Au(I)-Catalyzed Oxidative Functionalization of Yndiamides

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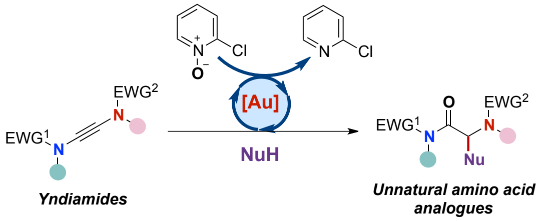


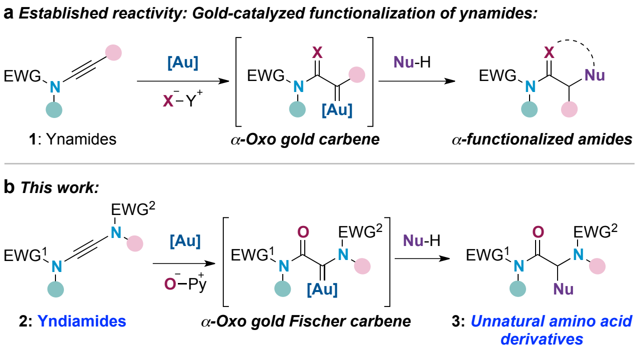
ABSTRACT: Yndiamides, underexplored cousins of ynamides, offer rich synthetic potential as doubly-nitrogenated two carbon building blocks. Here we report a gold-catalyzed oxidative functionalization of yndiamides to access unnatural amino acid derivatives, using a wide range of nucleophiles as a source of the amino acid sidechain. The transformation proceeds under mild conditions, is highly functional group tolerant, and displays excellent regioselectivity through subtle steric differentiation of the yndiamide nitrogen atom substituents.

Ynamides (**1**, Figure 1) are versatile functionalities that find widespread use in organic synthesis,[1] not least due to the electron-donating nitrogen atom which enhances both nucleophilicity and regioselectivity in their reactions.[1a-c] In stark contrast, yndiamides (**2**) – relatives of ynamides that feature an additional nitrogen substituent at the alkyne terminus – are barely explored despite their synthetic potential as diaminated, two carbon building blocks.[2] In previous work, we described the synthesis of yndiamides and their reactivity in transition metal catalyzed cycloisomerizations, which revealed them to be a rich source of azacycles.[2] However, their use in intermolecular bond-forming processes has not been studied.

Following Zhang and co-workers seminal reports on the generation of α-oxo gold carbenes with pyridine *N*-oxides,[3] Davies *et al.* described the first examples of equivalent oxidations of ynamides to α-imido gold carbenes.[4] This work led to an explosion of interest in gold-catalyzed oxidative ynamide functionalization, with wide variation of both the activating agent and nucleophile (Scheme 1a).[1e, 5] Pyridine *N*-oxides and related activators have since been employed as oxidants in a variety of other gold-catalyzed transformations of ynamides,[6] and have also been demonstrated as successful promoters of nucleophilic addition to ynamides under Brønsted acid catalysis.[7]

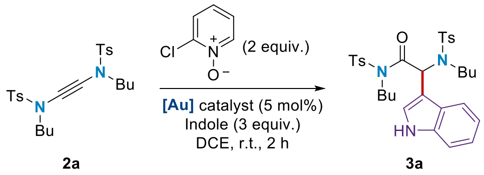
Ynamides are particularly well-suited to gold- or Brønsted acid-catalyzed oxidative functionalization via facile and regioselective generation of ketene iminium ion intermediates. Yn*di*amides **2** would be expected to benefit from similar activation of the alkyne, but their *pseudo*-symmetry poses a challenge for regioselective functionalization. Here we describe the development of an oxidative gold-catalyzed transformation of yndiamides to α-functionalized aminoamides **3** via α-oxo gold carbenes. These products correspond to unnatural amino acid derivatives, motifs that are of great importance both in medicinal chemistry[8] and in the modification of protein structure and function.[9] We also report the realization of regioselective yndiamide functionalizations, where subtle steric effects were found to outweigh electronic considerations.

Scheme 1. Gold(I)-catalyzed oxidative functionalization of ynamides, and concept of this work.



At the outset of our investigations, we tested the gold-catalyzed ynamide oxidative functionalization using Ph$_3$PAuNTf$_2$ as catalyst, as employed by Ye and co-workers,[6a] with yndiamide **2a** as substrate and 2-chloropyridine *N*-oxide as oxidant (Table 1, entry 1). To our delight, the desired product **3a** was isolated in good yield (72%), albeit accompanied by small amounts (~5%) of inseparable side products.[10] Changing the counterion (Ph$_3$PAuSbF$_6$, entry 2) led to an improvement in yield (80%), as did the use of a pre-formed NHC-Au(I) catalyst (IPrAuNTf$_2$, 82%, entry 3), but both exhibited equivalent side product formation. We suspected this might be due to competitive trapping of the putative gold-carbene intermediate by water;[10] pleasingly, use of anhydrous DCE and inclusion of 4Å molecular sieves suppressed side product formation, albeit at a cost to the reaction yield (59%, entry 4). While other gold(I) phosphine complexes offered no benefit (entries 5, 6), use of the NHC-gold(I) catalyst IPrAuNTf$_2$ afforded an excellent yield of **3a** (81%, entry 7).

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Yield (%)
1	PPh$_3$AuNTf$_2$	72[b]
2	PPh$_3$AuSbF$_6$	80[b]
3	IPrAuNTf$_2$[c]	82[b]
4[d]	PPh$_3$AuNTf$_2$	59
5	(4-MeOC$_6$H$_4$)$_3$PAuNTf$_2$	41
6	(4-FC$_6$H$_4$)$_3$PAuNTf$_2$	42
7	IPrAuNTf$_2$	81
8[e]	–	–
9[f]	**IPrAuNTf$_2$**	**84**
10[f]	HNTf$_2$ (10 mol%)	78

[a]Reactions conducted with **2a** (0.10 mmol), 0.05 M; catalysts LAuX were prepared *in situ* by pre-mixing the corresponding LAuCl and AgX salts, unless stated otherwise. Yields are isolated yields. DCE = 1,2-dichloroethane. [b] Product isolated with ~5% inseparable impurities.[10] [c] IPrAuNTf$_2$ was obtained commercially. [d] Entries 4–9 conducted in the presence of 4Å molecular sieves. [e] Reaction performed in absence of gold catalyst. [f] Reaction conducted at 0.5 M concentration, 1 h. IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene

No reaction was observed in the absence of gold catalyst (entry 8). Performing the reaction at higher concentration (0.5 M) led to complete conversion within 1 h and a slight increase in yield (84%, entry 9). We were also pleased to find that triflimide (10 mol%) enabled the formation of **3a** in good yield (78%, entry 10).[7a]

With optimized conditions in hand for both gold- and acid-catalyzed oxidative yndiamide functionalization, the scope of the reaction was explored with respect to the nucleophile (Figure 1). We first found that the gold-catalyzed reaction of yndiamide **2a** proved equally efficient at 1 mmol scale (0.48 g), delivering **3a** in 80% yield. The reaction also translated smoothly to pyrrole, affording the 2-substituted pyrrole aminoamide **3b** in good yield (66%). However, use of Brønsted acid catalyzed conditions resulted in a low yield of **3b** as a 2:1 mixture of C2 and C3 pyrrole regioisomers (31% combined yield), along with 25% of the double substitution product **4b**. The latter presumably arises by acid-promoted elimination of TsBuNH from the initially formed aminoamide **3b** to generate an intermediate pyrrolium ion, which is captured by a further equivalent of pyrrole nucleophile.

In light of this side reaction, we elected to perform the remainder of the substrate screen under gold catalysis. Pleasingly, a range of other indoles and pyrroles proved effective nucleophiles, affording products **3c**–**3h** in high yields (63–89%). The identities of four of these products were confirmed by X-ray crystallography.[11] For indoles **3c**–**3f** both electron-withdrawing and donating groups were tolerated on the indole ring, with exclusive addition at the 3-position. *N*-methyl pyrrole afforded a mixture of C2 and C3 adducts, while 2,5-dimethylpyrrole gave solely the expected C3 adduct in good yield (**3h**, 83%). *O*- or *S*-heterocycles were found to require additional activating substituents, with benzannulated heterocycles proceeding most efficiently (**3i**–**k**). No reaction was observed using the parent non-activated heterocycles (furan etc.) even at elevated temperatures.[10]

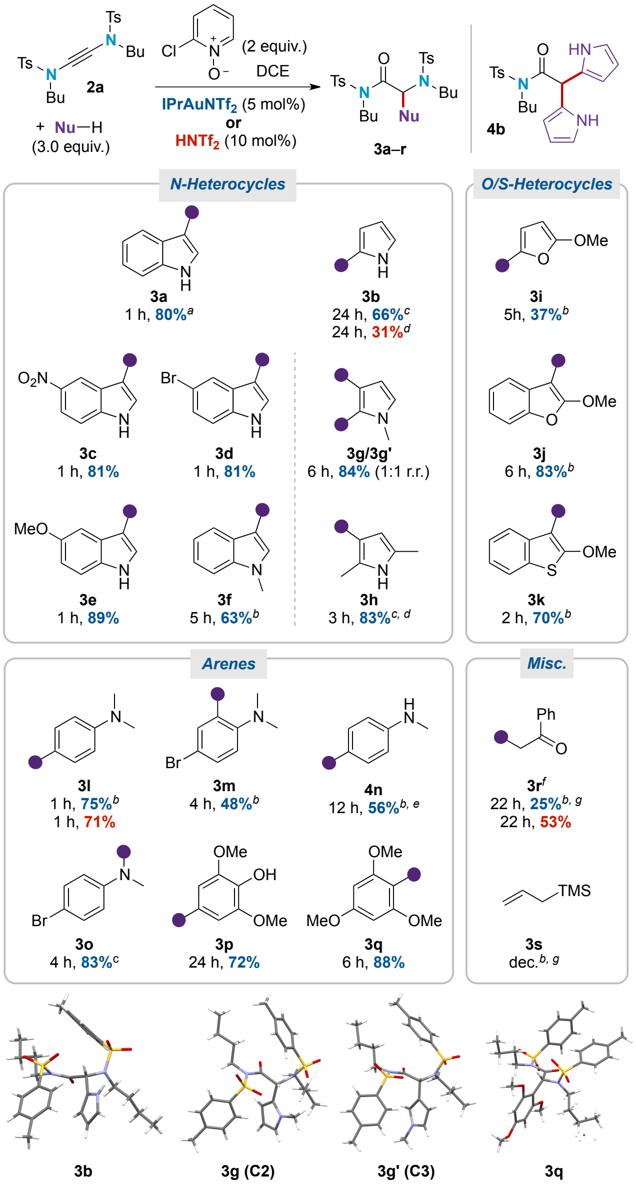
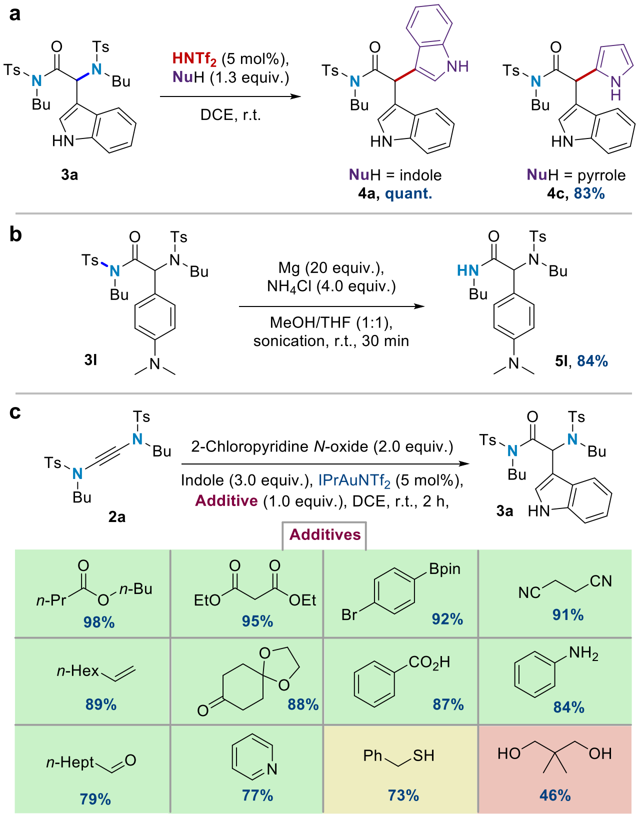


Figure 1. Nucleophile scope of Au(I)- or HNTf$_2$-catalyzed yndiamide oxidative functionalization. Unless otherwise stated all reactions were performed on 0.1 mmol scale at room temperature with [**2a**] = 0.5 M; Yields refer to isolated yields after full conversion of **2a** as indicated by TLC analysis; yields in blue obtained using IPrAuNTf$_2$, yields in red obtained using HNTf$_2$. [a] Reactions performed at 1 mmol scale. [b] Reactions performed at 80 °C. [c] Reactions performed at 0.4 mmol scale. [d] Reactions performed at 0.2 mmol scale. [e] Double addition product **4n** was isolated. [f] *tert*-butyldimethyl((1-phenylvinyl)oxy)silane was used as nucleophile. [g] Reaction treated with 1 M HCl for 30 min after full conversion to give the corresponding ketone. **3b, 3g, 3g'** and **3q** were determined by single crystal X-ray diffraction.[11]

An interesting reaction pattern was observed for anilines. *N,N*-disubstituted anilines react at the *para* position (**3l**, 75%), or at the *ortho* position when the *para* position is blocked (**3m**, 48%); interestingly, **3l** was obtained in comparable yield under Brønsted acid catalysis (71%). An *N*-monosubstituted aniline also reacted at the *para* position to give the double substitution product **4n**, but reacted

Scheme 2. Further transformations of α-aminoamides, and robustness test.[a]

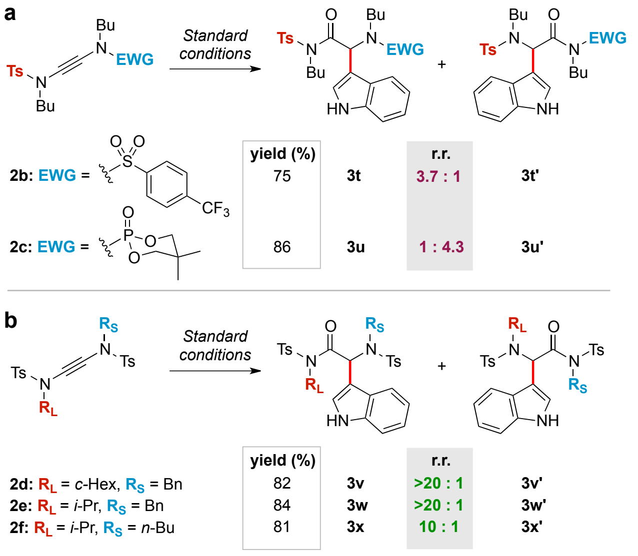


[a] Reactions in Scheme 2c were performed using 0.05 mol 2a in 0.1 mL anhydrous DCE; NMR yields of **3a** are stated, which were determined by quantitative ^{1}H NMR experiments with dimethylsulfone as the internal standard.

through the nitrogen atom when the *para* position was masked (single addition, **3o**). Finally, the parent aniline failed to produce any desired product, with only yndiamide decomposition observed.

Related methoxylated arenes displayed similar behaviour: while phenol and anisole proved unsuccessful, the more electron-rich 2,6-dimethoxyphenol gave **3p** in good yield (72%), albeit requiring an extended reaction time. Heightened reactivity was observed using 1,3,5-trimethoxybenzene, which delivered **3q** in excellent yield (91%). Two non-aryl carbon nucleophiles were also tested; while a silyl enol ether produced the desired product **3r** (in low yield), decomposition was observed using allyltrimethylsilane (**3s**). To our surprise, a significant increase in yield of **3r** was seen using 10 mol% $HNTf_2$ as catalyst (53%). The observation of double substitution under Brønsted acid catalyzed conditions (Figure 1, **4b**), offers potential for further functionalization of the mono-substituted aminoamide products. Indeed, a rapid and quantitative acid-catalyzed substitution of the α-sulfonamide group in **3a** using indole as nucleophile was achieved with just 5 mol% $HNTf_2$ promoter, giving *bis*-indole acetamide **4a** in quantitative yield (Scheme 2a). This transformation was also successful using pyrrole as the nucleophile, giving the bis-heteroarylated product **4c** in 83% yield. The two nitrogen atoms in yndiamide **3l** could also be further differentiated by selective detosylation[12] (Mg/NH_4Cl, Scheme 2b), affording a high yield of acetamide **5l** from aminoamide **3l** (84%). A robustness test[13] was also performed to assess functional group tolerance (Scheme 2c); pleasingly, the reaction tolerated 10 out of 12 external additives covering a range of functional groups, the exceptions being a thiol (73%) and 1,3-diol (46%). The latter induced the formation of unidentified side products, likely due to competing nucleophilic attack by the diol.

Scheme 3. Regioselectivity in gold-catalyzed oxidative functionalization of unsymmetrical yndiamides.[a]



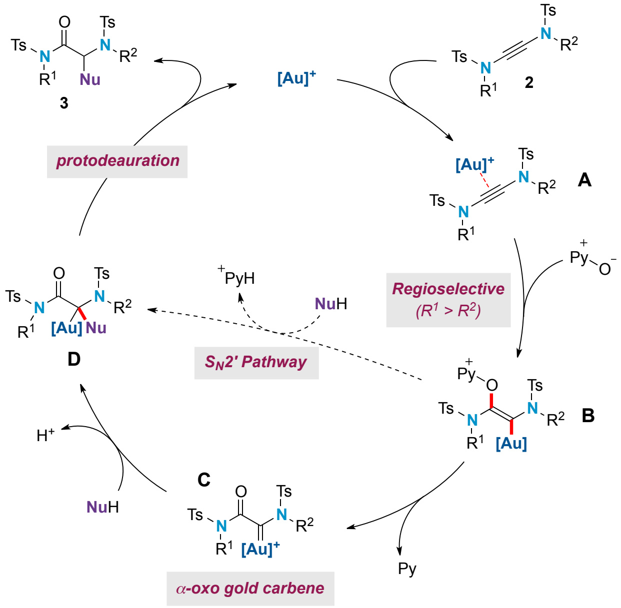
[a] Reactions conducted with 0.1 mmol yndiamide **2b**–**e**. Standard conditions: 2-chloropyridine *N*-oxide (2.0 equiv.), indole (3.0 equiv.), $IPrAuNTf_2$ (5 mol%), r.t., 2h. Yields in **a** refer to combined isolated yield of both isomers. Yields in **b** refer to isolated yield of the major isomer, apart from **3x**/**3x'** which were not separable. Regioisomer ratios (r.r.) were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. See the Supporting Information for details of assignment of regioisomers.

As noted, ynamide functionalizations typically benefit from high regioselectivity due to the inherent polarization of the alkyne. Achieving regiocontrol in yn<u>di</u>amide functionalization was likely to be more challenging but could arise through 'tuning' of the two electron withdrawing groups to render one 'end' of the alkyne more nucleophilic. As such, the unsymmetrical yndiamides **2b** and **2c** (Scheme 3a) were subjected to the oxidative functionalization using indole. However, only modest regioselectivity was achieved on replacing Ts with either a more (*p*-$F_3CC_6H_4SO_2$, **3t**/**3t'**, r.r. = 3.7:1) or less (phosphoryl, **3u**/**3u'**, r.r. = 1:4.3) electron-withdrawing group. We hypothesized that the use of other pyridine *N*-oxides might affect this ratio based on altered nucleophilicity. The use of pyridine *N*-oxide itself led to a significant reduction in yield, while 4-fluoropyridine *N*-oxide maintained similar reaction efficiency; however, neither improved the regioselectivity of the reaction.

An alternative solution to this problem is steric differentiation of the two nitrogen atoms (Scheme 3b). Accordingly, yndiamide **2d**, featuring cyclohexyl and benzyl substituents, delivered a single regioisomer of product **3v**. The extent of this steric influence was challenged using ynamides **2e** (*i*-Pr vs Bn) and **2f** (*i*-Pr vs *n*-Bu). This revealed that even a single methyl branch α- to the ynamide nitrogen atom is sufficient to impart high levels of regiocontrol in the functionalization. These results suggest that the gold complex preferentially engages the yndiamide proximal to the less-bulky nitrogen substituent, with the exceptional regioselectivity arising from minimisation of steric repulsion, rather than electronic factors.

Scheme 4 shows a proposed reaction mechanism for the gold-

Scheme 4. Proposed reaction mechanism.



catalyzed transformation. π-Acid activation of the yndiamide triple bond as gold complex **A** is followed by attack of 2-chloropyridine *N*-oxide to give intermediate **B**. Two pathways are then possible, the first of which involves formation of an α-oxo gold carbene **C** via spontaneous loss of pyridine, as has been proposed for other gold-catalyzed oxidative process on alkynes or ynamides. [3a, 6a, 14] Attack of the nucleophile on **C** then affords adduct **D**, protodeauration[15] of which gives product **3** and regenerates the gold catalyst. Attempts to trap the putative gold carbene via cyclopropanation were unsuccessful (see the Supporting Information), however the formation of such carbenes is known to be favored by the strong σ-donating but weak π-acidic nature of the IPr ligand.[16] Alternatively, **D** could arise directly from **B** via S_N2' displacement of the pyridine leaving group by the nucleophile.

In conclusion, we have developed a gold-catalyzed oxidative functionalization of yndiamides to afford unnatural amino amide derivatives. Remarkable regioselectivity could be induced by steric differentiation of the yndiamide substituents. The broad functional group tolerance of this transformation was highlighted by robustness tests, with the amide products being suitable for further derivatization including addition of a second heteroaromatic nucleophile. We anticipate that this mode of activation should become a significant addition to the field of yndiamide chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization of compounds synthesized (PDF); X-ray crystallography data for compounds (cif).

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Notes

The authors declare no conflicts of interest.

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