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(Triphenyl phosphite)gold(I)-Catalyzed Intermolecular Hydroamination of Alkenes and 1,3-Dienes[†]

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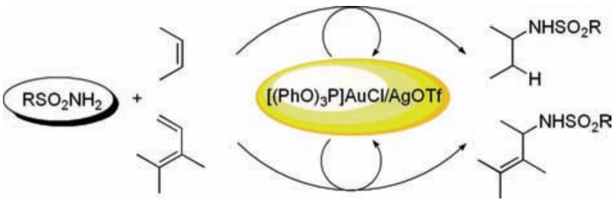
ABSTRACT



Intermolecular addition of different sulfonamides to alkenes and conjugated dienes can be carried out using a low loading of (triphenyl phosphite)gold(I) chloride and silver triflate as a catalytic mixture. The reaction can be performed under conventional thermal or microwave conditions and at rt in the case of dienes. Terminal alkenes undergo regioselective hydroamination at the internal carbon atom and dienes at the less substituted double bond.

Acid- and metal-promoted hydroamination of alkenes (AHA) is a general and atom-economical method for the synthesis of amines or derivatives.[1] Intramolecular hydroaminations are faster and more general than intermolecular processes. In the last case, the regioselectivity is difficult to control, not only for alkenes but also for 1,3-dienes, which can afford 1,2- and 1,4-addition products. Recently, TfOH,[2] (Ph$_3$P)AuCl/AgOTf,[3] [PtCl$_2$(CH$_2$═CH$_2$)]$_2$,[4] Cu(OTf)$_2$/dppe,[5] and Bi(OTf)$_3$/[Cu(CH$_3$CN)$_4$]PF$_6$[6] have been reported as catalysts for the addition of sulfonamides to alkenes[2,3a,c,4] and to 1,3-dienes.[2,3b,5,6] The gold(I)[7] complex (Ph$_3$P)AuCl/AgOTf has been used for the intermolecular hydroamination of alkenes and dienes.[3] However, metal-catalyzed intermolecular AHA required high loadings, generally 5−10 mol %. In the presence of triflic acid, a low loading (1 mol %) can be used as efficient catalyst, although regioisomeric mixtures and hydrovinylation products due to cationic intermediates are formed.[2] Therefore, a more efficient catalyst should be developed for the hydroamination of alkenes and dienes.

We envisaged that the use of stronger electron-withdrawing ligands would increase the interaction of the LAu$^+$ with the C−C double bond and consequently a greater catalytic activity. Here, we report that the simple (triphenyl phosphite)gold(I) chloride[8]/AgOTf can be used as a very efficient

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[†] Dedicated to Professor E. J. Corey on occasion of his 80th birthday.

(1) Recent reviews: (a) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. (b) Hultzsch, K. C. *Org. Biomol. Chem* **2005**, *3*, 1819–1824. (c) Roesky, P. W.; Müller, T. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 2708–2710. (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–704.

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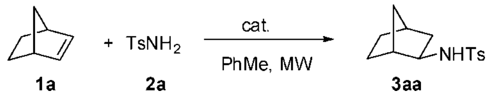
and general catalyst for the addition of sulfonamides to alkenes and dienes.

Preliminary studies about the catalytic activity of different gold(I) chloride complexes and AgOTf were screened for the addition of *p*-toluenesulfonamide ($TsNH_2$, **2a**) to norbornene (**1a**) in toluene under microwave heating (Table 1).

Table 1. Catalysts Studies for the Addition of $TsNH_2$ to Norbornene[a]



entry	cat. (mol %)	*T* (°C)	time (min)	convn[b] qa(%)
1	(Me_2S)AuCl/AgOTf (5)	90	30	96
2	(Ph_3P)AuCl/AgOTf (5)	85	15	99 (92)
3	(Ph_3P)AuCl/AgOTf (0.1)	90	30	58
4	[$(BTFP)_3P$]AuCl/AgOTf (5)	85	15	99
5	[$(PhO)_3P$]AuCl/AgOTf (5)	85	15	99
6	[$(PhO)_3P$]AuCl/AgOTf (1)	90	30	99
7	[$(PhO)_3P$]AuCl/AgOTf (0.1)	90	30	99
8	[$(PhO)_3P$]AuCl/AgOTf (0.05)	90	30	94 (90)
9	[$(PhO)_3P$]AuCl/AgOTf (0.01)	90	30	60
10	HOTf (0.1)	90	30	8

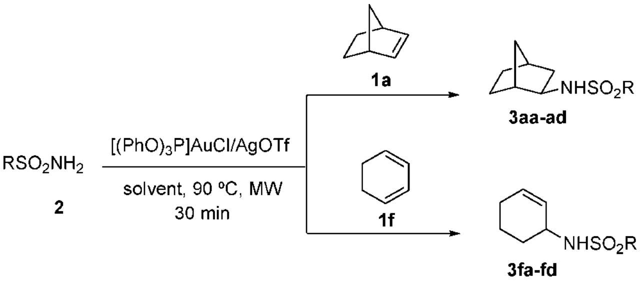
[a] Reactions were performed with $TsNH_2$ (171 mg, 1 mmol), norbornene (376 mg, 4 mmol), and catalyst (see column) in dry toluene (2 mL) under Ar in a microwave reactor (70 W, 10 psi) with air stream cooling. [b] Determined by GC, based on $TsNH_2$. The isolated yield after flash chromatography is shown in parentheses.

In the presence of the commonly used (Me_2S)AuCl/AgOTf and (Ph_3P)AuCl/AgOTf, the reaction took place in 30 and 15 min, respectively, affording *exo*-**3aa** in high yields, using 5 mol % loading (Table 1, entry 1 and 2). However, when the loading of the last catalyst was lowered to 0.1 mol %, only 58% conversion was observed at 90 °C after 30 min irradiation (Table 1, entry 3). The mixture of the gold(I) chloride complex formed with the strong electron-withdrawing tris[3,5-bis(trifluoromethyl)phenyl]phosphine [$(BTFP)_3P$][9] and AgOTf provided full conversion under the same reaction conditions (Table 1, compare entries 2 and 4).

Then, the gold(I) complex [$(PhO)_3P$]AuCl[8,10,11] derived from the inexpensive ligand triphenyl phosphite, which shows strong electron-withdrawing ability and is also an strong π-acceptor phosphorus ligand, was assayed. A 1:1 mixture of this complex and AgOTf[11] gave excellent conversions under different loadings, such as 5, 1, 0.1, and 0.05 mol % (Table 1, entries 5−8). However, when the amount of catalyst was decreased to 0.01 mol %, only 60% conversion was observed (Table 1, entry 9). For comparison, using TfOH (0.1 mol %) under the same reaction conditions gave a very low conversion (Table 1, compare entries 7 and 10).

The performance of [$(PhO)_3P$]AuCl/AgOTf as catalyst under the optimized reaction conditions was subsequently examined with norbornene (**1a**) and cyclohexa-1,3-diene (**1f**) using different nucleophiles (Table 2). Thus, hydroamination of norbornene with electron-rich 4-methyl- and 4-methoxybenzenesulfonamide gave rise to full conversion (Table 2, entries 1 and 2), whereas in the case of 4-nitrobenzenesulfonamide the reaction failed (Table 2, entry 3). The addition of methanesulfonamide was performed in dioxane due to solubility problems in toluene, affording product **3ad** in good yield (Table 2, entry 4). The hydroamination of cyclohexa-1,3-diene (**1f**) was performed with electron-rich 4-methyl- and 4-methoxybenzenesulfonamide with 1 mol % loading of catalysts affording products **3fa** and **3fb**, respectively, in good yields (Table 2, entries 5 and 6). In the case of methanesulfonamide, a 5 mol % loading of catalysts in dioxane was used, giving product **3fd** in good yield (Table 2, entry 7).

Table 2. Hydroamination of Norbornene and Cyclohexa-1,3-diene with Different Sulfonamides Catalyzed by [$(PhO)_3P$]AuCl/AgOTf [a]



entry	cat. mol %	sulfonamide	solvent	no.	convn[b] (%)
1	0.05	$TsNH_2$	PhMe	**3aa**	94 (90)
2	0.1	$4\text{-}MeOC_6H_4SO_2NH_2$	PhMe	**3ab**	99 (96[c])
3	5	$4\text{-}NO_2C_6H_4SO_2NH_2$	PhMe	**3ac**	0
4	5	$MeSO_2NH_2$	dioxane	**3ad**	98 (65)
5	1	$TsNH_2$	PhMe	**3fa**	66
6	1	$4\text{-}MeOC_6H_4SO_2NH_2$	dioxane	**3fb**	− (77)
7	5	$MeSO_2NH_2$	dioxane	**3fd**	85 (65)

[a] Reactions were performed with sulfonamide (1 mmol), diene (4 mmol), catalyst (see column) in dry solvent (2 mL) under Ar in a microwave reactor (70 W, 10 psi) with air stream cooling. [b] Determined by GC, based on sulfonamide. In parenthesis isolated yield after flash chromatography. [c] After recrystallization from hexane/EtOAc.

The study about the scope of this hydroamination reaction was carried out with different alkenes and dienes and $TsNH_2$ (**1a**) as nucleophile using [$(PhO)_3P$]AuCl/AgOTf as catalyst (Table 3). Norbornene gave product **3aa** with full conversion working also under thermal (14 h) or microwave (MW) (30 min) conditions with 0.05 mol % loading of catalyst (Table 3, entries 1 and 2). The same reaction catalyzed by (Ph_3P)AuCl/AgOTf needed a 5 mol % loading.[3a] In the case of cyclohexene and cyclooctene, the corresponding products

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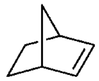
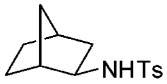
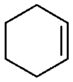
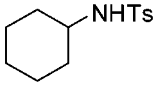
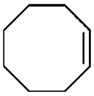
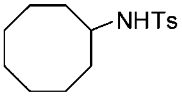
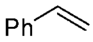
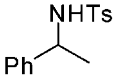
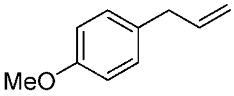
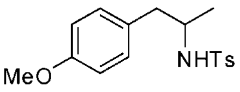
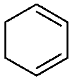
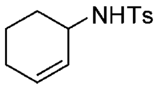
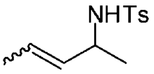
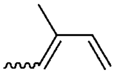
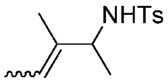
(10) [$(PhO)_3P$]AuCl/$AgSbF_6$ has been recently used as catalyst for the intramolecular hydroarylation of allenes: (a) Tarselli, M. A.; Gagné, M. R. *J. Org. Chem.* **2008**, *73*, 2439–2441.

(11) Kowala, C.; Swan, J. M. *Aust. J. Chem.* **1966**, *19*, 547–554.

Table 3. Hydroamination of Akenes and Dienes with $TsNH_2$ Catalyzed by $[(PhO)_3P]AuCl/AgOTf$ [a]

entry	alkene or diene	no.	solvent	cat. mol %	temp (°C)	time	product	no.	convn (%)[b]	Z/E[c]
1		**1a**	PhMe	0.05	85	14 h		**3aa**	99	-
2		**1a**	PhMe	0.05	90	30 min[d]		**3aa**	94 (90)	-
3		**1b**	PhMe	2	85	24 h		**3ba**	84 (64)	-
4		**1c**	PhMe	1	85	24 h		**3ca**	98 (75)	-
5		**1d**	PhMe	5	85	14 h		**3da**	61	-
6		**1d**	PhMe	5	90	30 min[d]		**3da**	78 (66)	-
7		**1e**	PhMe	5	85	24 h		**3ea**	99[e]	-
8		**1e**	PhMe	5	90	30 min[d]		**3ea**	95[e] (91)[e]	-
9		**1e**	PhMe	5[f]	90	30 min[d]		**3ea**	97[g] (75)[g]	-
10		**1f**	PhMe	0.1	85	14 h		**3fa**	68	-
11		**1f**	PhMe	0.1	90	20 min[d]		**3fa**	66	-
12		**1f**	CH_2Cl_2	1	25	24 h		**3fa**	99 (90)	-
13		**1g**[h]	PhMe	0.1	85	14 h		**3ga**	85	1/5
14		**1g**[h]	PhMe	0.1	90	30 min[d]		**3ga**	97 (85)	1/7
15		**1g**[h]	CH_2Cl_2	1	25	24 h		**3ga**	99 (65)	1/16
16		**1h**[i]	PhMe	0.1	85	14 h		**3ha**	98 (77)	1/6
17		**1h**[i]	PhMe	0.1[f]	85	14 h		**3ha**	21	1/49
18		**1h**[i]	PhMe	0.1	90	30 min[d]		**3ha**	84 (71)	1/6
19		**1h**[i]	PhMe	0.1[f]	90	30 min[d]		**3ha**	51	1/21
20		**1h**[i]	CH_2Cl_2	1	25	24 h		**3ha**	99 (86)	1/49
21		**1h**[i]	CH_2Cl_2	1[f]	25	24 h		**3ha**	93	1/49

[a] Reactions were performed with $TsNH_2$ (171 mg, 1 mmol), alkene or diene (4 mmol), and $[(PhO)_3P]AuCl/AgOTf$ (see column) in dry solvent (2 mL) under normal or MW heating and Ar atmosphere. [b] Determined by GC based on $TsNH_2$. The isolated yield after flash chromatography is shown in parentheses. [c] Relative ratio determined by ^1H NMR over the crude reaction mixture. [d] Under microwave heating (70 W, 10 psi) with air stream cooling. [e] A 10/1 mixture (determined by NMR) of compound **3ea** and the regioisomer *N*-[1-(4-methoxyphenyl)propyl]-4-toluenesulfonamide was obtained. [f] The reaction was performed with HOTf. [g] A 4/1 mixture (determined by NMR) of compound **3ea** and the regioisomer *N*-[1-(4-methoxyphenyl)propyl]-4-toluenesulfonamide was obtained. [h] *Z*/*E*: 1/1.8. [i] *Z*/*E*: 1/2.5.

3ba and **3ca** could only be obtained in good yields using conventional heating (85 °C) and a higher catalyst loading (Table 3, entries 3 and 4). When using styrene, the addition took place regioselectively, giving product **3da** in better yield under MW than under conventional heating (Table 3, entries 5 and 6). Regioselective addition to 1-allyl-4-methoxybenzene (**1e**) was also observed affording a 10/1 mixture of product **3ea** and *N*-[1-(4-methoxyphenyl) propyl]-4-toluenesulfonamide in good yields under both type of heating (Table 3, entries 7 and 8). The triflic acid catalyzed hydroamination of **1e** gave a 4/1 mixture of regioisomers in 75% isolated yield (Table 3, compare entries 8 and 9).

Conjugated dienes showed a higher reactivity than simple alkenes, the reaction being performed also at rt in CH_2Cl_2 as solvent. Thus, cyclohexa-1,3-diene gave product **3fa** in moderate yields under heating with only 0.1 mol % of gold(I) catalyst. However, at rt, the corresponding product was obtained in 90% yield after 1 d at rt with 1 mol % loading of catalyst (Table 3, entries 10−12). In the case of penta-1,3-diene (**1g**), which was purchased as a *Z*/*E* 1/1.8 diasteromer mixture, reacted with $TsNH_2$ in good yields providing regioselectively product **3ga** as mixture of diasteromers in a different ratio than the starting diene **1g** (Table 3, entries 13−15). Similar results were obtained with 3-methylpenta-1,3-diene (**1h**, *Z*/*E*: 1/2.5), which provided product **3ha** predominatly as *E*-diastereomers (Table 3, entries 16, 18, and 20). The highest *E*/*Z* ratio for acyclic dienes resulted at rt, products **3ga** and **3ha** being obtained in 16/1 and 49/1 ratios, respectively. Product **3ha** has been prepared previously using 5-fold of $(Ph_3P)AuCl/AgOTf$ (5 mol %).[3b]

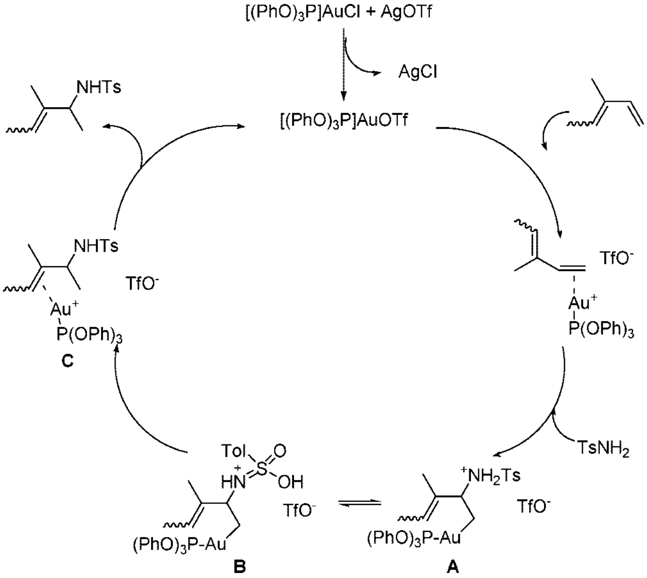
When the same reactions were performed using HOTf as catalyst, lower conversions were obtained under thermal conditions and similar results at rt (Table 3, entries 17, 19, and 21). The isomerization of the trisubstituted double bond was studied by NMR in the presence of the gold catalyst and in a paralell experiment with HOTf. After 1 h in $CDCl_3$, diene **1h** gave a 1/1 and 2/98 *E*/*Z* mixture with gold and HOTf, respectively. This means that the gold(I) complex was able to isomerize the double C−C bond. The presence of HOTf in the solution of $[(PhO)_3P]AuCl/AgOTf$ in $CDCl_3$ was not detected by ^{19}F NMR.

The formation of $[(PhO)_3P]Au^+(CH_3CN)$ ($m/z = 548$) by reaction of $[(PhO)_3P]AuCl$ and AgOTf in acetonitrile, was detected by ESI-MS. As has been proposed from calculations,[12] the interaction between the $[(PhO)_3P]Au^+$ cation and the TfO^- anion is very weak, which would therefore facilitate its substitution by the corresponding alkene or diene. From ^{31}P NMR studies it was observed that the ^{31}P signal of $[(PhO)_3P]AuCl$ at δ 109.93 was moved upfield at δ 95.11 in the case of the possible formation of $[(PhO)_3P]AuOTf$ due to the higher ionic character of the last complex. When the *Z*/*E* mixture of 3-methylpenta-1,3-diene (**1h**) was added to the $CDCl_3$ solution of $[(PhO)_3P]AuOTf$, the signal was moved downfield to δ 104.92, indicating the coordination of the diene to gold(I). In the case of the ^{13}C NMR studies of the supposed complex between the diene **1h** and gold(I), the signal intensity in the starting diene of the terminal CH_2 at δ 110.02 (*E*) and 112.97 (*Z*) diminished. This was probably due to the coordination of the terminal C−C double bond to gold(I). This coordination has been recently proposed by DFT calculations for the hydroamination reaction of **1h** with $CbzNH_2$.[12]

A plausible mechanism for the hydroamination of 1,3-dienes, which is in accordance with the proposal by Ujaque et al.,[12] is depicted in Scheme 1. After coordination of the diene to gold(I), the attack of the sulfonamide would give intermediates **A** and **B**. The regioselective nucleophile attack to the most coordinated double bond would give intermediate **A**, which can be in tautomeric equilibrium with **B** assisted by the triflate anion, as proposed by calculations for the benzyl carbamate addition.[12] When aniline, a nucleophile enable to participate in this tautomeric equilibrium, was allowed to react with **1h** under MW heating or at rt, the reaction failed. A direct proton transfer from N to the C atom has a high energy barrier according to these theoretical studies. After proton transfer to the C atom, intermediate **C** would be formed, and final decoordination would provide the product and regenerate the catalyst.

In conclusion, the studies described above demonstrate that $[(PhO)_3P]AuCl/AgOTf$ is a more efficient catalyst than HOTf or $(Ph_3P)AuCl/AgOTf$ for the intermolecular regioselective hydroamination of alkenes and dienes with different types of sulfonamides. The process can be performed with low catalyst loading in toluene as solvent either under conventional thermal conditions or under MW heating, in shorter reaction times, except for some cyclic alkenes. In addition, the reaction can also be performed at rt for 1,3-dienes.

Scheme 1. Proposed Reaction Mechanism for the Hydroamination of Diene **1h**



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Supporting Information Available: . Experimental procedure and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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