



Solvent effects in gold-catalysed A³-coupling reactions[☆]



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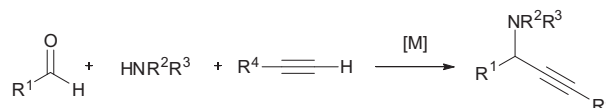
ABSTRACT

Gold-catalysed A³-reactions proceed efficiently when conducted in 2,2,2-trifluoroethanol as solvent. The rates of these reactions are accelerated considerably when conducted in a microwave reactor.

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The development of domino, multi-component and cascade reactions continues to be an area of intense academic interest¹ even though they were first documented over a century ago.² A particularly useful example is the 'A³-coupling reaction', an atom-economic, single step process for the preparation of synthetically useful propargyl amines^{3,4} from aldehydes, alkynes and amines (Scheme 1). This reaction is found to be catalysed by a number of transition metal complexes⁵ in a process that does not require the pre-generation of stoichiometric quantities of nucleophilic σ -alkyne organometallic reagents. The use of strong bases (Grignard or organolithium reagents) is therefore obviated in these reactions, a factor which contributes to their greater synthetic potential, flexibility and atom economy.

Concurrent with the development of multi-component reactions there has also been a resurgence of interest in the chemistry of gold, especially as applied to A³-coupling reactions.⁶ In their seminal Letter⁷ Wei and Li noted that the efficiency of gold-catalysed A³-reactions was greatly dependent upon the reaction conditions employed: reactions carried out at 100 °C in water for 12 h, using catalyst loadings of 1%, proved to be optimal for the substrates used in these initial investigations. The use of organic solvents (THF, DMF and toluene), rather than water, proceeded in lower conversions and with concomitant formation of undesired by-products.⁷



Scheme 1. Transition metal catalysed A³ coupling reaction.

Our interest^{8a,b} in the chemistry of organogold complexes encouraged us to investigate the use of complexes **1–4** in A³-coupling reactions and led us to question whether these complexes could be employed as homogeneous solutions in organic solvents. Complexes **1–4** (Fig. 1) used in this study were initially screened in a standard A³-reaction between benzaldehyde (1 mmol) and phenylacetylene (1.5 mmol) using either dibenzylamine or piperidine (1.1 mmol) as the amine partner, in a range of solvents at temperatures in the range between 40 °C and 60 °C.

Initial results indicated that the Au(III) complex **1** was catalytically active and resulted in quantitative conversion to the requisite A³-coupled product after 24 h in most of the solvents examined (Table 1, entries 1–4). Complexes **2**, **3** and **4** also promoted the A³-reaction, albeit at a much reduced rate, when the reactions were conducted in water (entries 6, 15 and 18; <20% conversion at 40 °C for 24 h). Most notably, exchange of water for chloroform as reaction medium afforded homogeneous reaction mixtures which resulted in a significant improvement in conversion rates, even when the less reactive catalysts **2** and **3** were employed (entries 9 and 16). Further studies clearly indicated that this was a solvent, rather than a temperature effect, as attempted coupling at 100 °C in water failed to force the reaction to go to completion (entries 7 and 8).

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Table 1
Solvent and catalyst screening experiments for A³ reactions

Entry	Catalysts	Solvent/T	Amine	Reaction time (h)	Conversion ^{a,b} , %
1	1	H ₂ O/40 °C	HNBn ₂	24	97 (85)
2	1	CHCl ₃ /60 °C	HNBn ₂	24	100
3	1	PhCF ₃ /60 °C	HNBn ₂	24	90
4	1	CF ₃ CH ₂ OH/40 °C	HNBn ₂	24	96 (84)
5	1	MeOH/40 °C	HNBn ₂	24	51
6	2	H ₂ O/40 °C	Piperidine	24	18
7	2	H ₂ O/60 °C	Piperidine	24	33
8	2	H ₂ O/100 °C	Piperidine	24	75
9	2	CHCl ₃ /60 °C	Piperidine	24	100
10	2	PhCF ₃ /60 °C	HNBn ₂	24	15
11	2	CF ₃ CH ₂ OH/60 °C	Piperidine	24	100
12	2	CF ₃ CH ₂ OH/60 °C	HNBn ₂	24	100
13	2	CF ₃ CH ₂ OH/40 °C	HNBn ₂	24	100
14	2	MeOH/40 °C	HNBn ₂	24	54
15	3	H ₂ O/40 °C	HNBn ₂	24	9
16	3	CHCl ₃ /60 °C	HNBn ₂	24	65
17	3	CF ₃ CH ₂ OH/60 °C	HNBn ₂	24	88
18	4	H ₂ O/40 °C	HNBn ₂	72	10
19	4	CHCl ₃ /60 °C	HNBn ₂	24	22
20	4	CHCl ₃ /60 °C	HNBn ₂	72	31
21	4	CHCl ₃ /60 °C	HNBn ₂	168	62
22	4	CF ₃ CH ₂ OH/40 °C	HNBn ₂	24	96
23	4	MeOH/40 °C	HNBn ₂	24	39
24	No catalyst	H ₂ O/40 °C	HNBn ₂	24	0
25	No catalyst	CHCl ₃ /60 °C	HNBn ₂	24	0
26	No catalyst	CF ₃ CH ₂ OH/40 °C	HNBn ₂	24	0
27	No catalyst	PhCF ₃ /60 °C	HNBn ₂	24	0

Reaction conditions: 1 mmol benzaldehyde, 1.1 mmol amine, 1.5 mmol phenylacetylene, 1 mol % catalyst, 2 mL solvent, 24 h.

^a Conversion determined by ¹H NMR analysis of the crude reaction mixtures based on benzaldehyde conversion.

^b Isolated yield.

It is conceivable that the increased rate observed for complex **2** when the reactions were conducted in chloroform was simply due to an improved solubility of the complex in this solvent. A similar rate enhancement was also observed when the sterically encumbered complex **4** was employed, although the degree of conversion plateaued at 62% even after extended reaction times (entries 19–21). The use of methanol⁹ or benzotrifluoride (PhCF₃; a nontoxic alternative¹⁰ to CH₂Cl₂ and CHCl₃) instead of chloroform proved to be deleterious to conversion rates. The fluorinated alcohol, 2,2,2-trifluoroethanol, (TFE) exhibits a number of unique properties ($pK_a = 12.4$; $E^N_T = 0.898$; $\alpha = 1.51$; $\beta = 0$; $N = -2.78$; $Y = 3.82$), and proved to have a pronounced effect on conversion rates of A³-reactions (entries 11–13, 17 and 22).

For the most active catalyst **1**, substitution of water by TFE had no appreciable effect upon the overall rate of conversion or isolated yield of A³-products (H₂O and TFE afford isolated yields of 85% and 84%; entries 1 and 4); these results which should be compared to the relatively poor outcome obtained using methanol as solvent (entry 5). A quite different result was encountered with the less active catalysts **3** and **4**. In the case of the least active catalyst **4**, near quantitative conversion to the desired A³-product was achieved when using TFE as solvent after 24 h at 40 °C (entry 22). This outcome should be compared to the poor conversions in either water (10% after 72 h at 40 °C; entry 18) or chloroform (62% conversion after 168 h at 60 °C; entry 21). A similar improvement in conversion, when compared to water as solvent, was also observed with **3** in combination with TFE as reaction solvent (entry 17). It should be noted that A³-coupling reactions did not proceed when conducted in the absence of gold in TFE (entries 24–27).

While there are numerous examples of microwave-assisted copper catalysed A³-reactions,¹² application of this technique to homogeneous, gold-catalysed A³-reactions is, to our knowledge, without literature precedent.¹³ The effect of microwave irradiation on gold-catalysed A³-reactions is tabulated above (Table 2).

Table 2
Screening experiments for microwave reactions

Entry	Catalysts	Solvent	Conversion ^a (%)
1	1	H ₂ O	89
2	1	CHCl ₃	43
3	1	PhCF ₃	33
4	1	Perfluorodecalin	76
5	1	CF ₃ CH ₂ OH	86
6	1	MeOH	50
7	1	PEG-400	61
8	2	H ₂ O	10
9	2	CHCl ₃	10
10	2	PhCF ₃	11
11	2	Perfluorodecalin	30
12	2	MeOH	40
13	2	PEG-400	27
14	2	CF ₃ CH ₂ OH	77

Reaction conditions: 1 mmol benzaldehyde, 1.1 mmol dibenzylamine, 1.5 mmol phenylacetylene, 1 mol % catalyst, 1 mL solvent, 100 °C, μ W, 30 min.

^a Conversion determined by ¹H NMR analysis of the crude reaction mixtures based on benzaldehyde conversion.

Highest conversions using **1** as catalyst were obtained when either H₂O (entry 1) or TFE (entry 5) were used as solvents. The use of either *cis/trans*-perfluorodecalin¹⁴ or PEG-400 (an environmentally benign solvent¹⁵) also proceeded with good efficiencies. This observation may facilitate the development of 'green', A³-coupling, reactions where the propargylamine product can be readily separated from the fluorosolvent and also enable recycling of a fluorosolvent catalyst.¹⁶ The effectiveness of **2**, which generally has a lower catalytic activity than **1** in A³-reactions, under the conditions of microwave activation, was also briefly investigated. Here the use of either water, chloroform or benzotrifluoride as solvent resulted in low conversion rates (entries 8–10) whereas reactions carried out in *cis/trans*-perfluorodecalin, methanol or PEG-400 resulted in

a slight enhancement in conversion rates (entries 11–13). Most startling however was the observation that, once again, the rate of A³-reactions are substantially accelerated when conducted in TFE as solvent (entry 14).

From this study, and in contrast to an earlier Letter,⁷ it is clear that the use of solvents, other than water, are compatible with efficient Au-catalysed A³-reactions. In particular we note that TFE has a beneficial effect upon both thermal and microwave-promoted gold-catalysed A³-reactions, such that these reactions can be driven to completion with short reaction times and without loss in yields. The TFE-modification does not require the use anaerobic conditions, proceeds efficiently in reagent grade solvents, and enables facile product isolation (TFE has a bp of 77 °C).

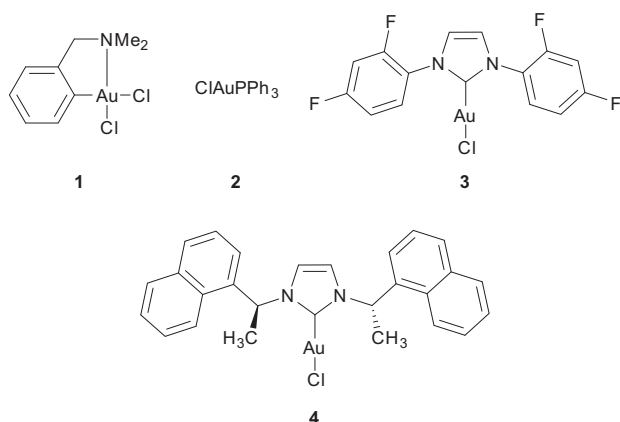
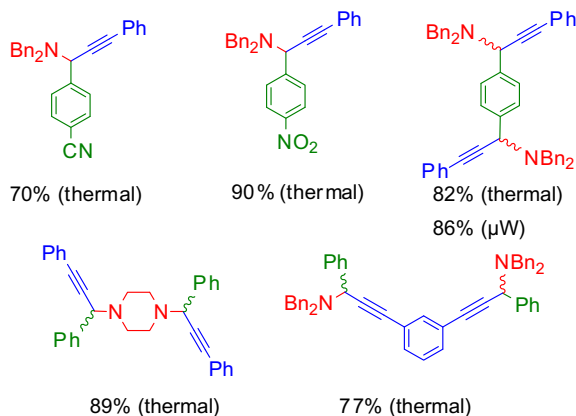


Figure 1. Gold complexes utilised in this investigation.



Thermal: CF₃CH₂OH, 40 °C, 24 h, 1 mol% **1**;
μW: CF₃CH₂OH, 30 min, 100 °C, 1 mol% **1**.

Figure 2. Representative A³-reactions conducted in TFE.

Table 3
Selected properties of solvents^{10,11}

Solvent	E _N ^T (polarity)	HBD	Dipole moment (D)
Perfluorodecalin	–	0	0
PhCF ₃	0.241	–	2.9
CH ₂ Cl ₂	0.309	0.13	1.57
CHCl ₃	0.259	0.1	1.2
PEG-400	0.575	0.31	4.3
MeOH	0.762	0.93	1.7
TFE	0.898	1.51	2.03
H ₂ O	1.0	1.17	1.87

We have also applied our standard reaction conditions to other A³-coupling reactions (Fig. 2). We find that either thermal or microwave activation proves to be effective in the promotion of these reactions in TFE and that product isolation using this solvent system proves to be trivial.¹⁷

Conclusions

Gold complexes **1–4** were found to be effective catalysts for the A³-coupling reaction. The use of TFE as solvent results in improved rates, an effect which can be further augmented by the application of microwave irradiation. We surmise that, in the case of TFE in particular, the observed solvent effects are due to a favourable combination of physical properties as listed in Table 3. TFE is a highly polar, H-bonding, nonnucleophilic solvent which presumably favours both initial iminium ion formation and subsequent capture with an acetylenic gold σ-complex.¹⁸ Studies are now underway for the development of recyclable, fluorine-tagged catalysts for use in A³-reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.10.141>.

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