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Gold(I)-Catalyzed Intramolecular Enantioselective Hydroarylation of Allenes with Indoles

Cong Liu and Ross A. Widenhoefer*

Duke University, French Family Science Center, Durham, North Carolina 27708-0346

rwidenho@chem.duke.edu

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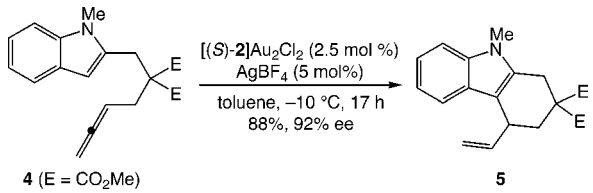
ABSTRACT



4 (E = CO_2Me) **5**

Treatment of 2-allenyl indole 4 with a catalytic 1:2 mixture of [(*S*)-2]Au_2Cl_2 [(*S*)-2 = (*S*)-3,5-*t*Bu-4-MeO-MeOBIPHEP] and $AgBF_4$ in toluene at −10 °C for 17 h led to isolation of tetrahydrocarbazole 5 in 88% yield with 92% ee. The protocol was effective for the cyclization of terminally disubstituted allenes and for the formation of seven-membered rings.

Transition-metal-catalyzed hydroarylation of C−C multiple bonds has attracted considerable attention as an atom-economical approach to the functionalization of arenes.[1] This interest has led to the development of a number of effective protocols for the hydroarylation of alkenes[2] and alkynes.[3] Likewise, a number of highly enantioselective Lewis acid catalyzed procedures have been developed for the hydroarylation of electron-deficient alkenes with electron-rich arenes.[4,5] In contrast, examples of the catalytic, enantioselective hydroarylation of electronically unactivated C−C multiple bonds remain scarce.[6,7] We have contributed to this area through the development of a Pt(II)-catalyzed protocol for the enantioselective, intramolecular hydroarylation of unactivated alkenes with indoles. As an example, treatment of the 2-(4-pentenyl)indole **1** with a catalytic 1:1 mixture of [(*S*)-**2**]$PtCl_2$ [(*S*)-**2** = (*S*)-3,5-*t*Bu-4-MeO-MeOBIPHEP] and AgOTf (10 mol %) at 60 °C for 20 h led to isolation of

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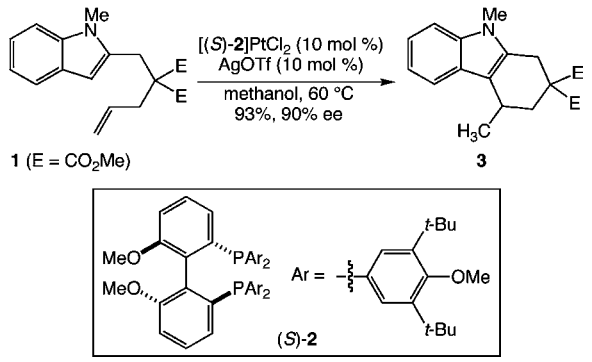
tetrahydrocarbazole **3** in 93% yield with 90% ee (Scheme 1). Unfortunately, this level of selectivity was not realized

Scheme 1

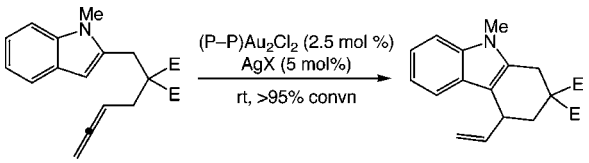


with other alkenyl indoles, and internal alkenes failed to undergo hydroarylation.

As an extension of our work in the area of gold(I)-catalyzed alkene hydroamination,[8,9] we have developed an effective procedure for the intramolecular hydroarylation of 2-allenyl indoles to form functionalized tricyclic indole derivatives catalyzed by a 1:1 mixture of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl and AgOTf (5 mol %).[9−12] We[13] and others[14] have developed enantioselective transformations catalyzed by chiral bis(gold) complexes of the form (P−P)Au$_2$X$_2$ (P−P = bidentate phosphine; X = anionic ligand or counterion). We therefore considered that chiral bis(gold)phosphine complexes might also catalyze the enantioselective intramolecular hydroarylation of allenes with indoles. Indeed, here we report the gold(I)-catalyzed enantioselective hydroarylation of 2-allenyl indoles to form functionalized tricyclic indole derivatives.

An initial experiment in the area of enantioselective allene hydroarylation was encouraging. Treatment of the 2-(4,5-hexadienyl)indole (**4**) with a catalytic 1:2 mixture of [(*S*)-BINAP]Au$_2$Cl$_2$ and AgOTf in dioxane at room temperature for 3.5 h led to complete consumption of **4** to form the 4-vinyltetrahydrocarbazole (**5**) as the exclusive product with 32% ee (Table 1, entry 1). Subsequent optimization with respect to phosphine, silver salt, and solvent led to identification of a 1:2 mixture of [(*S*)-**2**]Au$_2$Cl$_2$ and AgBF$_4$ in toluene as a more selective catalyst system for the hydroarylation of **4** (Table 1, entries 2−11). Decreasing the reaction temperature to −10 °C led to a marked improvement in enantioselectivity (Table 1, entry 12), although further decrease in reaction temperature led to incomplete conversion. In a preparative-scale reaction employing our optimized conditions, reaction of **4** (0.25 M) with a catalytic 1:2 mixture of [(*S*)-**2**]Au$_2$Cl$_2$ and AgBF$_4$ in toluene at −10 °C for 17 h led to isolation of **5** in in 88% yield with 92% ee (Table 2, entry 1).

Table 1. Effect of Ligand, Silver Salt, and Solvent on the Gold-Catalyzed Enantioselective Hydroarylation of **4**



entry	P−P	X	solvent	time (h)	ee (%)[a]
1	(*S*)-BINAP	OTf	dioxane	3.5	32
2	(*S*)-xylyl-BINAP	OTf	dioxane	2	42
3	(*S*)-MeO-BIPHEP	OTf	dioxane	3.5	48
4	(*S*)-MeO-BIPHEP	BF_4	dioxane	24	55
5	(*S*)-MeO-BIPHEP	SbF_6	dioxane	24	44
6	(*S*)-MeO-BIPHEP	ClO_4	dioxane	24	55
7	(*S*)-**2**	BF_4	dioxane	24	76
8	(*S*)-**2**	BF_4	THF	47	70
9	(*S*)-**2**	BF_4	MeCN	6	63
10	(*S*)-**2**	BF_4	MeOH	3	67
11	(*S*)-**2**	BF_4	toluene	2	81
12	(*S*)-**2**	BF_4	toluene	17	91[b]

[a] Enantiomeric excess determined by chiral HPLC analysis. [b] Reaction run at −10 °C.

2-Allenyl indoles that possessed either a 5-methoxy or 5-flouro group underwent gold-catalyzed hydroarylation to form the corresponding tetrahydrocarbazoles in good yield with modest enantioselectivity (Table 2, entries 2 and 3). The protocol also toleratered free hydroxyl groups in proximity to the allenyl moiety but again with modest enantioselectivity (Table 2, entry 4). Gratifyingly, 2-allenyl indole **6** that is disubstituted at the terminal allenyl carbon atom underwent enantioselective hydroarylation to form tetrahydrocarbazole **7** in 82% yield with 91% ee (Table 2, entry 5). Likewise, the 2-(5,6-heptadienyl)indole **8** underwent

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Table 2. Enantioselective Hydroarylation of 2-Allenyl Indoles (0.25 M) Catalyzed by a Mixture of [(*S*)-**2**]Au_2Cl_2 (2.5 mol %) and $AgBF_4$ (5 mol %) in Toluene at −10 °C for 18−24 h (E = CO_2Me)

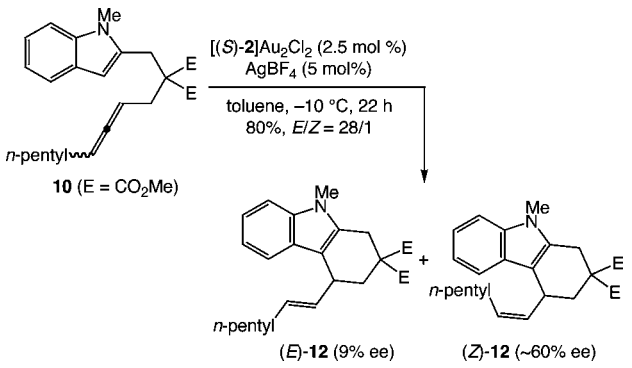
entry	allenyl indole	product	yield (%)[a]	ee (%)[b]
1	R = H (**4**)	**5**	88	92
2	R = OMe		85	78
3	R = F		90	75
4	R = CH_2OH		50	72
5	**6**	**7**	82	91
6[c]	**8**	**9**	80	91

[a] Isolated product of >95% purity. [b] Determined by chiral HPLC analysis. [c] Reaction run at room temperature.

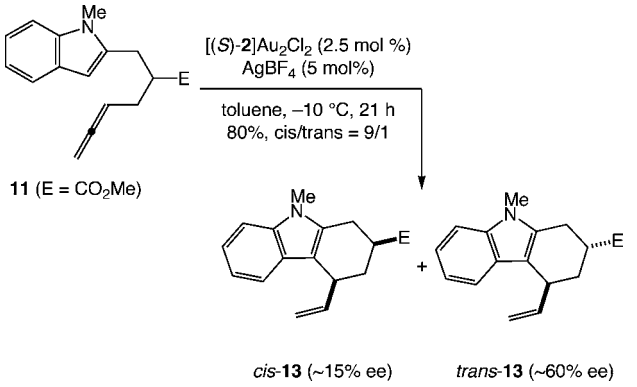
7-*exo*-*trig* cyclization at room temperature to form tricyclic indole **9** in 80% yield with 91% ee (Table 2, entry 6).

We have investigated the enantioselective hydroarylation of the 2-(4,5-undecadienyl) indole **10** and the 2-(2-methoxycarbonyl-4,5-hexadienyl) indole **11** to evaluate the effect of substrate chirality on the stereoselectivity of hydroarylation (Schemes 2 and 3). In both cases, the stereoselectivity of

Scheme 2



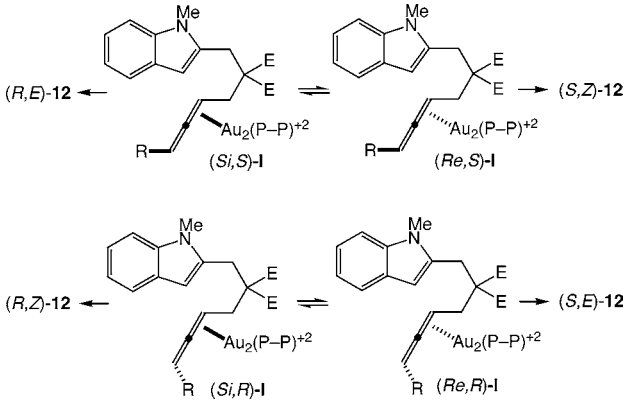
Scheme 3



hydroarylation was controlled predominantly by the substrate stereocenter(s). In the first case, gold-catalyzed cyclization of **10** led to isolation of a 28:1 mixture of *E*-**12** and *Z*-**12** in 80% combined yield with 9% and ∼60% ee,[15] respectively (Scheme 2). In the second case, gold-catalyzed cyclization of **11** led to isolation of a 9:1 mixture of *cis*-**13** and *trans*-**13** in 80% combined yield with ∼15% and ∼60% ee,[16] respectively (Scheme 3).

Our previous investigations of gold-catalyzed allene hydrofunctionalization have established mechanisms involving outer-sphere attack of the nucleophile on a gold-complexed allene followed by protonolysis of the resulting alkenyl gold complex with retention of configuration.[9,13] Therefore, predominant (>96%) formation of nearly racemic *E*-**12** from racemic **10** indicates that C−C bond formation occurs predominantly from gold allene intermediates (*si*,*S*)-**I** and (*re*,*R*)-**I** in which the gold atom is *cis* to the proximal alkyl group (Scheme 4).[17] In comparison, a purely catalyst-

Scheme 4



controlled process would proceed via cyclization of either the (*si*,*S*)-**I**/(*si*,*R*)-**I** or (*re*,*S*)-**I**/(*re*,*R*)-**I** pair leading to forma-

(15) The low concentration of *Z*-**12** precluded accurate determination of enantiomeric purity.

tion of a 1:1 mixture of enantiomerically pure homochiral diastereomers (Scheme 4). A similar analysis can be applied to the gold-catalyzed hydroarylation of **11**. In this case, predominant formation of *cis*-**13** with low enantiopurity indicates that C−C bond formation occurs primarily from the gold allene intermediates in which the gold atom is *trans* to the homoallylic ester group with negligible discrimination of the *si* and *re* faces of the allene by the chiral catalyst.[17]

Substrate control of stereoselectivity in the gold-catalyzed enantioselective hydroarylation of **10** and **11** stands in sharp contrast to the pronounced catalyst control of stereoselectivity in the gold-catalyzed intramolecular enantioselective hydroalkoxylation of chiral δ- and γ-hydroxy allenes.[13] In a particularly illustrative example, reaction of racemic 2,2-diphenyl-4,5-heptadien-1-ol with a catalytic 1:2 mixture of [(*S*)-**2**]Au_2Cl_2 and AgOTs led to isolation of a 1:1 mixture of (*E*)- and (*Z*)-4,4-diphenyl-2-(1-propenyl)tetrahydrofuran in 96% combined yield with 97% and 99% ee, respectively.[13] The disparate mechanisms of stereocontrol in the gold-catalyzed enantioselective hydrofunctionalization of chiral 2-allenyl indoles and chiral hydroxy allenes must result from the dissimilar hybridization and steric profiles of the respective nucleophiles.

In summary, we have developed an effective Au(I)-catalyzed protocol for the enantioselective hydroarylation of achiral 2-allenyl indoles and have shown that chiral allenyl indoles undergo hydroarylation with pronounced substrate control of stereoselectivity. We continue to work toward the identification of more selective and more general catalysts for enantioselective hydroarylation and toward the elucidation of the mechanisms of gold-catalyzed enantioselective hydrofunctionalization including the effect of the nucleophile on the selectivity of these transformations.

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Supporting Information Available: Experimental procedures, mechanistic schemes for the cyclization of **10** and **11**, and scans of chiral HPLC traces and NMR spectra for tricyclic indoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Determination of the enantiomeric purity of **13** was complicated by co-elution of one enantiomer of (*E*)-**13** with one enantiomer of (*Z*)-**13** on HPLC.

(17) See Supporting Information for a more detailed depiction of the pathways leading to all possible stereoisomers of **12** and **13** formed in the gold-catalyzed cyclization of **10** and **11**, respectively.