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Gold-Catalyzed Annulations of *N*-Aryl Ynamides with Benzisoxazoles to Construct 6*H*-Indolo[2,3-*b*]quinoline Cores

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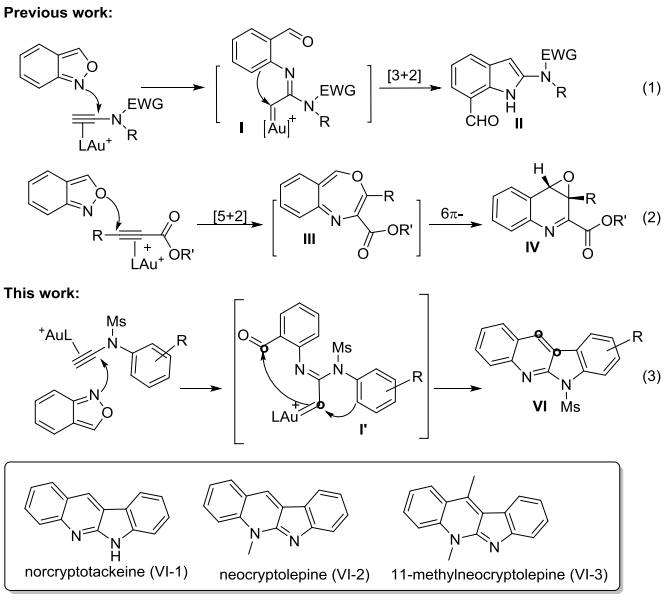
This work reports new annulations of *N*-aryl ynamides with benzisoxazoles to form 6*H*-indolo[2,3-*b*]quinoline derivatives. The synthetic utility of this new method is manifested by its applicability to access naturally occurring alkaloids including norcryptotackeines, neocryptolepine and 11-methylneocryptolepine. Our experimental data indicate that high-temperature conditions allow *N*-aryl nucleophiles to become conformationally flexible, rendering the attack at gold carbenes effective to generate reactive indoles that attacks again the benzaldehyde to furnish the observed products.

Interest in the gold-catalyzed annulations of isoxazoles or benzisoxazoles with alkynes is rapidly growing because of their easy access to five- and six-membered azacycles.[1-4] The reactions of isoxazoles[2] and benzisoxazoles[3] on the same alkynes typically afforded two distinct products. In the case of benzisoxazoles, Hashmi reported their [3+2]-annulations with ynamides via a *N*-attack regioselectivity to form *α*-iminogold carbenes **I**, further preceding to 2-amino-7-formylindole products **II**[3a]. In contrast, gold-catalyzed annulations of benzisoxazoles with propiolate derivatives proceeded through a distinct *O*-attack regioselectivity to enable [5+2]-annulation/6*π*-electrocyclization cascades, yielding valuable quinoline oxides **IV**[4]. In these reactions, gold *π*-alkynes bear no nucleophiles; we envisage that new reactions likely occur when these alkynes comprise a potent nucleophile to functionalize further gold carbene intermediates. To test this hypothesis, as depicted in eq 3, ynamides bearing an electron-rich *N*-aryl sulfonamide trigger a cascade reaction on gold carbene intermediates **I'**, involving a *N*-aryl attack at gold carbenes, then at the benzaldehyde sequentially to construct 6*H*-indolo[2.3-*b*]quinoline frameworks[5a,5b]. Such a framework matches well with several naturally occurring alkaloids such as norcryptotackeine, (**VI-1**) [5a,6a], neocryptolepine (**VI-2**) [6b,6c] and 11-methylneocryptolepine (**VI-3**) [6d], which exhibit potent activity in the treatment of infectious disease, fever and malaria. Application of our new method for the synthesis of these three bioactive molecules will be described herein.



In the gold-catalyzed annulations of benzisoxazole **2a** with ynamide **1a**, two possible products **3a** and **4a** are likely to form; the former arises from our new process (eq 3) whereas the latter is produced from the known system[3a] (eq 1). We tested the reactions with LAuCl/$AgSbF_6$ (L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr, PPh_3 and $P(OPh)_3$ (entries 1-4) in hot DCE (70 °C, 0.25 h); only P(*t*-Bu)$_2$(*o*-biphenyl)$AuSbF_6$ showed the chemoselectivity to yield 6*H*-indolo[2,3-*b*]quinoline **3a,** up to 88% yield, together with pyrrole derivative **4a** in only 7% yield. Herein, electron-rich $IPrAuNTf_2$ is envisaged to generate gold carbenes **I'** favorably (eq 3), but its tethered benzaldehyde becomes an active nucleophile to facilitate the formation of pyrrole product **4a**. Other silver salts such as $AgNTf_2$ and AgOTf were not chemoselective to afford compounds **3a** and **4a** in

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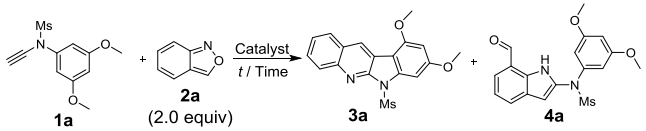
significant proportions (entries 5-6). As noted in entries 7-8, the reactions at mild temperatures 50 °C and 25 °C preferably delivered side product **4a** with 43% and 58% yields respectively (entries 7-8); this temperature-dependent chemoselectivity is attributed to the rigid conformation of a sulfonamide group at low temperatures, rendering its nucleophilic attack difficult. Other solvents gave **3a** in the following yields: toluene 70%, 1,4-dioxane 19% and MeCN 66% (entries 9-11). Under the condition entry 1, We examined the reaction with P(*t*-Bu)$_2$(o-biphenyl)AuCl alone that gave the desired product **3a** in 57% yield together with **4a** in 29% yield. (entry 12). Accordingly, the preferable chemoselectivity toward **3a** was affected largely by the nature of gold catalyst. $AgSbF_6$ (20 mol%) alone gave the undesired pyrrole derivative **4a** efficiently (entry 13). Compound **3a** was characterized by X-ray diffraction to confirm its 6*H*-indolo[2.3-*b*]quinoline framework.[7]

Table 1. Chemoselectivity affected by various gold catalysts

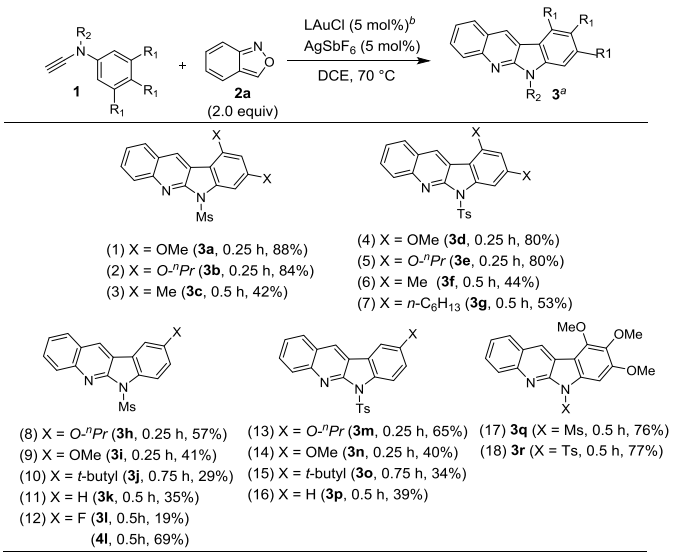


Entry	Catalyst (mol%)	Solvent	*t*(°C) /Time(h)	Isolated yiels (%)[a] 3a	4a
1	LAuCl (5)/$AgSbF_6$ (5)[b]	DCE	70/0.25	88	7
2	IPrAuCl (5)/$AgSbF_6$ (5)[c]	DCE	70/0.25	44	50
3	PPh_3AuCl (5)/$AgSbF_6$ (5)	DCE	70/0.25	68	21
4	$(PhO)_3$AuCl (5)/$AgSbF_6$ (5)	DCE	70/0.25	61	31
5	LAuCl (5)/$AgNTf_2$ (5)	DCE	70/0.25	52	47
6	LAuCl (5)/AgOTf (5)	DCE	70/0.25	57	39
7	LAuCl (5)/$AgSbF_6$ (5)	DCE	50/0.47	50	43
8	LAuCl (5)/$AgSbF_6$ (5)	DCE	25/0.75	35	58
9	LAuCl (5)/$AgSbF_6$ (5)	Toluene	70/0.25	70	24
10	LAuCl (5)/$AgSbF_6$ (5)	1,4-Dioxane	70/0.25	19	72
11	LAuCl (5)/$AgSbF_6$ (5)	MeCN	70/0.25	66	29
12	LAuCl (5)	DCE	70/0.25	57	29
13	$AgSbF_6$ (20)	DCE	70/0.25	8	88

1a (0.1 *M*, 1.0 equiv). [a]Product yields are obtained after purification from a silica column. [b]L = P(*t*-Bu)$_2$(*o*-biphenyl). [c]IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

These new annulations were tested further with various ynamides **1** and benzisoxazole **2a** to assess the reaction generality; the results are summarized in Scheme 1. Pyrrole products **4** would also be produced when the desired reactions (eq 3) became inefficient. For mesyl-derived 3,5-substituted phenyl sulfonamides **1a-1c** bearing X = O-^{n}Pr, OMe, Me, their resulting products **3a**-**3c** were obtained in 42%-88% yields (entries 1-3). These cascade annulations were successfully extended to their tosylate-derived products **3d-3f** with 44%-80% yields (entries 4-6). In comparison with 3,5-dimethylphenyl analogue **1f**, 3,5-di(*n*-hexyl)phenyl **3g** provided a slightly increased yield, i.e. 53% (entry 7). We tested the reactions with *para*-substituted phenyl derivatives **1h**-**1l** (X = O-^{n}*Pr*, OMe, *t*-butyl, F), their corresponding products **3h-3l** were obtained in 19-57% yield (entries 8-12). The fluoroderivative **1l** gave the desired product in 19% yield together with species 4l in 69% yield (entry 12). Notably, their tosyl-derived analogues gave improved yields (34-65%) of the desired compounds **3m-3p** (entries 13-16). Unsubstituted

Scheme 1. Catalytic Annulations with various N-arylynamides



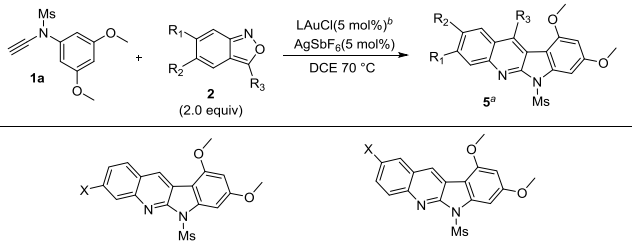
(1) X = OMe (**3a**, 0.25 h, 88%)
(2) X = O-^{n}*Pr* (**3b**, 0.25 h, 84%)
(3) X = Me (**3c**, 0.5 h, 42%)
(4) X = OMe (**3d**, 0.25 h, 80%)
(5) X = O-^{n}*Pr* (**3e**, 0.25 h, 80%)
(6) X = Me (**3f**, 0.5 h, 44%)
(7) X = *n*-C_6H_{13} (**3g**, 0.5 h, 53%)
(8) X = O-^{n}*Pr* (**3h**, 0.25 h, 57%)
(9) X = OMe (**3i**, 0.25 h, 41%)
(10) X = *t*-butyl (**3j**, 0.75 h, 29%)
(11) X = H (**3k**, 0.5 h, 35%)
(12) X = F (**3l**, 0.5h, 19%)
(**4l**, 0.5h, 69%)
(13) X = O-^{n}*Pr* (**3m**, 0.25 h, 65%)
(14) X = OMe (**3n**, 0.25 h, 40%)
(15) X = *t*-butyl (**3o**, 0.75 h, 34%)
(16) X = H (**3p**, 0.5 h, 39%)
(17) **3q** (X = Ms, 0.5 h, 76%)
(18) **3r** (X = Ts, 0.5 h, 77%)

1 (0.1 *M*, 1.0 equiv) [a]Product yields are obtained after purification from a silica column. [b]L= P(*t*-Bu)$_2$(*o*-biphenyl).

ynamides **1k** and **1p** were also applicable substrates to afford desired **3k** and **3p** in 35% and 39% yields respectively (entries 11 and 16). Finally, we tested the reactions on 3,4,5-trimethoxyyphenyl sulfonamides **1q** and **1r**, producing desired products **3q** and **3r** in 76-77% yields (entries 17-18).

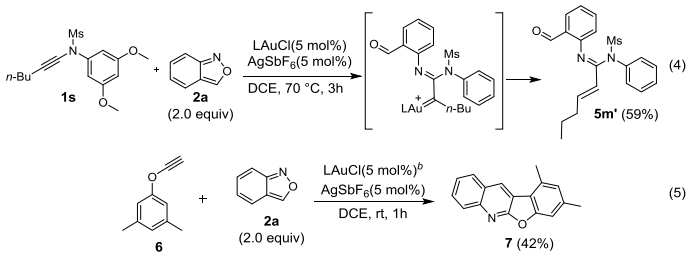
As shown in Scheme 2, the scope of these annulations is significantly expanded with various applicable benzisoxazoles **2a-2l**. For species **2a-2d** bearing various 6-substituted benzisoxazoles (X = Cl, Br, OMe, and Me), their annulations with model ynamide **1a** afforded the desired products **5a**-**5d** with reasonable yields (58%-77%, entries 1–4). In the case of 5-substituted benzisoxazoles (X = Cl, Br, OMe, Me and OCO_2Et), their corresponding products **5e**-**5i** were obtained in 44-78% yields (entries 5-9). The reaction of dioxolo benzoisoxazole **2j** with **1a** delivered desired **5j,** albeit in 38% yield (entry 10). We examined the reactions on 3-substituted benzisoxazoles **2k** and **2l** (X = Me, Ph), yielding the desired products **5k** and **5l** in 68-70% yields (entries 11-12).

Scheme 2. Catalytic Annulations with various benzisoxazoles



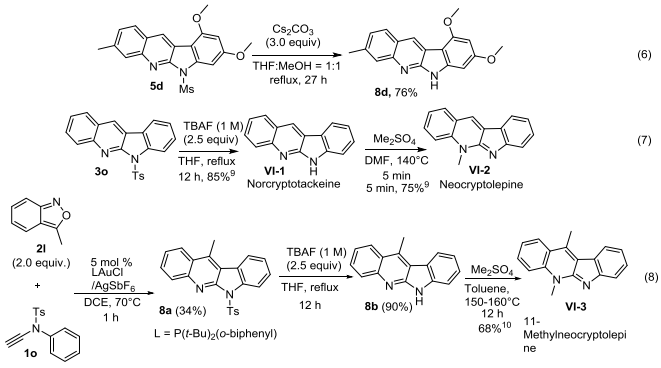
(1) X = Cl (**5a**, 0.25 h, 68%)
(2) X = Br (**5b**, 0.25 h, 61%)
(3) X = OMe (**5c**, 0.5 h, 77%)
(4) X = Me (**5d**, 0.25 h, 58%)
(5) X = Cl (**5e**, 0.5 h, 78%)
(6) X = Br (**5f**, 0.5h, 67%)
(7) X = OMe (**5g**, 0.5 h, 44%)
(8) X = Me (**5h**, 0.25 h, 60%)
(9) **5i** (0.5 h, 71%)
(10) **5j** (0.5 h, 38%)
(11) X = Me (**5k**, 0.25 h, 70%)
(12) X = Ph (**5l**, 0.25 h, 68%)

1 (0.1 *M*, 1.0 equiv) [a]Product yields are obtained after purification from a silica column. [b]L= P(*t*-Bu)$_2$(*o*-biphenyl).



We tested the reaction on one internal ynamide **1s** that reacted with benzisoxazole **2a,** in the presence of gold catalyst, to from compound **5m'** in 59% yield; this information confirms the intermediacy of gold carbene intermediates (eq 4). To expand the reaction scope, we examined such cascade annulations on phenoxyalkyne **6**,[8a] which reacted with benzisoxazole **2a** under standard conditions to yield distinct heterocyclic compound **7** in 42% yield (eq 5).

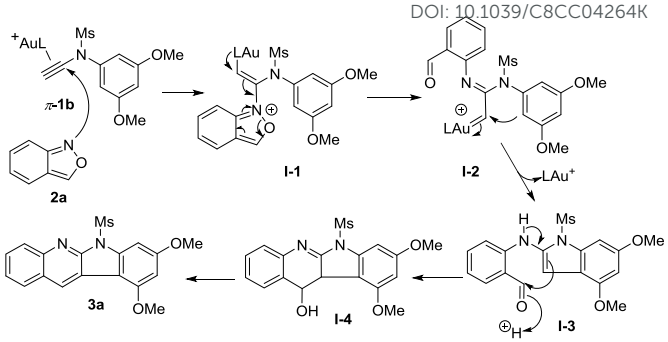
Indoloquinoline **5d** undergoes a facile deprotection to remove the mesyl group, producing **8d** in 76% yield (eq 6). Compound **5d** was treated with Cs_2CO_3 in THF/MeOH (1:1) under reflux in 27 h, from which we obtained compound **8d** in 76% yield. In the literature,[5a-5b,9] compound **VI-1** and its methy derivative, neocryptolepine **VI-2** were prepared smoothly from our resulting indolo[2,3-*b*]quinoline **3o** (eq 7). We launched a formal synthesis of the third target, methylneocryptolepine **VI-3** based on our new method. To our pleasure, gold-catalyzed reactions of 3-methylbenzisoxazole **2l** with ynamide **1o** in hot DCE (70 °C, 1 h) afforded desired **8a** in 34% yield, which was convertible to the key intermediate **8b** before preceeding to the desired alkaloid **VI-3** (eq 8)[10].



Scheme 3 shows a proposed mechanism of this gold catalysis. An initial *N*-attack[3] of benzisoxazoles **2a** at π-alkyne complexes **1a** yielded alkenylgold species **I-1**, further producing gold carbenes **I-2** via a cleavage of the N-O bond. At high temperatures, the *N*-aryl nucleophile is conformational flexible to attack gold carbenes **I-2** preferably, generating reactive indole species **I-3**. An addition of this indole at the benzaldehyde is expected to yield azacyclic product **3a** via dehydration of species **I-4**.

In summary, we have designed a new path for the gold-catalyzed annulations[11] of *N*-aryl ynamides[12-13] with benzisoxazoles to construct 6*H*-indolo[2,3-*b*]quinoline frameworks. Besides the electron-rich property of *N*-aryl group, the success of these reactions relies on the operations at high temperatures to enable a *N*-aryl group to attack gold carbenes,

Scheme 3. A plausible mechanism



forming indoles that attack again at the benzaldehyde. This high-temperature effect avoids the formation of 2-amino-7-formylindoles from the Hashmi's reaction.[3a] The utility of this method is manifested by a satisfactory range of *N*-aryl ynamides and benzisoxazoles. Our preliminary results indicate that a phenoxyethyne is also a applicable substrate. To manifest the utility of this new method, we have completed the formal synthesis of three naturally occurring alkaloids based on this new catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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