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Au-catalyzed Intramolecular Annulations Toward Fused Tricyclic [1,3]oxazino[3,4-*a*]indol-1-ones under Extremely Mild Conditions

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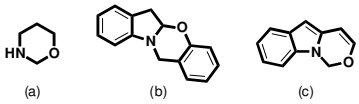
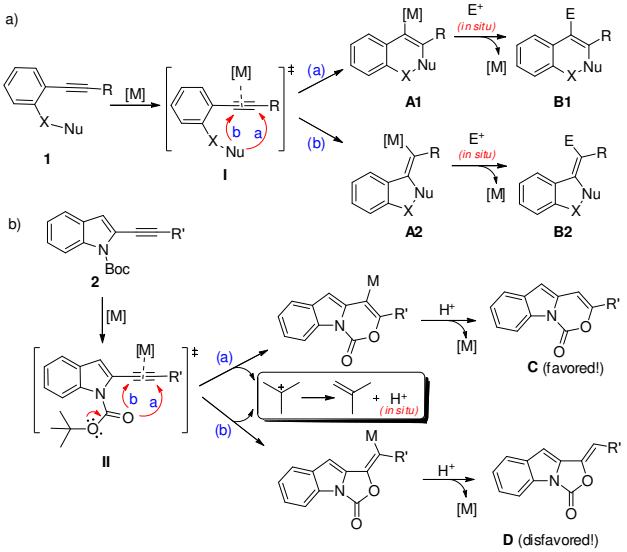
We report a general and efficient method for the rapid generation of tricyclic [1,3]oxazino[3,4-a]indol-1-ones under extremely mild conditions. The reaction is compatible with a wide range of functionalized indoles with different electronic natures. The blue light fluorescent emission properties of some titled fused-tricyclic compounds are briefly studied.

Substituted 1.3-oxazinane alkaloids are an important subclass of heterocycles due to their presence in a wide range of natural or bioactive molecules (Scheme 1a).[1] 1.3-Oxazinanes are versatile synthetic building blocks for organic synthesis, and they can be readily converted to *N*-alkyl- or *N*-H-functionalized 1,3-aminoalcohols in concise transformations.[2] 1.3-Oxazinanes with fused aromatic analogues are very closely related to optoelectronic material fields (Scheme 1b).[3] For instance, 1.3-oxazinane with a fused 3*H*-indole structure was found to be stable enough to tolerate hundreds of switching cycles in photochemical experiments with no sign of decomposition even in oxygenation conditions. Their excellent fatigue resistance has made the indole-based 1,3-oxazinanes attractive as photoresponsive photochromic filters and photonic devices.[4] Moreover, because the indole-based heterocycles generally display potent biological or medicinal activities, we envisioned that the incorporation of the indole moiety into the scaffold of 1,3-oxazinanes would be beneficial for subsequent biological evaluation or chemical genetic studies. While there are reports of polycyclic indole skeletons containing oxazinane structures,[5] there are currently lack of general method describing the synthesis of fused tricyclic [1,3]oxazino[3,4-*a*]indol-1-ones (Scheme 1c).



Scheme 1. (a) 1.3-Oxazinane. (b) fused indole-based tetracyclic compound that containing an 1.3-oxazinane. (c) fused tricyclic 1.3-oxazinane derivative.

We recently published studies regarding the transition-metal-catalyzed electrophilic cycloisomerization reaction of multiple alkynes **1** (Scheme 2a) to prepare functionalized carbocyclic and heterocyclic molecules **B** such as halo-substituted benzo[*a*]fluorenols,[6a] densely trisubstituted naphthelenes,[6b] 3-CF_3S-1-metheleneindenes,[6c] 2-vinyl-3-OAc-indenes,[6d] etc. The reactions were supposed to proceed by a stepwise mechanism and involve metal-coordination and activation of the alkyne triple bond (intermediate **I**), intramolecular nucleophilic attack on the cationic species to form the ring skeleton **A1** and **A2**, and subsequent de-metallation reactions by the *in situ* generated electrophiles $\mathbf{E}^+$ (Scheme 2a).



Scheme 2. (a) Published results in transition-metal-catalyzed electrophilic cyclization reactions. (b) Proposed synthethic route.

The facile nature of catalytic cycloisomerization strategies prompted us to imagine that a similar reaction using Boc-protected

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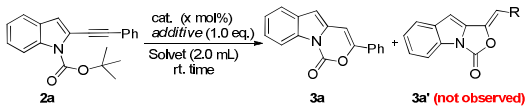
2-alkylindole **2** as a starting material would lead to the indole-based tricyclic product **C** or **D** (Scheme 2b). As shown in Scheme 2b, the reaction would commence with a *6-endo-dig* (path a) or *5-exo-dig* (path b) cyclization of a tethered carbamate onto a metalla-alkyne complex **II** followed by the formation of tricyclic ring systems with concurrent elimination of the carbocation *t*Bu$^+$. Isobutene would be released from the *tert*-butyl group and the *in situ*-generated proton could in turn work as an electrophile to induce the demetallation reaction to close the catalytic cycle. In this regard, we suggest that bond angles of 120° rather than 109.5° in the rigid indole-C2 atom in intermediacy **II** should force the putative *6-endo-dig* cyclization pathway to be a more favored one. This shows that product **C** is the major outcome.

The transition-metal-catalyzed intramolecular cyclizations of alkynes for the rapid generation of five-membered dioxolan-2-ones[7a,b] and 1,3-oxazolidin-2-ones[8a,b,9] and oxazinones have been realized. Gagosz *et al* reported a one-pot Cu(II) and Au(I) co-catalyzed sequential reaction of bromoalkyne with tert-butyloxycarbamate to give a diverse set of 1,5-disubstituted oxazolones.[9] Asao and co-workers reported a gold-catalyzed alkylation reaction of alcohols and aromatic compounds using *ortho*-alkynylbenzoic acid alkyl esters as starting materials.[10,11] Occhiato and co-workers reported a cyclic urethane derivatives synthesis via gold(I)-catalyzed cyclization of N-Boc-protected 6-alkynyl-3,4-dihydro-2H-pyridines.[12] However, the development of practical and efficient methods to prepare six-membered and indole-based fused tricyclic ring systems, especially from readily available starting materials and simple processing reactions, are still of highly desirable.

Results and Discussion

The NBoc-2-alkynylindole **2a** was first selected as a test substrate. Initially, the model reaction of indole **2a** under the catalysis of $AuCl_3$ in dichloromethane was examined.[13] To our delight, the desired product (compound **3a)** was isolated at very low yields (Table 1, entry 1). The targeted by-product **3a'** was not detected. Preliminary study indicated that alcoholic solvent was an optimal reaction medium; the yield of compound **3a** could be improved to 21% in ethanol (Table 1, entry 3). Notably, the silver catalyst was totally inert (Table 1, entry 4). We reasoned that the acidic condition would be necessary for the formation of the carbenium ion species because it was assumed to be involved in the annulation process. To this end, we were delighted to find that the addition of *p*-TsOH dramatically accelerated the transformation, and the desired compound **3a** was isolated in 58% or 75% yield when catalyzed via Ph_3PAuBF_4 or $AuCl_3$, respectively (Table 1, entries 5-6). No improved performance was observed when Brønsted acids such as MsOH, HOAc, or TFA were used (Table 1 entries 7-9). A similar result of 72% yield was obtained when using DCM as the solvent under the catalysis of $AuCl_3$ (Table 1 entry 10). Good results were obtained when a commercially available acidic gold catalyst, $HAuCl_4$, was evaluated. The desired product **2a** was isolated in 92% yield even in the absence of external acid additives (Table 1 entry 11). We next screened some other laboratory solvents using $HAuCl_4$ as the catalyst. The results indicate that ethanol was the most optimal reaction medium (Table 1 entries 14-18). Finally, the concentration of this intramolecular annulation reaction was also tested (Table 1 entries 19-20). Impressively, this reaction is easily handled and only requires the catalyst and environmentally friendly solvent to promote the expected transformation at room temperature.

Table 1. Optimization of the reaction conditions.[a]



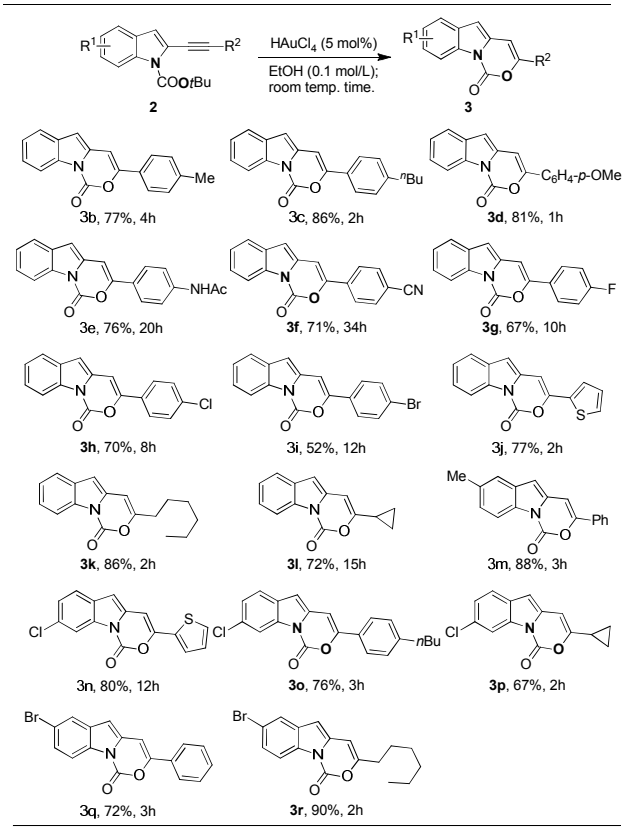
entry	cat. (x mol%)	additive (1.0 eq.)	solv.	time /h	**3a**/%[a]
1	$AuCl_3$ (5)	-	DCM	24	9
2	$AuCl_3$ (5)	-	Toluene	24	0
3	$AuCl_3$ (5)	-	EtOH	24	21
4	AgOTf (5)	-	EtOH	24	0
5	Ph_3PAuCl (2.5) + $AgBF_4$ (5)	*p*-TsOH	EtOH	2	58
6	$AuCl_3$ (5)	*p*-TsOH	EtOH	2.5	75
7	$AuCl_3$ (5)	MsOH	EtOH	4	43
8	$AuCl_3$ (5)	HOAc	EtOH	10	37
9	$AuCl_3$ (5)	TFA	EtOH	4.5	68
10	$AuCl_3$ (5)	*p*-TsOH	DCM	4	72
11	**$HAuCl_4$ (5)**	**-**	**EtOH**	**2.5**	**92**
12	$HAuCl_4$ (2)	-	EtOH	5	75
13	-	*p*-TsOH	EtOH	24	0
14	$HAuCl_4$ (5)	-	DCM	4	88
15	$HAuCl_4$ (5)	-	1,4-dioxane	4	84
16	$HAuCl_4$ (5)	-	HFIP	4	54
17	$HAuCl_4$ (5)	-	MeOH	4	87
18	$HAuCl_4$ (5)	-	*i*PrOH	14	86
19	$HAuCl_4$ (5)	-	EtOH	12	92[b]
20	$HAuCl_4$ (5)	-	EtOH	1.5	85[c]

[a] reaction conditions: 1a (0.20 mmol), catalyst (x mol%), additive (y eq.), solvent (2.0 mL, 0.10 M), room temp. [b] EtOH (3.0 mL); [c] EtOH (1.0 mL). *p*-TsOH = 4-methylbenzenesulfonic acid. MsOH = methanesulfonic acid. TFA = 2,2,2-trifluoroacetic acid. HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol.

Having defined the conditions needed for efficient transformation, we next examined a wide variety of NBoc-2-alkynylindoles (**2;** Table 2).[14] The reaction was found to have a good functional group tolence with respect to variation of the R^2

groups in substrate **2** as well as the existence of aryl-, heteroaryl-, alkyl, and cycloalkyl groups at this position. For example, when R^1 = H and the aryl group on R^2 contained electron-donating or -withdrawing substituents, the expected products **3b** to **3i** were obtained in 52-86% yields. Notably, the photoelectronically important CN group (**2f**)[15] and 2-thienyl group (**2j**)[16] can also be tolerated. This indicates that photochromic property studies might be conducted in the future with fluorescence spectroscopy.[4] The presence of a heteroaryl goup on the 2-thienyl substituent was also tolerated under standard conditions. This afforded the expected product **3j** in 77% yield. The efficiency of this reaction was not compromised when substrates containg alkyl groups such as *n*-hexyl or cyclopropyl substituent were added at the R^2 position. The corresponding products **3k** and **3l** were isolated in 86% and 72% yields, respectively.

Table 2. Scope of NBoc-2-alkynylindoles **2**.[a]

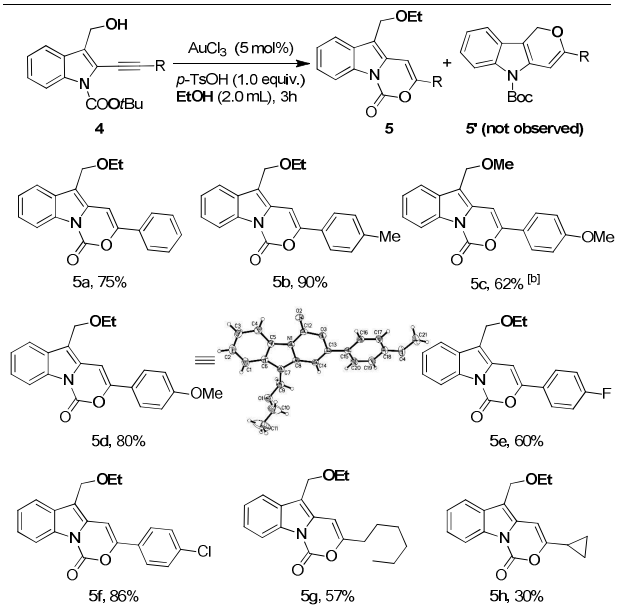


[a] Reaction conditions: **2** (0.20 mmol), $HAuCl_4$ (5 mol%), EtOH (2.0 mL, 0.10 M), rt; isolated yields based on **2**.

For the various substituents attached at the benzoid ring of the indole core structure, we were delighted to find that the electron-rich alkyl group and the electron-deficient halogen group (6-Cl and 5-Br) can be tolerated to give a structually divergent 1*H*-[1,3]oxazino[3,4-*a*]indol-1-ones (**3m**-**3r**) in good to excellent yields. Halogen groups such as chloro and bromo atoms are versatile synthetic handles in organic synthesis. Therefore, the existence of these groups suggest that further elaborations on the resulting products may be easily achieved via palladium-catalyzed cross-coupling reactions.

Interestingly, when substrate **4** contained a nucleophilic free hydroxoy group at the C3 position of the indole core structure, the cyclization reaction selectively occurred at the ester moiety, and the free OH group was alkylated with the alcoholic solvent to afford product **5**. Only modest yield of 63% could be obtained when using $HAuCl_4$ (5 mol%) as the cataylst for reaction of **4a** to **5a**, however, this could be improved to 75% yield when $AuCl_3$ (5.0 mol%) was used as the catalyst, *p*-TsOH (1.0 equiv.) as the acidic additive and DCM as the solvent. We presumed the HAuCl4 should be too acidic as compared with p-TsOH for the reaction of **4a** to **5a**. The structure of compound **5** was identified unambiguously by X-Ray diffraction analysis.[17] It should be noted that when running the reaction of **4** in nonalcoholic solvents such as dichloromethane or 1,4-dioxane, which were potential solvents for the cyclization reaction of **2a** (Table 1), the reaction became black soon and a complex mixture were observed. This result indicated that for the reaction of **4** to **5**, the etherization process of substrate **4** with alcohol should possibly happen first before the *6-endo-dig* cyclization.

Table 3. Annulation reaction of NBoc-3-hydroxymethylindoles **4**.[a]

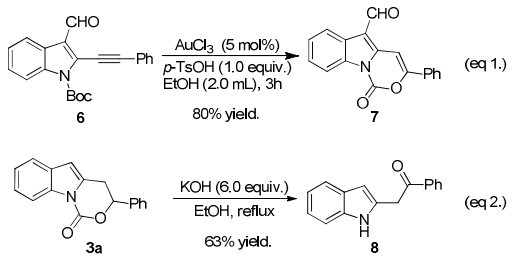


[a] reaction conditions: compound **4** (0.20 mmol, 1.0 equiv), $AuCl_3$ (5 mol%), *p*-TsOH (1.0 equiv), EtOH (2.0 mL, 0.10 M), rt, open air; isolated yields based on compound **4**. [b] MeOH (2.0 mL) instead of EtOH as the solvent.

This result is significant and deserves notice because it is widely accepted that the nucleophilic ability of the free OH group is much stronger than the oxygen atom in carbamate.[18] However, the *6-endo-dig* cyclization product **5** was found to be the only product, and compound **5'** was not observed. This result confirmed our hypothesis that the NBoc-2-alkynylindole structure is very rigid (scheme 1b) such that the nucleophilic oxygen is positioned and should be held close to the alkyne

reaction center. Therefore, the relative nucleophilicity is not necessarily the determining factor for the annulation reaction. For the hydroxyl group to attack the alkyne-gold complex, an *anti* relationship is needed, which might be sterically disfavoured by the Boc group. The yields of the alkyl substituted products **5g** and **5h** were only moderate, and were presumably due to the relatively low reactivity or the inherent strain of the corresponding starting materials.

The aldehyde group in the C3 position of the indole substrate can be successfully tolerated (Scheme 3, eq 1). When aldehyde **6** was cyclized, the expected product **7** was isolated in 80% yield. The aldehyde group was very reactive in organic synthesis, and the tolerance of this functional group suggested that additional transformations such as the Seyferth-Gilbert homologation[19] or reductive amination reactions should be possible to introduce diversity and complexity. Moreover, the 2-(1*H*-indol-2-yl)-1-phenylethanone **8** could be obtained in 63% yield when treating the compound **3a** in KOH-EtOH (Scheme 3, eq 2).



Scheme 3. Annulation reaction of the aldehyde substituted indole **6**. And ring expansion reaction of product **3a**.

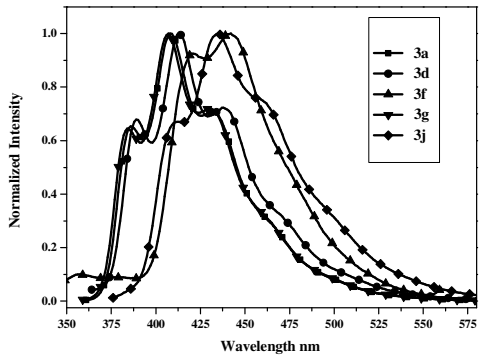


Figure 1. The fluorescence spectrum of compounds **3a**, **3d**, **3f**, **3g**, and **3j**. Experiments were carried out in a dilute solution of $CHCl_3$ (10^{-5} mol/L) at room temperature.

Table 4. Photophysical Properties Measured in $CHCl_3$ (10^{-5} mol/L).

compound	$\lambda_{max,em}$/nm	Φ_F [c]	τ_F (ns) [d]
3a	386, 409[a], 432[b]	0.572	1.24
3d	389, 412[a], 437[b]	0.666	1.18
3g	384, 407[a], 431[b]	0.496	1.53
3j	413, 434[a], 462[b]	0.76	2.12

[a] Referenced to the maximum emission peak. [b] referenced to the shoulder peak. [c] Absolute fluorescence quantum yields were recorded on a Hamamatsu Quantaurus-QY system. [d] Fluorescence life time studies were recorded on a Hamamatsu Quantaurus-Tau system.

To demonstrate the utility of the resulting tricyclic [1,3]oxazino[3,4-*a*]indol-1-ones, the fluorescence of compounds **3a**, **3d**, **3f**, **3g**, and **3j** were briefly studied (Figure 1). These compounds were selected to be representative because the fluorescence emission behaviours were largely dependent on the fluorophore with influence on the substituted groups.[20] The results showed that all of the compounds emitted from 400 nm to 450 nm (the maxinum emission wavelength were shown in table 4). In addition, distinct electronic effects in the emission spectra were also observed. For example, compound **3d** has an electron-donating methoxy group at the phenyl moiety, and it displayed a red-shift in emission wavelength versus **3a** (from 408 to 413 nm). Compound **3g** has an electron-deficient halogen group, and it produced a minor blue shift (406 nm) in the emission spectrum. Compounds **3f** and **3j** had an obvious red-shift because the largest emission peaks were located at 435 nm and 440 nm, respectively. The solution quantum yields of compounds **3a**, **3d**, **3g** and **3f** displayed efficiencies ranged from 0.49 to 0.76 (Table 4). This result indicated that flexible emission band tuning might be achieved simply by changing the electronic nature of the substituents. These were attached at the fluorophore core structure. In addition, lumophores based on **3a** as a matrix may play a crucial role in light emitting materials, environmental sensors or bio-probes in future work. More detailed photophysical characterization is currently underway.

Conclusions

In conclusion, photophysically and pharmaceutically important tricyclic [1,3]oxazino[3,4-a]indol-1-ones were constructed efficiently via a gold-catalyzed intramolecular cyclization of N-Boc-2-alkynylindoles under room temperature in alcoholic solvent. This reaction is easily handled because only the catalyst and environmentally friendly solvent are needed to promote the formal annulation. In addition, the reaction shows a high chemical selectivity toward 6-endo-dig cyclization because no 5-exo-dig cyclization was observed. This method highlights a facile one-step transformation from easily available starting materials to structurally diverse [1,3]oxazino[3,4-a]indol-1-ones. These are not readily available via conventional synthetic methods. The preliminary photophysical examinations revealed that some of the tricyclic products have blue fluorescence. This indicated that the fused polyaromatic compounds might be used as optoelectronic materials in future work.

Acknowledgements

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Keywords: gold-catalysis • intramolecular annulation • indole • 1*H*-[1,3]oxazino[3,4-*a*]indol-1-one • tricyclic compounds

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