Site-specific introduction of gold-carbenoids by intermolecular oxidation of ynamides or ynol ethers†‡

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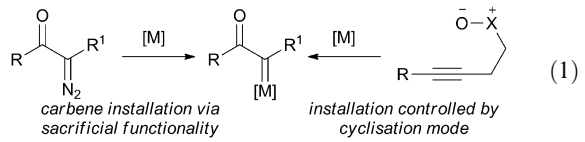
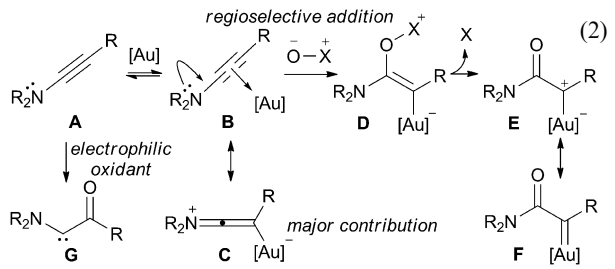
Ynamides and ynol ethers undergo intermolecular gold-catalysed reaction with a nucleophilic oxidant to access metal-carbenoid reactivity patterns. A site-specific oxidation/1,2-insertion cascade is used for a general access to functionalised α,β-unsaturated carboxylic acid derivatives and vinylogous carbimates.

Metal carbenes, generated by the site-specific metal-promoted decomposition of a reactive functionality such as a diazo group [eqn (1), LHS], are employed extensively across an array of useful transformations.[1,2] However, the need to introduce such potentially hazardous diazo functionality, often immediately prior to the carbene-based step, comes at the expense of synthetic efficiency and flexibility. In this paper we report a strategy that does not rely on the use of sacrificial functionality:[3] we show that the ynamide, or ynol ether, functional group can be employed as a direct equivalent to an α,α-disubstituted-diazo imide, or ester, for regiospecific access to gold-carbenoid reactivity patterns.



(1)

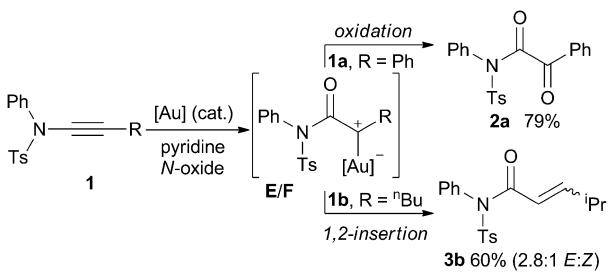


(2)

The activation of an alkyne by a π-acid has been used to trigger numerous intramolecular rearrangements involving metal carbenoids.[4] Of recent note, a range of new reactions have evolved from the use of tethered sulfoxide,[3,5] amine *N*-oxide[6] or nitrone[7] moieties to oxidise a metal-activated alkyne to an α-oxometal carbenoid [eqn (1), RHS]. We reasoned that an intermolecular equivalent, where the oxygen delivery system does not remain in the product, would provide the basis for greater synthetic applicability.[8] In the absence of the regiocontrol exerted by the cyclisation bias of an intramolecular process, we required an alternative method for the intermolecular reaction to ensure site-specificity of carbenoid introduction. To this end, we explored ynamides:[9] ready π-acid coordination to the electron-rich π-system generates a gold complex **B**. The electrophilic site of **B** is adjacent to the heteroatom due to the contribution from the favoured gold–ketene–iminium resonance form **C**.[10] Reaction of this complex with a suitably nucleophilic *external* oxidant could therefore generate intermediate **D**, which on cleavage of the O–X bond will generate an intermediate **E/F** that displays carbenoid character. By this principle, *ynamides might be employed as α,α′-disubstituted imidocarbenoids* [eqn (2)].

To test our reactivity hypothesis, two ynamides were reacted in the presence of a gold catalyst and an oxidant (Scheme 1). Pyridine-*N*-oxide was selected as an *O*-nucleophilic, stable, crystalline and commercial oxidant, the by-product of which is readily removed. To our delight, products of oxidation processes were observed. For substrate **1a** (R = Ph), the use of 2.2 eq. of pyridine-*N*-oxide led to the formation of oxoacetamide **2a** in good yield. The use of stoichiometric pyridine-*N*-oxide with substrate **1b** (R = ^{n}Bu) resulted in isolation of the α,β-unsaturated carboxylic acid derivative **3b**. Both transformations are consistent with the reactivity expected from the formation of a gold-carbenoid **E/F**, by subsequent oxidation[11] or 1,2-insertion respectively.[4,5b] Significantly, this strategy provides the opposite regiochemistry to that previously established in oxidative ynamide chemistry (eqn (2), **E/F** *vs.* **G**).[12]

While the formation of oxoacetamide **2a** complements the known oxidation of ynamides with electrophilic reagents,[13] the formation of α,β-unsaturated imide **3b** provides a new method to access this important structural motif and building block for organic synthesis.[14,15] The fact that ynamides **1** are now very readily prepared from accessible materials,[16] a sulfonamide



Scheme 1 Gold-catalysed oxidation reactions of ynamides. *Conditions*: $Ph_3PAuCl/AgOTs$ (**2a**: 10 mol%; **3b**: 5 mol%), pyridine *N*-oxide (**2a**: 2.2 eq.; **3b**: 1.0 eq.), CH_2Cl_2, RT.

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‡ Electronic supplementary information (ESI) available: Catalysis optimisation study; experimental details and analytical data for catalysis precursors and products; control reactions and a preliminary discussion of the interconversion of (*E*)/(*Z*)-**9b**. See DOI: 10.1039/c0cc02736g

and a terminal alkyne,[16c] means that this approach constitutes an interesting alternative to classical disconnections for the α,β-unsaturated imides **3**. We therefore decided to explore this transformation in greater detail.

Taking **1b** as the test substrate, we varied reaction parameters, maintaining a just-over stoichiometric equivalence of *N*-oxide for efficiency (see ESI‡). An array of gold(I) and gold(III) species proved to be active for this process, whilst platinum(II) salts, Brønsted acids and an electrophilic bromine source gave no reaction and/or degradation. We chose to take forward two sets of conditions: system A uses air-stable dichloro(pyridine-2-carboxylato)gold(III) precatalyst Au-**I**[17] in a chlorinated solvent at mildly-elevated temperature; system B avoids the use of chlorinated solvent, employing $AuBr_3$ precatalyst at room-temperature in THF.

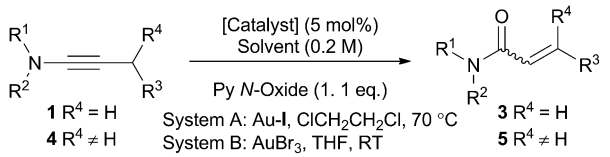
We subsequently prepared a range of ynamides to explore the scope of this transformation (Table 1). The reaction was successful using *N*-alkynylsulfonamides (entries 1–12) and *N*-alkynyloxazolidinones (entries 13–28). Both *N*-tosyl and *N*-mesityl substitution worked well, for instance **3b** and **3e**. Good to excellent yields were achieved across the substrates and in all cases the (*E*)-isomer was formed as the major, or sole product. The reaction tolerates a variety of functionality including alkyl chlorides (entries 3 and 4, 21 and 22), alkyl, benzyl and silyl ethers (entries 9 and 10, 17 and 18, 23 and 24), a phthalimido group (entries 19 and 20) and a thioester (entries 25 and 26). Synthetically valuable vinylogous carbimates **3d** and **3h** can also be prepared when employing substrates with an alkoxy group in the propargylic position (entries 5, 6 and 15). Similar yields were generally observed with both the catalysis systems. However, under conditions B more complex mixtures were obtained with silyl- and methyl-ether functionalised substrates **2h** and **2i**. In both cases, high yields of the desired product were obtained using system A (entries 15 and 17). *E* : *Z* selectivity varied with conditions to a moderate or significant effect though system B generally afforded greater *E* : *Z* selectivity. Trisubstituted olefins **5a** and **5b** can also be readily prepared in good yield applying either reaction system to both the *N*-alkynylsulfonamide **4a** (entries 11 and 12) and the *N*-alkynyloxazolidinone **4b** (entries 27 and 28).

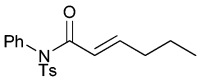
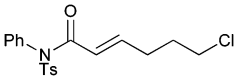
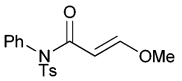
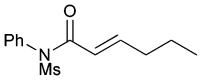
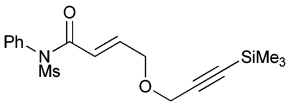
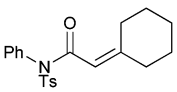
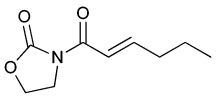
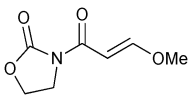
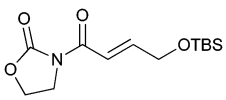
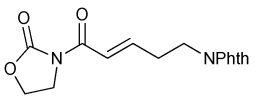
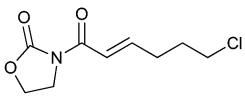
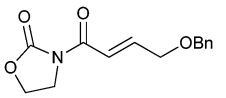
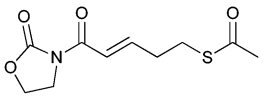
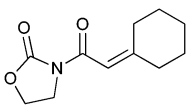
The reaction of **1f** in particular demonstrates exquisite chemoselectivity between the ynamide and alkyne groups, whilst the retention of the silyl appendage demonstrates the mildness of both sets of conditions (entries 9 and 10).

The generality of this reactivity pattern was further explored using an ynol ether in place of the ynamides.[18] Reaction of **6** afforded α,β,γ,δ-unsaturated carboxylic ester **7**, predominantly as the (*E*,*E*)-isomer (Scheme 2).[19]

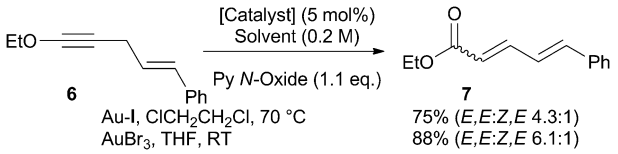
The presence of a stereogenic centre in the α,β-unsaturated imide or vinylogous carbimate products of catalysis would further enhance their utility as building blocks for organic synthesis. Non-racemic chiral ynamides **8a** and **8b** were tested under both sets of reaction conditions. In all cases, the desired vinylogous amides **9a** and **9b** were formed in high yield (Scheme 3). Intriguingly, whilst simple *N*-alkynyloxazolidinone **3h** had afforded only the (*E*)-isomer (Table 1, entry 13), reaction of the chiral analogue **8a** saw (*Z*)-**9a** formed in appreciable quantities (Scheme 3). The reactions of the more

Table 1 Synthesis of α,β-unsaturated imides

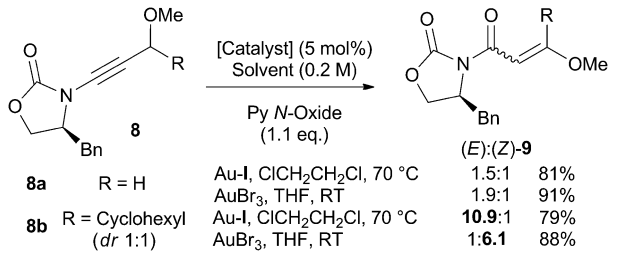


Entry	Product[a]		System[b]	Yield[c] [%] (*E* : *Z* ratio)
1		**3b**	A	71 (2.3 : 1)
2			B	70 (3.7 : 1)
3		**3c**	A	73 (1.9 : 1)
4			B	70 (3.5 : 1)
5		**3d**	A	70[d]
6			B	65[d]
7		**3e**	A	75 (3.0 : 1)
8			B	71 (4.0 : 1)
9		**3f**	A	66 (2.8 : 1)
10			B	68 (3.2 : 1)
11		**5a**	A	80
12			B	78
13		**3g**	A	63 (3.2 : 1)
14			B	70 (5.0 : 1)
15		**3h**	A	89[d]
16			B	—[e]
17		**3i**	A	75 (6.7 : 1)
18			B	—[e,f]
19		**3j**	A	68 (5.6 : 1)
20			B	75 (6.7 : 1)
21		**3k**	A	63 (2.9 : 1)
22			B	65 (4.0 : 1)
23		**3l**	A	73 (2.8 : 1)
24			B	68 (3.1 : 1)
25		**3m**	A	75 (2.6 : 1)
26			B	71 (7.7 : 1)
27		**5b**	A	81
28			B	81

[a] Mixtures of geometric isomers unless otherwise stated. [b] See ESI‡ for reaction times. [c] Isolated after flash chromatography, ratio of isomers determined by ^{1}H NMR spectroscopy. Isomers were separated for characterisation. [d] Only *E*-isomer was observed. [e] Major product is **3** in a complex mixture. [f] Starting material remaining.



Scheme 2 Use of an ynol ether in the gold-catalysed oxidation reactions.



Scheme 3 The oxidation/1,2-insertion reaction of chiral ynamides.

highly substituted ynamide **8b**, employed in the reaction as a 1 : 1 mixture of diastereomers, diverged significantly with choice of reaction conditions.

Whilst the use of moderately elevated temperature and Au-**I** (system A) afforded (*E*)-**9b** as the major isomer, a result consistent with those observed in Table 1, the room temperature reaction using $AuBr_3$ in THF (system B) afforded (*Z*)-**9b** as the major product. This stereoselective access to either geometric isomer of chiral β-methoxy unsaturated carboxylic imides from a mixture of diastereomers, could be of significant utility in synthesis.‡

In summary, we have demonstrated the gold-catalysed site-specific intermolecular oxidation of ynamides and ynol ethers. This method provides a means to access α-imido and α-ester metal carbenoid reactivity from these electron-rich π-systems. A general and efficient preparation of synthetically important α,β-unsaturated carboxylic ester and imide derivatives, as well as vinylogous carbimates is achieved from readily-accessible materials. The mild reaction conditions are tolerant of a wide range of functional groups, including other alkyne moieties. The general potential of this approach for diazo-free reaction development, as well as the specific synthetic utility of the reactions detailed herein, are under study in our lab.

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