ORGANIC LETTERS

2006
Vol. 8, No. 13
2707−2710

Phosphine Gold(I)-Catalyzed Hydroamination of Alkenes under Thermal and Microwave-Assisted Conditions

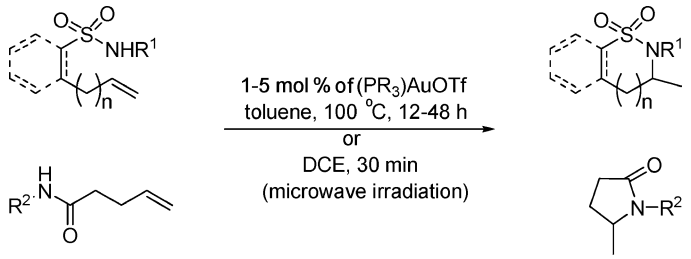
Xin-Yuan Liu, Cheng-Hui Li, and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

cmche@hku.hk

Received March 24, 2006

ABSTRACT



Phosphine gold(I) complexes catalyzed isomerization of terminal alkenes and hydroamination of unactivated alkenes under thermal and microwave-assisted conditions. This is the first example of the use of microwave radiation as a heat source for gold(I)-catalyzed organic reactions.

Gold complexes have increasingly been used as catalysts in a variety of organic transformations.[1,2] While the majority of such transformations draw on the propensity of Au(I) to activate alkynes toward nucleophilic addition,[3] reactions involving nucleophilic addition to unactivated alkenes catalyzed by Au(I) are sparse.[4,5] The catalytic addition of an organic N−H bond to alkenes or alkynes (hydroamination) to give nitrogen-containing molecules is of great interest to both the academic and industrial community.[6] In the literature, most amines are made in multistep syntheses, and as

(1) For reviews of homogeneous gold-catalyzed reactions, see: (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (c) Hoffman-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990.

(2) (a) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 325. (b) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529.

(3) (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (b) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (c) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (d) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563. (e) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (f) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (g) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (h) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (i) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (j) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155. (k) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (l) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (m) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (n) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (o) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. For a specific review on the activation of alkynes by gold catalysts, see: (p) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3.

(4) (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (b) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319. (c) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884.

(5) (a) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744. (d) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

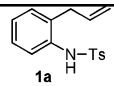
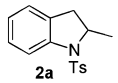
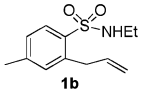
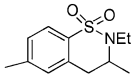
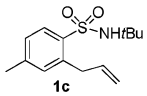
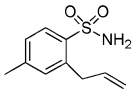
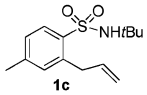
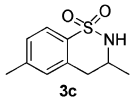
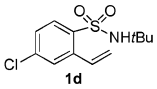
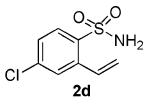
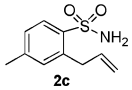
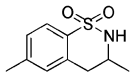
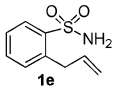
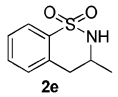
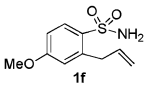
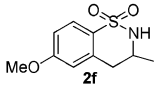
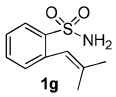
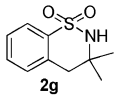
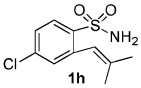
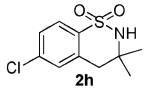
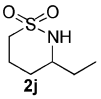
10.1021/ol060719x CCC: $33.50
Published on Web 06/03/2006

such, hydroamination offers an attractive alternative means to give organic nitrogen compounds. Addition of N−H bond to unactivated alkenes provides a pathway for N−C bond formation[6] and can be catalyzed under acidic conditions[7] or using Lewis acid metal catalysts that are likely to coordinate and activate the alkene toward nucleophilic addition.[8] However, most of the reported catalysts for hydroamination show limited scope of substrates, modest selectivity, and sluggish rates for reactions involving unactivated substrates, and in the case of palladium catalyst for hydroamination reaction, β-hydride elimination to afford unsaturated products is usually encountered as a side reaction.

Owing to the ability of Au(I) to activate alkenes,[5a] we conceived that Au(I) complexes could be potentially useful catalysts for intramolecular hydroamination of unactivated alkenes. During the preparation of this paper, He[5b,c] and Widenhoefer[5d] independently reported the utility of cationic Au^{I}−phosphine complexes as catalysts for hydroamination of unactivated alkenes, though the reported alkene substrates are different from those described in this work. However, the reported gold(I)-catalyzed hydroamination reactions require long reaction times that would be disadvantageous for its future application in high-throughput synthesis. We conceived that rapid and reliable microwave applications[9] could be advantageous for gold(I)-catalyzed intra- and intermolecular hydroamination of unactivated alkenes. Herein, we report gold(I)-catalyzed isomerization of terminal alkenes and highly efficient intra- and intermolecular hydroamination of unactivated alkenes under conventional thermal conditions as well as under microwave irradiation.

A study was performed to investigate the activity of different gold and AgOTf (OTf = trifluoromethane sulfonate) catalysts in the intramolecular hydroamination of tosylamide **1a** (Table 1, entry 1; see also Table S1 in Supporting Information). AgOTf, $(PPh_3)AuCl$, and $AuCl_3$/AgOTf all failed to give the desired product **2a** in good yields. While using a combination of 5 mol % of $(PPh_3)AuCl$ and AgOTf as a catalyst in toluene, the hydroamination product **2a** was formed in nearly quantitative yield. $[((PPh_3)Au)_3O]OTf$ and other $(PR_3)AuOTf$ catalysts can replace $(PPh_3)AuOTf$ as the catalyst with no significant decrease in product yield. Using 1 mol % of $(PCy_3)AuOTf$ or $Au_2(dcpm)(OTf)_2$ (dcpm = bis(dicyclohexylphosphino)methane), **2a** was exclusively formed after 36 h at 85 °C. However, $[(PPh_3)_2Au]^+$ or $[Au_2(dppm)_2]^{2+}$ (dppm = bis(diphenylphosphino)methane) did not show any catalytic activity under the same reaction condi-

Table 1. Intramolecular Hydroamination of Alkenes[a]

entry	substrate	T (°C)	time (h)	product	yield (%)[b]
1	 1a	80	12	 2a	99
2	 1b	100	24	 2b	95
3	 1c	60	12	 2c	90
4	 1c	100	48	 3c	99
5	 1d	60	12	 2d	100
6	 2c	100	48	 3c	99
7	 1e	100	48	 2e	95
8	 1f	100	48	 2f	99
9	 1g	100	12	 2g	99
10	 1h	100	12	 2h	99
11	 1i	100	72	 3i	95
12	 1j	100	48	 2j	88
13	 1k	100	72	 2k	95[c]

[a] In toluene, 5 mol % of $(PPh_3)AuCl$/AgOTf. [b] After column chromatography. [c] Yield was determined by ^1H NMR.

(6) For leading reviews, see: (a) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Nobis, M.; Drieβen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (e) Brunet, J.-J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: New York, 2001; p 91. (f) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795. (g) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (h) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935. (i) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (j) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367.

(7) (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471. (b) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

(8) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (b) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (d) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (e) Oe, Y.; Ohta, T.; Ito, Y. *Chem. Commun.* **2004**, 1620.

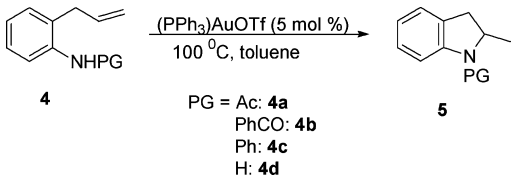
(9) (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (b) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653.

tions. Different solvents were screened, and toluene was found to be the best one.

Due to the therapeutic application of sulfonamide antibiotics,[10,11] we prepared a series of ortho-substituted benzenesulfonamides[12] as precursors for the preparation of cyclic sulfonamides (Table 1). When *N*-ethylbenzenesulfonamide **1b** was used as the substrate, the corresponding cyclic product **2b** was obtained in essentially quantitative yield at 100 °C for 24 h (entry 2). When *N*-*tert*-butylbenzenesulfonamide **1c** was heated in toluene at 60 °C in the presence of 5 mol % of $(PPh_3)AuOTf$, the *tert*-butyl group was cleaved (entry 3). Increasing the reaction temperature to 85 °C resulted in the formation of a 3:5 mixture of **2c** and **3c** with a total 99% yield. Hydroamination product **3c** was formed exclusively when the reaction temperature was increased to 100 °C and the reaction time was extended to 48 h (entry 4). When substrate **1d** was subjected to the same reaction conditions, the *tert*-butyl group was readily cleaved (entry 5). According to a previous report,[12] cleavage of the *tert*-butyl group in similar substrates was performed in the presence of anisole, and neat trifluoroacetic acid was used as the solvent. Here, the gold(I)-catalyzed cleavage of the *tert*-butyl group could be conducted under mild conditions.

We then examined the intramolecular hydroamination of *N*-unsubstituted sulfonamides. In the presence of 5 mol % of $(PPh_3)AuOTf$, a series of unsaturated sulfonamides **2c** and **1e**−**j** were found to readily undergo intramolecular hydroamination to give the corresponding products **3c** and **2e**−**j** in excellent yields (Table 1). In a number of cases, product yields were nearly quantitative (entries 6−10). Interestingly, substrates **1g** and **1h** bearing a bulky 2-methylpropenyl group were the most reactive and gave the corresponding products in 99% yield within 12 h (entries 9 and 10). When 2-vinylbenzenesulfonamide **2d** was used as the substrate, no reaction was observed. The substrate **1i**, which could form an unstable seven-membered ring intermediate or a six-membered ring through a stabilized cyclohexyl intermediate, gave a six-membered ring product **3i** along with the isomerized product **2i** (see Chart S1 in Supporting Information) in excellent yield within 24 h. Prolonged heating was necessary for the reaction to give **3i** as the only product (entry 11). When **1j** was used as the substrate, the six-membered ring product was formed exclusively in good yield (entry 12). The substrate **1k** failed to provide the hydroamination product, and the isomerized product **2k** was obtained instead. This could be due to steric hindrance on the terminal position of alkene and the instability of the five-membered intermediate (entry 13). On the basis of these results, migration of double bonds catalyzed by gold(I) occurred (entries 11−13). We extended this reaction to other nitrogen-containing molecules, such as acetamide (**4a**) and benzamide (**4b**), and aniline (**4c**), as well as free amine (**4d**); the reactions gave none or very low yields of the desired products (Scheme 1; see also Table S2 in Supporting Information).

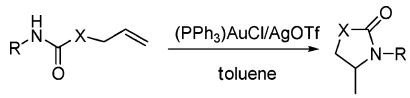
Scheme 1



4 PG = Ac: **4a**, PhCO: **4b**, Ph: **4c**, H: **4d** **5**

To elucidate the effect of electronic properties of the nitrogen and activating group on this reaction, we prepared benzamides **6a**−**e** as depicted in Table 2. Hashmi reported

Table 2. Intramolecular Hydroamination of Benzamides[a]



6 **7**

entry	substrate	R	X	*T* (°C)	time (h)	yield (%)[b]
1	**6a**	Ph	C	100	30	50
2[c]	**6a**	Ph	C	100	30	89
3[c]	**6b**	*p*-Cl−Ph	C	100	30	90
4[d]	**6c**	PhCO	C	100	30	60
5[d]	**6d**	Ts	C	60	24	40
6	**6e**	Ts	O	60	24	0[e]

[a] In toluene, 20 mol % of $(PPh_3)AuCl/AgOTf$. [b] Isolated yield. [c] In toluene, 100 mol % of $(PPh_3)AuCl/AgOTf$. [d] In toluene, 50 mol % of $(PPh_3)AuCl/AgOTf$. [e] *p*-Toluenesulfonamide was isolated.

conversion of propargylcarboxamides to 2,5-disubstituted oxazoles under mild reaction conditions via homogeneous catalysis by $AuCl_3$.[13] We found that substrate **6a** underwent conversion to cyclic product **7a** in 50% yield in the presence of 20 mol % of $(PPh_3)AuOTf$. When the reactions were conducted in the presence of a stoichiometric amount of $(PPh_3)AuOTf$, γ-lactams **7a** and **7b** were obtained in excellent yields (entries 2 and 3). When **6c** and **6d** were used as the substrates, the cyclic products were obtained in 60 and 40% yield, respectively, along with benzamide and *p*-toluenesulfonamide as byproducts (entries 4 and 5). According to previous reports,[7a,14] these substrates readily underwent cleavage of the amide bond under similar reaction conditions. The allyl alcohol-derived carbamate completely underwent cleavage of the amide bond to give the *p*-toluenesulfonamide (entry 6).

To shorten the reaction times, we subjected the reaction to microwave irradiation, which is known to accelerate transition metal-catalyzed homogeneous reactions.[9] Considerably shorter reaction times of less than 1 h were found for intramolecular hydroamination of unactivated alkenes cata-

(10) Bowman, W. C.; Rand, M. J. *Textbook of Pharmacology*, 2nd ed.; Blackwell: London, 1979; Chapter 34.
(11) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, 1996; Vols. 3 and 4.
(12) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327.
(13) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391.
(14) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622.

Table 3. Gold(I)-Catalyzed Intra- and Intermolecular Hydroamination under Microwave-Assisted Conditions[a]

entry	reactant A	reactant B	power (W)	time (min)	product (conversion)[b]	yield (%)[c]
1	**1a**	_	43	20	**2a** (86)	86
2	**1b**	_	43	40	**2b** (90)	90
3	**1g**	_	40	10	**2g** (100)	100
4	**1i**	_	43	40	**2i** and **3i** (95)	95(7:10)
5[d]	**6a**	_	43	30	**7a** (100)	57
6[d]	**6b**	_	43	30	**7b** (100)	60
7[d]	**6c**	_	43	30	**7c** (85)	60
8[e]	$TsNH_2$		43	40	**8a**[f] (90)	86(90)[g]
9[e]	TsNHEt		43	60	**8b**[f] (60)	50
10[e]	$TsNH_2$		30	40	**8c**[f] (50)	43(51)[g]
11[h]	$TsNH_2$		48	40	**8d**[f] (100)	95(89)[g]
12[h]			45	40	**8e**[f] (100)	93
13[h]			50	40	**8f**[f] (100)	97

[a] Reactions were conducted with 0.1 mmol of substrate and 5 mol % of $(PPh_3)AuCl/AgOTf$ in 1 mL of $ClCH_2CH_2Cl$ at 140 °C while being irradiated with microwave. [b] Conversion (%) was determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] Reactions were conducted with 0.1 mmol of substrate and 20 mol % of $(PCy_3)AuCl/AgOTf$ in 1 mL of $ClCH_2CH_2Cl$ at 140 °C while being irradiated with microwave. [e] Reactions were conducted with 0.1 mmol of $TsNH_2$, 0.4 mmol of alkenes, and 5 mol % of $(PPh_3)AuOTf$ in 1 mL of $ClCH_2CH_2Cl$ at 140 °C while being irradiated with microwave. [f] See Chart S1 in Supporting Information. [g] The yield in parentheses refers to a reaction performed under thermal conditions. [h] A 1:1 ratio of nucleophile and norbornene was used.

lyzed by gold(I) complexes, affording the corresponding products in good yields in each case (Table 3, entries 1−4). Using this procedure, benzamide derivatives (**6a**−**c**) were completely transformed, and the corresponding products were efficiently formed in moderate yields in the presence of 20 mol % of $(PCy_3)AuOTf$ within 30 min (Table 3, entries 5−7), while, for the same reactions under conventional thermal conditions, a stoichiometric amount of catalyst and a reaction time of 30 h were required (Table 2, entries 2−4). This result shows that gold(I)-catalyzed intramolecular hydroamination is efficient under microwave irradiation. We also examined the intermolecular hydroamination of unactivated alkenes under microwave irradiation (Table 3, entries 8−12). Noticeably, the reaction worked smoothly, and corresponding products could be isolated in excellent and moderate yields with reaction times of 40−60 min. We found that carboxylic acid can also be added to alkene to give ester in excellent yield in a reaction time of 40 min under similar reaction conditions (Table 3, entry 13).

In conclusion, a variety of phosphine gold(I) complexes have been demonstrated to be efficient catalyst for inter- and intramolecular hydroamination reactions of alkenes. The use of microwave radiation as a heat source allows a convenient access to the temperature needed to allow completion of the reaction in a much shorter time than that required under conventional thermal conditions. The microwave-assisted phosphine gold(I)-catalyzed organic reactions could provide an entry for further development of gold(I) organic catalysis in high-throughput synthesis.

Acknowledgment. We are thankful for the financial support of The University of Hong Kong (University Development Fund), Hong Kong Research Grants Council (HKU 7012/05P), and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (AoE/P-10/01).

Supporting Information Available: Experimental procedure, product characterizations, Table S1, Table S2, and Chart S1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060719X