Cyclisation

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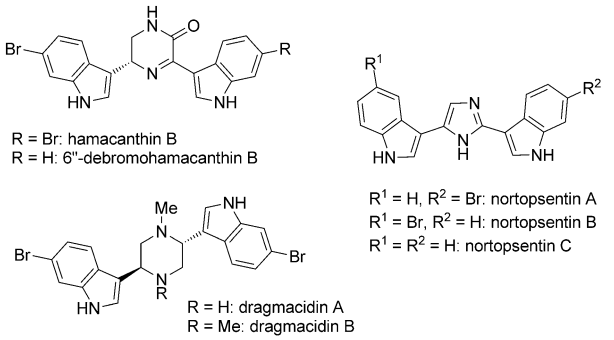
Gold-Catalyzed Intramolecular Regio- and Enantioselective Cycloisomerization of 1,1-Bis(indolyl)-5-alkynes**

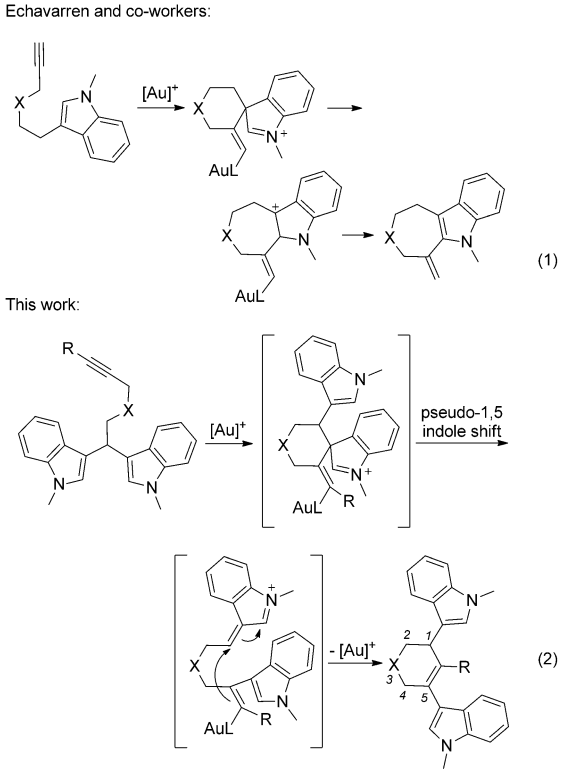
Long Huang, Hai-Bin Yang, Di-Han Zhang, Zhen Zhang, Xiang-Ying Tang, Qin Xu, and Min Shi**

Indole is one of the most intensively investigated aromatic heterocycle, because its derivatives are abundant in nature and possess various biological activities.[1] Among the large number of indoles, bis(indole) alkaloids, such as hamacanthins, nortopsentins, and dragmacidins (Scheme 1), are particularly abundant in marine sponges. In bis(indole) alkaloids, two indole moieties are connected to various heterocyclic units. Compounds with this structural motif exhibit a wide spectrum of pharmacological activities, including antibacterial, antiviral, and cytotoxic activities, which make bis(indole) alkaloids and their analogues attractive targets for biomedical and synthetic studies.[2]



Scheme 1. Examples of naturally occurring and pharmacologically active bis(indole) alkaloids.

Gold catalysis, which is currently a hot topic in homogeneous catalysis, can be well understood with the concept of carbophilic π-acids, which are widely employed in the activation of alkynes, allenes, and alkenes. However, in contrast to gold-catalyzed enantioselective transformations involving allenes, there are relatively few examples involving alkynes.[3–6] Echavarren and co-workers reported an elegant gold-catalyzed intramolecular reaction of indoles with alkynes, which proceeded through 6-*endo*-dig, 6-*exo*-dig, 7-*exo*-dig, and 8-*endo*-dig cyclizations and were highly dependent on the oxidation state of the gold catalyst. Further investigations by this group indicated that similar spirocyclic intermediates were probably involved in cyclizations of various other substrates [Scheme 2, Eq. (1)].[7] Recently,



Scheme 2. Intramolecular cycloaddition reactions of indole and alkyne.

tremendous efforts have been made toward the formation of useful aza-heterocyclic structures through the versatile intramolecular cyclization of indoles with alkynes.[8] Most of these efforts focused on the construction of indole-fused scaffolds, and Bandini and co-workers reported the only asymmetric variant in 2012.[8j] We developed an efficient protocol for the preparation of 1,1-bis(indolyl)-5-alkynes

[*] L. Huang, H.-B. Yang, D.-H. Zhang, Z. Zhang, Dr. X.-Y. Tang, Prof. Dr. M. Shi
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (China)
E-mail: Mshi@mail.sioc.ac.cn
Dr. Q. Xu, Prof. Dr. M. Shi
Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology
130 Mei Long Road, Shanghai 200237 (China)

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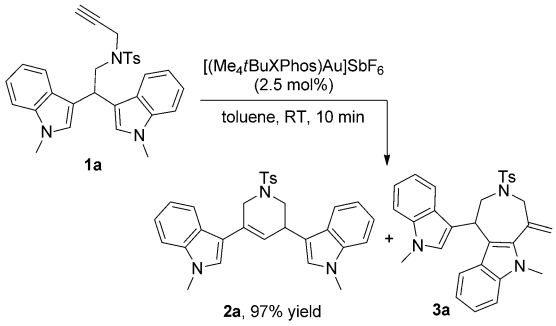
Supporting information for this article (including spectroscopic and HPLC data of the products shown in Tables 1–4) is available on the WWW under http://dx.doi.org/10.1002/anie.201302632.

through an acid-catalyzed intermolecular reaction of 5-alkynals with indoles (see Table S1 in the Supporting Information for details).[9e] Upon treatment of 1,1-bis-(indolyl)-5-alkyne with a gold catalyst, a bis(indole) cycloadduct was obtained [Scheme 2, Eq. (2)],[10] stemming from a gold-catalyzed 6-*endo*-dig cyclization and a pseudo 1,5 migration of the nucleophilic indole moiety (C–C bond cleavage) followed by nucleophilic attack of the in situ generated alkenyl–gold complex.[11] It also provided us with a strategy for the synthesis of six-membered rings from 5-alkynals with two indole moieties, rather than indole-fused cycloadducts (as reported previously), playing a key role in the annulation process.

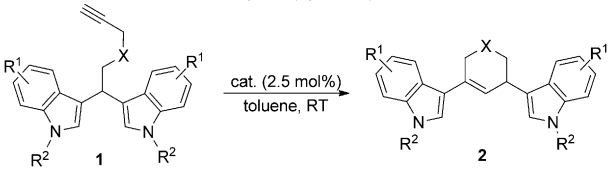
We first attempted the cyclization with 1,1-bis(indolyl)-5-hexyne **1a** as the model substrate, which was easily prepared from the reaction of 5-alkynal with indole using $BF_3{\cdot}Et_2O$ as the catalyst. The initial results and subsequent optimization of the reaction conditions are summarized in Table S2 in the Supporting Information. Cycloadduct **2a** was exclusively produced in 97% yield within 10 minutes (Scheme 3), when a gold complex with the electron-rich phosphine ligand Me_4*t*BuXPhos was employed as the catalyst.



Scheme 3. Optimized reaction conditions for the intramolecular cycloisomerization of 1,1-bis(indolyl)-5-hexyne **1a**.

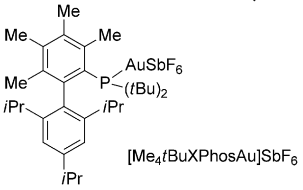
Having established the optimal reaction conditions for the formation of **2a** as the major product, we surveyed the substrate scope of the reaction by using variously substituted bis(indolyl)alkynes **1** (Table 1). Among tosylamide-linked substrates **1b**–**1l** (X = NTs), a variety of N-substituted indole moieties were well-tolerated, including those substituted with N-benzyl and N-allyl groups. The use of indoles **1c** and **1d** as nucleophiles provided the products in better yields and regioselectivities compared with N-nonsubstituted indole **1b** (Table 1, entries 1–3). Next, we found that substituents at positions 2, 4, 5, 6, and 7 of the *N*-methylindole backbone were also well tolerated, regardless of whether they were electron-donating or electron-withdrawing, furnishing the desired products in high yields and excellent regioselectivities (Table 1, entries 4–11). In the case of other N-sulfonated amines (X = NBs or NNs), the reactions also proceeded smoothly to give the desired products **2m** and **2n** in 89% and 97% yield, respectively (Table 1, entries 12 and 13). Substrates with *gem*-diester and oxygen atom linkers efficiently gave the desired cycloadducts **2o** and **2p** in 97% and 91% yields, respectively, (Table 1, entries 14 and 15), thus indicating the broad substrate scope of this reaction.

Table 1: Substrate scope of gold(I)-catalyzed intramolecular cycloisomerization of various 1,1-bis(indolyl)-5-hexynes.[a]



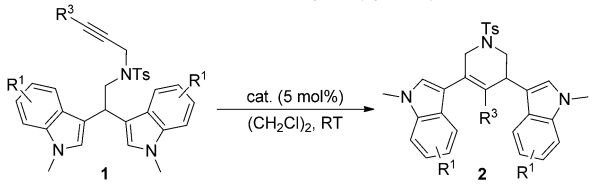
Ent.	1	X	R^1	R^2	*t* [min]	2	Yield [%][b]
1	**1b**	NTs	H	H	30	**2b**	90[c]
2	**1c**	NTs	H	Bn	≤5	**2c**	≥99
3	**1d**	NTs	H	allyl	120	**2d**	≥99
4	**1e**	NTs	2-Me	Me	10	**2e**	≥99
5	**1f**	NTs	4-Cl	Me	10	**2f**	90
6	**1g**	NTs	5-Cl	Me	10	**2g**	≥99
7	**1h**	NTs	5-Br	Me	10	**2h**	98
8	**1i**	NTs	5-Me	Me	10	**2i**	95
9	**1j**	NTs	5-OMe	Me	10	**2j**	97
10	**1k**	NTs	6-F	Me	10	**2k**	≥99
11	**1l**	NTs	7-Me	Me	60	**2l**	≥99
12	**1m**	NBs	H	Me	10	**2m**	89
13	**1n**	NNs	H	Me	10	**2n**	97
14	**1o**	$CH(CO_2Et)_2$	H	Me	≤5	**2o**	97
15	**1p**	O	H	Me	10	**2p**	91

[a] All reactions were carried out using **1** (0.1 mmol) in the presence of catalyst (2.5 mol%) in toluene (1.0 mL) unless otherwise specified. [b] Yield of isolated product. [c] **2**:**3** = 15:1, determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as internal standard. [d] Ts = 4-toluenesulfonyl, Ns = 4-nitrobenzenesulfonyl, Bs = 4-bromobenzenesulfonyl.



Au^I-catalyzed cyclizations of 1,1-bis(indolyl)-5-alkynes **1q**–**1u** were also explored under similar conditions (Table 2). The reactions of substrates **1q** and **1s**, which both bear an ester group at the alkyne moiety, proceeded smoothly to give the corresponding products **2q** and **2s** in good yields and excellent regioselectivities under identical conditions as those employed in Table 1 (Table 2, entries 1 and 3). The cyclization of **1r** was sluggish using Me_4*t*BuXPhosAuCl/AgOTf as the catalyst system, but was successfully catalyzed by [(PPh_3)AuCl]/AgOTf, giving **2r** in 78% yield and in a ratio of 4:1 with the corresponding regioisomer **3r** (Table 2, entry 2). The structures of **2r** and **3r** were unambiguously determined by X-ray diffraction (see the Supporting Information). Moreover, the previously employed reaction conditions were not suitable for the less reactive substrates **1t** and **1u**. According to recent investigations on ligand effects in gold catalysis, the use of an electron-poor ligand would favor the electronic activation of the alkyne in reactions, in which the activation of an unsaturated C–C bond is the rate-determining step.[6b] Further investigations revealed that both substrates produced the corresponding products **2t** and **2u** in

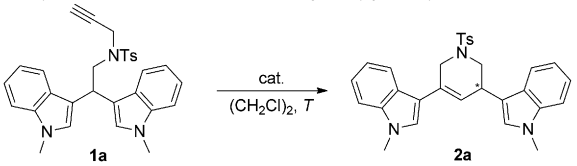
Table 2: Substrate scope of gold(I)-catalyzed intramolecular cycloisomerization of various internal 1,1-bis(indolyl)-5-alkynes.[a]



Ent.	**1**	R^1	R^3	Catalyst	*t* [h]	**2**	Yield [%][b]
1	**1q**	H	CO_2Et	[(Me_4tBuXPhos)AuCl]	3	**2q**	86[c]
2	**1r**	4-Cl	CO_2Et	[(PPh_3)AuCl]	1	**2r**	78[d]
3	**1s**	H	CO_2Ph	[(Me_4tBuXPhos)AuCl]	12	**2s**	77
4	**1t**	H	Me	[(JackiePhos)AuCl]	12	**2t**	71
5	**1u**	H	Ph	[(JackiePhos)AuCl]	6	**2u**	90
6	**1u**	H	Ph	[(IPr)AuCl]	3	**2u**	82

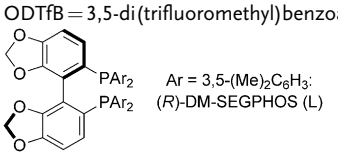
[a] The were carried out using **1** (0.1 mmol) in the presence of catalyst (5 mol%) and AgOTf (5 mol%) as co-catalyst in $(CH_2Cl)_2$ (1.0 mL). [b] Yield of isolated product. [c] **2**:**3** = 19:1. [d] **2**:**3** = 4:1. Ratios of **2**:**3** determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as internal standard. JackiePhos = 2-{bis[3,5-bis(trifluoromethyl)phenyl]phosphino}-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl.

Table 3: Selected optimization experiments of Au^I-catalyzed enantioselective cycloisomerization with 1,1-bis(indolyl)-5-alkyne **1a**.[a]



Ent.	Cat. (mol%)	*T*	*t*	**2a**:**3a**[b]	Yield [%][c]	*ee* [%][d]
1	[LAu_2Cl_2] (2.5)/AgOTf (5)	0°C	30 min	2.5:1	60	25
2	[LAu_2Cl_2] (2.5)/$AgBF_4$ (5)	0°C	5 h	5:1	74	31
3	[LAu_2Cl_2] (2.5)/$AgNTf_2$ (5)	0°C	30 min	12:1	67	30
4	[LAu_2Cl_2] (2.5)/$AgSbF_6$ (5)	0°C	1 h	8:1	66	44
5	[LAu_2Cl_2] (2.5)/AgOTs (5)	0°C	10 h	1.4:1	41	19
6	[LAu_2Cl_2] (5)/$AgSbF_6$ (5)	0°C	30 min	19:1	71	53
7[e]	[LAu_2Cl_2] (2.5)/AgOBz (5)	RT	7 days	–	–	–
8	[LAu_2Cl_2] (2.5)/AgODNB (5)	RT	7 days	6:1	50	81
9[e]	[LAu_2Cl_2] (5)/AgODNB (10)	RT	24 h	4:1	72	82
10[e]	[L(AuODNB)$_2$] (5)	RT	2 h	7:1	81	88
11[e]	[L(AuOPNB)$_2$] (5)	RT	2 days	9:1	68	88
12[e]	[L(AuOONB)$_2$] (5)	RT	3 h	5:1	80	85
13[e]	[L(AuODTfB)$_2$] (5)	RT	12 h	8:1	88	91

[a] The reactions were carried out with **1a** (0.1 mmol) and catalyst in $(CH_2Cl)_2$ (1.0 mL), unless otherwise specified. [b] Ratio determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated product **2a**. [d] *ee* value of product **2a**, determined by HPLC on a chiral stationary phase. [e] In 0.5 mL $(CH_2Cl)_2$. ODNB = 3,5-dinitrobenzoate, OPNB = 4-nitrobenzoate, OONB = 2-nitrobenzoate, ODTfB = 3,5-di(trifluoromethyl)benzoate.



good yields and excellent regioselectivities by employing the electron-poorer phosphine ligand JackiePhos (Table 2, entries 4 and 5). The use of [(IPr)AuCl]/AgOTf as the catalyst system gave **2u** also in good yield (Table 2, entry 6).

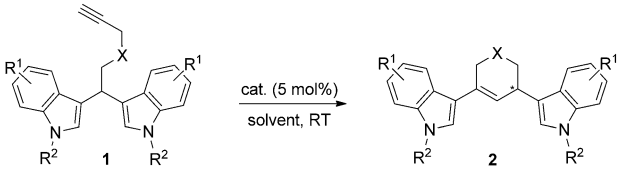
The results of our examination of the enantioselective cyclization of 1,1-bis(indolyl)-5-hexyne (**1a**) are shown in Table 3. Among the commonly used chiral phosphine ligands, use of (*R*)-DM-SEGPHOS resulted in the best enantioselectivity (see Tables S3–S5 in the Supporting Information for details). The examination of silver salts by carrying out the reaction in dichloroethane at 0°C showed that $AgSbF_6$ was the better co-catalyst compared with a range of other silver salts (Table 3, entries 1–5). Changing the ratio of [LAu_2Cl_2]/$AgSbF_6$ to 1:1 (5 mol% each, L = (*R*)-DM-SEGPHOS) improved the *ee* value to 53% (Table 3, entry 6). This increase in enantioselectivity led us to believe that the intact coordination of the counterion was crucial for stereoinduction (one counterion is Cl and the other is SbF_6). Inspired by a report of Toste and co-workers, we next investigated the cyclization using silver salts with benzoate counterions, because the catalyst systems could be easily modified both electronically and sterically by careful choice of these counterions.[5h] Use of silver benzoate did not lead to any product (Table 3, entry 7). We found a dramatic improvement on the *ee* value when silver 3,5-dinitrobenzoate was employed as the co-catalyst at room temperature, although the yield was only 50%, even after extending the reaction time (Table 3, entry 8). When the reaction was performed with an increased catalyst loading of 5 mol% and an increased concentration (0.5 mL of solvent) at room temperature, **2a** was obtained in 72% yield and 82% *ee* (Table 3, entry 9). Next, we synthesized [L(AuODNB)$_2$] and directly used it in this asymmetric gold catalysis, affording **2a** in 81% yield and 88% *ee* within 2 h (Table 3, entry 10). Further optimizations indicated that 3,5-di(trifluoromethyl)benzoate was the best counterion, producing **2a** in 88% yield with 91% *ee* and an 8:1 ratio of regioisomers (Table 3, entries 11–13).

During the exploration of the substrate scope, we realized that in some cases, the reaction should be performed in dichloromethane and in the presence of 5 mol% [L(AuODNB)$_2$] (L = (*R*)-DM-SEGPHOS), because some substrates are not soluble in dichloroethane and the reaction proceeds more quickly in the presence of [L(AuODNB)$_2$].[12] Thus, we developed two sets of reaction conditions for this enantioselective gold(I)-catalyzed 6-*endo*-dig cyclization: A) 5 mol% [L(AuODTfB)$_2$], 0.5 mL dichloromethane, and B) 5 mol% [L(AuODNB)$_2$], 0.5 mL dichloromethane. With these two sets of reaction conditions in hand, the substrate scope of the reactions was examined. Reactions of N-benzylated or N-allylated indole derivatives **1c** and **1d** provided the desired products **2c** and **2d**, respectively, in moderate yields and good enantio- and regioselectivities (Table 4, entries 1 and 2, respectively). A range of substituents at positions 4, 5, 6, and 7 of the indole moieties were well tolerated, affording the desired products in 65–90% yields with 60–96% *ee*, regardless of whether they were electron-donating or electron-withdrawing groups (Table 4, entries 3–9). Substrates with NBs and NNs linkers gave the desired products **2m** and **2n**, respectively, in 65–69% yields with 83–

84% *ee* and regioisomers in ratios of 4:1–5:1 (Table 4, entries 10 and 11). Substrate **1o**, which has a *gem*-diester linker, gave the corresponding product **2o** in 80% yield with 48% *ee* (Table 4, entry 12). It should be noted that the electron density and steric hindrance associated with the indole rings as well as the linker of 1,1-bis(indolyl)-5-hexyne were essential to the outcome of the reactions with regard to yields, enantioselectivities, and regioselectivities.[13]

In summary, we have developed a novel gold(I)-catalyzed 6-*endo*-dig cyclization of various 1,1-bis-(indolyl)-5-alkynes to give bis(indole) alkaloid analogues in good yields through a pseudo 1,5 migration of an indole moiety. This reaction is not only applicable to a wide range of terminal alkyne substrates, but also to various internal alkyne substrates by adjusting the electronic property of the catalyst through the choice of the phosphine ligands. Moreover, the use of chiral phosphine/gold(I) complexes $[L(AuODTfB)_2]$ or $[L(AuODNB)_2]$ (L = (*R*)-DM-SEGPHOS) enabled enantioselective 6-*endo*-dig cyclizations, affording the corresponding bis-(indole) alkaloid analogues in moderate to excellent yields (55–90%) and with moderate to good *ee* values (48–96%) together with satisfactory regioselectivities (3.5:1→20:1).

Table 4: Substrate scope of enantioselective Au^I-catalyzed cycloisomerization with various 1,1-bis(indolyl)-5-hexynes.



Ent.	1	X	R^1	R^2	Cond.[a]	*t* [days]	2:3[b]	2	Yield [%][c]	*ee* [%][d]
1	**1c**	NTs	H	Bn	B	1	7:1	**2c**	69	72
2	**1d**	NTs	H	allyl	A	4	6:1	**2d**	55	81
3	**1f**	NTs	4-Cl	Me	B	1	6:1	**2f**	74	60
4	**1g**	NTs	5-Cl	Me	B	0.5	>20:1	**2g**	90	96
5	**1h**	NTs	5-Br	Me	A	3	>20:1	**2h**	85	96
6	**1i**	NTs	5-Me	Me	B	1	4:1	**2i**	75	82
7	**1j**	NTs	5-MeO	Me	B	0.5	3.5:1	**2j**	68	83
8	**1k**	NTs	6-F	Me	A	2	3:1	**2k**	65	90
9	**1l**	NTs	7-Me	Me	A	2	5:1	**2l**	75	90
10	**1m**	NBs	H	Me	A	3	5:1	**2m**	65	83
11	**1n**	NNs	H	Me	A	2	4:1	**2n**	69	84
12	**1o**	$C(CO_2Et)_2$	H	Me	A	3	4:1	**2o**	80	48

[a] Conditions A: **1** (0.1 mmol), $[L(AuODTfB)_2]$ (5 mol%), $(CH_2Cl)_2$ (0.5 mL); conditions B: **1** (0.1 mmol), $[L(AuODNB)_2]$ (5 mol%), CH_2Cl_2 (0.5 mL). [b] Ratio determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase. Ts = 4-toluenesulfonyl, Ns = 4-nitrobenzenesulfonyl, Bs = 4-bromobenzenesulfonyl.

Experimental Section

General procedure for gold(I)-catalyzed cycloisomerization of 1,1-bis(indolyl)-5-alkynes: $[(Me_4tBuXPhos)Au]SbF_6$ (2.5 mol%) was added to a solution of 1,1-bis(indolyl)-5-alkyne **1** (0.1 mmol, 1.0 equiv) in $(CH_2Cl)_2$ (1.0 mL) in an Schlenk tube. The mixture was stirred at room temperature until the reaction was completed (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, eluent: petroleum ether/ethyl acetate = 8/1→4/1) to give the corresponding products **2** in moderate to excellent yields.

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Keywords: bis(indoles) · cycloisomerization · enantioselectivity · gold · regioselectivity

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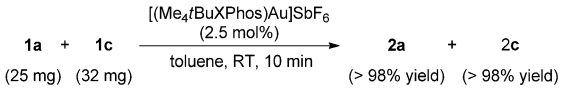

[12] During the course of our studies on the effect of the counterion on this enantioselective gold(I)-catalyzed 6-*endo*-dig cyclization, we concluded that the reaction rates became faster along with an increased acidity of the employed benzoates. pK_a values of various benzoic acids in water at 25 °C: benzoic acid: 4.204; 4-nitrobenzoic acid: 3.441; 3,5-dinitrobenzoic acid: 2.85; 2-nitrobenzoic acid: 2.18. J. A. Dean, *Lange's Handbook of Chemistry*, 15th ed., McGraw-Hill, New York, **1999**.

[13] Using conditions B, the corresponding bis(indole) alkaloid analogues **2b** and **2e** were obtained in 23% *ee* and 10% *ee*, respectively. As for substrate **1b**, we posited that the coordination of chiral gold(I)–benzoate complexes could be impacted by the exposed indole N–H, whereas the coordinated counterions were crucial to increase the transmission of chiral information. As for substrate **1e**, the chiral catalyst was too far away from the electrophilic site to induce chirality, because of the steric hindrance between the methyl group at position 2 of the iminium cation and the chiral phosphine gold(I) catalyst.

[14] CCDC 874179 (**1q**), 877836 (**2r**), and 878653 (**3r**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

