

Direct Access to Enantioenriched Spiroacetals through Asymmetric Relay Catalytic Three-Component Reaction

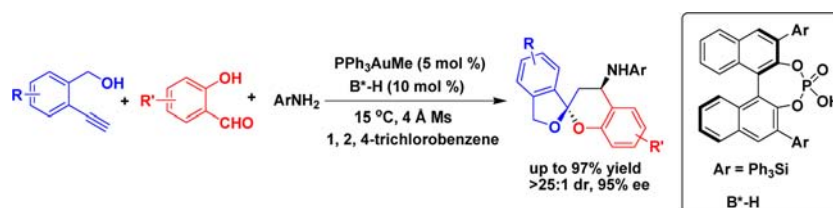
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ABSTRACT



The gold(I)/chiral Brønsted acid relay catalysis enabled a highly stereoselective three-component reaction of salicylaldehydes, anilines, and alkynols to give aromatic spiroacetals in high yields and stereoselectivities.

The spiroacetal moiety widely presented in a myriad of natural products essentially contributes to the bioactivity and represents a privileged scaffold in drug discovery.¹ Moreover, molecules containing the spiroacetal have been widely recognized as useful building blocks for the synthesis of a wide range of biologically active compounds,² such as berkelic acid (I), which shows a confrontation ovarian cancer effect, paecilospirone (II), which acts as an inhibitor of microtubule, and γ -rubromycin (III), which exhibits antibacterial properties (Figure 1). Consequently, efficient access to such a structural target has been in great demand. However, the methods investigated previously reported mostly on the diastereoselective spiroacetalizations from optically pure starting materials,³ and until very recently, the asymmetric catalytic variants from achiral

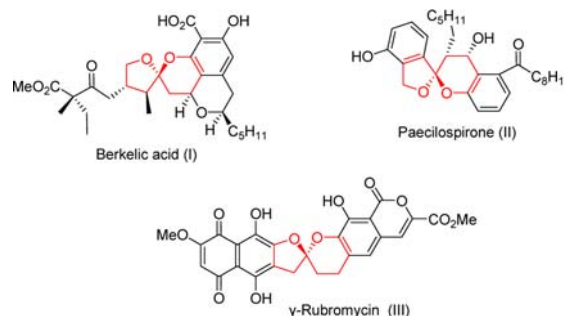


Figure 1. Nature products containing spiroacetal moiety.

materials to give optically active spiroacetal have not appeared.^{4,5} Ding and co-workers reported a nice synthesis of spiroacetals with excellent levels of stereoselectivity through asymmetric reductive acetalization of α,β -unsaturated ketones catalyzed by chiral iridium(I) complexes (eq 1, Scheme 1).^{4a} List identified a truly enantioselective

(1) For reviews see: (a) Perron, F.; Albizzati, K. F. *Chem. Rev.* **1989**, 89, 1617. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, 105, 4406.

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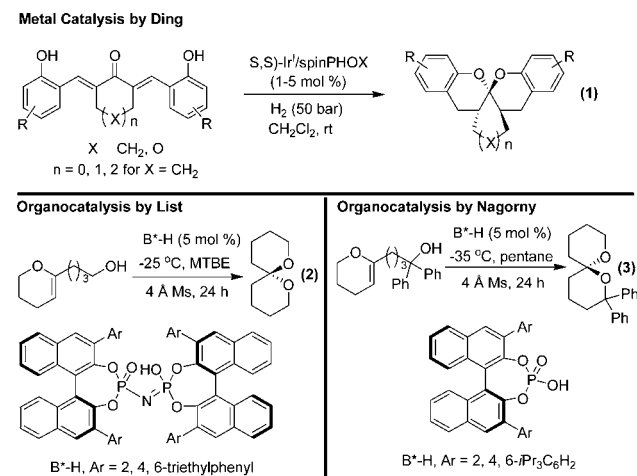
(3) (a) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.; Pettus, T. R. R. *Org. Lett.* **2008**, 10, 1477. (b) Wilson, Z. E.; Hubert, J. G.; Brimble, M. A. *Eur. J. Org. Chem.* **2011**, 3938. (c) Smith, M. J.; Furkert, D. P.; Sperry, J.; Brimble, M. A. *Synlett* **2011**, 1395. (d) Butkevich, A. N.; Corbu, A.; Meerpoel, L.; Stansfield, I.; Angibaud, P.; Bonnet, P.; Cossy, J. *Org. Lett.* **2012**, 14, 4998.

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acetalization of hydroxyalkyl-substituted enol ethers by using a newly designed chiral binol-based C_2 -symmetric imidodiphosphoric acid as the chiral catalyst, generating chiral spiroacetals in excellent stereoselectivity (eq 2, Scheme 1).^{4b} Subsequently, Nagorny established a similar binol-based phosphoric acid-catalyzed stereoselective acet-

Scheme 1. Typical Examples of Asymmetric Catalytic Access to Chiral Spiroacetals



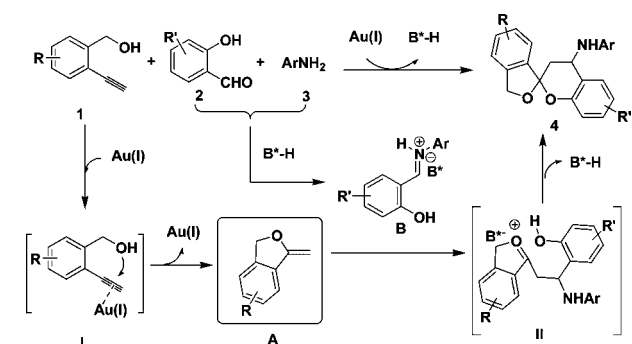
alization of hydroxyalkyl-substituted enol ethers (eq 3, Scheme 1).^{4c} Despite these successful examples, the union of readily available and easily accessible fragments instead of the preformed acetalization substrates into chiral spiroacetals under mild conditions, which actually provides a

(6) For reviews on combining organocatalysis with metal catalysis, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, 38, 2745. (b) de Armas, P.; Tejedor, D.; Garcia-Tellado, F. *Angew. Chem., Int. Ed.* **2010**, 49, 1013. (c) Rueping, M.; Koenigs, R. M.; Atodiresi, I. *Chem.—Eur. J.* **2010**, 16, 9350. (d) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (e) Zhou, J. *Chem. Asian J.* **2010**, 5, 422. (f) Han, Z.-Y.; Wang, C.; Gong, L.-Z. In *Science of Synthesis: Asymmetric Organocatalysis*; Maruoka, K., Ed.; Georg Thieme Verlag: Stuttgart, 2012; Vol. 2, p 697. (g) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, 18, 10212. (h) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem.* **2012**, 10, 211.

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more synthetically efficient access to the structurally complex targets, has been investigated even less and is thereby highly valuable to be disclosed.⁵ We will herein report a gold(I)/Brønsted acid relay catalytic three-component cascade reaction, providing an important alternative of known methods to directly access highly enantioenriched spiroacetals.

Scheme 2. Asymmetric Gold(I)/Brønsted Acid Relay Catalytic Synthesis of Spiroacetals



In the last decades, the metal/organo combined catalysis has turned out to be a robust strategy for the creation of new enantioselective transformations.^{6–8} In particular, the hybrid metal/organo relay catalysis was able to assemble readily available starting materials into structurally complex molecules, essentially avoiding additional laborious workup and purification process of the intermediates involved.⁸ We and others found that the combination of gold complexes and chiral phosphoric acids enabled a range of asymmetric cascade reactions.⁸ Recently, Barluenga developed a palladium(II)-catalyzed synthesis of racemic spiroacetals through a three-component cascade reaction.⁹ Inspired by this finding and our knowledge in gold/phosphoric acid binary catalysis,^{8d,h,k–m} we envisaged that the alkynols of type **1** are principally able to undergo a cyclization reaction to afford aromatic enol ethers **A** under the catalysis of a gold complex.^{8k} The intermediates **A** might participate in a formal [4 + 2] cyclization reaction, consisting of an asymmetric Mannich-type reaction

(8) For metal/organo relay catalysis, see: (a) Abillard, O.; Breit, B. *Adv. Synth. Catal.* **2007**, 349, 1891. (b) Chercheja, S.; Eilbracht, P. *Adv. Synth. Catal.* **2007**, 349, 1897. (c) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, 130, 14452. (d) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, 131, 9182. (e) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, 11, 4204. (f) Cai, Q.; Zhao, Z.-A.; You, S.-L. *Angew. Chem., Int. Ed.* **2009**, 48, 7428. (g) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, 131, 6354. (h) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, 12, 2266. (i) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G.; Duan, Y.; Fan, H.-J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, 133, 6126. (j) Chen, Q.-A.; Chen, M.-W.; Yu, C.-B.; Shi, L.; Wang, D.-S.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2011**, 133, 16432. (k) Han, Z.-Y.; Guo, R.; Wang, P.-S.; Chen, D.-F.; Xiao, H.; Gong, L.-Z. *Tetrahedron Lett.* **2011**, 52, 5963. (l) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, 134, 6532. (m) Wu, H.; He, Y.-P.; Gong, L.-Z. *Adv. Synth. Catal.* **2012**, 354, 975.

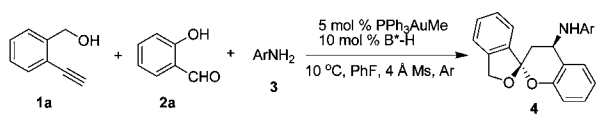
(9) Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, 48, 1644.


with salicylaldehydimines **B** in situ generated from the condensation between salicylaldehydes **2** and anilines **3**¹⁰ under the catalysis of chiral Brønsted acid¹¹ and a subsequent acetalization to result in the generation of corresponding aromatic spiroacetals (Scheme 2). As such, a series of enantioenriched aromatic spiroacetals would be directly afforded from easily accessible substrates.

The initial investigation of the proposed asymmetric relay catalytic three-component reaction was performed with (2-ethynylphenyl)methanol (**1a**), 2-hydroxybenzaldehyde (**2a**), and aniline (**3**) in the presence of a combined catalyst system^{8d} consisting of chiral gold phosphate and Brønsted acids prepared from PPh₃AuMe (5 mol %) and Brønsted acids prepared from PPh₃AuMe (5 mol %) and chiral phosphoric acid **5a** (10 mol %) and of 4 Å molecular sieves in fluorobenzene¹² at 10 °C (Table 1). The transformation proceeded smoothly and afforded *N*-phenyl-3'-*H*-spiro[chroman-2,1'-isobenzofuran]-4-amine (**4a**) in good yield (70%), but the enantioselectivity was poor (entry 1). Thus, various structurally diverse chiral phosphoric acids **5a–g** derived from 3,3'-disubstituted BINOLs were evaluated to identify the best organocatalyst (entries 2–7). Among them, the phosphoric acid **5g** bearing a sterically bulky substituents at 3,3'-positions turned out to be the preeminent catalyst and was able to provide the spiroacetal **4a** with high yield (83%) and moderate diastereoselectivity (3:1), while the major diastereomer of **4a** was obtained in 72% ee (entry 7). Interestingly, the chiral gold phosphate in situ generated from **5g** and PPh₃AuMe^{8d,e} was able to catalyze the reaction in 79% yield, but with a lower enantioselectivity (entry 8 vs 7). The results indicated that both gold phosphate and chiral phosphoric acid can catalyze the cascade reaction, but the chiral phosphoric acid plays a dominant role in the control of stereoselectivity in the Mannich-type reaction step (Scheme 2). A survey of solvents identified that the halogenated benzenes were beneficial to the stereocontrol (entries 9–11), and enantioselectivity could be enhanced to 80% ee by conducting the reaction in 1,2,4-trichlorobenzene (entry 11). Then, a variety of aniline derivatives (**3b–e**) were examined, and it was found that either electronically withdrawing or donating substituents were well tolerated (entries 12–15). In particular, the 3,5-dimethoxyaniline (**3e**) participated in the three-component reaction with the highest level of enantioselectivity (entry 15).


Under the optimal conditions, we next investigated the generality for salicylaldehydes (Table 2). A wide range of salicylaldehydes substituted with various substituents at the benzene ring were applicable to the reaction, giving

Table 1. Evaluation of Brønsted Acid Catalysts and Optimization of Reaction Conditions^a



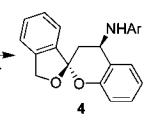


1a



2a

3



4

5a: Ar = 4-NO₂C₆H₄
5b: Ar = 4-ClC₆H₄
5c: Ar = 4-Biphenyl
5d: Ar = 1-Naphthyl
5e: Ar = 3, 5-(CF₃)₂C₆H₃
5f: Ar = Ph₂MeSi
5g: Ar = Ph₃Si

3a: Ar = Ph
3b: Ar = 4-MeOC₆H₄
3c: Ar = 4-MeC₆H₄
3d: Ar = 4-CF₃C₆H₄
3e: Ar = 3, 5-(MeO)₂C₆H₃

entry	B*-H	ArNH ₂	4	yield ^b (%)	dr ^c	ee ^d (%)
1	5a	3a	4a	70	3/1	1
2	5b	3a	4a	99	3/1	10
3	5c	3a	4a	65	3/1	21
4	5d	3a	4a	73	3/1	49
5	5e	3a	4a	93	3/1	19
6	5f	3a	4a	87	3/1	6
7	5g	3a	4a	83	3/1	72
8	5g	3a	4a	79	3/1	65 ^e
9	5g	3a	4a	80	4/1	74 ^f
10	5g	3a	4a	78	4.6/1	76 ^g
11	5g	3a	4a	84	4.5/1	80 ^h
12	5g	3b	4b	75	4.3/1	76 ^{h,i}
13	5g	3c	4c	83	4.7/1	74 ^{h,i}
14	5g	3d	4d	69	4.5/1	69 ^{h,i}
15	5g	3e	4e	88	6/1	85 ^{h,i}

^a Unless indicated otherwise, the reaction of **1** (0.12 mmol), **2** (0.11 mmol), and **3** (0.10 mmol) was carried out in PhF (1.0 mL) at 10 °C for 3 d under Ar in the presence of gold catalyst (5 mol %), Brønsted acid (10 mol %), and 4 Å Ms (50 mg). ^b Combined yield of both diastereomers. ^c The dr was determined by ¹H NMR. ^d The ee was determined by HPLC. ^e 5 mol % of **5g** was used. ^f In PhBr (1.0 mL). ^g In 1,3-dichlorobenzene (1.0 mL). ^h In 1,2,4-trichlorobenzene (1.0 mL) at 15 °C. ⁱ The compound details were described in the Supporting Information.

aromatic spiroacetals in up to 95% yield with > 25:1 dr and up to 91% ee (entries 1–7). A disubstituted salicylaldehyde with the chloro groups at both 4 and 6-positions underwent the reaction to furnish the corresponding **4f** in 81% yield and with 91% ee (entry 1). Notably, the position of the substituent on the benzene ring of the salicylaldehydes exhibited significant effect on both the diastereo- and enantioselectivities. For instance, 2-hydroxybenzaldehydes with a substituent at 4-position gave higher enantioselectivities than those with the substituent at either the 5- or 6-position (entries 3, 6, and 7 vs 2 and 5). Excellent diastereoselectivity (> 25:1), together with a high yield (83%) and high ee (85% ee), was obtained when 2-hydroxy-1-naphthaldehyde was employed as a reaction component (entry 4). Interestingly, the electron feature of the substituent on the benzene ring of 2-hydroxybenzaldehyde had very little effect on the stereoselectivities (entries 3, 6, and 7). Further investigation of the substrate scope was focused on the alkynols. Various alkynols with different aryl substituents, such as a 4-fluorophenyl and 4-bromophenyl group, were tolerated. Excellent enantioselectivities were also

(10) Salicylaldehydimines **B** can be easily afforded from the condensation of **2** and **3** catalyzed by Brønsted acid, while in the absence of the acid, the condensation will become very slow.

(11) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uruguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For reviews, see: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Terada, M. *Chem. Commun.* **2008**, 4097. (f) Terada, M. *Synthesis* **2010**, 1929. (h) Rueping, M.; Lin, M. Y. *Chem.—Eur. J.* **2010**, *16*, 4169. (i) Bernardi, L.; Comes-Franchini, M.; Fochi, M.; Leo, V.; Mazzanti, A.; Ricci, A. *Adv. Synth. Catal.* **2010**, *352*, 3399.

(12) For the use of fluorobenzene as the optimal solvent in gold/Brønsted acid relay catalysis, see ref 8l.

Table 2. Scope of Various Alkynols and Salicylaldehydes of the Cascade Multiple Components Reactions^a

entry	4	R	R'	yield ^b (%)	dr ^c	ee ^d (%)
1	4f	H	4,6-Cl ₂	81	10/1	91
2	4g	H	5-Cl	79	>25/1	80
3	4h	H	4-F	70	6/1	90
4	4i	H	^e	83	>25/1	85
5	4j	H	6-F	95	9/1	83
6	4k	H	4-Br	78	6.5/1	89
7	4l	H	4-Me	87	4/1	90
8	4m	4-F	4,6-Cl ₂	91	>25/1	90
9	4n	4-F	4-F	75	4.3/1	90
10	4o	4-F	4-Br	71	4.6/1	94
11	4p	4-F	4-Me	72	5/1	91
12	4q	5-F	4,6-Cl ₂	67	>25/1	81
13	4r	4-Cl	4,6-Cl ₂	87	9/1	92
14	4s	4-Cl	4-Me	92	4.3/1	92
15	4t	4-Cl	4-F	83	4/1	91
16	4u	4-Cl	4-Br	97	4/1	95
17	4v	5-Cl	4,6-Cl ₂	62	9/1	84
18	4w	4-Me	4,6-Cl ₂	94	>25/1	87
19	4x	4-Me	^e	87	6/1	86
20	4y	4-Me	4-Br	88	3.5/1	88

^a Unless indicated otherwise, the reaction of **1** (0.12 mmol), **2** (0.11 mmol), and **3e** (0.10 mmol) was carried out in 1,2,4-trichlorobenzene (1.0 mL) at 15 °C for 3 d under Ar in the presence of gold(I) catalyst (5 mol %), Brønsted acid (10 mol %), and 4 Å Ms (50 mg). ^b Combined yield of both diastereomers. ^c The dr was determined by ¹H NMR. ^d The ee was determined by HPLC. ^e 2-Hydroxy-1-naphthaldehyde was used.

obtained for those alkynols with different salicylaldehydes (Table 2, entries 8–20). Basically, the electron-withdrawing substituent, such as either the fluoride, chloride, or the bromide group, turned out to be beneficial to the enantioselectivities, whereas the presence of electron-donating substituents, such as the methyl group, was slightly deleterious to the reactivity (entries 8–11 and 13–16 vs 18–20). Moreover, the position of the substituent

on the benzene ring of alkynols also had considerable influence on the reactivity. Thus, the alkynols with a substituent at the 4-position provided the corresponding spiroacetals in excellent yield and enantioselectivities (up to 97% yield and 95% ee). However, comparably lower yields and enantioselectivities were obtained when 5-substituted alkynols were examined as substrates (entries 8–11 vs 12 and entries 13–16 vs 17). The configurations of **4i** were determined by X-ray crystallography analysis (see the Supporting Information).

A scale-up three-component reaction **1a** with 2-hydroxy-1-naphthaldehyde and **3e** proceeded smoothly under the catalysis of gold(I)/ Brønsted acid binary system to generate the enantioenriched spiroacetal **4i** in a maintained yield and stereoselectivity. After recrystallization, the enantiomeric purity of **4i** could be enhanced to >99% ee. The hydrogenolysis of the optically pure **4i** furnished 3'-H-spiro[chroman-2,1'-isobenzofuran] **6**, which is presented as the cyclic core unit in the natural product paecilospirone (**II**),^{3b,c} in 90% yield with 98% ee (see the Supporting Information).

In summary, we have disclosed an asymmetric relay catalytic multicomponent reaction by using gold(I) complex/ chiral phosphoric acid, which is able to assemble the readily available and easily accessible substrates, including salicylaldehydes, aniline, and alkynols into aromatic spiroacetals with high optical purity. The method provided an important alternative of known methods to directly access highly enantioenriched spiroacetals and would be potentially applied to the synthesis of spiroacetal motifs presented in natural products.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.