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Skeletal Rearrangements

1,2-*N*-Migration in a Gold-Catalysed Synthesis of Functionalised Indenes by the 1,1-Carboalkoxylation of Ynamides

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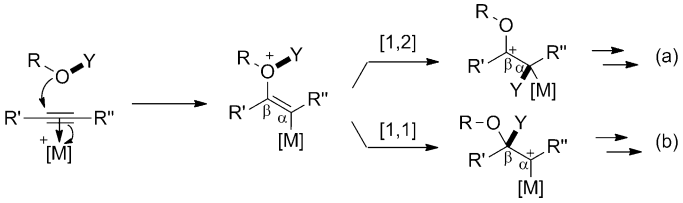
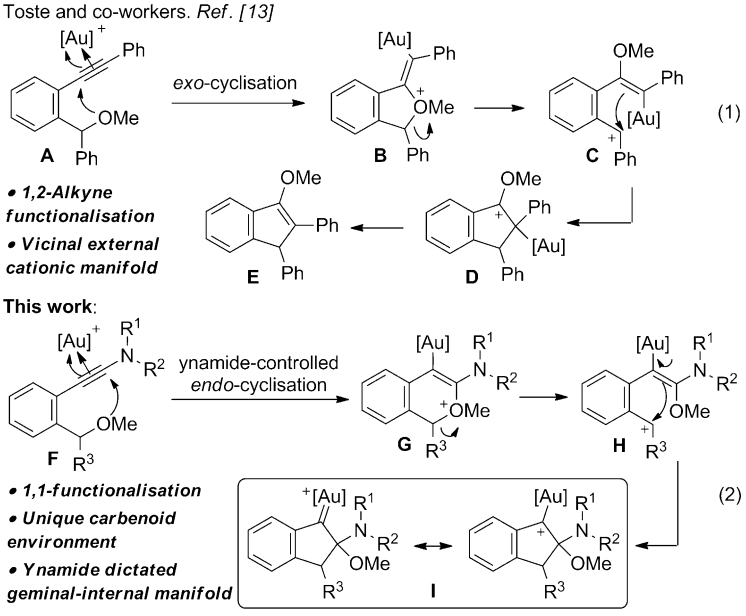
Abstract: Unique α-hemiaminal ether gold carbene intermediates were accessed by a gold-catalysed 1,1-carboalkoxylation strategy and evolved through a highly selective 1,2-*N*-migration. This skeletal rearrangement gave functionalised indenes, and isotopic labelling confirmed the rare C–N bond cleavage of the ynamide moiety. The effect of substituents on the migration has been explored, and a model is proposed to rationalise the observed selectivity.



Scheme 1. 1,2- and 1,1-carboalkoxylation pathways. Oxygen may be tethered to the alkyne through either R (resulting in external migration), or the migrating group Y (resulting in internal migration).

π-Acid-mediated alkyne carboalkoxylations are potent transformations for the rapid assembly of substituted carbo- and heterocyclic frameworks from simple precursors under mild reaction conditions.[1–3] Attack of an oxygen nucleophile onto a metal-activated π system is followed by cationic or sigmatropic migration from oxygen to carbon. Carbon–carbon bond formation can potentially occur α- or β- to the metal, as 1,2- or 1,1-carboalkoxylations, respectively (Scheme 1). The little-explored 1,1-pathway provides a complexity increasing and synthetically enticing non-diazo route to form a metal carbene (Scheme 1, path b).[4–5] Nakamura et al.'s seminal platinum- or palladium-catalysed cycloisomerisation of *o*-alkynyl benzaldehyde acetals[1c,d] was the only report of such processes, until very recent studies of Wang et al. on exploring catalyst control with terminal alkynes.[6]

Our interest in accessing carbenoid reactivity from ynamides led us to question whether the electronic bias of an ynamide might enforce a 1,1-carboalkoxylation pathway in systems in which the 1,2-pathway might be expected based on geometrical bias.[7] Although the use of ynamides in gold catalysis has rapidly increased over recent years, their carboalkoxylation chemistry had not previously been investigated.[8–10] During the final stages of this work, Hashmi and co-workers reported the formation of functionalised benzofurans by 1,2-external carboalkoxylation of phenol-derived ynamides (Scheme 1, path a).[8]



Scheme 2. Gold-catalysed carboalkoxylation: proposed ynamide-dictated carboalkoxylation mode.

For this study, we selected ynamides **F** to contrast with the 1,2-carboalkoxylations reported by Toste and co-workers using *o*-alkynylbenzylethers **A** (Scheme 2).[13] We envisaged that the electronic influence of **F** would divert the process down a 1,1-internal carboalkoxylation pathway by favouring a 6-*endo* cyclisation over the previously reported 5-*exo* pathway [Eq. (1) in

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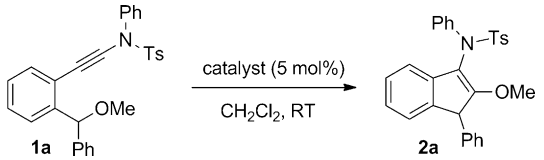
Table 1. Study of reaction conditions.[a]



Entry[a]	Catalyst	*t* [h]	Yield **1a** [%][b]	Yield **2a** [%][b]
1	AuCl	24	53	27
2	$PtCl_2$	24	>95	–
3	[Au**L**Cl_2][c]	24	17	63
4	$PPh_3AuCl/AgNTf_2$	6	–	79
5	*o*-biphenyl(*t*Bu)$_2$PAuCl/$AgNTf_2$	20	–	73
6	$(p\text{-}CF_3C_6H_4)_3PAuCl/AgNTf_2$	2	–	89
7	$(p\text{-}CF_3C_6H_4)_3PAuCl/AgBF_4$	2	–	88
8	$(p\text{-}CF_3C_6H_4)_3PAuCl/AgOTs$	6	–	78
9	$(p\text{-}CF_3C_6H_4)_3PAuCl$	24	>95	–
10	$(p\text{-}CF_3C_6H_4)_3PAuNTf_2$	2	–	88
11	$AgNTf_2$	24	>95	–
12	$HNTf_2$	24	66	–
13	$BF_3{\cdot}OEt_2$	24	31	–
14	SiO_2	24	80	–

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv), catalyst (5 mol%), CH_2Cl_2 (0.1 M), time as indicated. [b] Yields calculated by ^{1}H NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene). [c] **L** = Picolinate. Ts = toluene-4-sulfonyl.

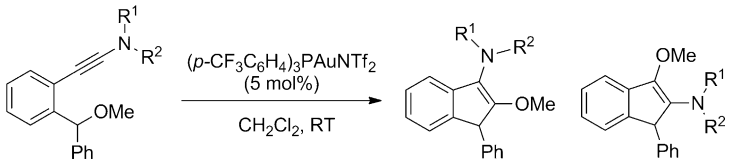
Scheme 2].[14] On fragmentation of **G**, vinyl gold **H** was predicted to form a unique gold carbene **I**, adjacent to a hemiaminal ether, through C–C bond formation β to the metal [Eq. (2) in Scheme 2]. From **I**, several outcomes could be envisaged to give functionalised indenes, of interest due to their function as core structures in many natural products[15] and pharmaceuticals,[16] as well as being useful ligands for transition metals.[17]

Our study commenced with ynamide **1a**, which reacted in the presence of AuCl to give *N*-indenyl sulfonamide **2a** as the sole product through a new skeletal rearrangement (Table 1, entry 1). No reaction was observed with $PtCl_2$; however, a Au^{III} complex gave a higher yield of **2a** (entries 2 and 3). Cationic gold(I)–phosphine complexes proved to be more effective, with complete conversion of **1a** and higher yields of **2a** (entries 4–8). The use of an electron-poor phosphine ligand was beneficial to both the reaction rate and yield relative to an electron-rich phosphine (Table 1, entry 6 vs. 4 and 5). The phosphine gold chloride alone was ineffective (entry 9), and little variation was observed on changing the silver salt (Table 1, entries 6–8). The study was continued with the preformed gold triflimidate complex, because it gave identical results to the complex formed in situ (entry 10 vs. 6). $AgNTf_2$ alone did not catalyse the reaction, and only degradation was observed in the presence of σ-Lewis or Brønsted acids (Table 1, entries 11–14).

Indene **2a** was thought to result from a 1,2-*N*-migration onto gold carbene **I**. Such processes are rare, and to the best of our knowledge, unreported in gold catalysis.[18–19] Doyle and co-workers recently reported *N*-migration of an endocyclic hydrazide on dediazotisation of β-methylene-β-silyloxy-β-amido-α-diazoacetates with a variety of metal catalysts.[20] For compound **2a**, a selective 1,2-migration of an exocyclic sulfonamide would occur from a β-methine-β-alkoxy-β-sulfonamido quaternary centre generated in unison with the gold carbene (Scheme 1, Eq. (2)). The relative migratory aptitude of different amide substituents was therefore probed further by using ynamides **1a–i** (Table 2).

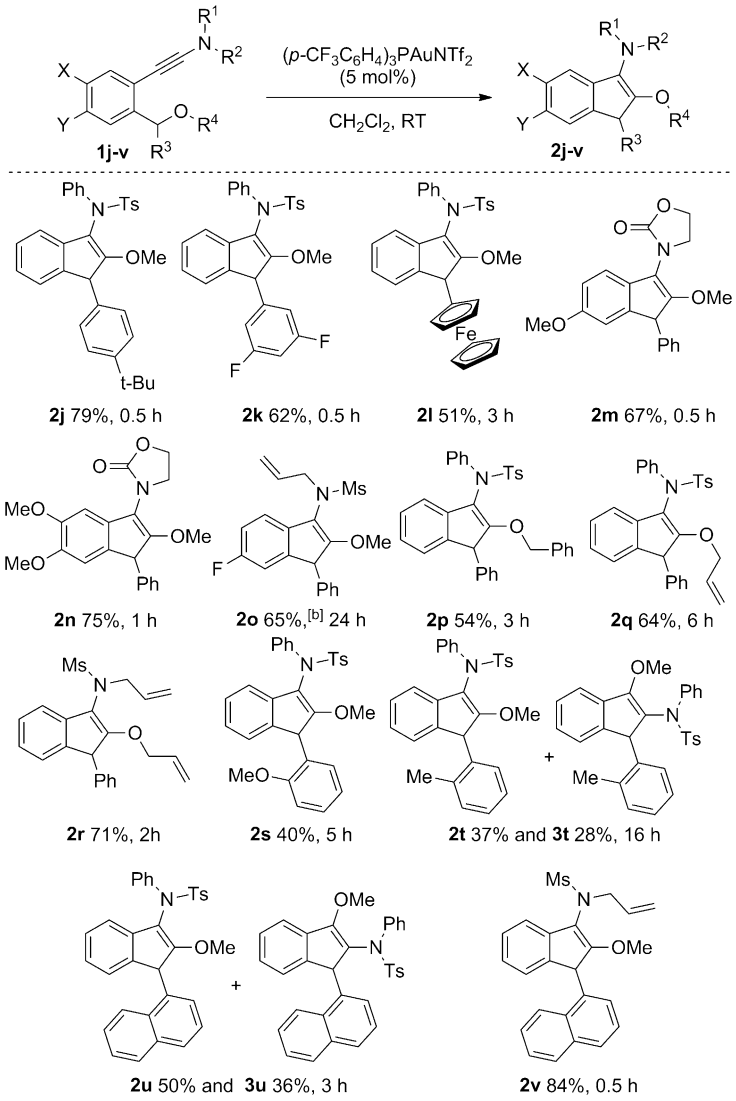
Sulfonylated aniline groups, including nosyl, generally worked well (Table 1, entries 1–3). *N*-Benzyl-substituted ynamide **1d** also underwent efficient cycloisomerisation affording **2d** in 72% yield (entry 4). In contrast, *N*-methyl-substituted ynamides were poorer substrates (entries 5 and 6): reactions of both methane- and 4-nitrobenzene sulfonamides **1e/f** were slow; products **2e/f** were only isolated in low yields, and similar quantities of the regioisomers **3e/f** were observed. A small amount of the isomer was also seen in the reaction of *N*-allyl methane sulfonamide **1g**, though a high yield of **2g** was obtained (entry 7). The use of other gold catalysts had relatively little impact on the outcome of this reaction (entries 7-9), and no products of cyclopropanation were observed.[21] A cyclic carbamate **1h** underwent the reaction cleanly with high selec-

Table 2. Study of the migrating group.[a]



Entry[a]	**1**: NR^1R^2	*t* [h]	Yield **2** [%][b]	Yield **3** [%][b]
1	**1a** NPhTs	2	78	–
2	**1b** $NPhSO_2Ph$	1	68[c,d]	–
3	**1c** NPhNs	0.75	76	–
4	**1d** NBnMs	3	72[d]	–
5	**1e** NMeMs	48	23	20[e]
6	**1f** NMeNs	24	29	23
7	**1g** N-allylMs	1	74	9
8[f]	**1g** N-allylMs	24	58	10
9[g]	**1g** N-allylMs	24	64	5
10	**1h** N(Ox)[h]	2	78	–
11	**1i** N(5-(*s*)Bn-Ox)[e]	24	–[i]	–

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), catalyst (5 mol%), CH_2Cl_2 (0.1 M), time as indicated. [b] Isolated yields after flash column chromatography unless otherwise stated. [c] 3 mmol, 1.4 g scale. [d] Isolated yield after recrystallisation without chromatography. [e] Yield calculated by ^{1}H NMR spectroscopy: present as an inseparable mixture with **1e**. [f] Catalyst: $(C_5F_5)_3PAuCl/AgNTf_2$. [g] Catalyst: [Au**L**Cl_2] **L** = picolinate. [h] Ox = 2-oxazolidinone. [i] 37% of **1i** remaining. Ms = methane sulfonyl, Ns = 4-nitrobenzene sulfonyl.



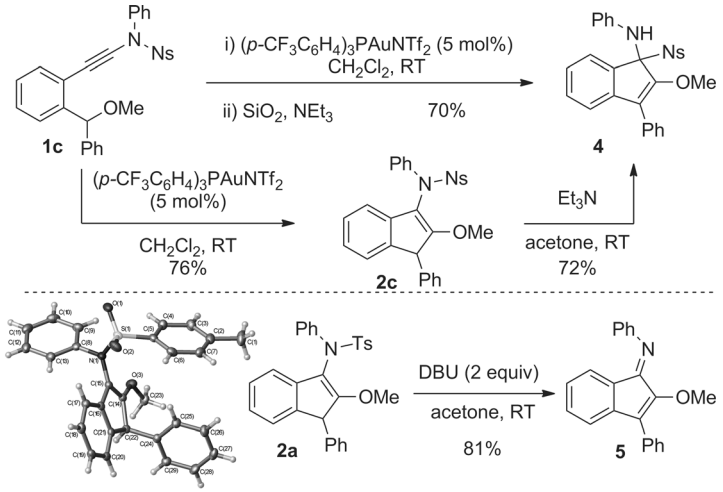
Scheme 3. Reaction scope. [a] Reaction conditions: **1** (0.2 mmol, 1 equiv), was reacted with $(p\text{-}CF_3C_6H_4)_3PAuNTf_2$ (5 mol%) in CH_2Cl_2 (0.1 M) at RT, time as indicated. [b] Using 10 mol% catalyst. Regioisomer **3o** also isolated in a 10% yield.

tivity for *N*-migration (entry 10). The use of a more hindered chiral benzyl substituted oxazolidinone derivative led to a complex reaction mixture alongside unreacted **1i** (entry 11). The practicality of this method was demonstrated by the gram-scale synthesis of **2b**, obtained after filtration to remove metal residues and then recrystallisation (entry 2).

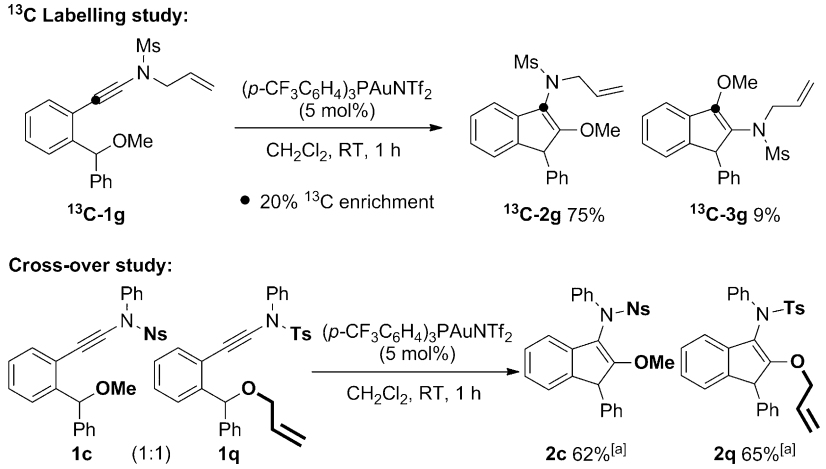
The impact of modification at other positions on the skeletal rearrangement was then explored (Scheme 3). Electron-donating and electron-withdrawing aryl groups (**2j** and **2k**) were well tolerated. Although complex mixtures were observed with furanyl or vinyl benzylic substituents, the ferrocene-substituted derivative **2l** could be prepared as a single regioisomer in moderate yield. Methoxy substitution on the core benzene ring was well tolerated at both the 3- and the 4- positions giving single products (**2m** and **2n**). The 4-fluoro-substituted variant required a longer reaction time (24 h) and an increased catalyst loading to achieve a good yield of **2o** alongside expected small amounts of regioisomer **3o** (Table 2, entry 7). Pleasingly, variation at the migrating alkoxy group was well tolerated with both *O*-benzyl and *O*-allyl substitution despite the possibility of direct external migration of an allylic or benzylic cation following initial nucleophilic attack (**2p**–**r**).[22] Increasing the steric bulk around the benzylic position with naphthyl, *o*-tolyl and *o*-anisole substituents (**2s**–**u**) saw a significant reduction in regioselectivity with an *N*-phenyl-*p*-tosyl substituted ynamide. However, the analogous ynamide **1v**, containing non-aromatic *N*-substituents gave a clean reaction, with **2v** formed as a single regioisomer in high yield.

The resulting functionalised indenes were found to be sensitive to basic conditions: *C*-sulfonylated indene-1-amine (**4**) was isolated in good yield when chromatographic purification of **2c** was attempted using triethylamine-treated silica gel to improve separation (Scheme 4), and could be deliberately prepared from **2c**. The product of double-bond migration was instead observed when carbamate **2n** was exposed to triethylamine (see the Supporting Information). Although **1a** did not rearrange in the presence of triethylamine, α-alkoxy conjugated imine **5** was isolated on treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). Single-crystal X-ray diffraction analysis of **2a** showed the indene and nitrogen to be resonance decoupled with the N–S bond aligned to the enol π system accounting for the ready elimination of the sulfonyl group.[23]

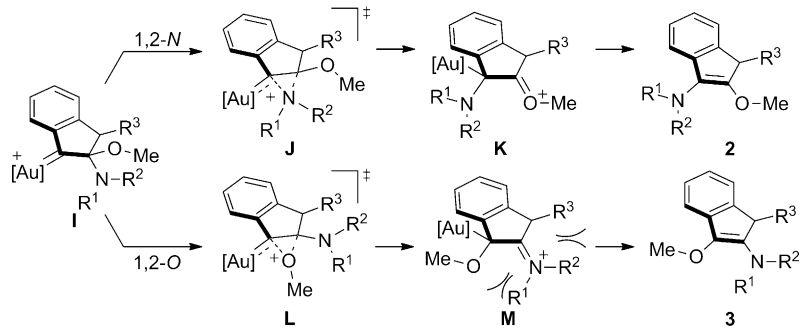
An isotopic-labelling study was carried out to support the mechanistic hypothesis. Ynamide **1g** was selected to allow isolation of both isomeric indenes, and a ^{13}C-enriched sample was prepared from ^{13}C-labelled benzoic acid (see the Supporting Informa-



Scheme 4. Base-mediated reactions of *N*-indenyl sulfonamides. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene. Crystal structure of **2a** with ellipsoids drawn at the 50% probability level.



Scheme 5. Mechanistic studies. [a] Yields calculated by ^{1}H NMR spectroscopy against a known quantity of internal standard (1,2,4,5-tetramethylbenzene).



Scheme 6. Proposed rationale for the observed regioselectivity.

tion). Cleavage of the ynamide C–N bond was confirmed with the formation of **^{13}C-2g**, in which nitrogen is connected to the ^{13}C-enriched carbon. Additionally, the absence of cross-over products when ynamides **1c** and **1q** were reacted together confirmed the intramolecular nature of this reaction (Scheme 5).

The formation of indenes **2** and **3** and the generally high selectivity for *N*- versus *O*-migration can be rationalised from the gold carbene **I** (Scheme 6). Fast, neighbouring-group-aided 1,2-migration must proceed with planarisation of both the α-C and the non-migrating heteroatom (**I**→**K** or **M**). Therefore, *N*-migration is favoured as iminium **M** would result in greater steric congestion than oxonium **K** due to the enforced proximity of its larger substituents with the adjacent groups. Because gold carbene **I** is expected to show considerable carbocationic character, nitrogen's greater ability to stabilise positive charge would also favour 1,2-*N* migration (**J** vs. **L**).[3,24] As high selectivity for *N*-migration of *N*-sp^2 carbamates and sulfonamides with electron-withdrawing groups was also observed, the late transition-state assessment (**K** vs. **M**) appears more accurate. This scenario can also explain why a loss in selectivity was observed with substrates such as **1e**, where the smaller substituents on nitrogen allow a planar configuration to be accessed affording isomer **3**.[25] The relative spatial positioning of the amide and alkoxy groups to the adjacent metal carbene may also have an impact on the migration, though as the relative stereochemistry in **I** is unknown, little comment can be made at this stage.[26] The reduced selectivity observed with *o*-substituted benzene units (**2s–u**) might be explained by stabilising π and through-space interactions[27] with the *N*-phenyl-*p*-toluene sulfonamide, so raising the barrier to *N*-migration. The high selectivity for *N*-migration with *N*-allyl-methane sulfonamide **2v**, incapable of such interactions, is in line with this hypothesis.

In conclusion, a cycloisomerisation of ynamides that features a rare C–N bond cleavage is reported. A 1,1-carboalkoxylation pathway is enforced by the electronic properties of ynamides to generate a unique α-hemiaminal ether carbene environment. Labelling studies confirmed a subsequent 1,2-*N*-migration with the high selectivity over 1,2-*O*-migration rationalised based on developing steric encumbrance. Further studies to harness the regiodetermining role of ynamides in cycloisomerisation reactions are ongoing.

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Keywords: carbenes · cycloisomerisation · gold · regioselectivity · ynamides

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