Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3763

www.rsc.org/obc

PAPER

Gold(I)-catalyzed intramolecular hydroamination and ring-opening of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinols†

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Received 21st February 2012, Accepted 12th March 2012
DOI: 10.1039/c2ob25512j

An interesting gold(I)-catalyzed intramolecular hydroamination and ring-opening of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinols has been described in this context. A variety of 4-substituted isoxazolidine derivatives were obtained in good to high yields through a highly regioselective cleavage of a carbon–carbon single bond in the cyclopropane.

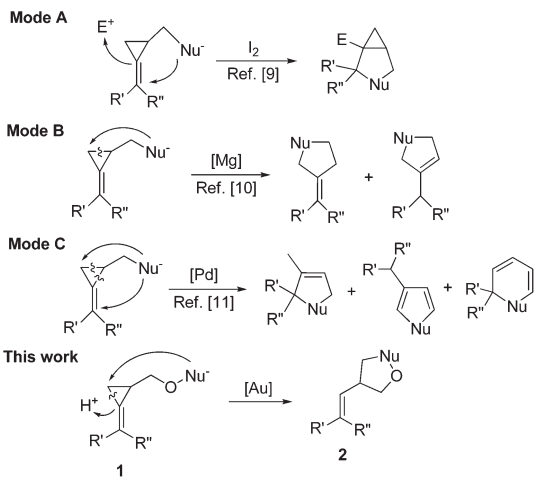
Introduction

Homogeneous catalysis mediated by gold complexes has received considerable attention in recent years,[1] and the core of these reactions rely on the interaction between gold catalysts and π-bonds of alkenes, alkynes, and allenes. The most common reaction pattern is the addition of nucleophiles to unsaturated C–C bonds, initially activated by the gold complex acting as a powerful soft catalyst, to efficiently construct new carbon–carbon or carbon–heteroatom bonds.[2–6] Methylenecyclopropanes (MCPs) are generally used as building blocks in organic synthesis for their accessibility as well as diverse reactivity driven by the relief of ring strain. Over the past few decades, a series of review articles have been published on the transformation of these *exo*-methylene three-membered carbocycles.[7] 2-(Arylmethylene)cyclopropylcarbinols are another kind of MCP bearing an additional hydroxymethyl group, and as demonstrated by our group, can undergo a variety of transformations triggered by the nucleophilic hydroxyl group under milder conditions.[8]

Several studies have focused on intramolecular nucleophilic addition of MCPs bearing a nucleophilic group (Scheme 1). Our group and Huang's group reported the efficient stereoselective synthesis of bicyclo[3.1.0]hexane from the reaction of 2-substituted MCPs with iodine (Mode A, Scheme 1).[9] Lautens *et al.* studied the MgI_2-mediated ring expansions of secondary MCP amides, which gave the isomeric five-membered unsaturated lactams (Mode B, Scheme 1).[10] Regioselective palladium-catalyzed ring-opening cycloisomerization of MCP ketones has been reported by Ma and co-workers (Mode C, Scheme 1).[11] In view of this, we designed and synthesized a novel type of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinols **1**, which contain a coordinative double bond and a strained carbocycle and tether an additional nucleophilic sulfonamide group. We envisioned that through an intramolecular hydroamination along with a highly regioselective C–C bond cleavage (proximal bond cleavage) of the cyclopropane in the presence of gold complex, isoxazolidines **2** could be formed. Isoxazolidines,[12] usually obtained by 1,3-dipolar cycloaddition of nitrones with alkenes, are valuable intermediates for the synthesis of natural products and possess very interesting biological properties.[13]

Results and discussion

Initial studies using sulfonamide-substituted 2-(arylmethylene) cyclopropylcarbinol **1a** [(*E*) configuration] as the substrate were aimed at determining the reaction outcome and subsequently optimizing the reaction conditions. The results are summarized in Table 1. We found that an interesting 4-substituted



Scheme 1 Intramolecular nucleophilic addition of 2-substituted MCPs. Nu = nucleophile, E = electrophile.

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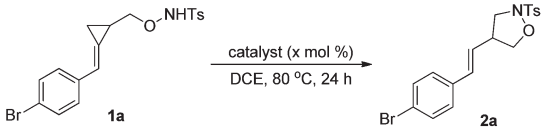
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds. CCDC reference number 816966. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25512j

Table 1 Optimization of reaction conditions for gold(I)-catalyzed intermolecular hydroamination and ring-opening



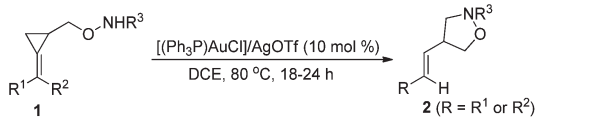
Entry[a]	Catalyst (x mol%)	Yield (%)[b] **2a**
1	[(Ph_3P)AuCl]/AgOTf (5)	59
2	[(Ph_3P)AuCl]/AgOTf (10)	95
3	[(Me_3P)AuCl]/AgOTf (10)	78
4	[(tBu$_3$P)AuCl]/AgOTf (10)	20
5	[(IPr)AuCl]/AgOTf (10)	32
6	[(*t*BuXPhos)Au(NCMe)]SbF_6 (10)	24
7	AgOTf (10)	81
8	[(Ph_3P)AuCl] (10)	NR[c]
9	HOTf (2)	18
10[d]	[(Ph_3P)AuCl]/AgOTf (10)	93

[a] [**1a**] = 0.05 M. [b] Isolated yield. [c] NR = no reaction. [d] 2,4,6-Tri-*tert*-butylpyrimidine (10 mol%) was added.

isoxazolidine derivative **2a** [(*E*) configuration] was formed in 59% yield using [(Ph_3P)AuCl]/AgOTf (5 mol%) as the catalyst in 1,2-dichloroethane (DCE) at 80 °C (Table 1, entry 1). The structure of compound **2a** was confirmed by NMR spectroscopic data and X-ray diffraction (see ESI†). Adding [(Ph_3P)AuCl]/AgOTf (10 mol%) afforded **2a** in 95% yield (Table 1, entry 2). Using [(Me_3P)AuCl], [(tBu$_3$P)AuCl] or [(IPr)AuCl] as a gold complex gave **2a** in 78%, 20% and 32% yields, respectively (Table 1, entries 3–5). In the presence of [(*t*BuXPhos)Au(NCMe)]SbF_6, **2a** could be also obtained in 24% yield (Table 1, entry 6). Control experiments indicated that using AgOTf alone as the catalyst gave **2a** in 81% yield and using [(Ph_3P)AuCl] alone as the catalyst did not promote the reaction (Table 1, entries 7 and 8). Moreover, in the presence of HOTf (2 mol%), **2a** could be formed in 18% yield as well (Table 1, entry 9). The addition of 2,4,6-tri-*tert*-butylpyrimidine (10 mol%, a proton scavenger) into the reaction system to exclude trace of HOTf gave **2a** in 93% yield (Table 1, entry 10). Therefore, the optimal reaction conditions have been identified to carry out the reaction in DCE at 80 °C using [(Ph_3P)AuCl]/AgOTf as the catalyst. Carrying out the reactions in other solvents, silver salts and different amounts of HOTf did not improve the reaction outcomes (see Table S1 in ESI†).

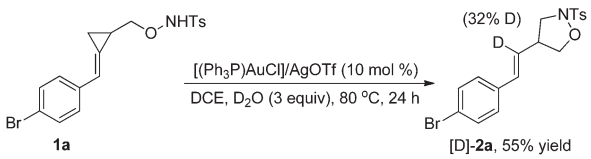
We next examined the substrate generality of this reaction under optimized conditions and the results are shown in Table 2. As can be seen from Table 2, for substrates **1b–1h** (R^3 = Ts) the reactions proceeded smoothly to furnish the desired products **2b–2h** in good yields, regardless of whether they have electron-rich, electron-poor, or electron-neutral aromatic rings at their alkene moieties (Table 2, entries 1–7). Changing the sulfonamide substitution R^3 to Bs and Ns produced the corresponding isoxazolidine derivative **2i** and **2j** in 64% and 67% yields, respectively (Table 2, entries 8 and 9). Further examination of substrate (*Z*)-**1k** and (*Z*)-**1l** revealed that the expected five-membered heterocycles **2i** and **2j** were formed in 79% and 84% yields, respectively (Table 2, entries 10 and 11). Only in the case of

Table 2 Substrate scope of the gold(I)-catalyzed intermolecular hydroamination and ring-opening of sulfonamide-substituted 2-methylenecyclopropylcarbinols **1**



Entry[a]	**1**	R^1	R^2	R^3	Yield (%)[b] **2**
1[c]	**1b**	C_6H_5	H	Ts	**2c**, 79
2	**1c**	4-ClC_6H_4	H	Ts	**2b**, 86
3	**1d**	4-FC_6H_4	H	Ts	**2d**, 83
4	**1e**	4-MeC_6H_4	H	Ts	**2e**, 78
5	**1f**	4-$MeOC_6H_4$	H	Ts	**2f**, 67
6	**1g**	3,4-$Cl_2C_6H_3$	H	Ts	**2g**, 50
7	**1h**	2,4-$Cl_2C_6H_3$	H	Ts	**2h**, 69
8	**1i**	4-BrC_6H_4	H	Bs	**2i**, 64
9	**1j**	4-BrC_6H_4	H	Ns	**2j**, 67
10	**1k**	H	4-BrC_6H_4	Bs	**2i**, 79
11	**1l**	H	4-BrC_6H_4	Ns	**2j**, 84
12	**1m**	$C_6H_5CH_2CH_2$	H	Ts	**Complex**

[a] All reactions were carried out using 1 (0.2 mmol) in the presence of [(Ph_3P)AuCl]/AgOTf (10 mol%) in DCE (2.0 mL) at 80 °C for 24 h. [b] Isolated yield. [c] In the presence of [(Ph_3P)AuCl]/$AgSbF_6$ (10 mol%). Ts = 4-toluenesulfonyl; Ns = 4-nitrobenzenesulfonyl; Bs = 4-bromobenzenesulfonyl.

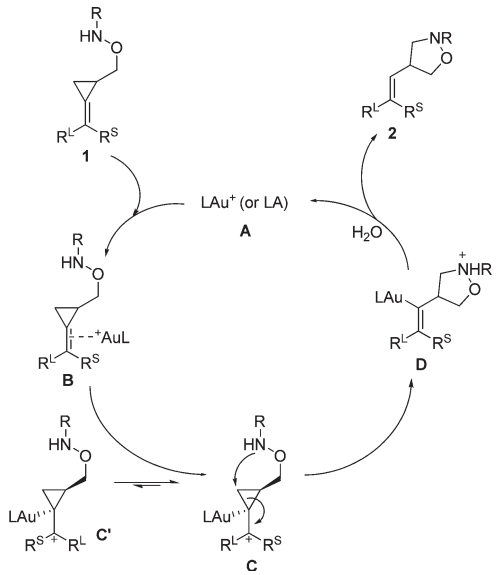


Scheme 2 Isotopic labeling experiments.

aliphatic MCP alcohol **1m** (R^1 = $C_6H_5CH_2CH_2$), complex product mixtures were formed under the standard conditions (Table 2, entry 12). The product structures of **2b–2j** were determined by NMR spectroscopic analysis, mass spectroscopy (MS), and HRMS (see ESI†). 2-(Arylmethylene)cyclopropyltosylamide **3a** (a simple tosyl amide without the oxygen atom) is inactive in this gold-catalyzed hydroamination (see ESI†).

To elucidate the cyclization mechanism, deuterium labeling experiment was performed as shown in Scheme 2. Carrying out the reaction of 2-(arylmethylene)cyclopropylcarbinol **1a** in D_2O (3 equiv.) led to the corresponding product [D]-**2a** in 55% yield along with 32% deuterium incorporation at its olefinic carbon atom.

A plausible mechanism for this reaction is outlined in Scheme 3 on the basis of the above deuterium labeling experiment.[14] Cationic Au(I) complex **A** (or Lewis acid) first coordinates to the alkene moiety of **1** [(*E*) or (*Z*) configuration] to give intermediate **B**, which then produces a carbocationic intermediate **C**. There might be an equilibrium between the intermediate **C** and intermediate **C′**, in which intermediate **C** is the preferred active species based on the formation of (*E*)-isoxazolidine products. The intermediate **C** undergoes a common intramolecular hydroamination along with the ring-opening of cyclopropane[15]



Scheme 3 A plausible reaction mechanism. L = ligand. LA = Lewis acid.

to give the corresponding five-membered heterocyclic intermediate **D**. The hydrolysis of intermediate **D** produces 4-substituted isoxazolidine derivative **2** and regenerates the Au(I) complex **A** to complete the catalytic cycle.

Conclusions

In summary, we have developed a novel gold(I)-catalyzed cyclization reaction to construct five-membered *N*,*O*-heterocyclic products from sulfonamide-substituted 2-(arylmethylene) cyclopropylcarbinol in good yields through a highly regioselective domino intramolecular hydroamination and ring-opening of cyclopropane. Further applications of this air- or moisture-tolerant reaction of a gold-catalyzed system and more detailed mechanistic investigation are under way in our laboratory.

Experimental

General remarks

^{1}H and ^{13}C NMR spectra were recorded at 400 (or 300) and 100 (or 75) MHz, respectively. Mass and HRMS spectra were recorded by ESI or EI method. The employed solvents were dry up by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

General procedure for Au(I)-catalyzed intramolecular hydroamination and ring-opening of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinols under the standard reaction conditions

Under an argon atmosphere, sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinol **1** (0.2 mmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (DCE) (2.0 mL) in an Schlenk tube, and (Ph_3P)AuCl/AgOTf (10 mol%) were added. Then, the reaction mixture was stirred at 80 °C until the reaction completed. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding products **2** in moderate to excellent yields.

Compound 1a. A white solid. Mp: 113–115 °C. IR (CH_2Cl_2) ν 3242, 2930, 1597, 1486, 1395, 1163, 1007, 817, 718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.30–1.35 (m, 1H, CH_2), 1.66–1.68 (m, 1H, CH_2), 1.83–1.92 (m, 1H, CH), 2.45 (s, 3H, CH_3), 3.86 (dd, J = 10.8 Hz, J = 7.8 Hz, 1H, CH_2), 4.02 (dd, J = 10.8 Hz, J = 6.3 Hz, 1H, CH_2), 6.72 (d, J = 1.2 Hz, 1H, CH), 7.14 (s, 1H, NH), 7.35 (d, J = 8.7 Hz, 4H, Ar), 7.44 (d, J = 8.7 Hz, 2H, Ar), 7.83 (d, J = 8.7 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 9.9, 11.8, 21.7, 79.3, 118.7, 120.9, 125.8, 128.2, 128.6, 129.7, 131.5, 133.4, 136.3, 144.9. MS (ESI) *m*/*z* 408 (M^+ + H). HRMS (ESI) Calcd for $C_{18}H_{19}NO_3SBr$ (M^+ + H): 408.0264, Found: 408.0261.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (11JC1402600), National Basic Research Program of China (973)-2010CB833302, and the National Natural Science Foundation of China for financial support (21072206, 20472096, 20872162, 20672127, 20732008 and 21121062).

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