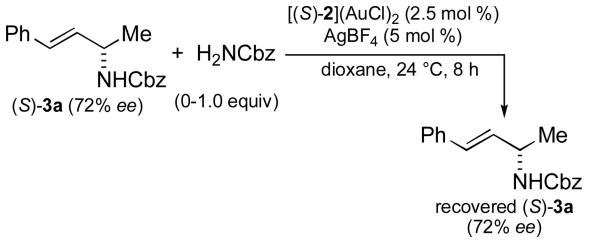
Congruent with our expectations, allene racemization occurred rapidly under reaction conditions. For example, periodic analysis of a solution of enantiomerically enriched (*S*)-**5b** (89% *ee*), benzyl carbamate, and a catalytic mixture of [(*S*)-**2**]$(AuCl)_2$ and $AgBF_4$ employing chiral stationary phase HPLC revealed complete racemization of (*S*)-**5b** prior to any detectable formation of **6b** (≤5 min; Table 3). Interestingly, continued analysis of the reaction mixture showed that the enantiopurity of **6b** decreased from 69% *ee* at 21% conversion to a terminal value of 59% *ee* at ≥74% conversion (Table 3). This phenomenon was not restricted to the formation of **6b** and the enantiopurity of **3a** formed in the gold-catalyzed reaction of **1** with benzyl carbamate likewise decreased from 78% *ee* at 22% conversion to a terminal value of 72% *ee* at ≥83% conversion.

Although we initially considered that racemization of **3a** or **6b** under reaction conditions was responsible for the conversion-dependent enantioselectivity displayed by the gold-catalyzed intermolecular EHA of **1** or **5b**, respectively, this possibility was excluded. For example, stirring a solution of (*S*)-**3a** (72% *ee*) and a catalytic 1:2 mixture of [(*S*)-**2**]$(AuCl)_2$ and $AgBF_4$ at room temperature for 8 h either in the presence (1 equiv) or absence of benzyl carbamate led to no detectable decrease in the enantiopurity of (*S*)-**3a** (eq 2). Rather, a pair of experiments pointed to the potentially deleterious effect of the *N*-allylic carbamate product on the enantioselectivity of intermolecular EHA. For example, treatment of a 1.5:1:1 mixture of **1**, benzyl carbamate, and (*S*)-**6c** with a catalytic mixture of [(*S*)-**2**]$(AuCl)_2$/$AgBF_4$ at 24 °C for 24 h led to isolation of (*S*)-**3a** in 75% yield with 74% *ee* (Scheme 1), which is nominally higher enantioselectivity than was realized in the absence of (*S*)-**6c** (Table 1, entry 10). However, the corresponding reaction of **1**, benzyl carbamate, and (*S*)-**6c** catalyzed by [(*R*)-**2**]$(AuCl)_2$/$AgBF_4$ led to isolation of (*R*)-**3a** in 71% yield with 62% *ee* (Scheme 1), which is considerably lower enantioselectivity than was observed in the absence of (*S*)-**6c**.



eq 2

Rapid allene racemization precluded stereochemical analysis of the gold-catalyzed intermolecular EHA of (*S*)-**5b** (Table 3). However, we have previously established the *anti*-stereochemistry of gold(I)-catalyzed intramolecular enantioselective allene hydrofunctionalization,[7,15] which is consistent with the outer-sphere addition of the nucleophile to a gold(I) π-allene complex. Although such a mechanism implicates one of the two gold centers of a bis(gold) catalyst in the allene activation/C–N bond formation process, there is no firm evidence that supports the direct participation of the second gold center in these steps.[10,16] There is, however, evidence that the ligation state of this spectator gold center can affect the enantioselectivity of gold-catalyzed hydrofunctionalization.[8] Given the non-coordinating nature of the BF_4^- counterion employed in the gold-catalyzed intermolecular EHA of allenes, the spectator gold center is presumably ligated with an allene, benzyl carbamate, or either enantiomer of the *N*-allylic carbamate product.[17] Therefore, the decreasing enantioselectivity of the gold-catalyzed intermolecular EHA of allenes with increasing conversion presumably reflects the increasing concentration of a less selective *N*-allylic carbamate ligated catalyst species.

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In summary, we have developed a gold(I)-catalyzed protocol for the stereoconvergent, intermolecular enantioselective hydroamination of chiral, racemic 1,3-disubstituted allenes with *N*-unsubstituted carbamates. In addition, the enantioselectivity versus conversion behavior of intermolecular EHA coupled with independent analysis of the effect of *N*-allylic carbamate on the enantioselectivity of these transformations suggests that the nature of the catalytically active species changes with increasing concentration of *N*-allylic carbamate. We continue to work toward the identification of more selective and more general catalytic systems for intermolecular EHA and toward the development of ligand-modulated enantioselective gold catalysis.

Acknowledgments

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References

1. For reviews on catalytic hydroamination, see: Chemler SR. Org. Biomol. Chem. 2009; 7:3009–3019. [PubMed: 20976023] Müller TE, Hultzsch KC, Yus M, Foubelo F, Tada M. Chem. Rev. 2008; 108:3795–3892. [PubMed: 18729420] Aillaud I, Collin J, Hannedouche J, Schulz E. Dalton Trans. 2007:5105–5118. [PubMed: 17985016] Widenhoefer RA, Han X. Eur. J. Org. Chem. 2006:4555–4563. Hultzsch KC. Org. Biomol. Chem. 2005; 3:1819–1824. [PubMed: 15889160] Hultzsch KC. Adv. Synth. Catal. 2005; 347:367–391..
2. For reviews regarding the synthesis of α-chiral allylic amines see: Hartwig JF, Stanley LM. Acc. Chem. Res. 2010; 43:1461–1475. [PubMed: 20873839] Trost BM, Zhang T, Sieber JD. Chem. Sci. 2010; 1:427–440. Lu Z, Ma S. Angew. Chem. Int. Ed. 2008; 47:258–297. Helmchen G, Dahnz A, Dübon P, Schelwies M, Weihofen R. Chem. Commun. 2007:675–691. Trost BM, Crawley ML. Chem. Rev. 2003; 103:2921–2943. [PubMed: 12914486] Hollis TK, Overman LE. J. Organomet. Chem. 1999; 576:290–299. Johannsen M, Jørgensen KA. Chem. Rev. 1998; 98:1689–1708. [PubMed: 11848944] Skucas E, Ngal M-Y, Komanduri V, Krische MJ. Acc. Chem. Res. 2007; 40:1394–1401. [PubMed: 17784728] Kobayashi S, Ishitani H. Chem. Rev. 1999; 99:1069–1094. [PubMed: 11749440] Bloch R. Chem. Rev. 1998; 98:1407–1438. [PubMed: 11848938] .
3. For notable examples of enantioselective, intermolecular hydroamination, see: Pan S, Endo K, Shibata T. Org. Lett. 2012; 14:780–783. [PubMed: 22256899] Reznichenko AL, Nguyen HN, Hultzsch KC. Angew. Chem. Int. Ed. 2010; 49:8984–8987. Zhang Z, Lee SD, Widenhoefer RA. J. Am. Chem. Soc. 2009; 131:5372–5373. [PubMed: 19326908] Zhou J, Hartwig JF. J. Am. Chem. Soc. 2008; 130:12220–12221. [PubMed: 18715004] Hu A, Ogasawara M, Sakamoto T, Okada A, Nakajima K, Takahashi T, Lin W. Adv. Synth. Catal. 2006; 348:2051–2056. Li K, Horton PN, Hursthouse MB, Hii KK. J. Organomet. Chem. 2003; 665:250–257. Utsunomiya M, Hartwig JF. J. Am. Chem. Soc. 2003; 125:14286–14287. [PubMed: 14624571] Löber O, Kawatsura M, Hartwig JF. J. Am. Chem. Soc. 2001; 123:4366–4367. [PubMed: 11457216] Kawatsura M, Hartwig JF. J. Am. Chem. Soc. 2000; 122:9546–9547. Dorta R, Egli P, Zürcher F, Togni A. J. Am. Chem. Soc. 1997; 119:10857–10858..
4. Yamamoto has reported the stereospecific, intermolecular hydroamination of chiral allenes: Nishina N, Yamamoto Y. Angew. Chem. Int. Ed. 2006; 45:3314–3317..
5. a) Beck JF, Schmidt JAR. RSC Advances. 2012; 2:128–131.b) Kinjo R, Donnadieu B, Bertrand G. Angew. Chem., Int. Ed. 2011; 50:5560–5563.c) Kuchenbeiser G, Shaffer AR, Zingales NC, Beck JF, Schmidt JAR. J. Organomet. Chem. 2011; 696:179–187.d) Duncan AN, Widenhoefer RA. Synlett. 2010:419–422. [PubMed: 21197142] e) Toups KL, Widenhoefer RA. Chem. Commun. 2010; 46:1712–1714.f) Zeng X, Frey GD, Kinjo R, Donnadieu B, Bertrand G. J. Am. Chem. Soc. 2009; 131:8690–8696. [PubMed: 19456108] g) Zeng X, Soleilhavoup M, Bertrand G. Org. Lett. 2009; 11:3166–3169. [PubMed: 19719176] h) Nishina N, Yamamoto Y. Tetrahedron. 2009; 65:1799–1808.i) Lavallo V, Frey GD, Donnadieu B, Soleilhavoup M, Bertrand G. Angew. Chem., Int. Ed. 2008; 47:5224–5228.j) Nishina N, Yamamoto Y. Tetrahedron Lett. 2008; 49:4908–4911.k) Nishina N, Yamamoto Y. Synlett. 2007:1767–1770.l) Ayinla RO, Schafer LL. Inorg. Chim. Acta.

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2006; 359:3097–3102.m) Anderson LL, Arnold J, Bergman RG. Org. Lett. 2004; 6:2519–2522. [PubMed: 15255680] n) Johnson JS, Bergman RG. J. Am. Chem. Soc. 2001; 123:2923–2924. [PubMed: 11456996] o) Al-Masum M, Meguro M, Yamamoto Y. Tetrahedron Lett. 1997; 38:6071–6074.p) Besson L, Goré J, Cazes B. Tetrahedron Lett. 1995; 36:3857–3860.q) Walsh PJ, Baranger AM, Bergman RG. J. Am. Chem. Soc. 1992; 114:1708–1719.

6. Kinder RE, Zhang Z, Widenhoefer RA. Org. Lett. 2008; 10:3157–3159. [PubMed: 18570376]
7. a) Li H, Lee SD, Widenhoefer RA. J. Organomet. Chem. 2011; 696:316–320. [PubMed: 21909160] b) Zhang Z, Bender CF, Widenhoefer RA. Org. Lett. 2007; 9:2887–2889. [PubMed: 17595096] c) Zhang Z, Bender CF, Widenhoefer RA. J. Am. Chem. Soc. 2007; 129:14148–14149. [PubMed: 17967025]
8. a) LaLonde RL, Wang ZJ, Mba M, Lackner AD, Toste FD. Angew. Chem. Int. Ed. 2010; 49:598–601.b) LaLonde RL, Sherry BD, Kang EJ, Toste FD. J. Am. Chem. Soc. 2007; 129:2452–2453. [PubMed: 17290999] c) Hamilton GL, Kang EJ, Mba M, Toste FD. Science. 2007; 317:496–499. [PubMed: 17656720]
9. For recent reviews of enantioselective gold(I) catalysis, see: Pradal A, Toullec PY, Michelet V. Synthesis. 2011:1501–1514. Sengupta S, Shi X. ChemCatChem. 2010; 2:609–619. Widenhoefer RA. Chem. Eur. J. 2008; 14:5382–5391. [PubMed: 18442031] Bongers N, Krause N. Angew. Chem. Int. Ed. 2008; 47:2178–2181..
10. Che has recently reported the gold(I)-catalyzed intermolecular enantioselective hydroarylation of 1,3-diarylallenes with indoles with up to 63% *ee*: Wang M-Z, Zhou C-Y, Guo Z, Wong EL-M, Wong M-K, Che C-M. Chem. Asian J. 2011; 6:812–824. [PubMed: 21344657] .
11. a) The absolute configuration of (*S*)-**3a** was determined by optical rotation {$[\alpha]_D^{25}$ –39.4 (*c* 0.19, CH_2Cl_2); lit. [for (*S*)-**3a**) $[\alpha]_D^{23}$ –55.4 (*c* 1.10, CH_2Cl_2)}.[11b] The absolute configurations of all remaining *N*-allylic carbamates were assigned by analogy; Hunt JCA, Laurent P, Moody CJ. J. Chem. Soc., Perkin Trans. 1. 2002:2378–2389..
12. a) Allenes depicted in Tables 1 and 2 were synthesized in two steps from 3-butyne-2-ol in 26–51% yield employing the procedures of Knochel[12b] and Myers, [12c] with the exception of **1** which was synthesized in one step from 4-phenyl-3-butyn-2-ol; Myers AG, Zheng B. J. Am. Chem. Soc. 1996; 118:4492–4493. Harrington-Frost N, Leuser H, Calaza MI, Kneisel FF, Knochel P. Org. Lett. 2003; 5:2111–2114. [PubMed: 12790541] .
13. Sulfonamides were less effective than were carbamates. For example, gold-catalyzed reaction of **1** with *p*-toluenesulfonamide at room temperature for 48 h formed (*E*)-4-methyl-*N*-(4-phenylbut-3-en-2-yl)benzenesulfonamide in 57% yield with 28 % *ee*.
14. For example, gold-catalyzed reaction of 1-phenyl-1,2-pentadiene with benzyl carbamate at room temperature for 48 h formed (*E*)-benzyl (1-phenylpent-1-en-3-yl)carbamate in 13% yield with 23 % *ee*.
15. Zhang Z, Widenhoefer RA. Angew. Chem. Int. Ed. 2007; 46:283–285.
16. Kim JH, Park S-W, Park SR, Lee S, Kang EJ. Chem. Asian J. 2011; 6:1982–1986. [PubMed: 21735554]
17. Brooner REM, Widenhoefer RA. Organometallics. 2012; 31:768–771.

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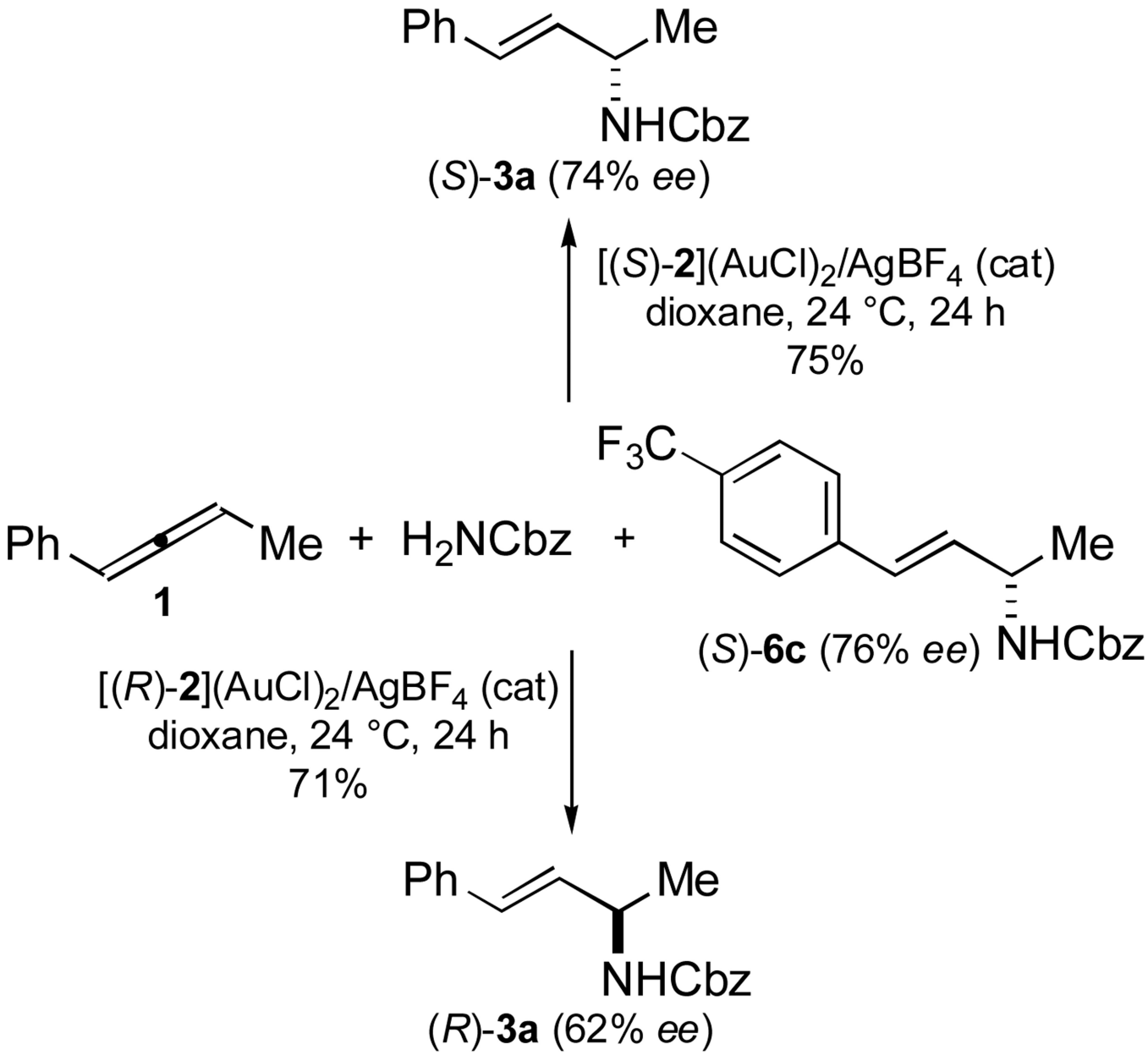

Scheme 1.

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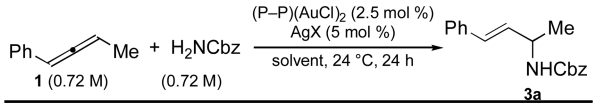
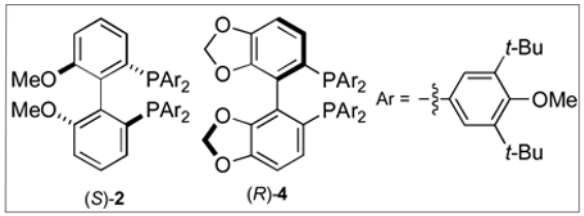
Table 1

Effect of supporting ligand, solvent, silver salt and allene concentration on the gold(I)-catalyzed enantioselective hydroamination of **1** with benzyl carbamate.



entry	P–P	AgX	solvent	yield (%)[a]	ee (%)	config
1	(*R*)-**2**	AgOTf	dioxane	35	50	*R*
2	(*R*)-**4**	AgOTf	dioxane	15	44	*R*
3	(*S*)-**2**	$AgSbF_6$	dioxane	20	60	*S*
4	(*S*)-**2**	$AgPF_6$	dioxane	12	66	*S*
5	(*S*)-**2**	$AgClO_4$	dioxane	49	63	*S*
6	(*S*)-**2**	$AgNTf_2$	dioxane	20	45	*S*
7	(*S*)-**2**	$AgBF_4$	dioxane	71	72	*S*
8	(*S*)-**2**	$AgBF_4$	toluene	65	50	*S*
9[b]	(*S*)-**2**	$AgBF_4$	THF	36	61	*S*
10[c]	(*S*)-**2**	$AgBF_4$	dioxane	89	72[d]	*S*



[a] Isolated yield; dr ≥25:1.

[b] [**1**] = [H_2NCbz] = 0.4 M, 48 h, GC yield.

[c] [**1**] = 1.1 M.

[d] 96% *ee* after recrystallization.

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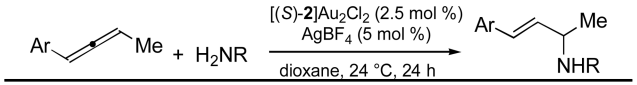
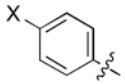
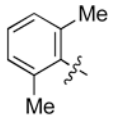
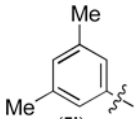
Table 2

Enantioselective hydroamination of allenes (1.1 M) with carbamates (0.71 M) catalyzed by a mixture of [(*S*)-**2**]$(AuCl)_2$ (2.5 mol %) and $AgBF_4$ (5 mol %) in dioxane at room temperature.



Entry	Ar	R[a]	Product	Yield [%][b]	*ee* [%][c]
1	Ph (**1**)	CO_2Me	**3b**	81	69
2	Ph (**1**)	Fmoc	**3c**	79	71
3	Ph (**1**)	Troc	**3d**	43	73
					
4	X = Me (**5a**)	Cbz	**6a**	97	72
5	X = OMe (**5b**)	Cbz	**6b**	85	60
6	X = CF_3 (**5c**)	Cbz	**6c**	82	76
7	X = Br (**5d**)	Cbz	**6d**	99	69[d]
8	X = Me (**5e**)	Cbz	**6e**	82	81
9[e]	X = *i*-Pr (**5f**)	Cbz	**6f**	80	81
10	X = Ph (**5g**)	Cbz	**6g**	86	86
11	X = Br (**5h**)	Cbz	**6h**	69	80
12[e]	 (**5i**)	Cbz	**6i**	42	92
13[e]	 (**5j**)	Cbz	**6j**	44	72

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[a] Cbz = benzyloxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl, Fmoc = fluorenylmethyloxycarbonyl.

[b] Isolated yield; dr ≥25:1.

[c] Enantiomeric excess determined by HPLC analysis on chiral support. Absolute configuration assigned as *S* based on analogy to (*S*)-**3a**.[11]

[d] 99% *ee* after recrystallization.

[e] Reaction run for 48 h.

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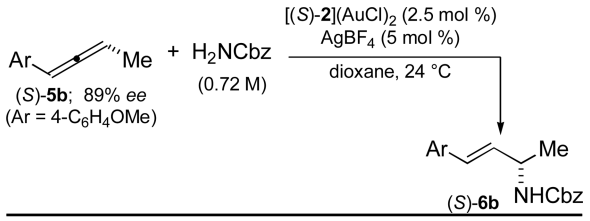
Table 3

Enantiopurity of allene and *N*-allylic carbamate as a function of conversion for the gold-catalyzed hydroamination of (*S*)-**5b** (89% *ee*).



Time [h]	Convn [%]	5b *ee* [%]	6b *ee* [%]
Š0.08	Š2	Š2	—
1	21	Š2	69
1.5	39	Š2	65
2.0	44	Š2	63
4.0	74	Š2	59
5.0	81	Š2	58
6.0	>90	Š2	59