Efficient ruthenium and copper cocatalzyed five-component coupling to form dipropargyl amines under mild conditions in water†

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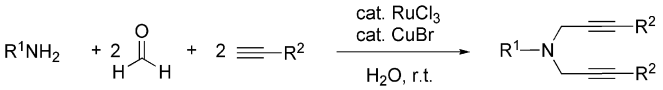
Dipropargyl amines are synthesized by a double direct alkynylation of primary followed by secondary imines formed *in situ* during an efficient, five-component, one-pot coupling reaction cocatalyzed by ruthenium and copper in water.

Propargyl amines are important components of biologically active compounds[1] and useful synthetic precursors.[2] Recently we and others have developed methods allowing for the direct alkynylation of imines formed *in situ* to generate propargyl amines in one step.[3–8] Depending on the substrates, this aldehyde–alkyne–amine coupling (A^3-coupling) can be successful using copper in solid phase systems,[3] copper-doped alumina with microwave assistance,[4] ruthenium–copper cocatalysis[5] and gold,[6] silver,[7] and iridium[8] catalysis. The ruthenium–copper, gold, and silver solution phase systems have shown greatest overall scope. Furthermore, the use of copper catalysis has led to the development of asymmetric A^3-couplings by us[9] and others.[10]

Dipropargyl amines are also important components of biologically active compounds.[11] Furthermore, the biological activity can differ significantly from the analogous compound with a monopropargyl amine substructure.[12] More importantly, dipropargyl amines have an important role in many current synthetic research efforts. These include various types of cycloaddition[13] and cycloisomerization[14] reactions, hydrative[15] and reductive[16] cyclizations, aza-Wittig rearrangements,[17] and macrocycle synthesis.[18] Yet, despite their widespread use, currently reported methods for the synthesis of dipropargyl amines have serious limitations. For example, the use of highly reactive bases such as sodium hydride,[19] or organometallic reagents[20] in a separate step limits the efficiency. An alternative has been to use propargyl bromides directly,[21] but these would also have to be pre-prepared in a separate step and can be difficult to handle. Ishii *et al.* recently reported an iridium catalyzed five component double A^3-coupling leading directly to dipropargyl amines.[22] Yet, with this system the terminal alkyne is limited to trimethylsilylacetylene and 1,4-dioxane or cyclopentyl methyl ether were required as solvents at temperatures exceeding 75 °C for up to 15 h to get satisfactory yields. Formation of dipropargyl amines by the microwave-assisted copper–alumina systems was also reported possible, but this methodology is limited to aminomethylation of alkynes.[4]

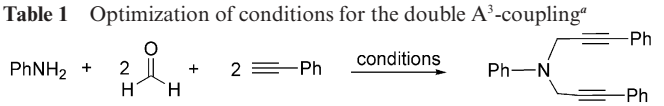
Herein we report the use of a ruthenium–copper cocatalyzed five component double A^3-coupling to synthesize dipropargyl amines from a range of simple amines, aldehydes, and alkynes in one pot under mild conditions in water (Scheme 1).



Scheme 1 Five component-coupling to form dipropargyl amines.

Initial screening of reaction conditions showed that increasing the reaction temperature can substantially decrease the yield (Table 1, entries 1–2, 4–6), indicating that side reactions are a problem. At 60 °C the yield is slightly better in toluene compared to water, whereas at room temperature, with increased reaction time, the opposite is true (Table 1, entries 4, 7, 10–11). This could indicate that hydrolysis of one or both of the imine intermediates is

Table 1 Optimization of conditions for the double A^3-coupling[a]



Entry	Catalyst loading	Solvent	Temp/time	Yield (%)[b]
1	$RuCl_3$ (6.4%) CuBr (15.3%)	Neat[c]	rt/20 h	82
2	$RuCl_3$ (6.7%) CuBr (17.7%)	Neat[c]	60 °C/20 h	62
3	$RuCl_3$ (5.9%) CuBr (15.4%)	H_2O[d]	60 °C/20 h	54
4	$RuCl_3$ (5.4%) CuBr (14.9%)	H_2O	60 °C/19 h	53
5	$RuCl_3$ (5.9%) CuBr (17.2%)	H_2O	100 °C/19 h	30
6	$RuCl_3$ (6.7%) CuBr (14.7%)	H_2O	rt/24 h	61
7	$RuCl_3$ (4.9%) CuBr (16.3%)	H_2O	rt/36 h	70
8	$RuCl_3$ (5.4%) CuBr (15.5%)	H_2O	rt/61 h	60
9	$RuCl_3$ (9.5%) CuBr (16.6%)	H_2O	rt/20 h	78
10	$RuCl_3$ (5.5%) CuBr (15.3%)	Toluene	rt/36 h	64
11	$RuCl_3$ (5.3%) CuBr (17.6%)	Toluene	60 °C/20 h	60

[a] 75 μL (0.82 mmol) aniline, 200 μL (1.8 mmol) phenylacetylene, 135 μL (1.8 mmol at 37 wt% in H_2O) formaldehyde, and 500 μL water were sealed in a tube containing the specified mol% of $RuCl_3$ and CuBr based on the moles of aniline and agitated for the time specified. [b] Yields based on NMR internal standard mesitylene. [c] 10 equivalents (900 μL) phenylacetylene used (reaction not strictly neat since 93 μL H_2O present from the 37 wt% formaldehyde). [d] Solids were sealed in a tube which was subsequently purged with nitrogen (liquids were degassed together by three freeze–pump–thaw cycles before transferring to solids under nitrogen by cannula).

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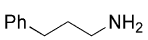
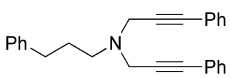
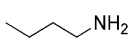
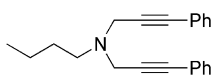
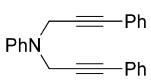
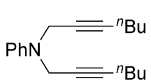
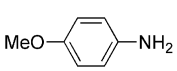
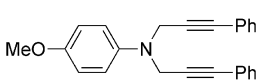
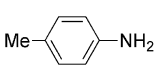
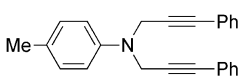
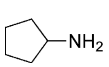
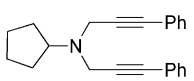
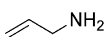
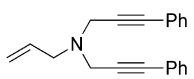
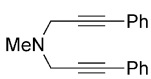
a major side reaction in water, which is enhanced by temperature substantially more than the desired A^3-coupling. The exclusion of oxygen from the reaction did not improve the yield (Table 1, entry 3) indicating that the Glaser-type alkyne coupling was not an important side reaction. When the reaction was performed neat at room temperature, the yield was increased considerably (Table 1, entries 1–2). This could indicate that even at room temperature imine hydrolysis is still a problem. The water in the neat examples comes from the formaldehyde solution, yet the A^3-coupling becomes more competitive over imine hydrolysis because there is now almost double the number of equivalents of alkyne relative to water. Increased temperature under these pseudo-neat conditions substantially decreased the yield (Table 1, entry 2). The conditions of entry 7 were used in preference to the neat conditions since it was not practical to perform the reaction neat with only 2.2 equivalents of alkyne due to insufficient mixing/stirring. Increasing the ruthenium catalyst loading to almost double can give an appreciable increase in yield, but whether or not this increased expense is worth an increase in yield of 8% is questionable. Optimum yield was obtained after reacting between 24–36 h at room temperature (Table 1, entries 6–8), and therefore lower temperatures were not attempted.

With optimized conditions (Table 1, entry 7) various substrates were examined. The yield was only modestly reduced upon using an aliphatic alkyne instead of phenylacetylene (Table 2, entries 3–4). The yield, however, was highly dependent upon the nature of the primary amine used. This substantiates the possibility that imine stability/hydrolysis is a critical factor influencing the yields. The linear aliphatic amines used gave the best yields (Table 2, entries 1–2). However, methyl amine gave the lowest yield (Table 2, entry 9), which could indicate that all or part of the reaction cycle occurs on the water surface since the propargyl amine/imine intermediates as well as methyl amine itself would be more soluble in water than any of the other corresponding amines/imines. The lower yield seen with cyclopentylamine (Table 2, entry 7) is likely the result of steric effects; whereas, allylamine could have undergone side reactions specific to the alkene functionality. Solid amines can be used directly even though the system was heterogeneous for all the reactions (Table 2, entries 5–6). A direct comparison of *para*-anisidine and *para*-toluidine shows that electron donation to the nitrogen improves the yield. Whether this is due to increased stability of the imine to hydrolysis is unclear. When formaldehyde was substituted with benzaldehyde in the reaction shown in Table 2, entry 3, only the monopropargyl amine coupling product was observed. Conditions are being optimized to allow for efficient double A^3-couplings using substituted aldehydes.

In conclusion we have developed a highly efficient method to synthesize a variety of dipropargyl amines under mild conditions.

Table 2 Synthesis of bis-propargyl amines *via* [Ru]–[Cu] catalyzed double A^3-coupling[a]

Entry	Amine	Alkyne	Product	Yield (%)[b]
1				84 (82)
2				79 (78)
3	$PhNH_2$			70 (62)
4	$PhNH_2$			63 (53)
5				63 (51)
6				47 (44)
7				45 (45)
8				60 (59)
9	$MeNH_2$			15

[a] Conditions used based on entry 7 in Table 1. All reactions were performed at 0.82 mmol scale with 2.2 equiv. alkyne, 2.2 equiv. formaldehyde, 5 mol% $RuCl_3$, 15 mol% CuBr, 500 μL H_2O, agitated at room temperature (22 °C) for 36 h; [b] Yields based on NMR with an internal standard (mesitylene) and isolated yields after column chromatography (50:1 hexanes : EtOAc) in parentheses.

The scope of the system and the application of the methodology are under investigation.

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