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Chiral Gold Complex-Catalyzed Hetero-Diels–Alder Reaction of Diazenes: Highly Enantioselective and General for Dienes

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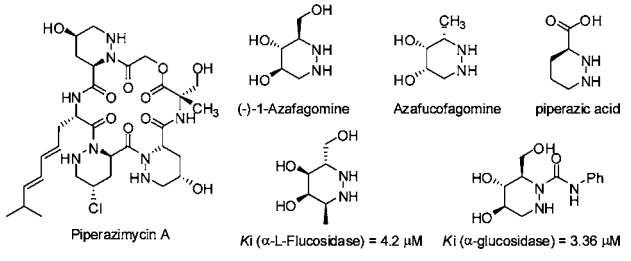
Supporting Information

ABSTRACT: A chiral gold(I) complex-catalyzed highly regio- and enantioselective azo hetero-Diels–Alder reaction has been developed. The chiral gold(I) complex acting as a Lewis acid exhibits high efficiency in the activation of urea-based diazene dienophiles. Moreover, this chiral gold catalyst also rendered a cascade intramolecular enyne cycloisomerization/asymmetric azo-HDA reaction.

The hetero-Diels–Alder (HDA) reaction is considered one of the most powerful methodologies for the construction of multifunctionalized heterocycles.[1] Among various enantioselective HDA reactions, those with diazene derivatives as dienophiles were able to produce optically active piperazines, which are important building blocks for the synthesis of natural products and constituents of core structural elements prevalently present in many bioactive compounds as shown in Scheme 1.[2] Moreover, the 1,4-diamine derivatives that can be

Scheme 1. The Natural Products and Bioactive Compounds Containing Piperazine Core Structure



accessed from piperazines have been applied to organic synthesis of many protease inhibitors.[3] However, highly enantioselective azo-HDA reactions involving diazene dienophiles are comparatively rare. Although endeavors have been devoted to reactions of this type for many years since Jørgensen reported a chiral copper complex-catalyzed HDA reaction with 22% ee,[4] so far, only one example reported by Yamamoto and co-workers, wherein the silver complex of BINAP enabled a highly enantioselective HDA reaction of diazene compounds, is most successful despite that only silyloxydienes were exploited as substrates.[5] Thus, the highly enantioseletive azo-HDA reactions of diazene tolerating a wide scope of dienes are still in great demand.

The great advances have been made in the asymmetric homogeneous gold catalysis[6] since the first enantioselective gold-catalyzed aldol reaction was described by Ito and co-workers.[7] Basically, gold(I) complexes could function either as a σ- or π-Lewis acid.[8] As π-Lewis acids, the chiral gold complexes have been identified to render a wide range of enantioselective transformations,[6,9] whereas relatively fewer examples have described the use of chiral gold(I) complex as σ-Lewis acids to control the stereochemistry by coordinating to heteroatoms (rather than C–C unsaturated bonds).[7,10] In particular, chiral gold(I) complexes have been successfully applied to facilitate asymmetric [4 + 2] cycloaddition reaction of allene-diene systems by coordination to carbon–carbon unsaturated bond,[11] but rarely been exploited to catalyze asymmetric Diels–Alder reaction by lowering LUMO of dienophiles by means of their σ-Lewis acidity. Hashmi and co-workers have demonstrated that a nonenantioselective tandem Diels–Alder reaction of *N*-phenyltriazoledione could occur under the catalysis of gold(III) complexes.[12] Herein, we will report the first chiral gold(I) complex-catalyzed highly enantioseletive azo-HDA reaction of diazene derivatives, wherein a broad spectrum of easily accessible dienes could be nicely tolerated. In addition, a cascade intramolecular enyne cycloisomerization/asymmetric azo-HDA reaction will also be described.

The initial investigation to validate our hypothesis started with a Diels–Alder reaction between commercially available 2,4-hexadiene (**1a**) and urea-based diazene dienophiles **2**, which were easily prepared from commercially available aryl isocyanates (ArNCO) and alkoxycarbonylhydrazine (H_2NNHCO_2R).[13] Since the chiral phosphoramidites have been convinced to be excellent ligands in asymmetric gold catalysis,[14] a BINOL-based phosphoramidite **3a** was first examined as the ligand of gold(I) catalyst in this reaction (Figure 1). To our delight, in the presence of 5 mol % of chiral gold(I) complex of the phosphoramidite **3a**, the HDA reaction of diene **1a** with the diazene **2a** proceeded smoothly to give the desired adduct **4a** in a high yield with 44% ee (Table 1, entry 1). However, the use of diazene **2b**, which was derived from **2a** by methylation, as dienophile led to no reaction (entry 2). The comparison of this result with that observed for **2a** indicated that the proton of the nitrogen of **2a** plays a crucial role in the reaction. The counterion of gold complexes was found to exert impact on the catalytic activities (entries 3–5) and the

Received: November 9, 2012
Published: February 19, 2013

   dx.doi.org/10.1021/ja3110472 | *J. Am. Chem. Soc.* 2013, 135, 3323–3326

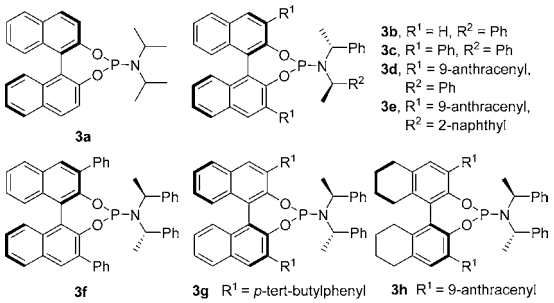
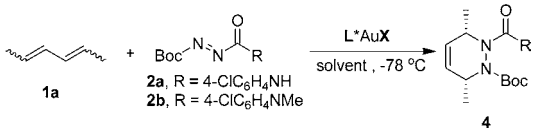


Figure 1. Chiral phosphoramidite ligands used in this study.

Table 1. Evaluation of Ligands and Optimization of Reaction Conditions[a]



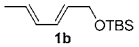
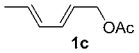
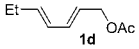
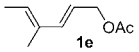
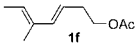
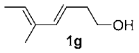
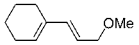
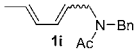
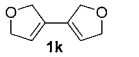
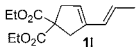
entry	L*/X	2	T (h)	yield (%)[b]	ee (%)[c]
1	3a/NTf_2	2a	25	99	−44
2	3a/NTf_2	2b	12	N.R.	--
3[d]	3a/SbF_6	2a	17	77	−37
4[d]	3a/OTf	2a	17	96	−42
5[d]	3a/PF_6	2a	34	50	−40
6	3b/NTf_2	2a	4	99	37
7	3c/NTf_2	2a	12	99	93
8	3d/NTf_2	2a	5	96	91
9	3e/NTf_2	2a	1	99	91
10	3f /NTf_2	2a	30	97	−56
11	3g/NTf_2	2a	12	95	−50
12	3h/NTf_2	2a	1	99	88
13[e]	3c/NTf_2	2a	4	96	94
14[e]	3d/NTf_2	2a	6	99	97
15[e,f]	3e/NTf_2	2a	6	89	99
16[e]	3h/NTf_2	2a	3	98	93

[a]The reaction of **1a** (0.3 mmol) and **2** (0.1 mmol) was carried out in dichloromethane at −78 °C in the presence of chiral gold catalyst (5 mol %). [b]Isolated yield. [c]Determined by HPLC. [d]The gold catalyst was prepared *in situ* from **L***AuCl and AgX. [e]In toluene. [f]**2a** was recovered.

bis(trifluoro-methylsulfonyl)amide (Tf_2N^-) enabled the gold complex to exhibit the highest catalytic performance (entry 1 vs 3−5). Then, the evaluation of other BINOL- and H_8−BINOL-derived phosphoramidites **3b−h** was conducted. The replacement of amine moiety on the phosphoramidite ligand with bis(1-phenylethyl)amine, as shown in **3b**, led to the generation of product with an inversed configuration (entry 6), which indicated that the amine moiety exerted striking influence on the control of stereochemistry. Moreover, it was identified that the introduction of different substituents to 3,3′-positions of the BINOL moiety has considerable impact on the stereoselection. Among the ligands screened, the chiral phosphoramidite **3c−3e** and **3h** were identified to deliver higher enantioselectivity than other analogues (entries 6−12). The examination of solvents found that the enantioselectivity could be generally improved to some degree in toluene while the chiral phosphoramidites **3d** and **3e** turned out to be most enantioselective (entries 13−16). Although the gold complex of **3e** showed higher levels of enantioselectivity than that of **3d**, it provided a slower reaction (entry 15 vs 14).

With the optimized reaction conditions in hand, we next explored the generality of the azo-HDA reaction (Table 2). 1,4-

Table 2. Substrate Scope[a]

entry	diene	T (h)	yield (%)[b]	4/4'	r.r.[c]	ee (%)[d]
1	 1b	5	99	**4b**	>20:1	97
2	 1c	17	94	**4c**	>20:1	99
3[h]	 1d	4	92	**4d**	20:1	96
4[e]	 1e	36	93	**4e'**	>20:1	94
5[f]	 1f	4	97	**4f'**	>20:1	96
6[h]	 1g	48	78	**4g'**	8:1	93
7	 1h	18	98	**4h'**	8:1	90
8[g,h]	 1i	4	99	**4i**	>20:1	98
9	 1j	18	98	**4j**	--	86
10	 1k	21	99	**4k**	--	99
11	 1l	22	95	**4l'**	>20:1	99

[a]Unless indicated otherwise, the reaction of **1** (0.15 mmol) and **2a** (0.1 mmol) was carried out at −78 °C in the presence of gold catalyst of phosphoramidite **3d** (5 mol %). [b]Isolated yield. [c]The regiomeric ratio was determined by ^{1}H NMR. [d]Determined by HPLC. [e]Gold catalyst of phosphoramidite **3h** was used. [f]Gold catalyst of phosphoramidite **3e** was used. [g]0.2 mmol of **1i** (*E*:*E*/*E*:*Z* = 8:1) was used. [h]In dichloromethane.

Dialkyl-substituted dienes **1b−1d** could undergo [4 + 2] cycloaddition to provide the corresponding chiral piperazines **4b−4d** in high yields and with excellent enantioselectivities ranging from 96% to 99% ee (entries 1−3). Significantly, the azo-HDA reaction involving trisubstituted dienes, as shown in **1e−1h** and **1l**, also proceeded smoothly to give rise to [4 + 2]-cycloaddition adducts in excellent enantiomeric excesses, but interestingly, with the reversed regioselectivity (entries 4−7 and 11). More importantly, the functional groups, such as ether, ester, and even the hydroxy group, were well tolerated (entries 1−7). Notably, the diene bearing a Lewis basic amide participated in the HDA reaction to afford the desired product in 99% yield with 98% ee (entry 8). A comparably lower enantioselectivity was observed in the case involving 1,3-cyclohexadiene (**1j**) as a substrate, but still with a high enantioselectivity of 86% ee (entry 9). The [4 + 2] cycloaddition of tetrasubstituted diene **1k** proceeded cleanly to give almost perfect yield and enantioselectivity (entry 10). The presence of ester groups in the trisubstituted diene as shown in **1l** could also be accommodated in high yield with

dx.doi.org/10.1021/ja3110472 | J. Am. Chem. Soc. 2013, 135, 3323−3326

excellent enantioselectivity (entry 11). It is worthy to mention that the use of the stereochemical mixtures of the dienes **1a** and **1i** rather than their pure form could also give high excellent stereoselectivities, which enhanced the synthetic importance of this reaction (Table 1 and Table 2, entry 8). The configurations of the **4c** and **4f′** were determined by X-ray analysis after derivation (see Supporting Information).

To investigate the coordination model[15] of diazene dienophile and gold complex, the DFT calculation was introduced.[16] The located complex structures were shown in Figure 2. The possibility of σ-coordination of the gold complex

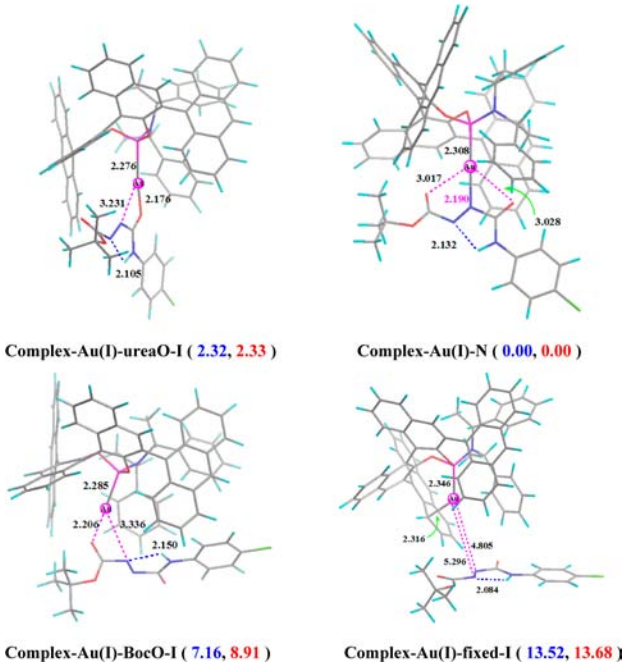
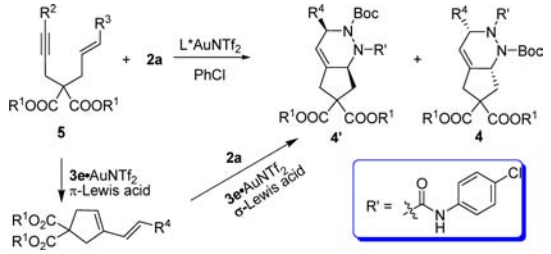


Figure 2. Optimized structures at the level of B3LYP with basis set 6-31G* for C, H, O, N, P, Cl and lanl2dz for Au atom, relative energies in enthalpy (blue) and Gibbs free energy (red), distances in angstrom.

to the carbonyl group of Boc was first ruled out due to its relatively lower stability. Instead of bonding with the carbonyl group of urea moiety as we initially proposed, it was found that the gold preferentially formed the σ-coordination bond with the azo moiety to lower the LUMO of the N−N double bond and thereby facilitated the HDA reaction. The efforts to seek the π-coordination of the gold complex to the N−N double bond of diazene always gave the σ-coordination of gold to either oxygen of the carbonyl or nitrogen of azo moiety. A restricted optimization by fixing the N−N double bond of the azo moiety and carbonyl groups in a same plane and approaching to P−Au bond perpendicularly resulted in a located π-coordination mode as shown in the complex-Au(I)-fixed-I (Figure 2). However, it is less stable than the σ-coordination of gold to nitrogen of azo moiety by about 13.5 kcal/mol.

Echavarren has established a very elegant gold(I)-catalyzed enyne cycloisomerization, which provided an efficient entry to access dienes of type **1l**.[17] Inspired by this finding, we envisaged that it is highly possible to establish an asymmetric gold-catalyzed cascade cycloisomerization/HDA reaction (Table 3). In this case, the chiral gold(I) complex actually acted sequentially as a π- and a σ-Lewis acid catalyst to promote the whole cascade reaction. To our delight, in the presence of 5 mol % of the gold(I) complex of the chiral phosphoramidite **3e**,

Table 3. Cascade Intramolecular Enyne Cycloisomerization/Asymmetric Azo HDA Reaction[a]



entry	5	R^1/ R^2/ R^3/ R^4	T (h)	yield (%)[b]	ee (%)[c]
1[d]	**5a**	Et/Me/H/Me	36	81(11)	94(12)
2[d,e]	**5b**	Bn/Me/H/Me	15	76(15)	80(6)
3[f]	**5c**	Me/H/Me/Me	3	96	95
4[f]	**5d**	Me/H/Et/Et	3	98	91
5[f]	**5e**	Me/H/*n*-Pr/*n*-Pr	5	98	86
6[f]	**5f**	Me/H/*i*-Pr/*i*-Pr	3	97	92
7[f]	**5g**	Me/H/C_2H_4Ph/C_2H_4Ph	21	95	90

[a]The reaction of **5** (0.15 mmol) and **2a** (0.1 mmol) was carried out in PhCl with gold catalyst of **3e** (5 mol %). [b]Isolated yield of **4′**, the data in parentheses are yields of minor products **4**. [c]Determined by HPLC, the data in parentheses are ee values of minor products **4**. [d]At 25 °C. [e]With gold catalyst of **3d** (5 mol %). [f]At −40 °C.

the enyne **5a** was able to undergo the cascade cycloisomerization/azo-Deils-Alder reaction at room temperature, giving the **4l′** in a 81% yield and with 94% ee and over 7/1 regioselectivity (entry 1). More importantly, the extension of the protocol to other enyne substrates was also successful. The dibenzyl 2-allyl-2-(but-2-ynyl)malonate **5b** underwent a smooth cascade reaction, but with a sacrificed stereoselectivity (entry 2). Significantly, the introduction of a substituent at the vinyl moiety of **5** was also able to participate in the enantioselective cascade reaction, to regiospecifically give the desired products in high levels of enantioselectivity of up to 95% ee, as exemplified by the cases involving enynes **5c**−**5g** (entries 3−7).

In conclusion, we have developed a highly regio- and enantioselective azo-HDA reaction catalyzed by chiral gold(I) complexes. The sterically demanding chiral phosphoramidites turned out to be the optimal ligands for the reaction. A broad scope of dienes was tolerated to afford structurally different piperazine derivatives with excellent enantioselectivities. More significantly, the π- and σ-coordination of the gold complex enables a cascade intramolecular enyne cycloisomerization/asymmetric azo-HDA reaction for a variety of enynes to give piperazine derivatives in high yields and excellent levels of stereoselectivity. Further studies will be focused on the reaction mechanism and transition states.

■ 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.

■ ACKNOWLEDGMENTS

We are grateful for financial support from NSFC (21232007, 21072181), MOST (973 project 2010CB833300), Ministry of Education, and CAS.

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