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Synthesis of 2-Spiropseudoindoxyls via an Intramolecular Nitroalkyne Redox−Dipolar Cycloaddition Cascade

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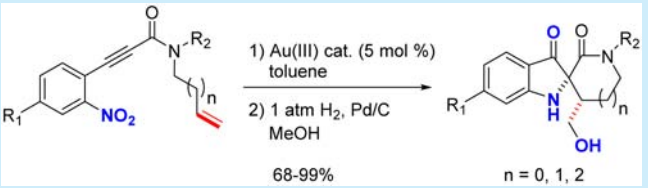
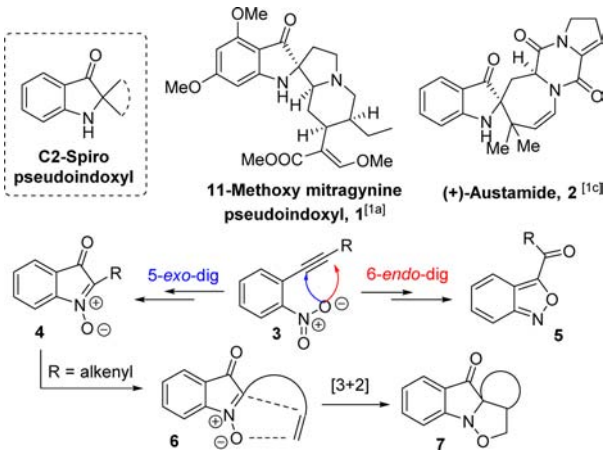
Supporting Information

ABSTRACT: Novel spiropseudoindoxyls were synthesized in high yields via a fully regioselective Au(III)-catalyzed cycloisomerization of easily obtainable *o*-nitrophenylpropiolamides, followed by an intramolecular dipolar cycloaddition as key steps. This one-pot cascade reaction resulted in new tetracyclic pseudoindoxyls, which were hydrogenated toward the title compounds as single diastereomers via N−O cleavage. The mechanism of the gold catalyzed cycloisomerization was studied by DFT and suggests a reaction path without the intermediacy of gold carbenoid species in these cases.



Pseudoindoxyls are important indole derivatives that represent a common feature of several indole alkaloids.[1] In particular, those containing a spirocyclic quaternary center at the C2 position are present in a number of natural products, as illustrated in Scheme 1. While the synthesis of related structures

Scheme 1



such as spirooxindoles with quaternary centers at the C3 position are very well described in the literature and show a broad range of bioactivity,[2] the pseudoindoxyl moiety currently is an underappreciated structure in the field of medicinal and organic chemistry. This can partially be attributed to the lack of selective, mild synthetic pathways toward this scaffold. The primary synthesis of pseudoindoxyls involves the oxidative rearrangement of the corresponding indoles.[1c,3] While milder methods have recently been developed, these syntheses are still limited by the use of protecting groups, low yields, or a lack of functional groups at the spirocyclic core structure.[4]

Because of our groups' ongoing interest in azepinone containing polyheterocycles,[5] a synthetic route toward novel spiropseudoindoxylazepinones and related structures was designed. A 5-*exo*-dig cycloisomerization of *o*-nitroalkynylbenzenes **3** would afford isatogen **4**, which in the presence of a double bond could undergo a [3 + 2] intramolecular cycloaddition reaction[6] toward polycylic spiropseudoindoxyls **7**. While some work has been done on *o*-nitroalkynylbenzene cycloisomerizations, these methods generally result in mixtures of isatogen **4** and anthranil **5** or require harsh conditions.[7] A fully selective, high-yielding 5-*exo*-dig cyclization under mild, catalytical conditions has not been reported to our knowledge. In addition, the combination of isatogen generation with an intramolecular dipolar cycloaddition has only very recently been described simultaneously with our research.[7e] In our approach an electron withdrawing alkyne substituent was chosen to direct the cyclization toward the exclusive formation of isatogens **4**.

For an initial evaluation of the cycloisomerization, model substrate **11** was chosen as it can be synthesized from commercially available substrates in a simple two-step process. A standard Sonogashira coupling of *o*-iodonitrobenzenes **8** with trimethylsilyl acetylene cleanly afforded *o*-nitroalkynylbenzenes **9**.[8] Deprotection of the TMS group with cesium fluoride and carboxylation with CO_2 formed the carboxylate anion *in situ*. Whereas an acidic workup afforded the corresponding acids **10**,[9] the addition of an alkenyl halide resulted in the desired ester **11** in good yields. The obtained pent-4-en-1-yl 3-(2-nitrophenyl)-propiolate **11** was subjected to various catalysts, as summarized in Table 1. Initial attempts to obtain the isatogen selectively via Au(I) catalysis proved unfruitful as both low conversions and mixtures of **12** and **13** were observed. Other transition metal

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Table 1[a]

entry	conditions	(11:12:13)[b]
1	$AuPPh_3Cl/AgNTf_2$ (5 mol %), CH_2Cl_2, rt	72:13:15
2	$AuPPh_3Cl/AgNTf_2$ (5 mol %), CH_3CN, rt	79:9:12
3	$AuPPh_3Cl/AgOTf$ (5 mol %), CH_2Cl_2, rt	75:11:14
4	$Pd(CH_3CN)_2Cl_2$ (5 mol %), CH_3CN, rt	25:75:0
5	$AuBr_3$ (5 mol %), CH_2Cl_2, rt	25:67:8
6	**17** (5 mol %), CH_2Cl_2, rt	20:80:0
7	**17 (5 mol %), toluene, rt**	**5:95:0**
8	$La(OTf)_3$ (5 mol %), rt	90:0:10
9	toluene, Δ	100:0:0

[a]Test reactions performed on a 0.4 mmol scale and allowed to stir overnight at room temperature. [b]Ratios as obtained via HPLC analysis.

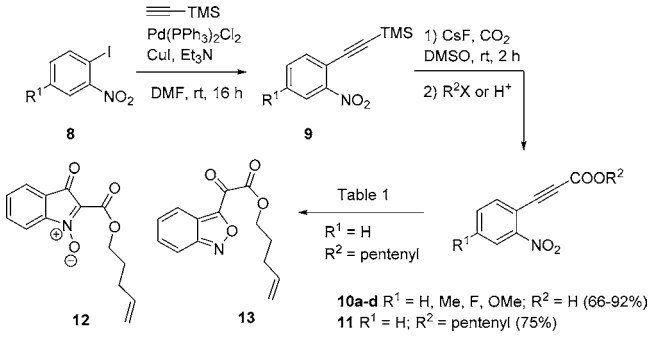
catalysts such as Pd(II) and Au(III) were also evaluated and proved to be more selective toward **12** than Au(I).

In particular, catalyst **17** was both fully selective and gave good conversion of **11**.[10] Anticipating on the need of refluxing temperatures for the cycloaddition, we tried the reaction in higher boiling solvents. To our surprise, even higher conversions were detected when using **17** in toluene (Table 1, entry 7). Control experiments with a Lewis acid (Table 1, entry 8) and heating (Table 1, entry 9) did not result in compound **12**.

With optimal conditions for isatogen formation in hand, the cycloaddition step was evaluated. Heating of **12** in refluxing toluene afforded full conversion to one new product, but MS and NMR analyses suggested dimer formation by intermolecular cycloadditions rather than the desired intramolecular cyclization, even at low concentrations.[11] The preference of esters to adopt a *trans* conformation was postulated as the main reason for this dimerization. Therefore, related cycloisomerizations were proposed using corresponding tertiary alkenylamides **14** bearing a steric substituent at nitrogen. It was believed that in these cases the intramolecular cycloaddition would be favored over the intermolecular dimerization.

The synthesis of amides **14** for evaluation in the gold-catalyzed cycloisomerization−cycloaddition domino reaction proved to be more difficult than anticipated. While the carboxylic acids **10** were readily available, as described in Scheme 2, standard

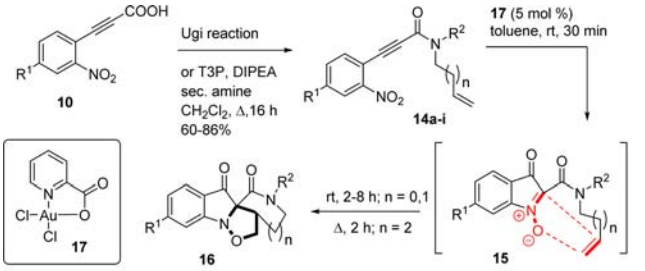
Scheme 2



conditions for amide bond synthesis (DCC/DMAP, EDC/HOBt, $SOCl_2$, $(COCl)_2$, HATU, and Yamaguchi activation) generally resulted in low conversions and/or very complex mixtures. Eventually, both the Ugi reaction[12] and amide bond formation via activation of **10** with T3P (*n*-propanephosphonic acid anhydride)[13] gave the desired amides **14** in satisfactory yields.

We were pleased to observe a clean, full conversion of **14d−g,i** ($n = 2$) to isatogen **15** upon treatment with catalytic amounts of Au(III) catalyst **17** in toluene at room temperature. Rather than isolating **15**, the crude mixture was subsequently refluxed, affording the desired polyheterocycles **16d−h** (Scheme 3). It

Scheme 3



16a n = 0, R^1 = H, R^2 = $CH_2C(O)NHt$-Bu(84%) **16e** n = 2, R^1 = Me, R^2 = $CH_2C(O)NHt$-Bu (78%)
16b n = 1, R^1 = H, R^2 = $CH_2C(O)NHt$-Bu (99%) **16f** n = 2, R^1 = F, R^2 = $CH_2C(O)NHt$-Bu (96%)
16c n = 1, R^1 = H, R^2 = Bn (80%) **16g** n = 2, R^1 = OMe, R^2 = $CH_2C(O)NcHex$ (77%)
16d n = 2, R^1 = H, R^2 = $CH_2C(O)NHt$-Bu (90%) **16h** n = 2, R^1 = H, R^2 = Bn (70%)

should be noted that the intermediate isatogen **15** was stable at room temperature and could be detected by NMR.[14] In the case of *N*-allyl and *N*-butenyl amides **14a-b,h** ($n = 0, 1$), the isatogen was unobservable because the cycloaddition toward **16a−c** occurs spontaneously at room temperature. In contrast to isatogen cycloadditions using alkene tethers without extra unsaturation,[7b] resulting in bridged cycloadducts, intermediates **15** only gave fused adducts **16**. This experimental result was also confirmed by preliminary DFT calculations.[14] To ensure a practical and efficient synthetic strategy, R^2 groups without additional stereocenters were chosen because the introduction of stereocenters at nitrogen of **14** was shown to give an inseparable mixture of diastereomers under the current conditions (see Supporting Information, **14c**). For a majority of the obtained spiropseudoindoxyl containing polyheterocycles **16**, a simple filtration through a silica plug to remove the catalyst resulted in products deemed pure via HPLC/NMR. Eliminating the need for column chromatography illustrates the excellent selectivity in both steps of this domino cyclization. This reaction proved equally successful in solvents that were not dried and without inert atmosphere. The conversion of **14** to **16** was also investigated under reflux conditions without gold catalyst **17**, but using equimolar TfOH instead. In these cases no conversion of **14** to **15** or **16** was observed, demonstrating the need for the gold catalyst.

Regarding the mechanism of the cycloisomerization, a gold carbenoid **22** has been assumed to be an intermediate for the isatogen formation.[15] To shed light on the mechanism of the Au(III)-catalyzed cycloisomerization, the free energy profile and geometries of reaction intermediates were calculated using DFT, including an implicit solvation correction for toluene.[16] In order to minimize computational cost, the substituents on the alkynamide were replaced by methyl groups. The Au(III) catalyst **17** was introduced in its active form (as monochloride Au-cation; the nicotine ligand is shown transparent in Figure 1) and shows a strong preference for the α-alkyne carbon. The catalyst is directed toward the nitro group, which deviates from a planar structure to interact with the Au center in **18**. The first, facile transition state $\mathbf{TS_a}$ shows a nucleophilic attack of the nitro oxygen atom on the electron poor alkyne to form the vinyl gold species **19** via an unconventional *syn*-addition.[16] Subsequently, as proposed in the literature for related Au(I)-catalyzed alkyne

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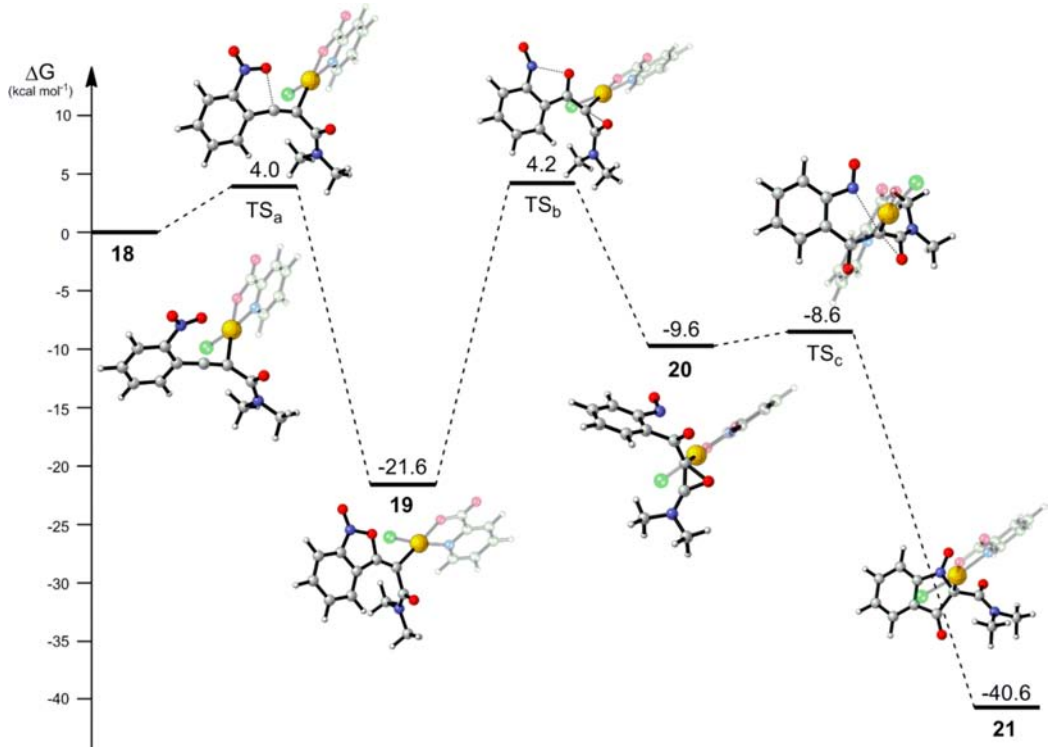
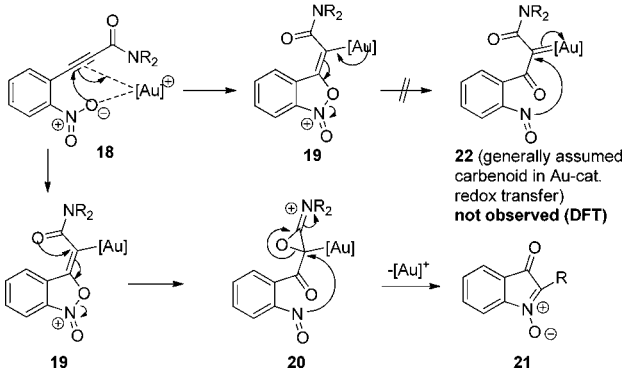


Figure 1. Proposed mechanism for the Au-catalyzed cycloisomerization, as calculated by DFT.

oxidations,[15] we expected the formation of a Au-carbenoid **22** after breaking of the N−O bond in **19** (Scheme 4).

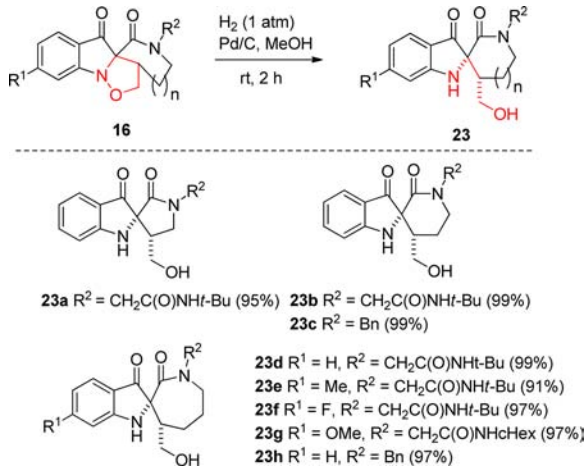
Scheme 4



Despite numerous attempts, we could not locate any Au(III)-carbenoid intermediate (or its mesomeric carbocation) such as **22** on the potential energy surface. Instead, our calculations indicate that the amide oxygen facilitates ring opening in **19** through TS_b via formation of the remarkable oxirane structure **20**, which is easily converted to the isatogen (**21**) through TS_c.[16] Intramolecular assistance of a nucleophile to facilitate the opening of vinyl gold intermediates is an interesting and rather unexplored pathway. The intermediacy of Au(I) carbenoids in alkyne transformations has been the subject of intense research in the last years, and the occurrence of these carbenoid species has been evidenced by DFT as well as experimental (NMR) techniques.[17] However, less conclusive information can be found regarding Au(III) carbenoid intermediates, which have also been proposed in various alkyne transformations.[18] We do not find evidence of such species in our case.

While a variety of spiropseudoindoxyls **16** was now readily available, all were still constrained by the isoxazolidine moiety, indicated in red in Scheme 5. Some reductive methods are

Scheme 5



available in the literature to cleave the N−O bond toward aminoalcohols,[19] but these conditions are generally not compatible with benzylic ketone functionalities. However, subjecting **16** to an atmospheric pressure of hydrogen in the presence of 10% Pd/C afforded spiropseudoindoxyls **23** in near quantitative yields as single diastereomers. The straightforward cleavage of the N−O bond offers a significant expansion for the synthetic scope of this method. This result was fortunate as benzylic ketones can be reduced under these conditions in some cases.[4a,20]

In conclusion, a Au(III)-catalyzed intramolecular nitroalkyne redoxtransfer was designed using *N*-alkenyl tethered alkynyla-

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mides as substrates to drive the cyclization exclusively toward the corresponding isatogens. A DFT mechanistic study suggests that no gold carbenoids are involved in such transformations, in contrast to their generally assumed intermediacy. Subsequently, the tethered alkene moiety engaged in an intramolecular dipolar cycloaddition. This one-pot procedure gave rise to several examples of unprecedented polyheterocycles with remarkable efficiency and high yields. Finally, the obtained strained polycyclic indolinones were easily transformed into new 2-spiropseudoindoxyls via hydrogenative cleavage of the N−O bond. A full exploration of this chemistry and the application of these types of 2-spiropseudoindoxyls as a class of compounds with potential as new scaffolds in medicinal chemistry is under investigation and will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data (^{1}H and ^{13}C NMR spectra) for all new compounds, and further discussion regarding dimer and isatogen formation. Additional computational data regarding **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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