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Solvent effects in gold-catalysed A^3-coupling reactions

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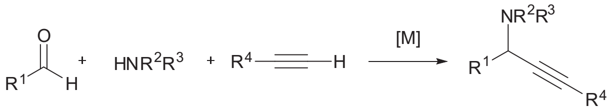
ABSTRACT

Gold-catalysed A^3-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.

The development of domino, multi-component and cascade reactions continues to be an area of intense academic interest[1] even though they were first documented over a century ago.[2] A particularly useful example is the 'A^3-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 complexes[5] 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 A^3-coupling reactions.[6] In their seminal Letter[7] Wei and Li noted that the efficiency of gold-catalysed A^3-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 A^3 coupling reaction.

Our interest[8a,b] in the chemistry of organogold complexes encouraged us to investigate the use of complexes **1**–**4** in A^3-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 A^3-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 A^3-coupled product after 24 h in most of the solvents examined (Table 1, entries 1–4). Complexes **2**, **3** and **4** also promoted the A^3-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 A^3 reactions

Entry	Catalysts	Solvent/*T*	Amine	Reaction time (h)	Conversion[a,b], %
1	**1**	H_2O/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_3CH_2OH/40 °C	$HNBn_2$	24	96 (84)
5	**1**	MeOH/40 °C	$HNBn_2$	24	51
6	**2**	H_2O/40 °C	Piperidine	24	18
7	**2**	H_2O/60 °C	Piperidine	24	33
8	**2**	H_2O/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_3CH_2OH/60 °C	Piperidine	24	100
12	**2**	CF_3CH_2OH/60 °C	$HNBn_2$	24	100
13	**2**	CF_3CH_2OH/40 °C	$HNBn_2$	24	100
14	**2**	MeOH/40 °C	$HNBn_2$	24	54
15	**3**	H_2O/40 °C	$HNBn_2$	24	9
16	**3**	$CHCl_3$/60 °C	$HNBn_2$	24	65
17	**3**	CF_3CH_2OH/60 °C	$HNBn_2$	24	88
18	**4**	H_2O/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_3CH_2OH/40 °C	$HNBn_2$	24	96
23	**4**	MeOH/40 °C	$HNBn_2$	24	39
24	No catalyst	H_2O/40 °C	$HNBn_2$	24	0
25	No catalyst	$CHCl_3$/60 °C	$HNBn_2$	24	0
26	No catalyst	CF_3CH_2OH/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 methanol[9] or benzotrifluroride ($PhCF_3$; a nontoxic alternative[10] to CH_2Cl_2 and $CHCl_3$) 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 A^3-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 A^3-products (H_2O 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 A^3-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 A^3-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 A^3-reactions,[12] application of this technique to homogeneous, gold-catalysed A^3-reactions is, to our knowledge, without literature precedent.[13] The effect of microwave irradiation on gold-catalysed A^3-reactions is tabulated above (Table 2). Highest conversions using **1** as catalyst were obtained when either H_2O (entry 1) or TFE (entry 5) were used as solvents. The use of either *cis*/*trans*-perfluorodecalin[14] or PEG-400 (an environmentally benign solvent[15]) also proceeded with good efficiencies. This observation may facilitate the development of 'green', A^3-coupling, reactions where the propargylamine product can be readily separated from the fluorous solvent and also enable recycling of a fluorous catalyst.[16] The effectiveness of **2**, which generally has a lower catalytic activity than **1** in A^3-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

Table 2
Screening experiments for microwave reactions

Entry	Catalysts	Solvent	Conversion[a] (%)
1	**1**	H_2O	89
2	**1**	$CHCl_3$	43
3	**1**	$PhCF_3$	33
4	**1**	Perfluorodecalin	76
5	**1**	CF_3CH_2OH	86
6	**1**	MeOH	50
7	**1**	PEG-400	61
8	**2**	H_2O	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_3CH_2OH	77

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

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