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Gold and BINOL-Phosphoric Acid Catalyzed Enantioselective Hydroamination/*N*-Sulfonyliminium Cyclization Cascade

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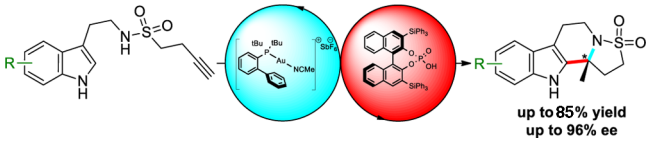
ABSTRACT



A highly enantioselective hydroamination/*N*-sulfonyliminium cyclization cascade is reported using a combination of gold(I) and chiral phosphoric acid catalysts. An initial 5-*exo*-dig hydroamination and a subsequent phosphoric acid catalyzed cyclization process provide access to complex sulfonamide scaffolds in excellent yield and high enantiocontrol. The method can be extended to lactam derivatives, with excellent yields and enantiomeric excesses of up to 93% ee.

Enantioselective cascade processes exploiting one-pot combinations of gold and chiral binol phosphoric acid (**BPA**) catalysts to govern both the reaction pathway and stereocontrol are becoming useful in synthesis. Recently, reactions exploiting the ability of gold to facilitate cycloisomerization, isomerization, and tautomerism in combination with phosphoric acid or phosphate catalyzed hydrogenation, Pictet–Spengler, or (*N*-acyl) iminium ion cyclization processes have been reported.[1,2] To this end, our group recently described a cascade process comprising alkynoic acid and tryptamine starting materials giving rise to polycyclic products with high enantioselectivities.[3] In continuation of this work, we wished to examine the compatibility of a gold catalyzed hydroamination with an enantioselective phosphoric acid catalyzed *N*-sulfonyliminium cyclization, a sequence that has no precedent.

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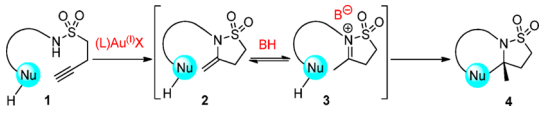
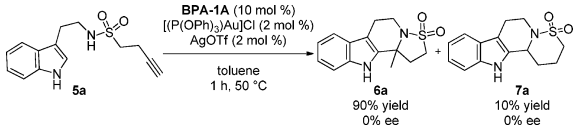
Scheme 1. Concept of Dual Catalytic Gold and Organic Phosphoric Acid Enantioselective Cyclization Cascade



Scheme 2. Proof of Principle Study in the *N*-Sulfonyliminium Cyclization Cascade



The proposed concept is depicted in Scheme 1 for an internal alkyl sulfonamide residue possessing a terminal alkyne **1**. Our initial choice of sulfonamide over carboxylic acid amide was influenced in part by their abundance in medicinally relevant compounds[4] and by the lack of such motifs in enantioselective cascade processes. We envisaged a novel alkyne hydroamination process to form isothiazolidine-1,1-dioxide (**2**), which could take place under gold(I) catalysis.[5,6] Protonation would then afford the *N*-sulfonyliminium intermediate **3**, which through tight ion pairing/general base catalysis with the conjugate base of the chiral phosphoric acid would facilitate an enantiofacially selective cyclization, thus providing a novel route to polycyclic isothiazolidine-1,1-dioxide moieties of type **4** (Scheme 1).[7−10] Herein we report our findings.

Proof of principle was first established after a brief screen of metal complexes by adding $[P(OPh)_3]AuCl$ (2 mol %) and AgOTf (2 mol %) in one portion to a mixture of sulfonamide **5a** and **BPA-1A** (10 mol %, Table 1) in toluene at 50 °C (Scheme 2). The reaction furnished the cascade products **6a** and **7a** (5-*exo* and 6-*endo* respectively in 9:1 ratio) with quantitative mass return at a faster rate than previously reported in *N*-acyliminium cyclization cascades.[3] Unfortunately, no enantioselectivity was witnessed. However, we later confirmed that this was due to a competing gold catalyzed background reaction;[11] treatment of sulfonamide **5a** with $[P(OPh)_3]AuCl$ (3 mol %) and AgOTf (3 mol %) at 60 °C in toluene afforded cyclization products **6a** and **7a** in quantitative yield as a 9:1 mixture of regioisomers respectively.[12] A range of alternative alkynophilic Lewis acidic metal complexes were screened in an attempt to slow the undesirable background process. Pleasingly, with Echavarren's catalyst[13] (**8**), **6a** was afforded in 56% yield and 73% ee (Table 1, entry 4). A brief solvent screen (Table 1, entries 4−8) identified toluene as the best solvent for enantioselectivity when compared with other aprotic solvents.[14] To further minimize the competitive gold catalyzed background reaction and improve efficiency, the loading of gold catalyst **8** was decreased to 2 mol % (Table 1, entry 9), which indeed resulted in an increase in product enantiomeric excess. Performing the reaction at 60 °C, rather than at 100 °C, afforded higher yields of the desired reaction product but with reduced enantiomeric excess (Table 1, entries 9 and 11). However, due to the increased lifespan of the gold catalyst under these conditions we were able to lower the gold catalyst loading even further to 0.5−1.0 mol %, which proved beneficial to both reaction yield and enantioselectivity (Table 1, entries 12 and 13). A subsequent screen of chiral BPA derivatives provided no enhancement in enantioselectivity (Table 1, entries 15−17) and confirmed **BPA-1A** was optimal for the enantioselective cascade process.

With optimized conditions in hand a variety of substituted indole sulfonamide derivatives were cyclized with good to excellent yields and enantioselectivities up to 96% ee (Figure 1). The reaction was found to tolerate electron-withdrawing halides at various positions around the ring (**6b** to **6f**) and the electron-deficient 5-nitrile derivative (**6g**), albeit at a slower reaction rate in the latter

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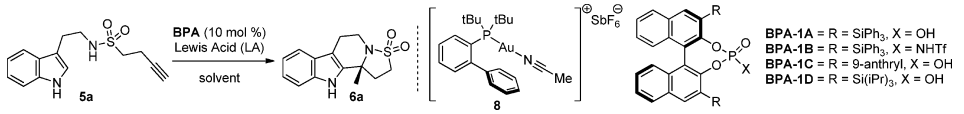
Table 1. Optimization Studies



entry[a]	LA cat.	LA (mol %)	BPA (mol %)	acid (mol %)	solvent	temp (°C)	yield (%)[b]	ee (%)
1	$[P(OPh)_3]AuOTf$	2	**1A**	10	toluene	100	26	17
2[c]	[NHC]AuOTf[d]	7	**1A**	10	toluene	100	71	52
3[e]	$Cu(OTf)_2$	20	**1A**	10	toluene	100	54	17
4[f]	**8**	5	**1A**	10	toluene	100	56	73
5	**8**	5	**1A**	10	$(CH_2Cl)_2$	60	83	46
6	**8**	5	**1A**	10	MeCN	60	77	53
7	**8**	5	**1A**	10	hexane	60	14	27
8	**8**	5	**1A**	10	THF	60	83	0
9	**8**	2	**1A**	10	toluene	100	68	87
10	**8**	2	**1A**	10	toluene	95	68	85
11	**8**	2	**1A**	10	toluene	60	82	81
12	**8**	1	**1A**	10	toluene	60	84	88
13	**8**	0.5	**1A**	10	toluene	60	78	88
14	**8**	0.1	**1A**	10	toluene	60	21	92
15	**8**	1	**1B**	10	toluene	60	83	45
16	**8**	1	**1C**	10	toluene	60	85	71
17	**8**	1	**1D**	10	toluene	60	79	45

[a] All reactions proceeded for 20 h at 7 mM concentration (with respect to **5a**) unless otherwise stated. No change in regioselectivity (9:1, **6a:7a**) was witnessed throughout optimization. [b] Isolated yield. [c] Initial LA catalyst loading of 2 mol %; after 48 h additional LA was charged (5 mol %) and reacted for a further 12.5 h. [d] [NHC]AuOTf = {Au[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]OTf}. [e] 52 h reaction. [f] Reaction complete after 1 h.

case due to its poor solubility in the reaction solvent. Substrates containing electron-donating groups (**6h** to **6k**) were also found to work well. These derivatives demonstrated that all the possible positions around the carbocycle of the indole ring could be substituted without significant detriment to enantioselectivity or yield.

To further test the flexibility of this new methodology, attempts were made to perform the reaction cascade on the chain extended amide analogue **9a**. Pleasingly, using 5 mol % of **8** and 10 mol % **BPA-1A** in refluxing toluene gave desired product **10a** in 50% ee and 79% yield as a single regioisomer. Successful optimization of the enantioselectivity was achieved through lowering the loading of the gold catalyst (see Supporting Information); with 1 mol % of gold catalyst **8**, lactam **10a** was formed in 86% yield and 66% ee.

A collection of examples were examined to test the effects of electron withdrawing (**10b**) and donating (**10c** and **10d**) substituents in this variant of our cascade process. Pleasingly the reactions proceeded with good to excellent yields and with enantiomeric excesses up to 93% (Figure 2).

From the data collected during the development of our method (Table 1) and literature precedent, we propose the mechanism of the reaction proceeds through two sequential and independent catalyzed transformations (Scheme 3). A gold(I) complex activates alkyne **5** through π acid/base interactions lowering the energy of the alkyne LUMO,[15] which allows the sulfonamide to attack selectively in a 5-*exo* fashion, presumably due to the gold alkyne bond being skewed toward the terminal end of the alkyne due

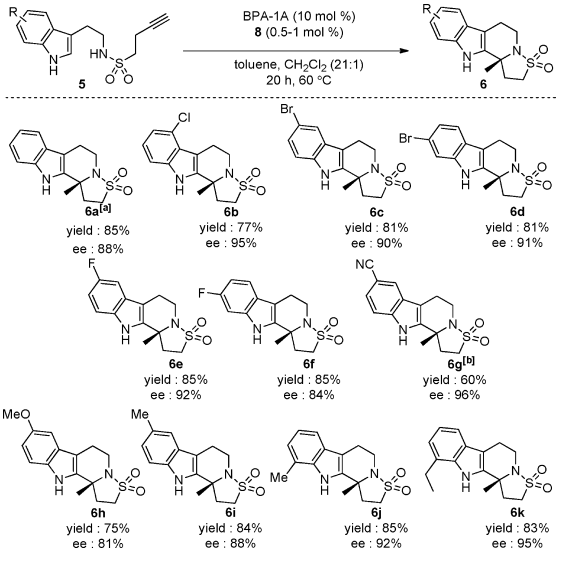


Figure 1. Substrate scope. [a] In all examples products of 5-*exo*cyclization (**6**) were separated from 6-*endo* cyclization regioisomers (**7**) by FCC (9:1 crude ratio). Compound **7a** was fully characterized in order to confirm the structure of the minor regioisomer. [b] Reaction time 60 h.

to sterics.[16] Protodeauration forms enesulfonamide **11**. At this juncture intermediate **11** can take two potential pathways: (i) gold catalyzed nonenantioselective *N*-sulfonyliminium cyclization via **12**[17,18] or (ii) the enantioselective **BPA** catalyzed *N*-sulfonyliminium cyclization via **13**. Evidence

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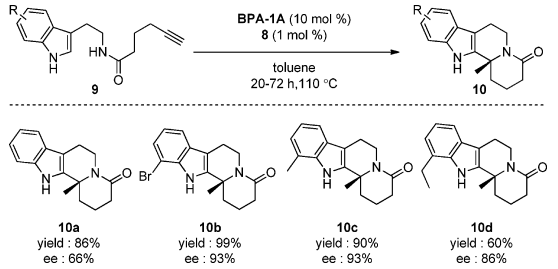
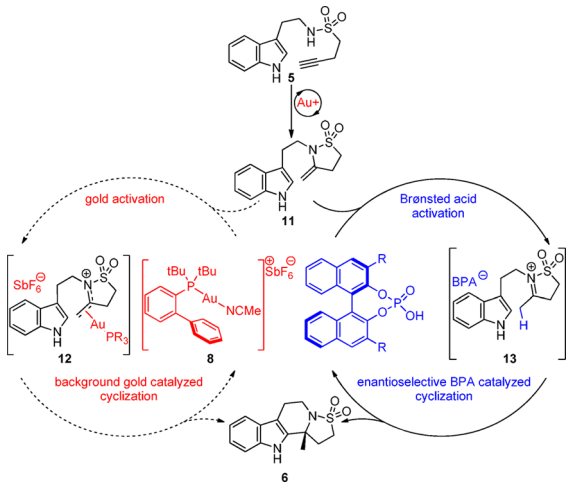


Figure 2. Application to δ-lactam synthesis *via* a 6-*exo*-cyclization cascade.

Scheme 3. Proposed Cascade Mechanism



that the enantioselective reaction pathway passes through an *N*-sulfonyliminium intermediate (not a gold(I) phosphate catalyzed intermediate[19]) came from an independent study (Scheme 4). Ketone **14** was prepared and treated with **BPA-1A** at 10 mol % in refluxing toluene. Product **6a** was obtained in quantitative yield in 92% ee. That the sense and magnitude of the enantioselectivity in this reaction were the same as those in the cascade (Table 1, entry 14) points to a common intermediate **13**.

The absolute stereochemistry was assigned by single crystal X-ray diffraction of the 3-bromobenzylated compound, **15a** (derived from **6a**) and the lactam **10b** (Figure 3). The absolute stereochemical configurations of

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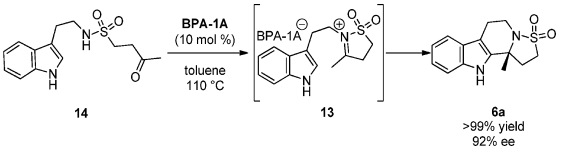
Scheme 4. Evidence for *N*-Sulfonyliminium Intermediate



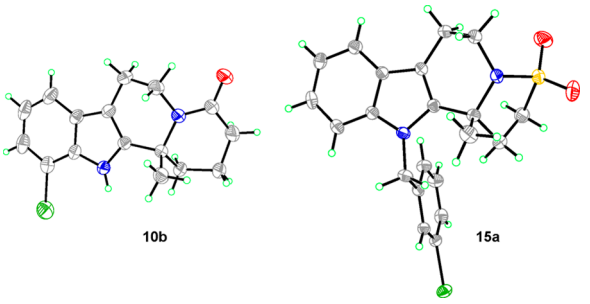


Figure 3. Thermal ellipsoid plot of **15a** and **10b** determined using single crystal X-ray diffraction data (1 equiv of **15a** and solvent (**10b**) omitted for clarity). C, gray; Br, green; N, blue; O, red; S, yellow.

the remaining derivatives were assigned by analogy and match the configuration of our previous findings.[3]

In conclusion we have developed a highly enantioselective *N*-sulfonyliminium cyclization cascade that allows access to complex and unusual sulfonamide scaffolds in excellent yield. We have also proven that this methodology can be used to create different ring systems of various sizes with most cases providing excellent yields and enantiomeric excesses. Mechanistic understanding has allowed us to control the background gold catalyzed reaction. Investigations into the development of more diverse cores possessing a range of different tethered nucleophiles are underway in our laboratory, and the results will be disclosed in due course.

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Supporting Information Available. Experimental procedures and characterization of compounds are available with copies of ^{1}H and ^{13}C NMR spectra for all new compounds, as well as HPLC and X-ray data where applicable. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.