Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201504697
Internationale Ausgabe: DOI: 10.1002/anie.201504697

Dual Catalysis for the Redox Annulation of Nitroalkynes with Indoles: Enantioselective Construction of Indolin-3-ones Bearing Quaternary Stereocenters

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Abstract: *The enantioselective redox annulation of nitroalkynes with indoles is enabled by gold/chiral phosphoric acid dual catalysis. A range of indolin-3-one derivatives bearing quaternary stereocenters at the C2 position were afforded in good yields and excellent enantioselectivities (up to 96% ee) from readily available starting materials.*

Indoles and oxindoles are unique substructures that frequently occur in natural alkaloids and biologically active molecules.[1] Numerous methods have been developed for the construction of optically active 2-oxindoles (indolin-2-ones).[2] In sharp contrast, reliable approaches towards the asymmetric synthesis of structurally similar indolin-3-ones are very limited.[3] Indeed, indolin-3-one derivatives that bear quaternary stereocenters at the C2 position are very intriguing for their widespread occurrence in natural products, such as (−)-isatisine A, (−)-isatisine A acetonide, strobilanthoside A, (−)-trigonoliimine C, (+)-austamide, and halichrome A (Figure 1).[4] A few elegant procedures have been established for their synthesis, but most of them rely on transformations of preexisting indolin-3-one ring systems.[3] Consequently, the development of straightforward and efficient methods to chiral indolin-3-ones, in particular from readily available starting materials, is highly desirable.

Recently, dual catalysis employing transition metals and chiral phosphoric acids (CPAs) has appeared as an attractive strategy for asymmetric catalysis.[5] Based on this strategy, enantioselective transformations of metal carbenoids generated from diazo compounds have been well developed, including multicomponent reactions of nucleophiles, electrophiles, and diazoacetates via zwitterionic intermediates,[6,7] enantioselective N–H or S–H insertion reactions with diazo compounds,[8] and sequential processes combining carbonyl ylide formation and reduction.[9] In comparison, asymmetric transformations of α-oxo metal carbenoids, which can be generated by transition-metal-catalyzed redox reactions of alkynes, have remained much less exploited.[10] We noticed that intramolecular redox annulations of nitroalkynes are involved in several attractive reactions, including isatogen formation and dipolar cycloaddition cascade reactions.[11] The formation of an α-oxo metal carbenoid was generally proposed as the initial step in these reactions. We thus envisaged that an enantioselective redox annulation of nitroalkynes with indoles might be realized by gold/CPA dual catalysis.[12] As proposed in Scheme 1, the desired product

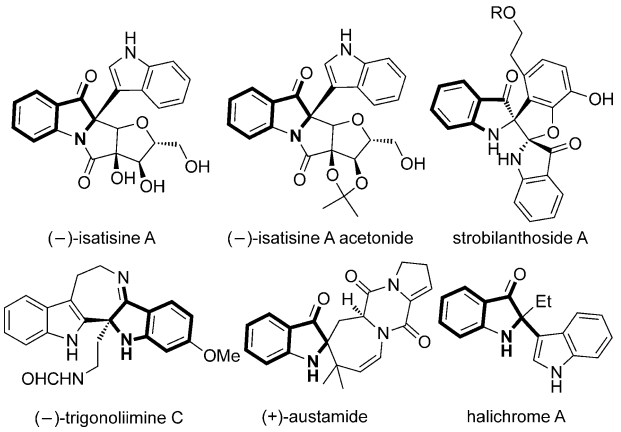
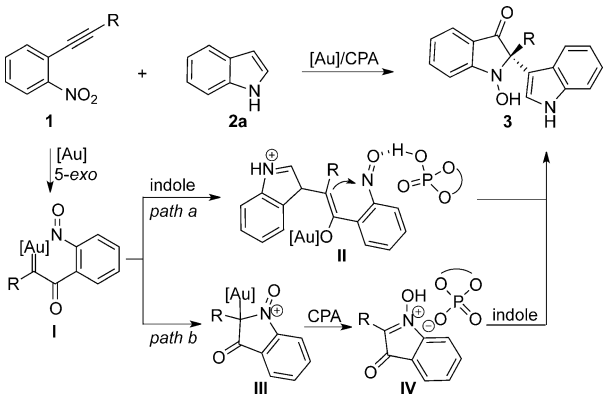


Figure 1. Selected natural products with an indol-3-one framework.



Scheme 1. Proposed redox annulation reaction of nitroalkynes with indoles.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504697.

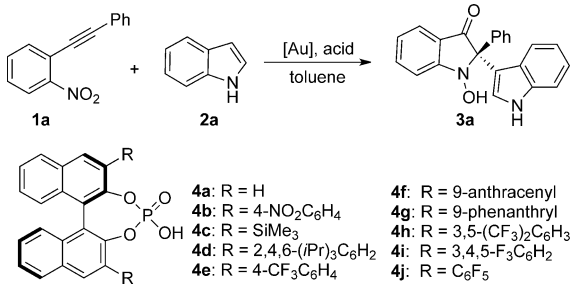
could be afforded either via zwitterionic intermediate **II** (path a; formed by the intermolecular interception of α-oxo gold carbenoid **I** with the indole) or via chiral ion pair **IV** (path b; generated by intramolecular trapping of the nitroso group in **I** followed by protonation). Herein, we report gold/CPA-catalyzed enantioselective redox annulation reactions of nitroalkynes with indoles. A range of indolin-3-ones with

quaternary stereocenters at the C2 position were afforded in good yields and excellent enantioselectivities (up to 96% *ee*) from readily available starting materials.

At the outset, we chose 1-nitro-2-(phenylethynyl)benzene (**1a**) and indole (**2a**) as the model substrates to optimize the reaction conditions. An initial reaction in the presence of $AuCl_3$ (7 mol%) and trifluoroacetic acid (TFA) furnished the desired product **3a** in 95% yield (Table 1, entry 1), but the use of a catalytic amount of TFA led to a decreased yield (entry 2). We then moved our attention to chiral Brønsted acids to develop an enantioselective version. A range of BINOL-based phosphoric acids **4** were thus tested in combination with $AuCl_3$. As expected, the reactions proceeded smoothly to afford the desired products; the use of CPAs with fluorine substituents led to better yields and enantioselectivities, probably owing to their higher acidity (entries 7 and 10–12). In particular, the desired product was obtained in 90% yield and 68% *ee* when CPA **4j** was used (entry 12). Lowering the temperature to 0°C slightly improved the enantioselectivity (entry 13). An examination of various gold catalysts revealed that $[PPh_3AuCl]/AgNTf_2$ (Tf = trifluoromethanesulfonyl) was much inferior and gave only a trace amount of the product (entry 14). $AuBr_3$ also failed to give a satisfying result (entry 15). However, to our delight, the reactions were favorably influenced by the addition of molecular sieves (entries 16–18), and the enantioselectivity of **3a** was remarkably improved to 95% *ee* when 3 Å molecular sieves were added (entry 18).[13]

With the optimized reaction conditions in hand, we then investigated the nitroalkyne and indole scope. First, indole derivatives with various substituents were subjected to the reaction with **1a** (Table 2, entries 1–11). Both electron-withdrawing and electron-donating substituents on the indole ring were well tolerated, mostly affording the desired products in excellent enantioselectivities. Electron-withdrawing substituents generally led to higher enantioselectivities but lower yields than electron-donating groups (**3b**, **3c**, **3e**, and **3h**–**3j** vs. **3f** and **3g**). However, a lower enantioselectivity was observed for the reaction of 5-bromo-substituted indole **2d**, even at −20°C (entry 4). A few substituted nitroalkynes were then reacted with indole. Substrates with aryl substituents (R^2) attached to the alkyne moiety afforded the products in good yields and enantioselectivities (entries 12 and 13), whereas a cyclopropyl group resulted in poor yield and enantioselectivity (entry 14). Furthermore, the halogenated nitroalkynes **1e** and **1f** reacted well with various indoles, furnishing the corresponding products in good yields and excellent enantioselectivities (entries 15–20).

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



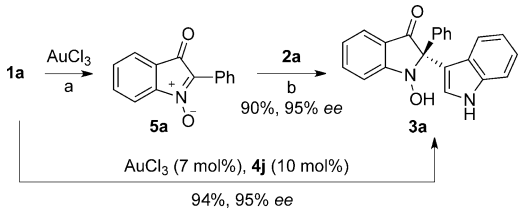
Entry	[Au]	Acid	*T* [°C]	Yield[b] [%]	*ee*[c] [%]
1[d]	$AuCl_3$	TFA	25	95	–
2	$AuCl_3$	TFA	25	60	–
3	$AuCl_3$	**4a**	25	80	13
4	$AuCl_3$	**4b**	25	NR	–
5	$AuCl_3$	**4c**	25	10	3
6	$AuCl_3$	**4d**	25	30	33
7	$AuCl_3$	**4e**	25	87	57
8	$AuCl_3$	**4f**	25	24	40
9	$AuCl_3$	**4g**	25	35	33
10	$AuCl_3$	**4h**	25	89	58
11	$AuCl_3$	**4i**	25	78	55
12	$AuCl_3$	**4j**	25	90	68
13	$AuCl_3$	**4j**	0	88	71
14	$[PPh_3AuNTf_2]$	**4j**	0	trace	–
15	$AuBr_3$	**4j**	0	54	45
16[e]	$AuCl_3$	**4j**	0	85	87
17[f]	$AuCl_3$	**4j**	0	87	78
18[g]	$AuCl_3$	**4j**	0	94	95

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Au] (7 mol%), and acid (10 mol%) in toluene (0.1 M). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] TFA (1.0 equiv). [e] With 5 Å molecular sieves (100 mg). [f] With 4 Å molecular sieves (100 mg). [g] With 3 Å molecular sieves (100 mg).

Table 2: Nitroalkyne and indole scope.[a]

Entry	R^1/R^2 (**1**)	R^3 (**2**)	Yield[b] [%]	*ee*[c] [%]
1	H/Ph (**1a**)	H (**2a**)	94 (**3a**)	95
2	H/Ph (**1a**)	5-F (**2b**)	86 (**3b**)	91
3	H/Ph (**1a**)	5-Cl (**2c**)	80 (**3c**)	95
4[d]	H/Ph (**1a**)	5-Br (**2d**)	79 (**3d**)	86
5	H/Ph (**1a**)	5-CO_2Me (**2e**)	65 (**3e**)	96
6[d]	H/Ph (**1a**)	5-OMe (**2f**)	92 (**3f**)	86
7	H/Ph (**1a**)	5-Me (**2g**)	96 (**3g**)	87
8[d]	H/Ph (**1a**)	6-F (**2h**)	81 (**3h**)	89
9	H/Ph (**1a**)	6-Cl (**2i**)	71 (**3i**)	91
10	H/Ph (**1a**)	6-Br (**2j**)	70 (**3j**)	90
11	H/Ph (**1a**)	7-Me (**2k**)	96 (**3k**)	93
12[d]	H/4-*n*PrC_6H_4 (**1b**)	H (**2a**)	73 (**3l**)	90
13	H/3-MeC_6H_4 (**1c**)	H (**2a**)	83 (**3m**)	93
14	H/cyclopropyl (**1d**)	H (**2a**)	65 (**3n**)	55
15	4-F/Ph (**1e**)	H (**2a**)	80 (**3o**)	85
16	4-F/Ph (**1e**)	6-Cl (**2i**)	75 (**3p**)	93
17	4-F/Ph (**1e**)	6-Br (**2j**)	76 (**3q**)	95
18	5-Cl/Ph (**1f**)	H (**2a**)	70 (**3r**)	94
19	5-Cl/Ph (**1f**)	5-F (**2b**)	70 (**3s**)	96
20	5-Cl/Ph (**1f**)	6-Cl (**2i**)	75 (**3t**)	95

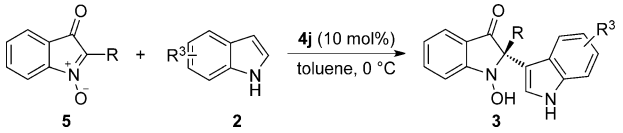
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $AuCl_3$ (7 mol%), **4j** (10 mol%), and 3 Å molecular sieves (150 mg) in toluene (0.1 M) at 0°C for 15–20 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At −20°C. M.S. = molecular sieves.



Scheme 2. Control reaction. Reaction conditions: a) $AuCl_3$ (7 mol%), 25°C, 3 h; b) **4j** (10 mol%), 3 Å molecular sieves (150 mg), 0°C, 15 h.

To understand the possible reaction mechanism, a control reaction was carried out. As shown in Scheme 2, isatogen **5a** was detected as the sole product in the absence of indole and chiral phosphoric acid with 7 mol% of $AuCl_3$ as the catalyst, which is consistent with literature precedents.[11a] Subsequent introduction of indole **2a**, CPA **4j** (10 mol%), and 3 Å molecular sieves to the reaction system at 0°C afforded **3a** in 90% yield and 95% *ee*, which is comparable to the results obtained under the optimized reaction conditions (Table 2, entry 1). These observations suggest that the reaction might proceed according to dual-catalysis path b (Scheme 1), although path a cannot be ruled out at this stage. As implied by the results of the control reaction, we then tested the direct addition of indoles to a series of isatogens **5**, which constitutes the first example of asymmetric Friedel–Crafts reactions using nitrones as alkylating reagents.[14,15] As shown in Table 3, the corresponding *N*-hydroxy indolin-3-ones **3** were generally afforded in excellent yields and enantioselectivities.

Table 3: Substrate scope of the Friedel–Crafts reaction between isatogens **5** and indoles.[a]

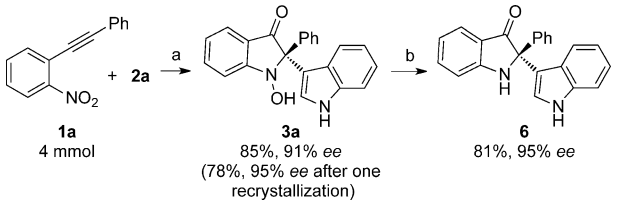


5 **2** **3**

Entry	R	R^3	Yield[b] [%]	*ee*[c] [%]
1	Ph (**5a**)	5-F (**2b**)	92 (**3b**)	93
2	Ph (**5a**)	5-Cl (**2c**)	93 (**3c**)	94
3	Ph (**5a**)	5-Br (**2d**)	90 (**3d**)	89
4	Ph (**5a**)	5-Me (**2g**)	91 (**3g**)	91
5	Ph (**5a**)	6-F (**2h**)	93 (**3h**)	90
6	Ph (**5a**)	6-Cl (**2i**)	92 (**3i**)	93
7	Ph (**5a**)	6-Br (**2j**)	91 (**3j**)	95
8	Ph (**5a**)	7-Me (**2k**)	92 (**3k**)	90
9	4-MeC_6H_4 (**5b**)	H (**2a**)	95 (**3u**)	91
10	4-FC_6H_4 (**5c**)	H (**2a**)	94 (**3v**)	95
11	*n*Bu (**5d**)	H (**2a**)	95 (**3w**)	53

[a] Reaction conditions: **5** (0.3 mmol), **2** (0.6 mmol), **4j** (10 mol%), and 3 Å molecular sieves (150 mg) in toluene (0.1 M) at 0°C for 12–20 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

The enantioselective redox annulation reaction could be easily scaled up under the optimized reaction conditions to give product **3a** in 85% yield and 91% *ee* (Scheme 3). The enantiopurity was further improved to 95% *ee* by a simple recrystallization. Subsequent cleavage of the N–O bond in **3a** to liberate the free amine was conducted using $N_2H_4{\cdot}H_2O$ as a reducing agent, which furnished indolin-3-one **6** in 81% yield and without any reduction in enantiopurity.[16]



Scheme 3. Reaction scale-up and further transformation. Reaction conditions: a) **1a** (4 mmol), **2a** (8 mmol), $AuCl_3$ (7 mol%), **4j** (10 mol%), and 3 Å molecular sieves (1.0 g) in toluene (30 mL) at 0°C for 18 h; b) **3a** (0.2 mmol), $N_2H_4{\cdot}H_2O$ (1.6 mmol) in MeOH (6.0 mL) at 80°C for 6 h.

In summary, we have successfully developed an efficient redox annulation reaction of nitroalkynes and indoles by gold/chiral phosphoric acid dual catalysis, which provides facile access to indolin-3-ones bearing C2 quaternary stereocenters in high yields and excellent enantioselectivities. This method is practical and straightforward as it can be easily scaled up and readily available starting materials are used. Moreover, the first asymmetric Friedel–Crafts reaction that employs nitrones as the alkylating reagents was developed.

Acknowledgements

We are grateful for generous support from the National Natural Science Foundation of P. R. China (21372202, 21402175), the New Century Excellent Talents in University (NCET-12-1086), and the Zhejiang Natural Science Fund for Distinguished Young Scholars (R14B020005).

Keywords: asymmetric catalysis · carbenoids · chiral phosphoric acids · gold · indolinones

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11205–11208
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[16] The absolute configuration of product **6** was determined to be *S* by comparison with its optical rotation/X-ray structure reported in Ref. [3b].

Received: May 27, 2015
Published online: August 5, 2015

