

Hybrid Metal/Organo Relay Catalysis Enables Enynes To Be Latent Dienes for Asymmetric Diels–Alder Reaction

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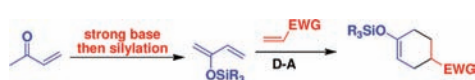
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S Supporting Information

ABSTRACT: The hybrid Au(I)/Brønsted acid binary catalyst system enables enynes to serve as latent 1,3-silyloxydienes capable of participating in the first cascade hydrosilylation of an enynyl silanol/asymmetric Diels–Alder reaction. A variety of polycyclic compounds bearing multistereogenic centers were obtained in high yields and excellent enantioselectivities from the relay catalytic cascade reaction between (2-(but-3-en-1-ynyl)phenyl) silanols and quinones catalyzed by the combined achiral gold complex and chiral *N*-triflyl phosphoramidate.

The Diels–Alder reaction is undoubtedly one of the most important and fascinating transformations in organic chemistry.¹ 1,3-Silyloxydienes have proven to be extraordinarily useful building blocks due to their high reactivity in a Diels–Alder reaction, providing an efficient entry to cyclohexanone derivatives.² So far, the most used method to prepare dienes of this type is the silylation of unsaturated carbonyls (Scheme 1).³

Scheme 1. Classical Synthesis of 1,3-Silyloxydienes for Diels–Alder Reaction

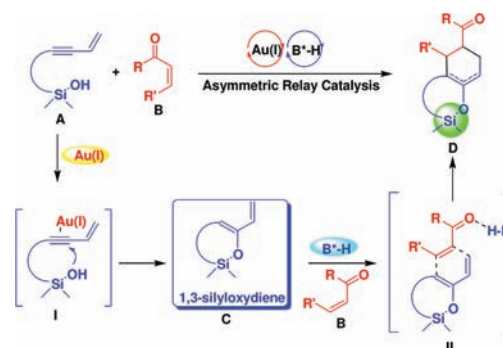


Although it is reliable and practical, the method basically requires a stoichiometric or more amounts of strong bases. A Diels–Alder reaction of 2-siloxy-1,3-butadiene catalytically generated from readily available precursors would be a highly appealing alternative and is arguably valuable in organic synthesis. However, an approach to realize such a Diels–Alder reaction has not been available, yet. As a proof of concept, we will herein describe a hybrid metal/organo relay catalytic reaction that comprises the first catalytic formation of 1,3-silyloxydiene from enynes and a Brønsted acid catalyzed asymmetric Diels–Alder reaction.

The greatest challenge that needs to circumvent for the validation of the concept is to find mild conditions that tolerate both the catalytic generation of dienes and the subsequent asymmetric Diels–Alder reaction. However, the classical synthesis of 1,3-silyloxydienes including the method shown in Scheme 1 is apparently far from requisites to realize the one-pot sequential diene formation and asymmetric Diels–Alder reaction. Recently, many endeavors have been devoted to the

development of asymmetric relay catalytic transformations by using metal/organo binary catalyst systems.^{4–6} Indeed, such a strategy has rendered the birth of a large number of unprecedented enantioselective processes and thereby has become an important research orientation in synthetic organic chemistry. We have found that gold(I) complexes and phosphoric acids are highly compatible and, more importantly, can synergistically afford some asymmetric cascade reactions.^{5d,h,k} Moreover, the gold-catalyzed hydroxylation of a carbon–carbon triple bond has been well established.⁷ Thus, we envisioned that the gold complex might be able to catalyze an intramolecular hydrosilylation of enynyl silanol of type **A**, giving a reactive silyloxydiene **C**, which could subsequently participate in an asymmetric Diels–Alder reaction with an electron deficient olefin **B** catalyzed by a chiral Brønsted acid (Scheme 2). As such, an asymmetric Diels–Alder reaction using enynes as latent 1,3-silyloxydienes turns out to be feasible.

Scheme 2. Combination of Catalytic Diene Generation and Asymmetric Diels–Alder Reaction in One Operation through Metal/Organo Relay Catalysis



Although the addition of either water or alcohols across a carbon–carbon triple bond has long been established by using transition metal catalysts,^{7,8} surprisingly, similar addition reactions using silanols as nucleophiles that produce synthetically useful silyl enol ethers or 1,3-silyloxydienes (with enynes) have been rarely reported.⁹ To validate the concept, an intramolecular hydrosilylation of (2-(but-3-en-1-ynyl)phenyl)dimethylsilanol (**1a**) was first explored using gold

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complexes as catalysts.¹⁰ However, the initial trials had met with problems. Under the catalysis of either Ph₃PAuOTf or Ph₃PAuNTf₂, the enynyl silanol **1a** was completely converted into silicon ether **3a** at room temperature (Table 1, entries 1

Table 1. Gold Catalyzed Intramolecular Hydrosilyxylation of (2-(But-3-en-1-ynyl)phenyl) Dimethylsilanol (1a**)^a**

entry	Au(I)	time (h)	solvent	conv. (%) ^b	2a/3a
1	Ph ₃ PAuOTf	5	CH ₂ Cl ₂	>99	<1:99
2	Ph ₃ PAuNTf ₂	5	CH ₂ Cl ₂	>99	<1:99
3	Ph ₃ PAuMe/6a	5	CH ₂ Cl ₂	33	50:50 ^c
4	8	5	CH ₂ Cl ₂	>99	85:15
5	8	8	PhCH ₃	>99	>95:5
6	8	8	PhF	>99	>95:5

^aUnless indicated otherwise, the reaction of **1a** (0.05 mmol) was carried out in presence of a gold catalyst (6 mol %) at room temperature. ^bThe conversion of the reaction and the ratio of **2a/3a** were determined by ¹H NMR. ^c6 mol % of **6a** was used.

and **2**). This homocoupling of silanols probably impeded the exploration of the hydrosilyxylation reaction between silanol and alkynes. Encouragingly, a gold phosphate, which was generated *in situ* from Ph₃PAuMe and phosphoric acid **6a**,¹¹ was able to yield a mixture of the desired 1,1-dimethyl-3-vinyl-1H-benzo[c][1,2]oxasiline **2a** and the silicon ether **3a** although the reaction proceed sluggishly (entry 3). To our delight, the gold complex **8** prepared from a bulky phosphine ligand¹² was able to efficiently inhibit the homocoupling process and provided the silyloxydiene **2a** in majority (entry 4). The screening of solvents found that either toluene or fluorobenzene was suitable media to give a high chemoselectivity in favor of the desired diene **2a** (>95:5, entries 5–6).

After establishing the optimized conditions for the efficient and chemoselective generation of the 1,3-silyloxydiene, we turned our attention to the asymmetric relay catalytic cascade reaction between the enynyl silanol **1a** and naphthoquinone **4** in the presence of the combined catalyst of the gold complex **8** and a chiral Brønsted acid (Table 2). Delightedly, the chiral phosphoric acid **6a** indeed rendered the cascade reaction to proceed in dichloroethane. The desired polycyclic compound **5a** was isolated as a single diastereomer in a moderate yield, but with poor enantioselectivity (entry 1). More interestingly, in comparison with the usual Diels–Alder reaction, an olefin migration occurred in this case presumably due to the conjugated stabilization energy between the aryl group and the carbon–carbon double bond. However, an effort to identify the optimal catalyst by evaluating 3,3'-disubstituted BINOL-based phosphoric acid failed to attain satisfactory results (entries 2 and 3). Thus, we turned our attention to examining chiral *N*-triflyl phosphoramides,¹³ which have proven to be efficient catalysts for the asymmetric Diels–Alder reaction between linear 1,3-silyloxydienes and ethyl vinyl ketone as demonstrated by Yamamoto and co-workers.¹⁴ To our delight, a drastic increase in both yield and enantioselectivity was observed using these stronger Brønsted acids compared to the corresponding phosphoric acids (entries 4–7). Notably, upon exploitation of phosphoramidate **7c** as a catalyst, the product **5a** can be obtained in 82% yield and with 71% *ee* (entry 6). We

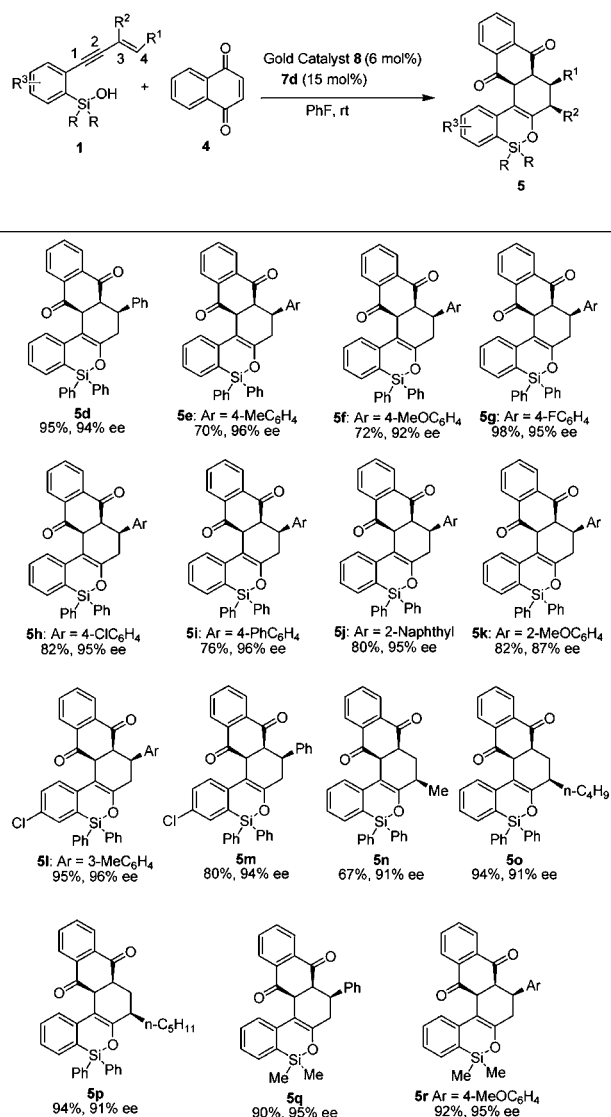
Table 2. Evaluation of Brønsted Acid Catalysts and Optimization of Reaction Conditions^a

entry	1	solvent	B*–H	time (h)	yield (%) ^b	<i>ee</i> (%) ^c
1	1a	DCE	6a	72	54	3
2	1a	DCE	6b	72	trace	–
3	1a	DCE	6c	72	30	27
4	1a	DCE	7a	72	52	13
5	1a	DCE	7b	72	22	56
6	1a	DCE	7c	72	82	71
7	1a	DCE	7d	72	76	65
8	1b	DCE	7c	96	57	67
9	1c	DCE	7c	72	68	79
10	1c	toluene	7c	48	65	83
11	1c	PhF	7d	9	81	88 ^d
12	1c	PhF	7d	12	65	89 ^{d,e}
13	1c	PhF	7d	11	85	89 ^{d,f}
14	1c	PhF	–	240	trace	– ^{e,f}

^aUnless indicated otherwise, the reaction of **1** (0.05 mmol) and **4** (0.1 mmol) was carried out at 35 °C in the presence of gold catalyst (6 mol %) and Brønsted acid (10 mol %). ^bIsolated yield. ^cThe *ee* was determined by HPLC. ^d15 mol % of Brønsted acid was used. ^eThe reaction was carried out at room temperature. ^f0.2 mmol of **4** was used.

then investigated the reaction involving (2-(but-3-en-1-ynyl)phenyl)diethylsilanol (**1b**) and (2-(but-3-en-1-ynyl)phenyl)diphenylsilanol (**1c**) under the catalysis of **7c** (entries 8 and 9). An improved enantioselectivity was observed in the case using **1c** as the substrate (entry 9). Variation of the solvent from dichloromethane to toluene could further improve the enantioselectivity from 79% to 83% *ee* (entry 9 vs 10). In particular, the product **5c** could be obtained in 81% yield and 88% *ee* using 3,3'-di(1-pyrenyl) BINOL-based phosphoramidate **7d** as the catalyst in fluorobenzene (entry 11). Finally, a further enhanced result (85% yield, 89% *ee*) could be achieved by tuning the equivalent of naphthoquinone and using 15 mol % of **7d** (entries 12–13). Interestingly, the Diels–Alder reaction between the 1,3-silyloxydiene **2c** *in situ* generated from **1c** and **4** did not occur in the presence of the gold complex alone (entry 14), implying that the Diels–Alder reaction was solely accelerated by the Brønsted acid.

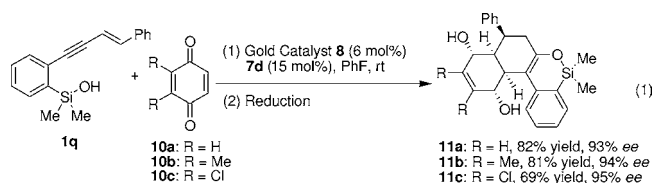
Under the optimized reaction conditions, we explored the generality of this asymmetric relay catalytic cascade reaction. As shown in Table 3, a (2-(but-3-en-1-ynyl)phenyl)diphenylsilanol derivative **1d** bearing a phenyl group at C4 underwent a smooth sequential intramolecular hydrosilyxylation/asymmetric Diels–Alder reaction to provide product **5d** in an excellent yield and enantioselectivity (95% yield, 94% *ee*). Significantly, the asymmetric relay catalytic reaction tolerated a wide spectrum of enynyl diphenylsilanols bearing either an

Table 3. Substrate Scope^a

^aUnless indicated otherwise, the reaction of **1** (0.05 mmol) and **4** (0.2 mmol) was carried out at room temperature in the presence of **8** (6 mol %) and **7d** (15 mol %) for 12 h.

electron-donating or -withdrawing aryl substituent at C4, giving rise to the desired polycyclic compound **5e–5k** in high yields of up to 98% and excellent enantioselectivities of up to 96% *ee*. The variation of the substituent on the phenylacetylene moiety was also tolerable (**5l** and **5m**). The enynyl diphenylsilanols with an alkyl substituent at C3 also underwent the cascade reaction cleanly, furnishing the desired products in high yields (67–94%) and excellent enantioselectivities (91% *ee*). Interestingly, enynyl dimethylsilanols **1q** and **1r** with an aryl substituent at C4 also provided the products **5q** and **5r** with satisfactory results (90–92% yields and 95% *ee*'s). Notably, scale-up reactions of **1d** (up to 804 mg) with naphthoquinone **4** also proceeded smoothly to give **5d** in high yield without erosion of the enantioselectivity (see Supporting Information (SI)). The configurations of **5d** were determined by X-ray crystallography analysis of its monoketoxime derivative **9**, and the relative configuration of **5n** was tentatively assigned to be *syn* by NOESY analysis (see SI).

In addition to naphthoquinone **4**, benzoquinone derivatives **10a–10c** also showed good reactivity toward the 1,3-silyloxydiene catalytically generated from **1q** and could participate in a smooth relay catalytic cascade reaction, after a one-pot diastereoselective reduction with diisobutylaluminum hydride to give **11a** to **11c** in 69–82% yields and with 93–96% *ee* (eq 1). The relative configuration of **11** was tentatively assigned by NOESY analysis (see SI).



In conclusion, we have demonstrated that the hybrid Au(I)/Brønsted acid binary catalyst system enables both (2-(but-3-en-1-ynyl)phenyl) dialkylsilanol and (2-(but-3-en-1-ynyl)phenyl) diarylsilanol derivatives to be latent 2-siloxy-1,3-butadienes and allows them to participate in the first asymmetric relay catalytic cascade intramolecular hydrosilylation/asymmetric Diels–Alder reaction. This relay catalytic process provides an unprecedented alternative to traditional Diels–Alder reactions for the efficient preparation of highly enantioenriched polycyclic compounds. Moreover, we developed a new 3,3'-di-(1-pyrenyl) BINOL-based phosphoramidate, which may potentially be a useful catalyst for asymmetric Diels–Alder reactions. Further investigations focused on tandem reactions involving intermolecular alkyne hydrosilylation are underway.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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