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Silver-catalysed intramolecular hydroamination of alkynes with trichloroacetimidates†

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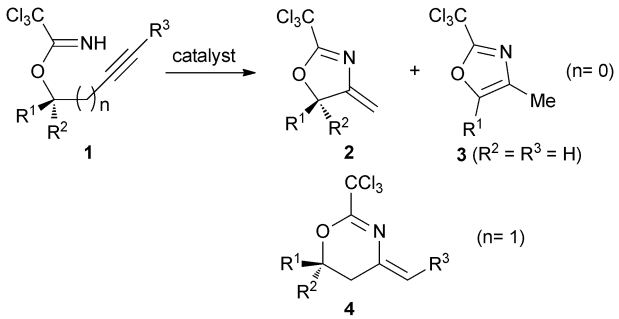
Silver(I) complexes catalyse the intramolecular addition of trichloroacetimidates to alkynes. In the absence of a ligand, the selectivity of the reaction is dependent upon the nature of the counter-anion and solvent. The introduction of non-chelating nitrogeneous ligands suppresses competitive Brønsted acid catalysis, improving the yield and selectivity of the reaction.

The intramolecular cyclisation of (homo)propargylic trichloroacetimidates **1** can occur *via* a hydroamination reaction to furnish heterocycles **2**, **3** (n = 0) and **4** (n = 1) (Scheme 1). To date, only gold catalysts have been reported to be effective for these reactions: Shin and co-workers[1] were the first to report the use of a cationic phosphine–gold(I) complex to effect the cyclisation of sixteen acyclic substrates to *exo*-methylene-substituted heterocycles **2** and **4** with good to excellent yields. In contrast, the catalytic activity of $AuCl_3$ is limited to the cyclisation of just two substrates,[2] proceeding *via* the *exo*-methylene **2** intermediate to afford oxazole **3** as the final product.

As part of our programme to explore the use of less expensive coinage metal catalysts for the heterofunctionalisation of C=C bonds, we investigated the application of Ag catalysis to this particular type of hydroamination reaction.[3–9] Prior to this, Ag-catalysed reactions of (relatively unactivated) alkynes were limited to the addition of alkyl and aryl amine substrates.[10–16]

Using unsubstituted **1a** as the model substrate, a total of eleven silver salts AgX or Ag_2Y were initially assessed using DCE as the solvent, where X = OAc, TFA, NO_3, SbF_6, PF_6, BF_4, OTf, OTs; Y = CO_3, O, SO_4 (Table S1 in the ESI,† with selected examples given in Table 1). The preliminary study revealed a strong counteranion effect on catalytic activity. None of the di-silver salts (Ag_2Y) were active and, with the exception of $AgNO_3$ and $AgPF_6$, all other AgX salts afforded quantitative conversion of **1a** within 6 h at room temperature. Notably, the selectivity of the reaction is also dictated by the counteranion X. For example, the use of AgTFA afforded the 4-methylene-dihydrooxazole product **2a** exclusively (Table 1, entry 1), while the use of AgOTf favoured the formation of the aromatic oxazole **3a** (entry 2). In all cases, only low to moderate yields were obtained for the reactions performed in DCE, due to formation of intractable side products. In an attempt to suppress the side reactions, the experiments were repeated using other solvents (see also Table S1, ESI†); the use of acetonitrile facilitated the reaction catalysed by AgTFA, where the formation of **2a** improved from 14 to 76% (entry 1 *vs.* entry 3). On the other hand, switching between DCE and acetone prompted a change in selectivity from **3a** to **2a** in the AgOTf-catalysed reaction (entries 2 and 6).

The isomerisation of **2a** to **3a** was reported to occur slowly under ambient conditions.[1] In this study, it was found that while TfOH is not catalytically active in the cyclisation (Table 1, entry 8), the aromatisation of **2a** to **3a** was complete within 5 h in the presence of 5 mol% of TfOH. With this in mind, the



Shin (2006):

$Au[P(C_6F_5)_3]Cl$ (5 mol%), $AgSbF_6$ (5 mol%), DCE, 0 °C - r.t., 3-9 h.

16 examples, n = 0, 1.

Hashmi (2006):

$AuCl_3$ (0.01-3 mol%), $CHCl_3$, 3 days

2 examples, n = 0, $R^1 = R^2 = R^3 = H$ (82%); $R^1 = R^3 = H$, $R^2 = Me$ (29%)

Scheme 1 Previous reports of intramolecular hydroamination of alkynes by trichloroacetimidates.

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† Electronic supplementary information (ESI) available: Experimental procedures, extensive optimisation tables and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3cc45500a

Table 1 Initial screening of catalytic conditions[a]

Entry	[Cat.]	Solvent	Conversion[b]/%	**2a**[b]/%	**3a**[b]/%
1	AgTFA	DCE	100	14	—
2	AgOTf	DCE	100	—	46
3	AgTFA	MeCN	100	76	—
4	AgOTf	MeCN	100	18	15
5	AgTFA	Acetone	62	22	—
6	AgOTf	Acetone	100	40	—
7	AgOTf/PS[c]	DCE	100	80	—
8	TfOH[d]	DCE	—	—	—
9	$[Ag(py)_2]$OTf	DCE	100	83	—
10	$[Ag(py)_2]$OTf	MeCN	100	83	—
11	$[Ag(py)_2]$OTf	Acetone	100	87	—
12	$[Ag(py)_2]$OTf	CH_2Cl_2	100	83	—

[a] Substrate **1a** (80.2 mg, 0.4 mmol), AgX (0.04 mmol, 10 mol%), solvent (as indicated, 1 mL), room temperature, 6 h. [b] Determined by ^{1}H NMR spectroscopy, using 1,3,5-trimethoxybenzene as internal standard. [c] PS = proton sponge (5 mol%), 40 °C, 3 h. [d] 10 mol%.

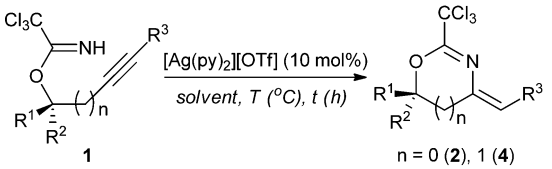
AgOTf-catalysed cyclisation of **1a** was performed in the presence of a non-coordinating base (proton sponge), which afforded **2a** exclusively with 80% conversion (entries 2 *vs.* 7), showing that selective formation of the *exo*-methylene product **2** can be attained by Ag-catalysis, so long as the attendant Brønsted acidity can be suppressed. Guided by this, $[Ag(py)_2][OTf]$[17] was subsequently prepared and evaluated as a catalyst. Pleasingly, the use of the pyridine-ligated silver salt afforded **2a** as the sole product. Furthermore, the catalyst is not only air- and moisture-stable, but also readily soluble in a number of solvents, allowing good results to be obtained consistently across a number of different reaction media, with no deleterious effect on conversion or selectivity (Table 1, entries 9–12).

The scope of the new catalyst was investigated with a number of substrates (Table 2), and the results were compared with those previously achieved using cationic gold complexes. With substrates containing alkyl substituents at the propargylic position (R^1 and/or R^2 = alkyl), very comparable results were attained using the silver catalyst at ambient temperature (entries 1–5). On the other hand, substrates **1** (where n = 0) containing aryl substituents at the propargylic position (R^1 = Ar) or internal alkynes ($R^3 \neq$ H) were reported to be inert towards gold catalysis.[1] Thus, we were surprised to detect a low level of conversion in the cyclisation of the phenyl-substituted **1f** to **2f** (entry 6) at an elevated temperature of 60 °C. Even more pleasingly, good conversions can be obtained with substrates containing bromide and silyl substituents at the terminal alkyne position in good conversions[18] (entries 7 and 8, respectively).

In comparison, 6-*exo-dig* cyclisations with homopropargylic substrates (where n = 1) were equally facile at room temperature and the products can be isolated in good yields. Both alkyl and aryl substituents can be accommodated at R^1 (Table 2, entries 9–14). Once again, conversions of internal alkyne substrates **1g** and **1h** were slow, which can be improved by increasing catalyst loading (entries 15 and 16).

The ability of the silver catalyst to promote reactions with internal alkynes is particularly noteworthy. It also provides a means of establishing the stereochemical pathway of the addition step. The products were obtained as *Z*-isomers exclusively, determined by NOE experiments performed on the trimethylsilyl-substituted

Table 2 5- and 6-*exo-dig* cyclisations of (homo)propargylic trichloroacetimidates[a]



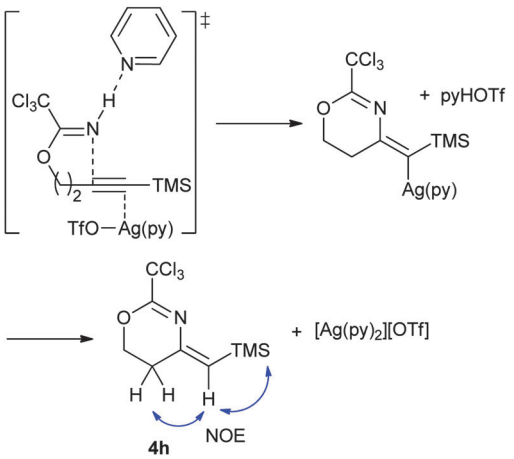
1 n = 0 (**2**), 1 (**4**)

Entry	R^1, R^2, R^3	n	Solvent	T/°C	t/h	Product	Yield[b]
1	H, H, H	0	Acetone	23	6	**2a**	87 (67)
2	Me, H, H	0	Acetone	23	6	**2b**	85 (74)
3	Et, H, H	0	Acetone	23	6	**2c**	>99 (86)
4	i-Pr, H, H	0	Acetone	23	6	**2d**	87 (82)
5	Me, Me, H	0	Acetone	23	6	**2e**	89 (79)
6	H, H, Ph	0	MeCN	60	7	**2f**	29
7	H, H, $SiMe_3$	0	MeCN	60	7	**2g**	82 (72)
8	H, H, Br	0	Acetone	23	6	**2h**	77 (30)
9	H, H, H	1	Acetone	23	6	**4a**	93 (76)
10	Me, H, H	1	Acetone	23	6	**4b**	97 (93)
11	Et, H, H	1	Acetone	23	6	**4c**	99 (91)
12	Ph, H, H	1	Acetone	23	6	**4d**	94 (90)
13	4-ClC_6H_4, H, H	1	Acetone	23	6	**4e**	96 (87)
14	4-$CF_3C_6H_4$, H, H	1	Acetone	23	6	**4f**	73 (70)
15	H, H, Ph	1	Acetone	56	7	**4g**	31
16[c]	H, H, $SiMe_3$	1	Acetone	56	8	**4h**	80 (71)

[a] General reaction conditions: substrate **1** (0.4 mmol), $[Ag(py)_2][OTf]$ (0.04 mmol, 10 mol%), solvent (1 mL). [b] Determined by ^{1}H NMR spectroscopy, using 1,3,5-trimethoxybenzene as internal standard. Isolated yields are indicated in parentheses. [c] 20 mol% catalyst used.

product **4h** (ESI†). This is commensurate with a mechanism whereby the addition of the N–H bond occurs in an *exo*-metallic fashion to a π-coordinated alkyne (Scheme 2). The putative (vinyl)silver complex then undergoes protonolysis to afford an overall *anti*-addition across the C≡C bond.

The ability of one of the pyridines to dissociate from the metal during the reaction appears to be key to reactivity, as the reaction did not proceed when a chelating ligand was used, *i.e.* [(phen)Ag][OTf] (phen = phenanthroline, Table S1, ESI†). Inherently, the dissociation of a pyridine is necessary to create a vacant coordination site for effective catalysis. In this case, we believe that the primary role of the liberated pyridine is to act as a Brønsted base to sequester triflic acid, thus preventing isomerisation to the aromatic heterocycles (**3**) and competitive side reactions,



Scheme 2 Proposed mechanism leading to the observed stereoselectivity.

e.g. proto-desilylation of the silyl-substituted substrates and products. It may also have additional roles in the proton-transfer processes, as indicated in Scheme 2.

The silver-catalysed intramolecular hydroamination addition of trichloroacetimidates to alkynes has been achieved for the first time, whereby the nature of the counteranion, solvent and ligand was found to have profound effects on catalytic turnover and selectivity. Encouragingly, the $[Ag(py)_2][OTf]$ complex is found to be highly effective for the cyclisation of internal alkynes to afford vinyl-bromide and silane products, which had not been possible using gold catalysts. The potential applications of these intermediates for organic synthesis (*e.g. via* cross coupling chemistry) are currently being investigated, and will be reported in due course.

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18 The bromo-product **2h** decomposes during the isolation procedure.

