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Chiral Brønsted Acid from a Cationic Gold(I) Complex: Catalytic Enantioselective Protonation of Silyl Enol Ethers of Ketones

Cheol Hong Cheon, Osamu Kanno, and F. Dean Toste*

Department of Chemistry, University of California, Berkeley, California 94720

Abstract

A chiral Brønsted acid has been developed from cationic gold(I) disphosphine complex in the presence of alcoholic solvent and applied to enantioselective protonation reaction of silyl enol ethers of ketones. Various optically active cyclic ketones were obtained in excellent yields and high enantioselectivities including cyclic ketones bearing aliphatic substrates at the α -position. Furthermore, the application of this Brønsted acid was extended to the first Brønsted acid-catalyzed enantioselective protonation reaction of silyl enol ethers of acyclic substrates, regardless of their E/Z ratio.

Over the past decade gold catalysis has attracted significant attention from synthetic community.¹ More recently, notable progress has been made in asymmetric catalysis using homogenous gold(I) complexes. In general, enantioselective reactions have relied on the ability of cationic gold(I) complex π -donor ligands such as alkynes, allenes, and alkenes and activate them toward nucleophilic attack.^{2–4} In contrast, similar σ -complexes of cationic gold complexes with σ -donor ligands have been little explored in asymmetric catalysis, although there have been several reports of reactivity differences in gold catalysis in the presence of protic additives.⁵ Very recently, we found that alcoholic additive have a dramatic effect on the regio- and enantioselectivity in gold-catalyzed hydroamination of 1,3-dienes.⁶ For example, in the absence of alcohol, 1,2-addition products were obtained as exclusive products with very poor enantioselectivity, whereas in the presence of an alcohol additive 1,4-addition products were obtained in good yields and high enantioselectivity (eq 1).

(1)

We hypothesized that in the absence of alcohol, the cationic gold(I) directly activates the 1,3-diene towards nucleophilic attack leading to the 1,2-addition products. On the other hand, in the presence of alcohol, cationic gold(I) forms σ -complex with alcohol to generate chiral Brønsted acid activated by complexation with gold; a so called, Lewis acid activated Brønsted acid (LBA).⁷ Based on these observations, we envisioned that a new chiral Brønsted acid could be generated by complexation of alcohol with cationic gold,

CORRESPONDING AUTHOR: fdtoste@berkeley.edu.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

significantly enhancing the acidity of the original alcohol. Herein we describe the development of a chiral LBA derived from cationic gold complex and its application to enantioselective protonation reaction of silyl enol ethers of ketones.^{8–11}

We began our investigation by examining the protonation reaction of silyl enol ether **4a**, catalyzed by 3 mol% (*R*)-DTBM-SEGPHOS(AuCl)₂ activated by 3 mol% AgBF₄, in isopropanol as a solvent. Under these conditions, the desired protonation product **5a** was obtained in quantitative yield and 87% ee (Table 1, entry 1). Encouraged by this initial result, we examined other chiral diphosphine(bis)gold complexes as catalysts for the enantioselective protonation reaction (entries 1–6). Among the gold(I) complexes tested, the (*R*)-BINAP-derived complex proved to generate the most selective catalyst for the asymmetric protonation reaction (entry 5).

With BINAP as the diphosphine ligand on gold, we next examined the effect of counterions on the protonation reaction (entries 4, 7–11). Generation of the cationic gold(I) complex proved essential for the protonation reaction, as no protonation was observed without AgBF₄ (entry 12), or when a more coordinating counterion was used (entry 7). On the other hand, reactive catalysts were generated from non-coordinating anions (entries 4, 8–11), with tetrafluoroborate providing the protonation adduct with highest enantioselectivity. Furthermore, the catalyst derived from the monocationic gold(I) complex proved more selective than the one from dicationic gold complex (entries 5 and 13). We also investigated the possibility of protonation catalyzed by a Brønsted acid derived from AgBF₄·BINAP complex; however, this silver-based Brønsted acid was not reactive enough to protonate silyl enol ether **4a** (entry 14).¹² Finally, the enantioselectivity could be further increased by changing the solvent from isopropanol to ethanol (entry 15).¹³

With these optimized conditions, we first investigated the scope of the gold-catalyzed enantioselective protonation reaction of silyl enol ethers of cyclic ketones (Table 2). Various silyl enol ethers from 2-aryl cyclic ketones could be employed in the enantioselective protonation reaction and the corresponding ketones were obtained with excellent yields and high enantioselectivities (entries 1–5). The cationic gold(I)-derived LBA could be further applied to the protonation reaction of silyl enol ethers of 2-alkyl cyclic ketones (entries 6–7). Tetralone and indanone analogs bearing a methyl group at the 2-position were obtained in quantitative yields and excellent enantioselectivity. It is noteworthy that the ring size of cyclic ketones had little effect on reactivity and high levels of enantioselectivity were obtained regardless of ring size (entries 1 vs 5, 6 vs 7).

Although several examples of Brønsted acid-catalyzed enantioselective protonation reactions of silyl enol ethers of cyclic ketones have been reported,^{9–11} to the best of our knowledge, *there have been no reports of Brønsted acid-catalyzed enantioselective protonation reaction of silyl enol ethers of acyclic ketones.*^{14,15} Therefore, we next examined the use of our gold(I)-based catalytic system in the enantioselective protonation of these more challenging substrates. The first anticipated challenge with acyclic substrates is the stereochemistry of starting silyl enol ethers. In contrast to cyclic ketones having only one isomer of silyl enol ethers, acyclic ketones can generate both (*E*) and (*Z*) silyl enol ethers. Since the transition states for the protonation of the diastereomeric silyl enol ether are different, we anticipated that it might be important to diastereoselectively generate the silyl enol ethers.^{8e} Furthermore, the acyclic substrates generally have more conformational flexibility than the corresponding cyclic ones, which can also lead to lower asymmetric induction.

With these challenges in mind, we examined our LBA-catalyzed asymmetric protonation reactions of silyl enol ethers of acyclic substrates (Table 3). First, we attempted to

synthesize stereochemically pure silyl enol ether **6a** of 2-phenyl propiophenone. After several unsuccessful attempts to obtain stereochemically pure silyl enol ether of 2-phenyl propiophenone,¹⁶ we decided to apply a mixture of (*E*) and (*Z*) silyl enol ethers to enantioselective protonation reaction under the standard condition developed for protonation reaction of cyclic substrates. To our surprise, the protonation product was obtained in nearly quantitative yield and 92 % ee despite a 2:1 isomeric ratio of the silyl enol ether substrate (entry 1, Table 3).

With this rather unexpected result in hand, we moved our attention to other acyclic substrates under those reaction conditions. Several other silyl enol ethers from 2-aryl propiophenones were prepared as a mixture of *E/Z* isomers. Protonation products, however, were obtained in excellent yields and high enantioselectivities regardless of the ratio of *E/Z* in the starting silyl enol ethers (entries 2–8). Electronic effects had little impact on enantioselectivity (entries 1–4), although electron-withdrawing substituents required somewhat longer reaction times (entry 4). Acyclic ketones bearing bulky aryl groups at the *alpha*-position, such as *ortho*-substituted aryl group, are tolerated, albeit with slightly lower enantioselectivity (entries 6–8). We further examined the effect of substituents on the aromatic ring of 2-phenyl propiophenone (entries 1, 9–11). Substituents on the phenyl ring have little effect on enantioselectivity (entries 1, 9–10), although the silyl enol ether with an electron-withdrawing substituents decreased reacted more slowly in the protonation reaction (entry 11). Furthermore, alkyl substituted silyl enol ether **6l** could also be employed in the gold-catalyzed protonation reaction with only slightly lower enantioselectivity (entry 12). The catalyst system was also effective for the protonation of the silyl enol ether of 2-phenyl butyrophenone (**6m**), providing the desired ketone in 91% yield and 85% ee (entry 13). However, the silyl enol ether possessing two alkyl groups at the *alpha*-position provided the protonation product in poor enantioselectivity (entry 14).¹⁷

Several experiments were conducted in order to gain insight into the reaction mechanism. First, we tested the possibility that the reaction proceeded by protonation of a gold enolate^{18,19} generated transmetalation of the silyl enol ether; however, silyl enol ether **6a** remained intact and we could not detect any gold enolate formation on treatment the cationic gold complex in the absence of alcohol. A second possible scenario is selective protonation of a rapidly equilibrating mixture of silyl enol ether isomers, in which the isomerization is catalyzed by either protonation or the cationic gold complex.²⁰ However, we did not observe any isomerization between silyl enol ethers by either LBA or the cationic gold complex and the ratio of *E/Z* isomers did not remain constant during the protonation reaction (Figure 1). The third scenario is that the gold-derived LBA discriminates both isomers and approaches both silyl enol ethers from the same prochiral face, which results in very high enantioselectivity regardless of a ratio of (*E*) and (*Z*) silyl enol ethers. This scenario is consistent with the observation that the enantioselectivity of the reaction remains constant, despite the changing ratio of olefin isomers (Figure 1). Similarly, protonation of the silyl enol ether of 2-phenyl propiophenone with different *E/Z* ratios, produced ketone **7a** with comparable the yields and enantioselectivities (eq 2).

(2)

In conclusion, we have developed the first gold-catalyzed enantioselective protonation reaction. The chiral Brønsted acids derived from cationic gold-complexes and an alcohol were applied to enantioselective protonation reaction of silyl enol ethers of ketones. Various silyl enol ethers from cyclic ketones could be applied to this catalytic system and the desired protonation products were obtained in excellent yields and high enantioselectivities. Furthermore, the catalytic system could be extended to the first enantioselective protonation reactions of silyl enol ethers of acyclic ketones. The silyl enol ethers of acyclic ketones afforded the corresponding ketones in high enantioselectivities even with a mixture of (*E*) and (*Z*) isomers of silyl enol ethers. Mechanistic studies suggest that a gold-derived LBA selectively protonates silyl enol ethers from the same prochiral face regardless of their stereochemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

- For recent reviews on gold catalyzed reactions, see: (a) Shapiro ND, Toste FD. *Synlett*. 2010:675. [PubMed: 21135915] (b) Wang S, Zhang G, Zhang L. *Synlett*. 2010:692. (c) Fürstner A. *Chem. Soc. Rev.* 2009; 38:3208. [PubMed: 19847352] (d) Shen HC. *Tetrahedron*. 2008; 64:7847. (e) Gorin DJ, Sherry BD, Toste FD. *Chem. Rev.* 2008; 108:3351. [PubMed: 18652511] (f) Li Z, Brouwer C, He C. *Chem. Rev.* 2008; 108:3239. [PubMed: 18613729] (g) Gorin DJ, Toste FD. *Nature*. 2007; 446:395. [PubMed: 17377576] (h) Hashmi ASK, Hutchings GJ. *Angew. Chem., Int. Ed.* 2006; 45:7896.
- For recent examples see: (a) Gonzalez AZ, Benitez D, Tkatchouk E, Goddard WA III, Toste FD. *J. Am. Chem. Soc.* 2011; 133:5500. [PubMed: 21428409] (b) Sethofer SG, Mayer T, Toste FD. *J. Am. Chem. Soc.* 2010; 132:8276. [PubMed: 20518531] (c) Martinez A, Carcia-Garcia P, Fernandez-Rodriguez, Sanz R. *Angew. Chem., Int. Ed.* 2010; 49:4633. (d) Liu F, Qian DY, Li L, Zhao XL, Zhang JL. *Angew. Chem. Int. Ed.* 2010; 49:6669. (e) Teller H, Flugge S, Goddard R, Fürstner A. *Angew. Chem., Int. Ed.* 2010; 49:1949. (f) LaLonde RL, Wang ZJ, Lackner AD, Toste FD. *Angew. Chem., Int. Ed.* 2010; 49:598. (g) Gonzalez AZ, Toste FD. *Org. Lett.* 2010; 12:200. [PubMed: 19961192] For reviews on enantioselective gold catalysis, see: (h) Sengupta S, Shi X. *ChemCatChem*. 2010; 2:609. (i) Widenhoefer RA. *Chem. Eur. J.* 2008; 14:5382. (j) Pradal A, Toullec PY, Michelet V. *Synthesis*. 2011:1501.
- For examples that are proposed to proceed to mechanisms other than π -activation see: (a) Campbell MJ, Toste FD. *Chem. Sci.* 2011; 2:1369. (b) Melhado AD, Amarante GW, Wang ZJ, Luparia M, Toste FD. *J. Am. Chem. Soc.* 2011; 133:3517. [PubMed: 21341677] (c) Martin-Rodriguez M, Najera C, Sansano JM, Wu F-L. *Tetrahedron: Asymmetry*. 2010; 21:1184. (d) Melhado AD, Luparia M, Toste FD. *J. Am. Chem. Soc.* 2007; 129:12638. [PubMed: 17900190] (e) Ito Y, Sawamura M, Hayashi T. *J. Am. Chem. Soc.* 1986; 108:6405.
- For recent reports of activation of alkenes with gold complex, see: (a) LaLonde RL, Brenzovich WE, Benitez D, Tkatchouk E, Kelly K, Goddard WA, Toste FD. *Chem. Sci.* 2010; 1:226. For enantioselective alkene hydroamination see: (b) Zhang Z, Lee SD, Widenhoefer RA. *J. Am. Chem. Soc.* 2009; 131:5372. [PubMed: 19326908] For a review, see: (c) Widenhoefer RA, Han X. *Eur. J. Org. Chem.* 2006:4555.
- (a) Luzung MR, Mauleon P, Toste FD. *J. Am. Chem. Soc.* 2007; 129:12402. [PubMed: 17887681] (b) Shi FQ, Li X, Xia Y, Zhang L, Yu ZX. *J. Am. Chem. Soc.* 2007; 129:15503. [PubMed:

- 18027935] (c) Marion N, Carlqvist P, Gealageas R, de Fremont P, Maseras F, Nolan SP. Chem. Eur. J. 2007; 13:6437.
6. Kanno O, Kuriyama W, Wang ZJ, Toste FD. *submitted*.
7. Yamamoto introduced the concept of Lewis acid Assisted Brønsted acid (LBA) catalysis. For reviews of combined acids, see: (a) Yamamoto H, Futatsugi K. Angew. Chem., Int. Ed. 2005; 44:1924. (b) Ishibashi H, Ishihara K, Yamamoto H. Chem. Rec. 2002; 2:177. [PubMed: 12112869]
8. For reviews of enantioselective protonation reactions, see: (a) Mohr JT, Hong AY, Stoltz BM. Nature Chem. 2009; 1:359. [PubMed: 20428461] (b) Duhamel L, Duhamel P, Plaquevent JC. Tetrahedron: Asymmetry. 2004; 15:3653. (c) Eames J, Weerasooriya N. Tetrahedron: Asymmetry. 2001; 12:1. (d) Yanagisawa A, Yamamoto H, Jacobsen EN, Pfaltz A, Yamamoto H. Comprehensive Asymmetric Synthesis III. 1999 Heidelberg Springer:1295. (e) Fehr C. Angew. Chem., Int. Ed. 1996; 35:2566.
9. For LBA catalyzed enantioselective protonation reactions, see: (a) Cheon CH, Imahori T, Yamamoto H. Chem. Commun. 2010:6980. (b) Nakashima D, Yamamoto H. Synlett. 2006:150. (c) Ishihara K, Nakashima D, Hiraiwa Y, Yamamoto H. J. Am. Chem. Soc. 2003; 125:24. [PubMed: 12515493] (d) Nakamura S, Kaneeda M, Ishihara K, Yamamoto H. J. Am. Chem. Soc. 2000; 122:8120. (e) Ishihara K, Nakamura S, Yamamoto H. Croat. Chem. Acta. 1998; 69:513. (f) Ishihara K, Ishida Y, Nakamura S, Yamamoto H. Synlett. 1997:758. (g) Ishihara K, Nakamura S, Kaneeda M, Yamamoto H. J. Am. Chem. Soc. 1996; 118:12874. (h) Ishihara K, Kaneeda M, Yamamoto H. J. Am. Chem. Soc. 1994; 116:11179.
10. For other examples of enantioselective protonation reactions of silyl enol ethers, see: (a) with organocatalyst, see: Poisson T, Dalla V, Marsais F, Dupas G, Oudeyer S, Levacher V. Angew. Chem., Int. Ed. 2007; 46:7090. (b) with chiral Brønsted acid, see: Cheon CH, Yamamoto H. J. Am. Chem. Soc. 2008; 130:9246. [PubMed: 18582053]
11. Another example of asymmetric protonation of silyl enol ether with BINAP·AgF complex, see: Yanagisawa A, Touge T, Arai T. Angew. Chem., Int. Ed. 2005; 44:1546.
12. We investigated the possibility that the protonation reaction was catalyzed by an LBA generated from AgBF₄ and alcohol in the absence of chiral phosphine ligand. However, under these conditions, the silver-derived LBA did not catalyze the protonation reaction.
13. See Supporting Information for additional details information.
14. Enantioselective protonation reaction of acyclic substrates was reported by Yamamoto; however, substrates employed can have only single isomer of silyl enol ethers, such as bis(trimethylsilyl)ketene acetals. See ref. 9(d).
15. Fu has reported an alternative method for the synthesis of acyclic α -aryl ketones via enantioselective α -arylation of acyclic ketones, see: (a) Lou S, Fu GC. J. Am. Chem. Soc. 2010; 132:1264. [PubMed: 20050651] (b) Lundin PM, Esquivias J, Fu GC. Angew. Chem., Int. Ed. 2009; 48:154.
16. Silyl enol ether of 2-phenyl propiophenone were obtained in different ratios of (*E*)- and (*Z*)-isomers depending on the reaction conditions. Soft enolization (TMSOTf, NEt₃) gave the silyl enol ether in 1:3 ratio, whereas hard enolization (LDA/TMSCl) gave the silyl enol ether with 1:2 ratio. For more detailed information, see Supporting Information.
17. Under the standard conditions, the gold-catalyzed protonation reaction of the silyl ketene acetal of methyl 2-phenylpropionate gave racemic product.

18. For an example of formation of gold(I) enolate, see: Nesmeyanov AN, Grandberg KI, Dyadchenko VP, Lemenovskii DA, Perevalova EG. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1974:1206.
19. For examples of gold-catalyzed reactions of silyl enol ethers that do not involve formation of gold enolates, see: (a) Staben ST, Kennedy-Smith JJ, Huang D, Corkey B, LaLonde RL, Toste FD. *Angew. Chem., Int. Ed.* 2006; 45:5991. (b) Linghu X, Kennedy-Smith JJ, Toste FD. *Angew. Chem., Int. Ed.* 2007; 46:7671. (c) Lee K, Lee PH. *Adv. Synth. Catal.* 2007; 349:2092. (d) Ito H, Ohmiya H, Sawamura M. *Org. Lett.* 2010; 12:4380. [PubMed: 20822100]
20. For isomerization between (*E*) and (*Z*) isomers of enol ethers in a gold catalyzed reactions, see: Teles JH, Brode S, Chabanas M. *Angew. Chem., Int. Ed.* 1998; 37:1415.

Figure 1.
Enantioselectivity and E/Z ratio during protonation reaction of **6a** with LBA.

Table 1

Optimization of Reaction conditions

entry	P	AgX	conversion (%) ^a	ee (%) ^b
1	1a	AgBF ₄	100	87
2	1b	AgBF ₄	70	87
3	1c	AgBF ₄	100	83
4	2a	AgBF ₄	100	36
5	3a	AgBF ₄	100	88
6	3b	AgBF ₄	100	70
7	3a	AgOBz	N. R.	N. D.
8	3a	AgNTf ₂	100	86
9	3a	AgOTf	100	86
10	3a	AgClO ₄	100	84
11	3a	AgSbF ₆	100	82
12	3a	-	N.R.	N. D.
13 ^c	3a	AgBF ₄	100	83
14 ^d	3a	AgBF ₄	N.R.	N. D.
15 ^e	3a	AgBF ₄	100	93

^a Conversion was determined by ¹H NMR.

^b Enantiomeric excess (ee) was determined by HPLC using chiral IC column.

^c 6 mol% of AgBF₄ was used.

^d Reaction was carried out in the absence of gold.

^e EtOH was used as solvent.

^f Absolute stereochemistry was determined by comparison of optical rotation.¹³

Table 2

Substrate Scope for Cyclic Ketones

entry	n	R ¹	yield (%) ^a	ee (%) ^b
1	1	Ph (4a)	96	93
2 ^c	1	4-MeOPh (4b)	98	90
3 ^c	1	4-MePh (4c)	95	91
4	1	2-naphthyl (4d)	94	94
5 ^d	2	Ph (4e)	95	94
6	1	Me (4f)	96	93
7	0	Me (4g)	97	94

^a Isolated yield.

^b Determined by chiral HPLC.

^c Reaction was conducted at -24 °C.

^d Reaction was carried out in EtOH without CH₂Cl₂.

^e Absolute stereochemistry was established by comparison of optical rotations of known compounds **4a** and **4f**. The absolute stereochemistry of the remaining of compounds was assigned by analogy.¹³

Table 3

Substrate Scope for Acyclic Ketones

entry	silyl enol ether	<i>E/Z</i> ^c	yield (%) ^a	ee (%) ^b
1	R ³ = Ph (6a)	2:1	97	92
2 ^e	R ³ = 4-MeOPh (6b)	5:1	98	95
3	R ³ = 4-MePh (6c)	2:1	95	95
4 ^d	R ³ = 4-CF ₃ Ph (6d)	1:1	92	92
5	R ³ = 2-naphthyl (6e)	2:1	95	94
6	R ³ = 1-naphthyl (6f)	3:1	91	86
7 ^e	R ³ = 2-MeOPh (6g)	3:1	94	90
8	R ³ = 2-MePh (6h)	2:1	93	85
9	R ¹ = 4-MeOPh (6i)	3:1	94	89
10	R ¹ = 4-MePh (6j)	3:1	95	90
11 ^d	R ¹ = 4-CF ₃ Ph (6k)	3:1	82	88
12	R ¹ = <i>t</i> -Bu (6l)	1:1	89	84
13	R ² = Ph (6m)	1:1	91	85
14	R ² = Me (6n)	4:1	94	17

^a Isolated yield.

^b Determined by chiral HPLC.

^c ratio of major silyl enol ether to minor silyl enol ether.

^d Reaction was carried out in EtOH without CH₂Cl₂.

^e Reaction time was 24 h.

^f Absolute stereochemistry was determined by comparison of optical rotation of known compound **6a** and absolute stereochemistry of the rest of compounds were assigned by analogy.¹³