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Gold(I)-Catalyzed Synthesis of Tetrahydrocarbazoles *via* Cascade [3,3]-Propargylic Rearrangement/[4+2] Cycloaddition of Vinylindoles and Propargylic Esters

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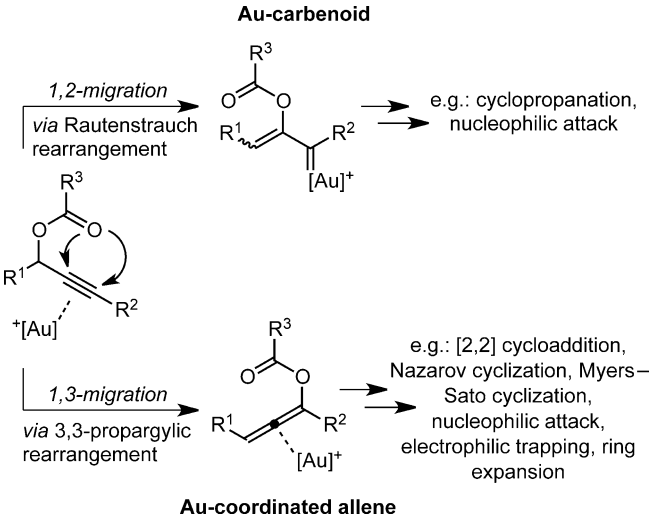
Abstract: A gold(I)-catalyzed cascade [3,3]-propargylic rearrangement and [4+2] cycloaddition reaction of 2-vinylindoles with propargylic esters is reported. The reaction leads to the synthesis of highly substituted tetrahydrocarbazole derivatives in high yields and diasteroselectivities. Furthermore, a preliminary screening for an asymmetric version of this reaction is described.

Keywords: cycloaddition; gold; nitrogen heterocycles; rearrangement

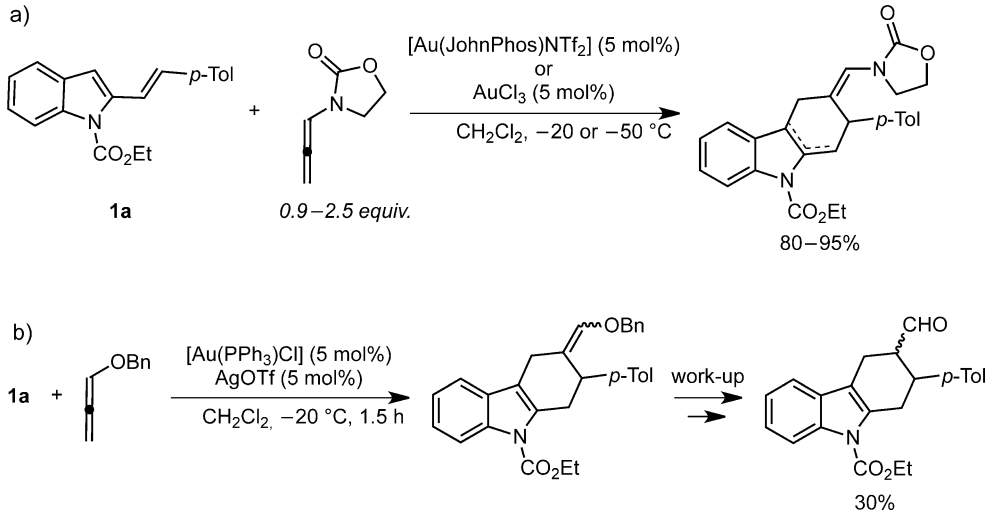
Introduction

The synthesis of heterocyclic compounds through metal-catalyzed cascade reactions has become one of the most active research topics in synthetic organic chemistry.[1] Among metals, gold catalysts have proved to be a useful tool for the preparation of various heterocycles in a simple and selective manner.[2] Moreover, gold catalysts can promote cascade reactions allowing for the construction of molecular complexity from simple starting materials. In particular, the ability of gold to induce propargylic esters rearrangements[3] has permitted the development of cascade reactions initiated by 1,2-migrations or 3,3-propargylic rearrangements (Scheme 1).[4] Thus, the syntheses of different heterocycles such as pyrrolines,[5] pyrrolidines,[6] indoles,[7] isoindoles,[8] pyridines,[9] piperidines,[10] quinolones,[11] azepines,[12] and lactams (pyrrolidin-2-ones)[13] have been achieved on the basis of this strategy. Recently, we reported the preparation of tetrahydrocarbazole derivatives by means of gold-catalyzed intermolecular [4+2] cycloaddition reactions.[14] These products indeed represent an interesting class of compounds and building blocks for the synthesis of alkaloids and biologically active molecules.[15]

In particular we found that modulation of the conditions, for example, gold species, stoichiometry and temperature, in the reaction between 2-vinylindoles and *N*-allenamides allowed for the selective preparation of non-aromatized and aromatized carbazole derivatives (Scheme 2a).[14b] The scope of this transfor-

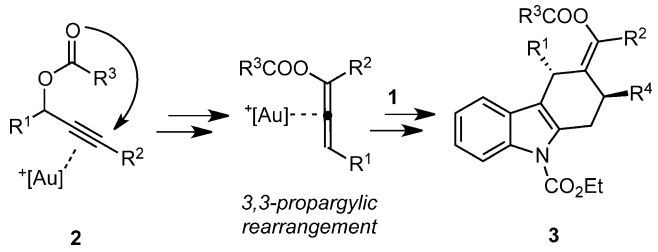


Scheme 1. Gold(I)-catalyzed propargylic esters rearrangements in cascade processes.



Scheme 2. Reaction of 2-vinylindole **1a** and a) *N*-allenamides b) allenyl benzyl ether.

mation was broad considering the nature of vinylindoles, but limited to *N*-allenamides as dienophiles. In fact, the use of other allenyl derivatives, such as allenyl ethers, led to unsatisfactory results in terms of *E/Z* selectivity and yield. For example, the reaction of vinylindole **1a** and allenyl benzyl ether led to a mixture of *E/Z*-vinyl benzyl ether carbazoles, as observed in the ^{1}H NMR of the crude mixture besides unreacted **1a**. Furthermore, purification of the reaction crude led to isolation of the corresponding aldehydes, arising from hydrolysis of the vinyl ether group, as a 1:1 mixture of diasteroisomers (Scheme 2b). To address these difficulties, we envisioned the possibility of using allenyl esters as allenyl ether surrogates. The formation of cycloaddition compounds bearing a more stable vinyl ester function might facilitate the isolation and purification of the corresponding tetrahydrocarbazoles. Allenyl esters can be prepared and isolated in high yields from propargylic esters *via* 3,3-rearrangements in the presence of poor electrophilic cationic gold(I) species.[16] Interestingly, the use of a more electrophilic gold catalyst enables not only the generation of the allenyl ester but also its subsequent activation for further transformations. We thought that this latter approach would be more suitable for our purposes as both the [3,3]-propargylic rearrangement and [4+2]cycloaddition could be catalyzed by the same gold species (Scheme 3) giving access to functionalized products in a single flask operation *via* a cascade reaction.



Scheme 3. Proposed cascade [3,3]-propargylic rearrangement and [4+2]cycloaddition leading to **3**.

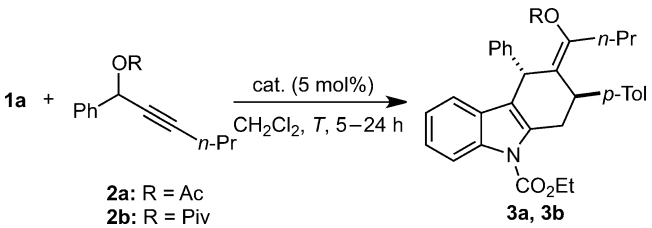
Herein, we report the results obtained in the gold-catalyzed reaction of 2-vinylindoles **1** and propargylic esters **2** for the selective synthesis of substituted tetrahydrocarbazoles **3**. To the best of our knowledge this is the first intermolecular example of this type of gold-catalyzed cascade process.

Results and Discussion

To test our proposal we started our investigation using 2-vinylindole **1a** and propargylic esters **2a** or **2b** in a model reaction in order to evaluate the activity of various gold species. The obtained results are summarized in Table 1.

At the outset, we selected as catalysts [Au(IPr)(SbF_6)(CH_3CN)] and [Au(JohnPhos)(NTf_2)] on the basis of the results obtained in the cycloaddition reaction between 2-vinylindoles and *N*-allenamides.[14b] However, under these conditions the reaction failed to give the desired compounds and vinylindole **1a** was recovered beside small amounts of the rearranged propargylic ester **2a** (entries 1 and 2). On moving to a more electrophilic gold(I) phosphite such as cationic tris(2,4-di-*tert*-butylphenyl)phosphite gold(I) generated *in situ* by chloride abstraction with silver triflimide, tetrahydrocarbazole **3a** was isolated in 31% as single diasteroisomer (entry 3). By increasing the amount of **2a** to 1.5 equivalents, the reaction yield was improved to 52% (entry 4). We next investigated the role of the counterions derived from the silver salts (entries 5–7).[17] In all cases tested the

Table 1. Screening of reaction conditions for the synthesis of **3a** and **3b**.[a]

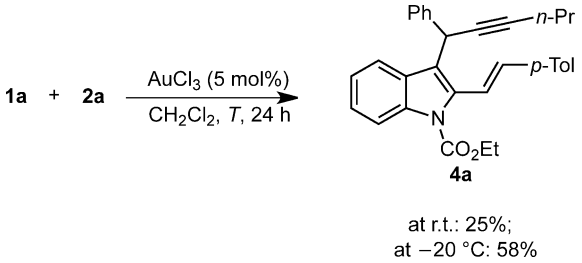


Entry	**2**, equiv.	Catalyst	*T* [°C]	*t* [h]	Yield[b]
1	**2a**, 1.1	[Au(IPr)(SbF_6)]	r.t.	24	–[c]
2	**2a**, 1.1	[Au(JohnPhos)(NTf_2)]	−20	24	–[c]
3	**2a**, 1.1	[AuP($ArO)_3$Cl]/$AgNTf_2$	−20	24	31%
4	**2a**, 1.5	[AuP($ArO)_3$Cl]/$AgNTf_2$	−20	24	52%
5	**2a**, 1.5	[AuP($ArO)_3$Cl]/$AgSbF_6$	−20	24	39%
6	**2a**, 1.5	[AuP($ArO)_3$Cl]AgOTf	−20	24	15%
7	**2a**, 1.5	[AuP($ArO)_3$OTFA]	−20	24	–[c]
8	**2a**, 1.5	[AuP($ArO)_3$Cl]/$AgNTf_2$	−35	24	64%
9	**2a**, 2.0	[AuP($ArO)_3$Cl]/$AgNTf_2$	−35	24	57%
10	**2b**, 1.5	[AuP($ArO)_3$Cl]/$AgNTf_2$	−35	5	75%
11	**2b**, 1.5	$AgNTf_2$	−35	24	–[c]
12	**2a**, 1.5	[$PtCl_2(C_2H_4)]_2$	−20	24	–[c]

[a] *Reaction conditions:* catalyst (5 mol%), 2-vinylindole (1.0 equiv.), propargylic ester (1.1–2 equiv.) in CH_2Cl_2 (0.1 M).
[b] Isolated yield.
[c] 2-Vinylindole **1a** was recovered unreacted after 24 h. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; JohnPhos = (2-biphenyl)di-*tert*-butylphosphine; Ar = 2,4-di-*tert*-butylphenyl.

yields were lower than in the presence of triflimide. In particular, when using less coordinating species such as hexafluoroantimonate and triflate, the product **3a** was isolated in 39% and 15% yield, respectively, (entries 5 and 6). The strongly coordinating trifluoroacetate proved to be totally ineffective (entry 7). A further improvement in the yield of **3a** was then obtained by decreasing the reaction temperature down to −35 °C (entry 8), while the use of even larger amounts of **2a** (2.0 equivalents) did not affect the yield (entry 9). Not only propargylic acetate **2a** but also the corresponding pivalate **2b** was tested. In particular, the use of this bulkier carboxylate at −35 °C was favorable for the course of the reaction, yielding **3b** in a satisfactory 75% yield in a reduced reaction time (entry 10). In order to exclude catalysis by silver(I) salts, we reacted **1a** and **2b** in the presence of $AgNTf_2$ but formation of **3a** was not detected after 24 h (entry 11). In addition we tested the activity of a Pt(II) species and also in this case **3a** was not observed (entry 12).[18]

The structure of tetrahydrocarbazole **3a**, showing a relative *trans* configuration of substituents at positions 3 and 5 and a *cis* configuration at the exocyclic



Scheme 4. Effect of $AuCl_3$ in the reaction between **1a** and **2a**.

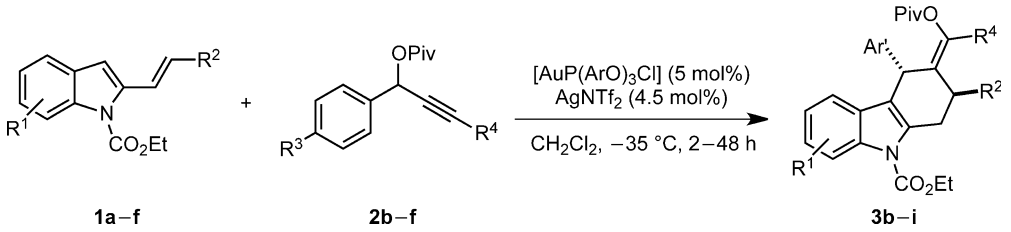
double bond, was assigned on the base of 2D-NMR analysis (see the Supporting Information).

Besides cationic gold(I) catalysts, also the activity of gold(III) chloride[19] was tested (Scheme 4) as it was effective in catalyzing the cycloaddition of 2-vinylindoles **1** with allenamides.[14b] However, the reaction of **1a** and **2a** in the presence of 5 mol% of $AuCl_3$ afforded the substituted indole **4a**, arising from nucleophilic substitution on propargylic acetate **2a**. Also in this case the decrease of the temperature to −20 °C produced a higher yield of the isolated product.

According to the screening, the reaction conditions reported in Table 1, entry 10 were selected to study the scope of the present transformation. The obtained results are summarized in Table 2.

In Table 2, entry 1 reports the best result for the cycloaddition reaction of **1a** with **2b**, obtained during the reaction conditions screening (see Table 1). Arenes bearing both electron-donating or electron-withdrawing groups were well tolerated as R^2 substituents in the vinylindole yielding compounds **3c** and **3d** in 72% and 79% yields, respectively (entries 2 and 3). Similarly, alkyl-substituted 2-vinylindole **1d** led to the formation of the tetrahydrocarbazole **3e** in 86% yield (entry 4). The substitution on the indole ring ($R^1 \neq H$) was more problematic. We observed in fact that the introduction of a methoxy group, like in vinylindoles **1e** and **1f**, was tolerated only in the C-6 position. For instance, 2-vinylindole **1e** afforded the corresponding carbazole **3f** in good yield (entry 5). On the contrary, C-5 substituted **1f** was not converted to any product and was completely recovered after 24 h (entry 6). Modifications of the propargylic esters were also probed. Thus, the electronic properties of the aryl group R^3 were modified by the introduction of EWG and EDG. Good results were obtained in the presence of fluorine (**2c**) or methyl (**2d**) substituents and the corresponding products **3g** and **3h** were isolated in 65% and 70% yields, respectively (entries 7 and 8). Instead a strong EDG, such as methoxy (**2e**), was not tolerated. In this case unreacted 2-vinylindole **1a** was quantitatively recovered (entry 9). Finally we verified that primary alkyl groups are the best R^4 substituents. A secondary alkyl chain such as isopropyl (**2f**) totally inhibits the reaction, while ter-

Table 2. Scope of the reaction between 2-vinylindoles **1** and propargylic esters **2** under gold(I) catalysis.[a]



1a–f **2b–f** **3b–i**

Entry	**1**	R^1	R^2	**2**	R^3	R^4	*t* [h]	**3**	Yield[b]
1	**1a**	H	4-Me-C_6H_4	**2b**	H	*n*-Pr	5	**3b**	75%
2	**1b**	H	4-MeO-C_6H_4	**2b**	H	*n*-Pr	2	**3c**	72%
3	**1c**	H	4-F-C_6H_4	**2b**	H	*n*-Pr	24	**3d**	79%
4	**1d**	H	Me	**2b**	H	*n*-Pr	21	**3e**	86%
5	**1e**	6-MeO	4-Me-C_6H_4	**2b**	H	*n*-Pr	23	**3f**	70%
6	**1f**	5-MeO	4-Me-C_6H_4	**2b**	H	*n*-Pr	24	–	–[c]
7	**1a**	H	4-Me-C_6H_4	**2c**	4-F	*n*-Pr	3	**3g**	65%
8	**1a**	H	4-Me-C_6H_4	**2d**	Me	*n*-Pr	4	**3h**	70%
9	**1a**	H	4-Me-C_6H_4	**2e**	MeO	*n*-Pr	24	–	–[c]
10	**1a**	H	4-Me-C_6H_4	**2f**	H	*i*Pr	48	–	–[c]
11	**1a**	H	4-Me-C_6H_4	**2g**	H	H	24	**3i**	35%[d]

[a] *Reaction conditions:* gold catalyst (5 mol%), $AgNTf_2$ (4.5 mol%), 2-vinylindole (1.0 equiv.), propargylic ester (1.5 equiv.) in CH_2Cl_2 (0.1 M).
[b] Isolated yield.
[c] Starting vinylindole was quantitatively recovered beside a mixture of unidentified products probably arising from decomposition of the allene intermediate.
[d] Besides a mixture of unidentified products. Ar = 2,4-di-*tert*-butylphenyl.

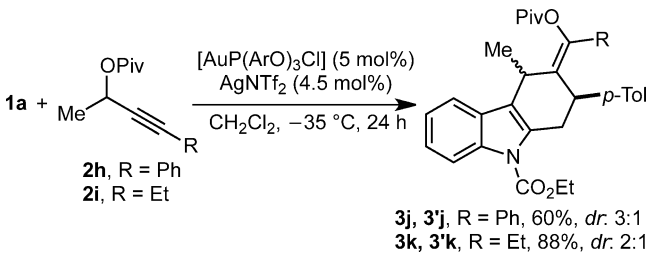
minal alkyne (**2g**) gave rise to carbazole **3i** in modest 35% yield (entries 10 and 11).

Further investigations pointed out the strong influence of the propargylic ester substituents on the stereoselectivity of the reaction.

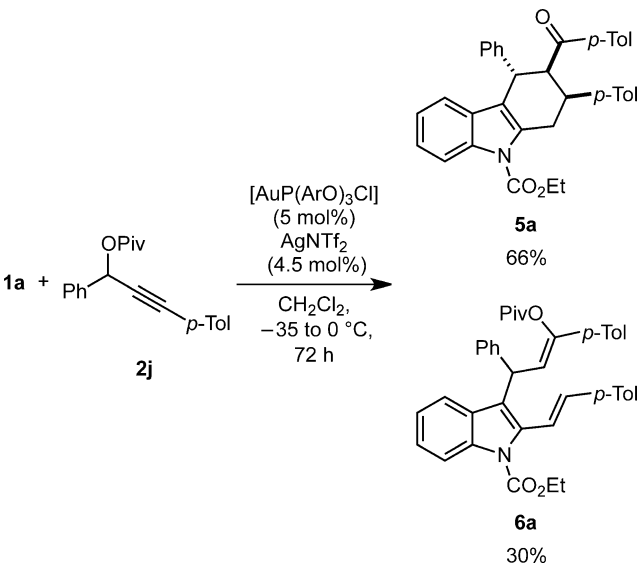
As reported in Scheme 5, when a methyl group is introduced at the propargylic position (**2h** and **2i** in Scheme 5), the reaction proceeded with good yields but the corresponding tetrahydrocarbazoles were obtained as a mixture of diasteroisomers.

Furthermore, we also evaluated the behavior of propargylic ester **2j** bearing aryl substituents both in the propargylic and alkyne positions. In this case the reaction was extremely slow and the expected tetrahydrocarbazole **3** was not observed. Instead, we isolated the corresponding hydrolyzed product **5a** and the hydroarylated indole **6a** in good combined yield (96%, **5a**:**6a** = 2:1) (Scheme 6). It is worth mentioning that, despite of compound **5a** having three consecutive stereocenters, one of them being enolizable, it was isolated as a single diasteroisomer.

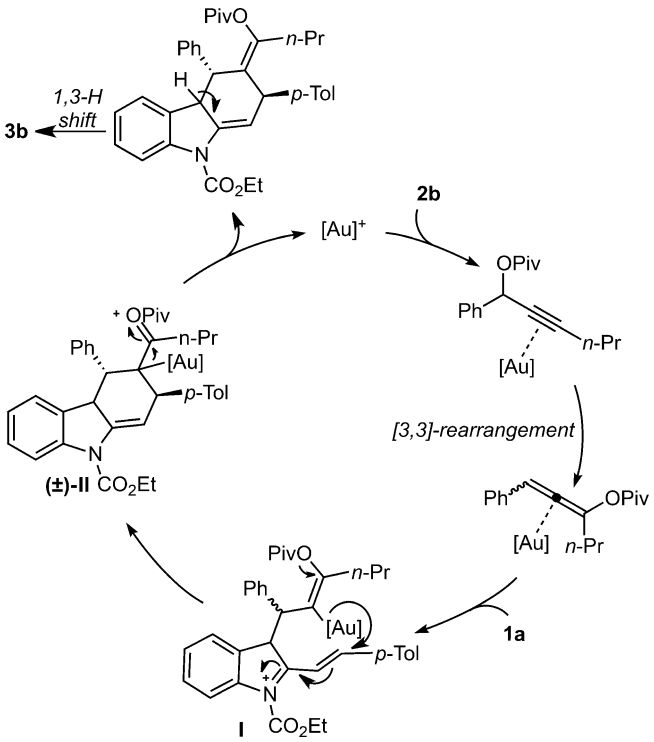
Based on previous reports,[20] the mechanism that we propose for the formation of tetrahydrocarbazoles **3a–i** is reported in Scheme 7 using **3b** as a model compound. Activation of the propargylic ester by the cat-



Scheme 5. Reactions between **1a** and propargylic esters **2h** and **2i**.

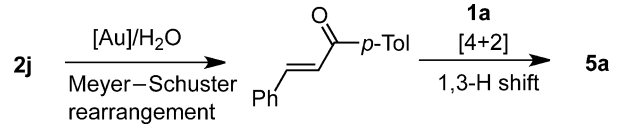


Scheme 6. Reaction between **1a** and propargylic ester **2j**.

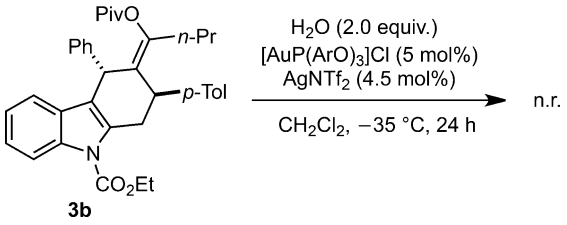


Scheme 7. Proposed reaction mechanism.

ionic gold(I) catalyst triggered the [3,3]-sigmatropic rearrangement leading to the corresponding gold-activated allene. This species, in equilibrium with oxonium resonance forms,[21] reacted with 2-vinylindole **1a** to give intermediate **I**. Subsequent cyclization led to carbazole (±)-**II** with complete *trans* diasteroselectivity, probably owing to a constrained arrangement between *p*-tolyl and phenyl groups during the cyclization step. Final elimination of $[Au]^+$ and 1,3-H shift afforded product **3b** and regenerated the catalytic species. The lack of diasteroselection observed in the reaction with propargyl esters **2h** and **2i** is probably related to a less constrained arrangement of the substituents in intermediate **I**. On the other side, in the case of propargylic ester **2j**, we supposed the cyclization step leading to (±)-**II** was slower. Thus, we assumed aromatization and protodeauration of intermediate **I** to form **6a**. Moreover, compound **5a** could arise from a hydrolytic process[22] involving **2j** and affording an α,β-unsaturated carbonyl compound, *via* a Meyer–Schuster rearrangement,[23] able to undergo a gold-catalyzed intramolecular diastereoselective cycloaddition reaction (Scheme 8).[14a] A potential hydrolysis of the final tetrahydrocarbazole in the reaction medium cannot be ruled out, but, in our opinion, it is unlikely because when we reacted **3b** in the presence of 2 equivalents of water, under standard reaction conditions, no product arising from hydrolytic processes was observed (Scheme 9).



Scheme 8. Plausible mechanism for the formation of **5a**.



Scheme 9. Reaction of **3b** in the presence of Au(I) and water.

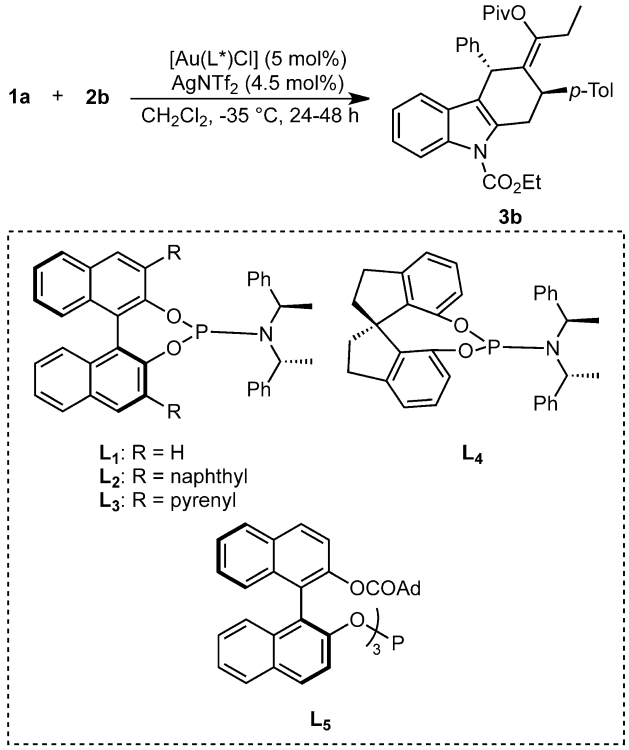
As a final study, we decided also to test the proposed cascade reaction in the presence of chiral gold(I) catalysts. In particular, we selected gold phosphoroamidites or phosphites considering the excellent results recently reported with these monodentate ligands in closely related transformations.[24] A preliminary screening of the reaction conditions is summarized in Table 3.

At the outset, we observed that a gold(I) catalyst bearing a BINOL-derived phosphoramidite $\mathbf{L_1}$ was efficiently catalyzing the reaction but with a poor enantiomeric ratio of 40:60 (entry 1). The introduction of bulky aromatic rings at the C3,C′3 position of BINOL ligands ($\mathbf{L_2}$ and $\mathbf{L_3}$) improved the enantioselectivity up to *e.r.* of 81:19, but was associated with lower yields and prolonged reaction times (entries 2 and 3). Spirobiindane ligand $\mathbf{L_4}$ was confirming this tendency to produce good *e.r.* of 86:14 but in 48 h and in a modest 37% yield. Interestingly, the addition of 4 Å molecular sieves to the reaction mixture allowed for the synthesis of **3b** in 62% yield, with similar enantioselectivity (entries 4 and 5). Finally we tested also a chiral phosphite ligand $\mathbf{L_5}$, which revealed to be the poorest catalyst both in terms of yield and enantioselection (entry 6).

Conclusions

In conclusion, we have reported an unprecedented intermolecular gold(I)-catalyzed cascade reaction for the synthesis of highly functionalized tetrahydrocarbazoles from 2-vinylindoles and propargylic esters. Whereas the [3,3]-rearrangement of propargylic esters and their subsequent intramolecular reactions with electrophilic double bonds are well documented in the literature, their intermolecular reactivities are less well described. This method is involving a [3,3]-propargylic rearrangement followed by a formal [4+2] cy-

Table 3. Reaction between **1a** and **2b** in the presence of chiral gold(I) catalysts.[a]



Entry	L*	Additive	*t*, [h]	Yield[b]	*e.r.*[c]
1	L_1	-	24	90%	40:60
2	L_2	-	24	42%	80:20
3	L_3	-	48	47%	81:19
4	L_4	-	48	42%	84:16
5	L_4	4 Å MS	48	62%	85:15
6	L_5	-	24	33%	57:43

[a] *Reaction conditions:* gold catalyst (5 mol%), $AgNTf_2$ (4.5 mol%), 2-vinylindole (1.0 equiv.) in CH_2Cl_2 (0.1 M).
[b] Isolated yield.
[c] Measured by HPLC of isolated **3b**.

cloaddition and represents a complementary approach for the preparation of this relevant class of heterocycles. The reaction showed quite a broad scope and very good diasteroselectivity. Moreover, the results reported in this study demonstrate once again the usefulness of easily achievable 2-vinylindoles as valuable scaffolds for the synthesis of more complex and intriguing compounds. A preliminary screening with chiral phosphoramidites ligands has revealed also the possibility of an asymmetric version of this transformation with good enantiomeric ratios. Further studies for improving the enantioselectivity, as well as, for the search of new gold-catalyzed cascade reactions involving vinyl heteroaromatics as substrates are in progress in our laboratories.

Experimental Section

Typical Procedure for the Synthesis of Tetrahydrocarbazoles 3

To a solution of $[AuP(ArO)_3Cl]$ (0.01 mmol, 5.0 mol%) and $AgNTf_2$ (0.009 mmol, 4.5 mol%) in CH_2Cl_2 (1 mL), 2-vinylindole **1a–f** (0.2 mmol, 1.0 equiv.) was added and the mixture was cooled to −35 °C. Then, a solution of propargylic ester **2a–j** (0.3 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL, final concentration *ca.* 0.1 M) was added and the reaction mixture was stirred at the same temperature until disappearance of the starting materials (checked by TLC). The reaction was quenched with PPh_3 (0.03 mmol, 15 mol%) and the solvent was removed under vacuum. Purification by column chromatography (SiO_2, hexane/ethyl acetate 95:5 to 90:10) yielded the corresponding tetrahydrocarbazole **3a–k**.

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