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Gold(I)-Catalyzed Dimerization of 3-Diazooxindoles Towards Isoindigos

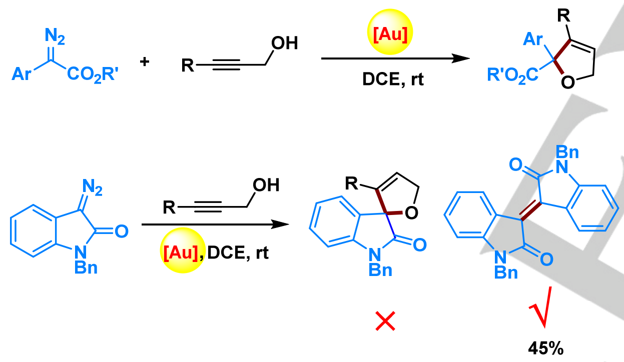
Xinbo Yao,[a] Tao Wang,*[a] and Zunting Zhang*[a]

Abstract: A gold-catalyzed dimerization of 3-diazooxindoles was developed, delivering isoindigos as products. The reaction shows broad substrate scope and functional group tolerance by affording various substituted isoindigos. Moreover, the method also exhibited high efficiency on a gram-scale reaction.

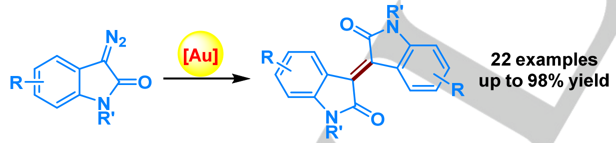
Introduction

Benefited from the explosive development of gold catalysis[1] in the last decade, a variety of transformations based on diazo compounds[2] has been achieved under gold catalysis. There have been reports on the gold-catalyzed cycloaddition,[3] cyclopropenation,[4] cyclopropanation,[5] C−H insertion[6] and O−H insertion[7] of diazo compounds. Recent results showed the advantage of gold catalysis in the carbene transfer from diazo compounds. For example, Zhang and Liu reported the gold-catalyzed chemoselective aryl C-H insertion over O-H insertion of phenol derivatives with diazo compounds.[6d] Sun and co-workers made great efforts on the gold-catalyzed coupling of diazo compounds.[8] Very recently, Zhou reported the stereoselective gold-catalyzed coupling of diazo reagents and fluorinated enol silyl ethers, delivering tetrasubstituted alkenes as products.[9] To make our efforts on gold catalysis,[10] in 2015 we reported the gold-catalyzed synthesis of 2,5-dihydrofurans via a formal [4 + 1] cycloaddition of *α*-diazoesters and propargyl alcohols (Scheme 1a).[10a] The reaction worked well for aryl diazoacetates, however, no expected spiro dihydrofuran product was obtained when diazooxindole was subjected to the standard conditions. Instead, a dimerization product, isoindigo, was obtained in moderate yield (Scheme 1a). As literature present, isoindigos play important roles in both pharmaceuticals and material science. For example, meisoindigo (Figure 1) shows anti-angiogenesis effects on chronic myelogenous leukemia in vitro.[11] Natura is proved to be an cyclin-dependent kinases (CDKs) inhibitor.[12] In addition, isoindigo-based materials were also wildly used in organic solar cells (OSCs) and field-effect transistors (FETs).[13] For an example, Figure 1 shows the first application of isoindigo-based materials ((iI)TT$_2$) to OPVs.[14] The importance of isoindigos in pharmaceuticals and material science inspired us to investigate the dimerization of diazooxindoles. Herein, we want to report the preparation of isoindigos *via* the dimerization of 3-diazooxindoles under gold catalysis.

(a) Our previous work



(b) This exploration



Scheme 1. Our previous work and this exploration.

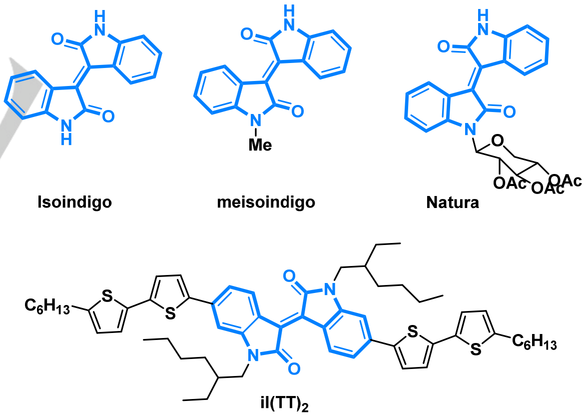


Figure 1. Representative examples of isoindigos in pharmaceuticals and organic photovoltaics (OPVs).

Results and Discussion

In our previous work, it was found that unprotected 3-diazooxindole completely decomposed in the presence of a gold catalyst while 1-benzyl-3-diazoindolin-2-one (**1a**) afforded **2a** in 45% yield (Scheme 1a).[10a] Based on this result, we optimized the reaction conditions for the dimerization by using **1a** as model substrate. The results were summarized in Table 1. Firstly, a variety of gold catalyst was examined. A gold catalyst with a steric bulk ligand, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), was found highly efficiency for the dimerization of **1a**, delivering isoindigo **2a** in 60% isolated yield

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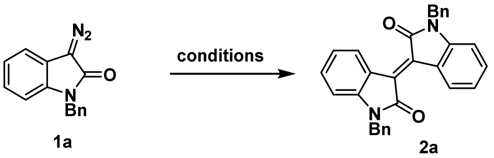
Table 1. Reaction Optimization. [a]



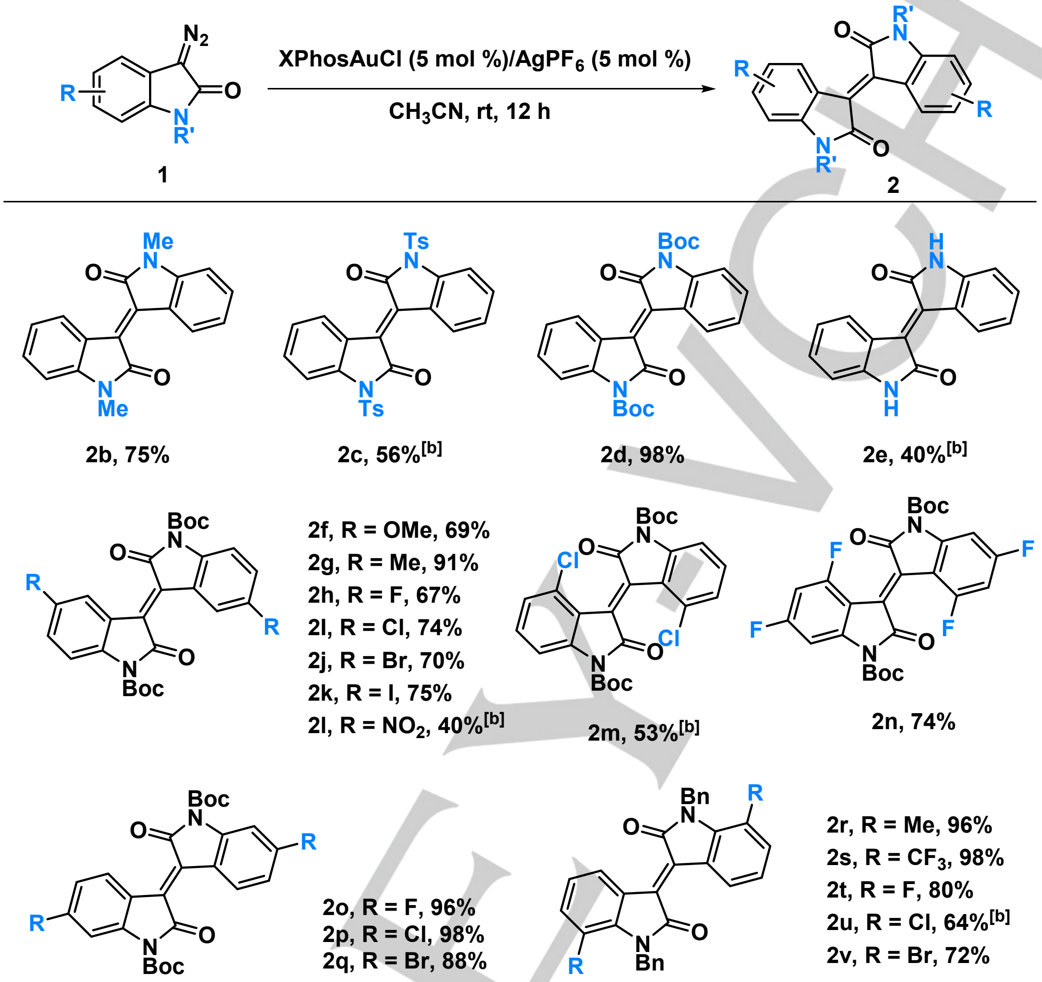
1a 2a

Entry	Catalyst (5 mol %)	Solvent/Time	Yield[b]
1	$PPh_3AuCl/AgNTf_2$	DCM/0.5 h	14%[c]
2	$JohnPhosAuCl/AgNTf_2$	DCM/0.5 h	30%[c]
3	$SPhosAuCl/AgNTf_2$	DCM/0.5 h	30%[c]
4	$XPhosAuCl/AgNTf_2$	DCM/0.5 h	60%[c]
5[d]	$BinapAu_2Cl_2/AgNTf_2$	DCM/0.5 h	15%[c]
6	(2,4-*t*Bu-PhO)$_3$PAuCl/AgNTf$_2$	DCM/0.5 h	35%[c]
7	$IPrAuCl/AgNTf_2$	DCM/0.5 h	41%[c]
8	$XPhosAuCl/AgSbF_6$	DCM/0.5 h	69%[c]
9	XPhosAuCl/AgOTf	DCM/0.5 h	60%[c]
10	$XPhosAuCl/AgBF_4$	DCM/0.5 h	65%[c]
11	$XPhosAuCl/AgPF_6$	DCM/0.5 h	80%
12	$XPhosAuCl/AgPF_6$	DCE/0.5 h	66%
13	$XPhosAuCl/AgPF_6$	Toluene/0.5 h	74%
14	$XPhosAuCl/AgPF_6$	THF/2 h	73%
15	$XPhosAuCl/AgPF_6$	CH_3CN/6 h	84%
16	$AgNTf_2$	DCM/0.5 h	23%[c]
17	$AgNTf_2$/XPhos	DCM/12 h	trace[e]
18	$[Rh(CH_3(CH_2)_6CO_2)_2]_2$	DCM/12 h	trace[c]
19	$Cu(OTf)_2$	DCM/12 h	45%[c]
20	$Cu(acac)_2$	DCM/2 h	NR
21	CuI	DCM/2 h	NR
22	$Cu(CH_3CN)_4BF_4$	DCM/4 h	45%[c]
23	$Cu(CH_3CN)_4PF_6$	DCM/4 h	43%[c]
24	$CuCl_2$	DCM/12 h	NR

[a] Reaction conditions: For entries 1-15 and entry 17, **1a** (49.9 mg, 0.2 mmol) was added to the stirring solution of the corresponding catalyst (0.01 mmol) in 2 mL of solvent at room temperature. For entries 18-24 and entry 16, the corresponding catalyst (0.01 mmol) was added to the solution of **1a** (49.9 mg, 0.2 mmol) in 2 mL of dichloromethane. After **1a** was fully consumed (monitored by TLC) or the time mentioned in each entry, the solvent was removed via rotary evaporation. The residue was purified by column chromatography on silica gel (dichloromethane was used as the eluting solvent) to afford **2a** as product. [b] Yields of isolated products. [c] The decomposition of **1a** is the main competing process of dimerization. [d] 2.5 mol % of $BinapAu_2Cl_2$ was added in combination with 5 mol % of $AgNTf_2$. [e] The conversion rate of **1a** was less than 90%.

(Table 1, entry 4). $BinapAu_2Cl_2$ (Binap = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene), (2,4-*t*Bu-$C_6H_3O)_3PAuCl$ and IPrAuCl [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)] were also tested together with $AgNTf_2$ (entries 5-7), respectively. However, no improvement was observed for the dimerization. A main reason accounting for the low yield was the decomposition of **1a**. By replacing $AgNTf_2$ with other silver salts to active the gold catalyst by chloride abstraction, the reaction was improved in some degree.[15] For example, when XPhosAuCl was used in combination with $AgSbF_6$, the reaction afforded **2a** in 69% yield (entry 8). When $AgPF_6$ was added to active XPhosAuCl, the reaction was dramatically improved affording **2a** in 80% yield (entry 11). A subsequent solvent screening revealed that the use of acetonitrile as solvent could further improved the transformation by preventing **1a** from decomposition (entry 15). $AgNTf_2$ was also capable of catalyzing this reaction, but only gave **2a** in 23% yield (entry 16). The addition of ligands (XPhos) in a 1:1 ratio to $AgNTf_2$ resulted in incompletely conversion of **1a**, delivering just trace amount of **2a** (entry 17). Other Lewis acids which were reported to be effective in the transformation of diazo compounds were examined (entries 18-24). The use of rhodium octanoate dimmer as catalyst also gave trace amount of **2a** due to the decomposition of **1a** (entry 18). Copper salts were also tested, among which $Cu(OTf)_2$, $Cu(CH_3CN)_4BF_4$ and $Cu(CH_3CN)_4PF_4$ exhibited a similarly catalytic efficiency, delivering **2a** in moderate yields (entries 19-24).

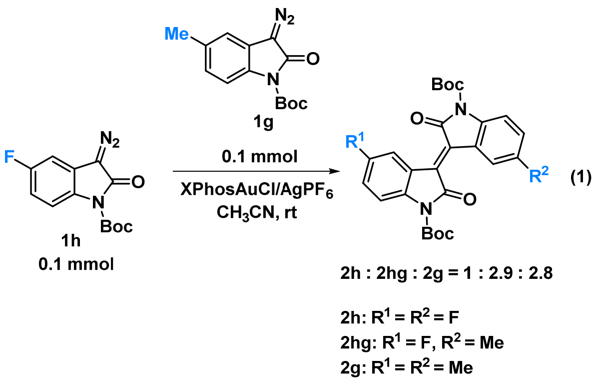
With the optimized conditions in hand, the scope of the substrates was explored (Scheme 2). At first, the protecting group on the nitrogen atom was explored. A methyl protected substrate gave **2b** in 75% yield, while a tosyl (Ts) protected product **2c** was obtained in only 56% yield. To our delight, when a *t*-butyloxy carbonyl (Boc) group was installed to nitrogen atom, the reaction worked smoothly affording **2d** in quantitative yield (98%). It was found that the existing of a Boc group dramatically increase the solubility of both the starting material and the product. In addition, as a protecting group, Boc is facile to be installed and removed. When unprotected 3-diazooxindole was subjected to the standard conditions, the corresponding isoindigo (**2e**) was obtained in only 40% yield. The substrate suffered from decomposition, resulting the poor yield of the product. Various of Boc protected 3-diazooxindoles were prepared and was subjected to the standard conditions to further explore the scope of the dimerization reaction. Firstly, a variety of substituents was introduced to the 5-position of 3-diazooxindole. Under standard conditions, the substrates afforded corresponding isoindigos in good to excellent yields (**2f-2l**). It was found that the substrates with electron-donating group in their 5-positions gave corresponding isoindigos in better yields than those with electron-withdrawing groups (for example **2g** *Vs*



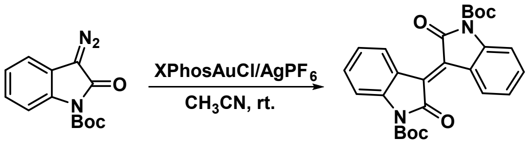
Scheme 2. Reaction Scope for the Synthesis of isoindigos. [a] Unless otherwise noted, reactions were performed on 0.3 mmol scale in 3 mL of CH_3CN with XPhosAuCl (5 mol %) and $AgPF_6$ (5 mol %) at room temperature for 12 h; the yields given are isolated yields. [b] The decomposition of the corresponding 3-diazooxindole resulted in the relatively lower yield of the product.

2l). 3-Diazooxindoles bearing substituents in 4-positions were also explored, which afforded corresponding isoindigos in good yields (**2m** and **2n**). **2p** and **2q** are often used starting materials for the preparation of isoindigo-based conjugated polymers, which could be obtained in good to excellent yields *via* the dimerization of corresponding 3-diazooxindoles under gold catalysis. In case of 3-diazooxindoles bearing substituents in 7-positions, because *N*-Boc protected substrates were difficult to prepared, *N*-Bn protected substrates were explored. The reactions worked well to deliver corresponding isoindigo products in good to excellent yields (**2r**-**2v**).

Two different 3-diazooxindoles, **1g** and **1h**, were subjected to the standard conditions (eq 1). By HPLC analysis, three products were observed in a 1:2.9:2.8 ratio (**2h**:**2hg**:**2g**). A cross-coupling product **2hg** and a homocoupling product **2g** were found as main products. The result suggests that the relatively electron-rich 3-diazooxindole **1g** is prior to the relatively electron-deficient 3-diazooxindole **1h** to attack the gold-carbenoid generated from **1g** and **1h** in the presence of a gold catalyst. This result is consistent with previous investigations of Davies[16] and Sun.[8a]



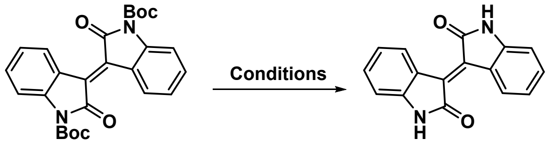
A gram-scale reaction of **1d** afforded **2d** in 88% yield when 5 mol % of catalyst was added. When the catalyst loading decreased to 3 mol %, **2d** was obtained in a slight lower yield (eq 2). The Boc group was easily removed when **2d** was subjected to LiBr or HCl conditions. Especially when **2d** was treated with HCl in ethyl acetate (EA), **2e** was obtained in nearly quantitative yield (95%, eq 3).



(2)

1d
1.037 g (4 mmol)

2d
0.8177 g, 88% yield (5 mol % catalyst)
0.7489 g, 81% yield (3 mol % catalyst)



(3)

2d **2e**

Condition A: LiBr (3 equiv), CH$_3$CN, 65 ^{o}C, 5 h, 76% yield
Condition B: HCl, EA, rt, 6 h, 95% yield

Conclusions

In conclusion, a highly efficient gold-catalyzed dimerization of 3-diazooxindoles was developed. The reaction shows its advantage in rapid construction of various substituted isoindigos in gram-scale under mild conditions. Taking the importance of isoindigos into account, the reaction shows its potent application in both pharmaceuticals and material science.

Experimental Section

General procedure for the gold-catalyzed dimerization of 3-Diazooxindoles

3-Diazooxindole (0.3 mmol) was added successively to a stirring suspension of XPhosAuCl (10.6 mg, 15.0 μmol) and AgPF$_6$ (3.8 mg, 15.0 μmol) in acetonitrile (3.0 mL) at room temperature. The solution was then stirred at room temperature for 12 hours. After evaporation, the residue was purified by column chromatography on silica gel (dichloromethane was used as the eluting solvent) affording the desired product.

(*E*)-1,1'-Dibenzyl-[3,3'-biindolinylidene]-2,2'-dione (**2a**)[17] : Yield: 75%, ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 9.23 (d, 2 H, *J* = 7.8 Hz), 7.33-7.25 (m, 12 H), 7.04 (t, 2 H, *J* = 7.8 Hz), 6.71 (d, 2 H, *J* = 7.8 Hz), 5.02 (s, 4 H) ppm.

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Keywords: gold catalysis • diazo compounds • dimerization • isoindigo • coupling

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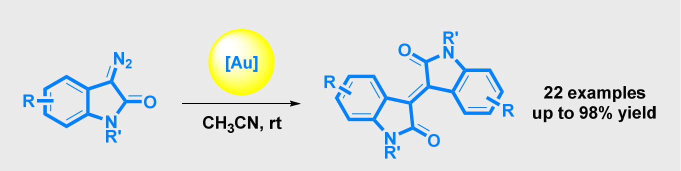
COMMUNICATION



Isoindigos were prepared *via* a gold-catalyzed dimerization of 3-diazooxindoles. Besides broad substrate scope and functional group tolerance, the reaction also exhibited high efficiency on a gram-scale reaction.

Gold Catalysis

Xinbo Yao, Tao Wang, and Zunting Zhang**

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