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Gold(I)- and Brønsted Acid-Catalyzed Ring-Opening of Unactivated Vinylcyclopropanes with Sulfonamides

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Abstract: The gold(I)- or Brønsted acid-catalyzed reaction of unactivated vinylcyclopropanes (VCPs) with sulfonamides affords useful homoallylic amine derivatives. This ring-opening reaction occurs in a highly selective manner affording in the case of α-phenyl-substituted VCPs products with the *E*-configuration exclusively.

Keywords: catalysis; gold; hydroamination; ring-opening; vinylcyclopropanes

Unactivated vinylcyclopropanes (VCPs) are potentially best-suited substrates for transition metal-catalyzed reactions involving ring-opening processes. However, only a limited number of such transformations has been reported so far. These include the classical rearrangement to cyclopentenes and related reactions,[1a–c] [5+2] cycloadditions,[1d,e] couplings with aldehydes,[1f] and a silaboration reaction.[1g] However, the ring-opening of unactivated VCPs using nitrogen nucleophiles remains vastly unexplored, despite its great potential as a new complementary carbon-nitrogen bond-forming reaction.[2]

Transition metal-catalyzed hydroamination is an extremely attractive and challenging process for the synthesis of amines, having witnessed an increasing academic and industrial interest, thus evolving to a highly active research area in the past decade.[3,4] Gold complexes have been shown very recently to exhibit unique properties in the activation of unsaturated carbon-carbon bonds and have been used in the catalytic hydroamination of a series of alkynes, allenes, 1,3-dienes and simple alkenes, thus affording 1,2-addition products.[5] Despite these achievements, an extension of the scope of possible substrates for hydroamination reactions is still very desirable.

As part of our continuing efforts in this area, we describe herein the first gold(I)-catalyzed highly stereoselective intermolecular ring-opening of unactivated VCPs with sulfonamides. This hydroamination reaction provides an alternative approach for the preparation of useful derivatives of homoallylic amines that are widely used in the synthesis of bioactive heterocycles.[6,7]

Initially, we chose VCP **1a** and benzenesulfonamide for a study of the corresponding hydroamination in the presence of gold complexes. Thus, compound *E*-**2aa**[8] was identified as the main product isolated from the reaction mixtures.[9] Moreover, the *E* configuration was confirmed by an X-ray crystallographic study of its analogue **2ab** whose structure is shown in Figure 1.[10]

Further optimizations of this reaction were carried out by screening various metal catalysts, solvents and conditions (Table 1). We found that by using 10 mol% $AuCl(PPh_3)$/AgOTf and 3 equivs. of **1a** in toluene at 50 °C (entry 14), **2aa** could be isolated in 73% yield. Interestingly, the yield of **2aa** did not drastically

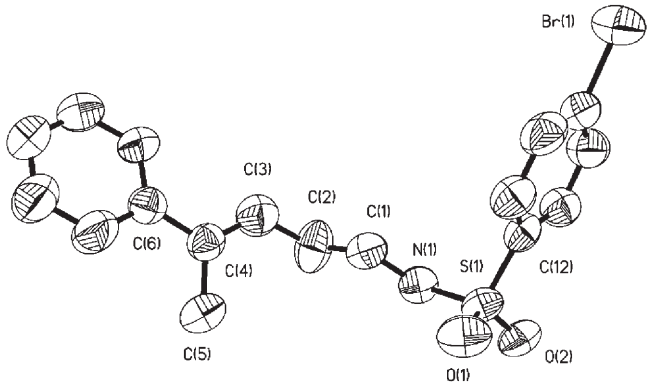
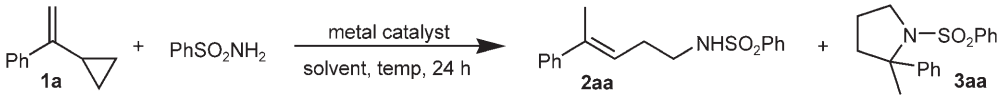


Figure 1. ORTEP representation of compund ***E*-2ab** (probability ellipsoids at the 50% level). Selected bond lengths (Å) and angles (°): S(1)–N(1), 1.609(4); N(1)–C(1), 1.472(6); C(3)–C(4), 1.320(7); C(1)–N(1)–S(1), 120.7(3).

Table 1. Optimization of reaction conditions.[a]



Entry	Metal catalyst	Solvent	Yield [%] of **2aa**/**3aa**[b]
1	-	toluene	-
2	$AuCl_3$/3 AgOTf	toluene	-/64
3	$AuCl(PEt_3)$/AgOTf	toluene	39/-
4	$AuCl(PCy_3)$/AgOTf	toluene	51/-
5	$AuCl(PPh_3)$/AgOTf	toluene	53/-
6	$AuCl[P(p\text{-}Tol)_3]$/AgOTf	toluene	48/-
7[c]	AuCl(L)/AgOTf	toluene	32/-
8	$AuCl[P(p\text{-}ClC_6H_4)_3]$/AgOTf	toluene	-/48
9	$AuCl[P(C_6F_5)_3]$/AgOTf	toluene	-/63
10[d]	$AuCl(PPh_3)$/AgOTf	THF	-
11	$AuCl(PPh_3)$/AgOTf	$Cl(CH_2)_2Cl$	-/42
12[e]	$AuCl(PPh_3)$/AgOTf	toluene	-
13[f]	$AuCl(PPh_3)$/AgOTf	toluene	-/37
14[g]	$AuCl(PPh_3)$/AgOTf	toluene	73/-

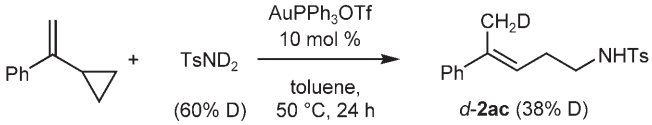
[a] 0.2 mmol $PhSO_2NH_2$, 0.3 mmol **1a**, 0.02 mmol metal catalyst, 2.0 mL solvent, 50 °C, 24 h.
[b] Isolated yield.
[c] L = (2-biphenyl)-di-*tert*-butylphosphine.
[d] Polymer formed.
[e] Room temperature.
[f] 80 °C.
[g] 0.6 mmol **1a**.

change when using gold(I) complexes containing electron-rich and/or more sterically demanding phosphine ligands (entries 3, 4, 6, and 7 *vs.* 5). On the other hand, catalysts with electron-deficient arylphosphines led to the preferred formation of product **3aa**, isolated in moderate yields (entries 8 and 9).[11] Moreover, metal salts such as $AuCl_3$, AgOTf, and $Pd(OAc)_2$ were found to be catalytically inactive.

With the optimized conditions in hand, we examined the scope of this gold(I)-catalyzed ring-opening with a variety of amines and unactivated VCPs (Table 2). Thus, for a series of nitrogen nucleophiles, including aniline, benzamide, a benzotriazole and substituted sulfonamides, TsNHMe gave excellent yield of ring-opening product **2ae** (entry 5), while aniline and benzamide did not show any conversion in 24 h. The large reactivity differences of these nucleophiles may be attributed to differences in basicity and solubility.[3f] With TsNHMe as nucleophile, we were delighted to find that a variety of VCPs, both bearing aryl or alkyl substitutents can be successfully hydroaminated to form ring-opened products in high yields. The electronic nature of the *para*-substituent on the phenyl ring of substrates of type **1a** has a significant impact on their reactivity, with trifluoromethyl leading to a slow reaction and only a moderate yield, and methoxy affording a complex mixture (entries 10 and 11, respectively). Furthermore, this ring-opening reaction also could be extended to trisubstituted VCPs, although in these cases both more elevated temperatures and a prolonged reaction time were necessary (entries 14 and 16).

To gain a first insight into the reaction mechanism, we performed experiments with the deuterated sulfonamide $TsND_2$, at a deuteration degree of 60 %. As depicted in Scheme 1, the deuterium label is found in the product *d*-**2ac** at the methyl position exclusively, with a level of deuterium incorporation of 38 % based on ^1H (700 MHz), ^{13}C NMR and ^{13}C-^1H HZQC spectroscopic analysis. The relatively low deuterium content may be attributed to D/H exchange of $TsND_2$ with adventitious proton sources in the reaction mixture[12] and/or to a weak kinetic isotope effect. Moreover, competition experiments using the VCPs **1a**–**f** allowed to establish a clean linear free energy relationship. The corresponding Hammett plot is shown in Figure 2 and indicates that, for example, the methyl substituted substrate **1b** reacts *ca.* 35 times faster than the analogous trifluoromethyl derivative **1f**.

Further investigations revealed that the Brønsted acid HOTf also can catalyze the ring-opening reaction



Scheme 1. Deuterium labelling experiment.

Table 2. Ring-opening of unactivated VCPs **1** with RR′NH.[a]

Entry	RR′NH	VCPs, **1**: R^1, R^2, R^3	Yield of **2**[b] [%]
1	$PhSO_2NH_2$	H, H, Ph (**1a**)	73 (**2aa**)
2	*p*Br-$C_6H_4SO_2NH_2$	**1a**	30 (**2ab**)
3	$TsNH_2$	**1a**	33 (**2ac**)
4	1,2,3-benzotriazole	**1a**	10 (**2ad**)
5	TsNHMe	**1a**	97 (**2ae**)
6	TsNHMe	H, H, *p*-Me-C_6H_4 (**1b**)	99 (**2ba**)
7	TsNHMe	H, H, *p*-(*t*-Bu)-C_6H_4 (**1c**)	90 (**2ca**)
8	TsNHMe	H, H, *p*-Cl-C_6H_4 (**1d**)	96 (**2da**)
9	TsNHMe	H, H, *p*-F-C_6H_4 (**1e**)	96 (**2ea**)
10	TsNHMe	H, H, *p*-CF_3-C_6H_4 (**1f**)	58 (**2fa**)
11[c]	TsNHMe	H, H, *p*-MeO-C_6H_4 (**1g**)	N.D. (**2ga**)
12	TsNHMe	H, H, 2-naphthyl (**1h**)	99 (**2ha**)
13[d]	TsNHMe	H, H, phenylethyl (**1i**)	80 (**2ia**)
14	TsNHMe	H(Me), Me(H), Ph **(1j)**	76 (**2ja**)
15[e]	TsNHMe	Ph, H, H (**1k**)	57 (**2ka**)
16[e]	TsNHMe	Ph(Me), Me(Ph), H (**1l**)	54 (**2la**)
17[f]	TsNHMe	H, H, cyclohexyl (**1m**)	99 (**2ma**)

[a] 0.2 mmol amine, 0.6 mmol **1**, 0.02 mmol $AuPPh_3OTf$, 2.0 mL toluene, 50 °C, 24 h.
[b] Isolated yield.
[c] Complete conversion, unidentified mixture, room temperature.
[d] *dr* = 80:20.
[e] 80 °C, 1.0 mmol **1**, 63 h.
[f] *dr* = 86:14.

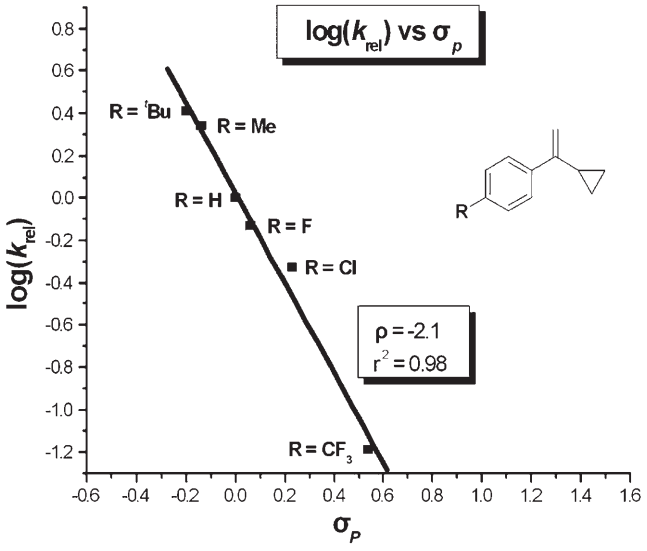


Figure 2. Hammett plot for the ring-opening of **1a–f** with TsNHMe using PPh_3/AuOTf as catalyst.

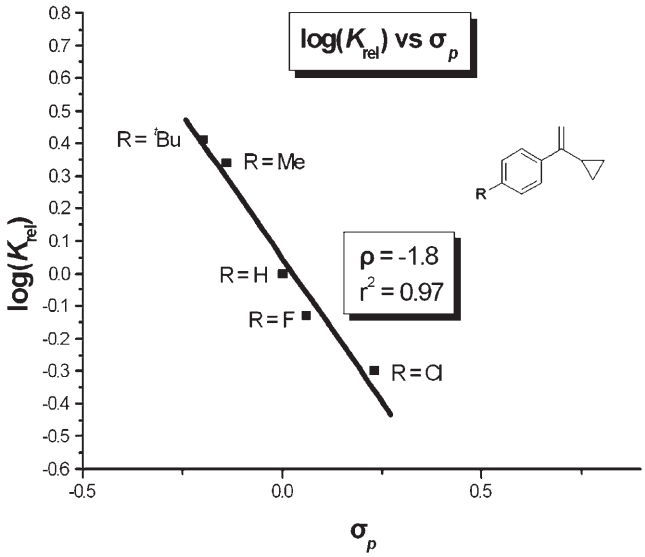
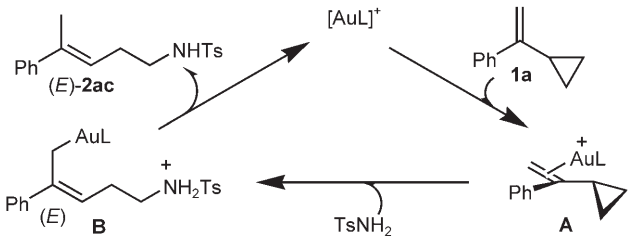


Figure 3. Hammett plot for the ring- opening of **1a–e** with TsNHMe using HOTf as catalyst.

affording very similar results when compared to the PPh_3/AuOTf catalyst under otherwise the same conditions and at the same concentration level.[13] Thus, employing 10 mol% HOTf as catalyst, the ring-opening of **1a** with TsNHMe gave 92% yield at 50 °C in 24 h. Furthermore, competition experiments using HOTf as catalyst also established a clean linear free energy relationship, shown in Figure 3, displaying a ρ value of −1.8, comparable to the value of −2.1 found when using the Au catalyt.

Thus, the question arose, whether PPh_3/AuOTf or HOTf, possibly generated from the reaction of the gold(I) precursor with sulfonamide, is the only true catalyst. However, based on He's recent results,[13a] it appears unlikely that the *in situ* reaction of PPh_3/AuOTf with $TsNH_2$ may generate HOTf in a suffi-



Scheme 2. Plausible simplified reaction mechanism for the Au(I)-catalyzed ring-opening of VCP **1a**.

ciently large concentration to account for the activity observed when operating with 10 mol% HOTf. Therefore, after having verified that AgOTf alone is not a catalyst, we assume that the cationic gold(I) complex is the main catalytically active species generated *in situ*. Thus, it is reasonable to assume that the activation of the VCP occurs *via* coordination of the olefinic bond to the cationic Au(I) species, thus forming an intermediate of type **A** (Scheme 2).[14] This should be favored by electron-donating groups at the *para*-position of the phenyl ring in derivatives of **1a** and could account for the strongly negative slope displayed by the Hammett plot. The regiospecific deuterium incorporation observed in the experiment with $TsND_2$ invokes the formation of an intermediate of type **B**, an Au(I)-primary alkyl derivative. Its protonolysis leads to product formation and regeneration of the catalytically active species. However, it still remains unclear how the crucial ring-opening step exactly occurs.

In summary, we have found a new gold(I)-catalyzed intermolecular ring-opening of unactivated VCPs with sulfonamides, constituting a new synthetic access to useful derivatives of homoallylic amines. The same reaction is also efficiently catalyzed by HOTf,[15] thus making it more convenient for synthetic purposes.

Experimental Section

General Procedures for Gold(I)- or HOTf-Catalyzed Ring-Opening of Unactivated VCPs with Sulfonamides

***Gold(I)*-catalyzed ring-opening reaction:** To a suspension of $AuPPh_3OTf$, prepared *in situ* from $AuCl(PPh_3)$ (10.0 mg, 0.02 mmol) and AgOTf (5.6 mg, 0.02 mmol) in 2 mL of toluene, TsNHMe was added (39 mg, 0.2 mmol), followed by α-phenylvinylcyclopropane **1a** (88 mg, 0.6 mmol). The resulting mixture was stirred for 24 h at 50 °C. Then, the reaction mixture was cooled to room temperature, evaporated under vacuum, and the residue was purified by silica gel column chromatography (eluent: EtOAc/petroleum ether = 1/3) to afford the product **2ae** as a colorless liquid; yield: 63 mg (97%).

HOTf-catalyzed ring-opening reaction: To the solution of α-phenylvinylcyclopropane **1a** (88 mg, 0.6 mmol) and TsNHMe (39 mg, 0.2 mmol) in 2 mL toluene at 50 °C, HOTf (3.0 mg, 0.02 mmol) was added using a micro-syringe. The resulting solution was stirred for 24 h. Then, the reaction mixture was cooled to room temperature, evaporated and the residue was purified by silica gel column chromatography (eluent: EtOAc/petroleum ether = 1/3) to afford the product **2ae** as a colorless liquid; yield: 60 mg (92%).

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References

[1] a) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197; b) G. Zuo, J. Louie, *Angew. Chem. Int. Ed.* **2004**, *43*, 2277; c) G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5798; d) P. A. Wender, L. O. Haustedt, J. Lim, J. A. Love, T. J. Williams, J.-Y. Yoon, *J. Am. Chem. Soc.* **2006**, *128*, 6302; e) B. M. Trost, H. C. Shen, D. B. Horne, F. D. Toste, B. G. Steinmetz, C. Koradin, *Chem. Eur. J.* **2005**, *11*, 2577; f) T. Tsuritani, H Shinokubo, K. Oshima, *Synlett* **2002**, 978; g) M. Suginome, T. Matsuda, T. Yoshimoto, Y. Ito, *Organometallics* **2002**, *21*, 1537.

[2] R. C. Larock, E. K. Yum, *Tetrahedron* **1996**, *52*, 2743.

[3] For recent representative examples of hydroamination reactions, see: a) N. Sakai, A. Ridder, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 8134; b) A. M. Johns, M. Utsunomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 1828; c) N. T. Patil, L. M. Lutete, H. Wu, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 4270; d) J. G. Taylor, N. Whittall, K. K. Hii, *Org. Lett.* **2006**, *8*, 3561; e) H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 1611; f) D. Karshtedt, A. T. Bell, T. D. Tilley, *J. Am. Chem. Soc.* **2005**, *127*, 12640.

[4] For recent reviews on hydroamination, see: a) K. C. Hultzsch, *Adv. Synth. Catal.* **2005**, *347*, 367; b) K. C. Hultzsch, *Org. Biomol. Chem.* **2005**, *3*, 1819; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; d) S. Hong, T. J. Marks, *Acc. Chem. Res.* **2004**, *37*, 673; e) J. J. Brunet, D. Neibecker, in: *Catalytic Heterofunctionalization*, (Eds.: A. Togni, H. Grützmacher) Wiley-VCH, Weinheim, **2001**, pp 91–141.

[5] For hydroamination reactions catalyzed by gold complexes, see: a) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555, and references cited therein; b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066; c) X.-Y. Liu, C.-H. Li, C.-M. Che, *Org. Lett.* **2006**, *8*, 2707; d) R. A. Widenhoefer, C. F. Bender, *Org. Lett.* **2006**, *8*. 5303; e) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634; f) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, 4905; for a

recent review on gold catalysis, see: g) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896.
[6] a) S. Gischig, A. Togni, *Eur. J. Inorg. Chem.* **2005**, 4745; b) L. Fadini, A. Togni, *Chem. Commun.* **2003**, 30; c) H. M. Senn, P. E. Blochl, A. Togni, *J. Am. Chem. Soc.* **2000**, *122*, 4098; d) R. Dorta, P. Egli, F. Zurcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857.
[7] For the synthesis of homoallylic amine derivatives, see: a) E. C. Burger, J. A. Tunge, *J. Am. Chem. Soc.* **2006**, *128*, 10002; b) R. Hirabayashi, C. Ogawa, M. Sugiura, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 9493.
[8] The configuration of **2aa** was assigned as *E* based on its ^{1}H-^{1}H NOESY NMR experiments; see Supporting Information.
[9] A similar ring-opening reaction leading to homoallylic amine derivatives has been observed recently by Carreira and co-workers in the Co- or Mn-catalyzed radical hydrohydrazination of vinylcyclopropanes. However, there is no experimental evidence that the Au-catalyzed reaction takes place *via* radical intermediates; see: J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693.
[10] Crystallographic data (excluding structure factors) for the structure of compound **2ab** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-622306. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].
[11] Very recently, Shi et al. reported the synthesis of pyrrolidines *via* an Au-catalyzed domino ring-opening/ring-closing reaction of methylene-cyclopropanes with sulfonamides, in which compounds of type **2** occur as intermediates; see: M. Shi, L.-P. Liu, J. Tang, *Org. Lett.* **2006**, *8*, 4043.
[12] For similar observations, see: Y. Chen, M. Shi, *J. Org. Chem.* **2004**, *69*, 426.
[13] For very recent N–H and O–H addition to simple olefins catalyzed by Brønsted acids, see: a) Zi. Li, J. Zhang, C. Brouwer, C.-G. Yang, N. W. Reich, C. He, *Org. Lett.* **200**6, 8, 4175; b) D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya, J. F. Hartwig, *Org. Lett.* **2006**, *8*, 4179; c) Y. Yin, G. Zhao, *J. Fluorine Chem.* **2007**, *128*, 40.
[14] M. A. Cinellu, G. Minghetti, S. Stoccoro, A. Zucca, M. Manassero, *Chem. Commun.* **2004**, 1618.
[15] For previous reports discussing gold *versus* Brønsted catalysis, see: a) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247; b) J. Liu, E. Muth, U. Flörke, G. Henkel, K. Merz, J. Sauvageau, G. Dyker, *Adv. Synth. Catal.* **2006**, *348*, 456; c) G. Dyker, D. Hildebrandt, D. Kadzimirsz, K. Merz, *Chem. Commun.* **2006**, 661.

