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# A systematic study on the Cadiot–Chodkiewicz cross coupling reaction for the selective and efficient synthesis of hetero-diynes†

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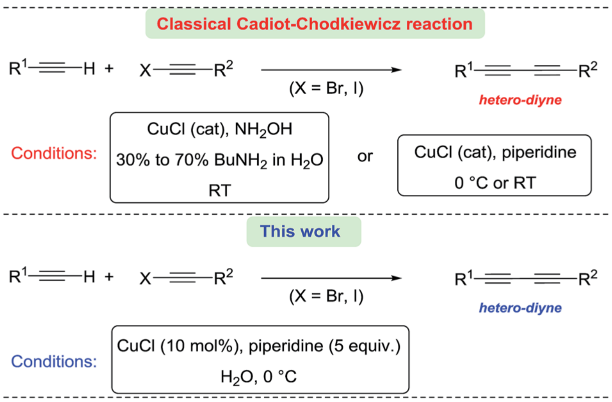
Mild reaction conditions for the Cadiot–Chodkiewicz cross coupling process have been developed for the highly selective and efficient synthesis of unsymmetrical diynes. The most abundant, economic, environmentally friendly, green solvent, water was employed as the sole reaction medium in combination with a minimal amount (5 equiv.) of piperidine base. The reported new reaction conditions provide operational simplicity, high selectivity for hetero coupling (>97%), use of water, and low basicity of the reaction medium compared to commonly used highly basic conditions, *i.e.*, 30–70% amine in water or 100% piperidine. Various sensitive functional groups were found to be highly compatible with the developed low basic reaction conditions. This study supports the fact that the Cadiot–Chodkiewicz cross coupling can be a greener reaction, has a very broad substrate scope, but has always been employed in non-green highly basic conditions and with limited substrate scope.

## Introduction

Water is a nontoxic, non-flammable, economic and green solvent, possessing unique properties.[1] Many natural and biological transformations have been carried out in water.[2] The unique properties of water make it highly appealing for biomimetic synthetic chemistry. Water as a solvent to promote organic transformations has been largely explored in the past two decades due to its fascinating advantages over traditional organic solvents, such as relative abundance, low cost, and non-toxicity.[3] The pioneering work of Breslow[4] and Sharpless[5] inspired the development of catalysis and green protocols in water for the synthesis of highly functionalized and biologically important compounds. Despite these advantages, most of the organic transformations are incompatible with water since most of the organic compounds do not dissolve in water and solubility is generally considered a prerequisite for reactivity.

The 1,3-diynes (symmetric and unsymmetrical) and polyynes are very important in synthetic organic and materials chemistry. These are the common structural motifs of a large variety of biologically active natural products[6] and supramolecular materials.[7] The synthesis of unsymmetrical diynes is more challenging and important as compared to symmetrical diynes in terms of selectivity and applications. The most commonly used procedure for the preparation of unsymmetrical diynes and polyynes is the Cadiot–Chodkiewicz cross-coupling reaction, a copper-catalyzed process between terminal alkynes and haloalkynes (Scheme 1).[8]

However, though the reaction is successful in many situations,[9–11] there are still some disadvantages, such as (a) poor selectivity for heterocoupling (b) basicity of the reaction medium is very high (70% to 100%) and (c) conditions are not very general for divergent substrates. Various modifications have been reported to help in suppressing the formation of the unwanted homocoupled products but they use costly reagents like Pd-catalysts along with Cu and they are very substrate specific *etc.* In this context, our aim was to develop economic, environmentally friendly, operationally simple and yet highly selective reaction conditions for the Cadiot–Chodkiewicz cross coupling. Here in we report a systematic study on the Cadiot–



Scheme 1 Reaction conditions in (a) classical Cadiot–Chodkiewicz cross coupling and (b) this work.

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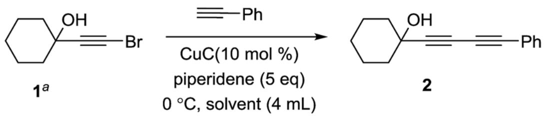
Chodkiewicz reaction, which resulted in the development of reaction conditions with water as the sole solvent and 5 equivalents of piperidine base, for the highly synthesis of unsymmetrical diynes.

## Results and discussion

Initially, we screened divergently polarized organic solvents and water for the reaction (Table 1). We have chosen bromopropargyl alcohol **1** and phenyl acetylene as substrates, piperidine (5 equivalents) as base, CuCl (0.1 eq.) as catalyst and 0 °C temperature as reaction conditions for this study.

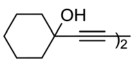
When the reaction was carried out in freshly degassed neat piperidine as in the literature[12] (Table 1, entry 1), the cross coupled diyne **2** was formed in 63% yield along with 13% of homodiyne **3**. Keeping this outcome as the reference, we next studied various solvents. In dichloromethane ($CH_2Cl_2$), with 5 equivalents of piperidine (Table 1, entry 2), the reaction was quicker (15 min) and selective (68%) towards **2**, as there was no detection of **3**. Acetone was equally good for the formation of **2** but gave about 10% of homodimer **3**. Various chlorinated solvents such as $CHCl_3$ (79% of **2**), 1,2-dichloroethane (1,2-DCE, 82% of **2**), and 1,2-dichlorobenzene (1,2-DCB, 72% of **2**) were screened (Table 1, entries 4–6). All of them were found to be highly selective and efficient for the formation of unsymmetrical diyne **2**. It is surprising and noteworthy that, in case of all the chlorinated solvents screened, no trace of the **3** was detected. We next carried out this reaction in highly polar solvents like MeOH, EtOAc, $CH_3CN$, and THF (Table 1, entries 7–10 respectively). These solvents with the exception of $CH_3CN$ (77%) resulted in a very selective cross coupling reaction but in relatively less yields (52–63%). When hexane, a nonpolar solvent was employed (entry 11), cross coupling was quick and efficient (70%) but gave 5% of homo-coupled diol **3**. These observations and outcomes clearly indicate that, there is no need to use the amine base as solvent or in excess amounts during the Cadiot–Chodkiewicz coupling and this reaction can be equally efficient and selective in common organic solvents with few equivalents of amine.

Table 1 Solvent screening for Cadiot–Chodkiewicz reaction



**1**[a] → **2**

| S. No | Solvent | Time (min) | Yield of **2**[b] (%) |
|---|---|---|---|
| 1 | Piperidine | 30 | 63 (13)[c] |
| 2 | $CH_2Cl_2$ | 15 | 68 |
| 3 | Acetone | 15 | 68 (10)[c] |
| 4 | $CHCl_3$ | 15 | 79 |
| 5 | 1,2-DCE | 15 | 82 |
| 6 | 1,2-DCB | 15 | 72 |
| 7 | MeOH | 15 | 63 |
| 8 | EtOAc | 30 | 54 |
| 9 | $CH_3CN$ | 15 | 77 |
| 10 | THF | 30 | 52 |
| 11 | Hexane | 15 | 70 (5)[c] |
| 12 | Water[h] | 15 | 82 |
| 13 | Distilled water | 15 | 82 |
| 14[d] | Water | 15 | 78 |
| 15[e] | Water | 15 | 82 (5) |
| 16[f] | Water | 15 | 76 |
| 17[g] | Water | 25 | 78 (3) |



homodimer **3**

[a] All the reactions were carried out with 0.2 mmol of **1** and 0.22 mmol of phenyl acetylene. [b] Isolated yields after column chromatography. [c] Numbers in paranthesis are isolated yields of homodimer **3**. [d] CuCl was in 5 mol%. [e] CuCl was in 20 mol%. [f] 7 mL of water was used. [g] 10 mL of water was used. [h] Normal water from tap.

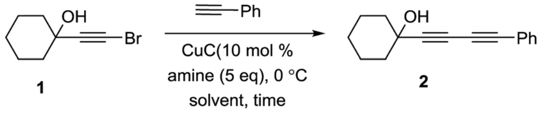
We next carried out this reaction in normal water as well as distilled water to make the process more environmentally benign and economic. To our delight the reaction was highly selective and efficient (82%) for the formation of heterodiyne **2** (Table 1, entries 12 & 13), as compared to any organic solvent. Furthermore, even trace amount of **3** was not detected. We next changed the amount of CuCl employing water as the solvent. In case of 5 mol% (entry 14) the yield of the **2** was reduced on the other hand 20 mol% (entry 15) was equally efficient as 10 mol% but gave 5% of homodimer **3**. When we increased the amount of water (entries 16 & 17) from 4 mL to 7 mL, with 5 equivalents of piperidine and 10 mol% of CuCl, the yield of the **2** was reduced (76%), whereas with 10 mL water, reaction was a bit slow and low yielding along with 3% of **3**. Hence, among all the solvents screened acetonitrile, chloroform, 1,2-DCE and water were found to be selective and efficient for cross coupling product.

Next screening study for various amine bases was carried out in water and 1,2-DCE by keeping the amount of base as 5 equivalents. When water was employed as the solvent (Table 2A), all the four amine bases screened, such as pyridine, $^nBuNH_2$, $^iPr_2NH$ and $Et_3N$ underwent the coupling reaction in about 15–30 min. But, the process was less efficient (57–77% yields of **2**) and less selective (6–12% of homo-diynol **3**) towards heterodiyne **2** (entries 2–5) compared to piperidine (entry 1). Similar results were observed when the same amines were screened in 1,2-DCE as the solvent (Table 2B). Hence piperidine was found to be the best amine for the Cadiot–Chodkiewicz cross coupling reaction irrespective of the nature of the solvent used.

After finding out the best solvent (water) and best amine (piperidine) then we wished to determine the optimal amount of piperidine base required to synthesize hetero-diynes selectively and efficiently. According to the currently existing and well accepted mechanism for Cadiot–Chodkiewicz coupling reaction, at least in one equivalent of base is required. But in the literature, amine is always used either as the solvent or in large excess *i.e.* at least 20 equivalents. However, use of excess amine base is not adherable and affordable. Hence, we have undertaken this task to reduce the equivalents of amine required for better reaction conditions.

Accordingly, we carried out the reaction in water as well as 1,2-DCE employing piperidine in variable amounts as shown in Table 3A and B. When 1 equiv., of piperidine was employed (Table 3A, entry 1) in water, the reaction was relatively slower (1 h) than with 5 equiv., (Table 3A, entry 4) and resulted in the

Table 2 Amine screening for Cadiot–Chodkiewicz reaction in water and 1,2-DCE$^a$



A

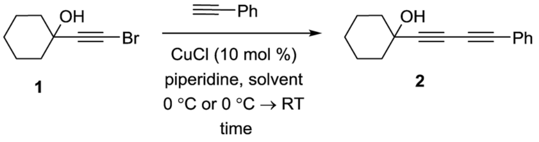
| S. No | Solvent | Amine | Time (min) | Yield of **2**$^b$ (%) | Dimmer **3**$^b$ (%) |
|---|---|---|---|---|---|
| 1 | Water | Piperidine | 15 | 82 | — |
| 2 | Water | Et$_3$N | 60 | 57 | 12 |
| 3 | Water | $^i$Pr$_2$NH | 70 | 66 | 7 |
| 4 | Water | $^n$BuNH$_2$ | 60 | 77 | 7 |
| 5 | Water | Pyridine | 90 | 65 | 6 |

B

| S. No | Solvent | Amine | Time (min) | Yield of **2**$^b$ (%) | Dimmer **3**$^b$ (%) |
|---|---|---|---|---|---|
| 1 | 1,2-DCE | Piperidine | 15 | 82 | — |
| 2 | 1,2-DCE | Et$_3$N | 15 | 63 | 10 |
| 3 | 1,2-DCE | $^i$Pr$_2$NH | 15 | 45 | 25 |
| 4 | 1,2-DCE | $^n$BuNH$_2$ | 15 | 34 | 25 |
| 5 | 1,2-DCE | Pyridine | 15 | 23 | 30 |

[a] Conditions: all the reactions were carried out with 0.2 mmol of **1** and 0.22 mmol of phenyl acetylene, either in degassed water or 1,2-DCE (2 mL/0.1 mmol of **1**). [b] Isolated yields after column chromatography.

Table 3 Optimization study for amount of piperidine in water and 1,2-DCE$^a$



A

| S. No | Solvent | Piperidine equiv. | Time (h) | **2**$^b$ (%) | **3**$^b$ (%) | rsm **1**$^b$ (%) |
|---|---|---|---|---|---|---|
| 1$^c$ | Water | 1.0 | 1 | 65 | 7 | 10 |
| 2$^c$ | Water | 3.0 | 1/4 | 72 | 5 | — |
| 3$^c$ | Water | 4.0 | 1/4 | 80 | — | — |
| 4$^c$ | Water | 5.0 | 1/4 | 82 | — | — |
| 5 | Water | 7.0 | 1/4 | 78 | 8 | — |
| 6 | Water | 10.0 | 1/4 | 81 | 3 | — |

B

| S. No | Solvent | Piperidine equiv. | Time (h) | **2**$^b$ (%) | **3**$^b$ (%) | rsm **1**$^b$ (%) |
|---|---|---|---|---|---|---|
| 1$^d$ | 1,2-DCE | 0.2 | 5 | 37 | 15 | 25 |
| 2$^d$ | 1,2-DCE | 0.5 | 5 | 59 | 12 | 10 |
| 3$^c$ | 1,2-DCE | 1.0 | 3 | 62 | 12 | 5 |
| 4$^c$ | 1,2-DCE | 3.0 | 1/4 | 78 | ~2% | — |
| 5$^c$ | 1,2-DCE | 4.0 | 1/4 | 80 | — | — |
| 6$^c$ | 1,2-DCE | 5.0 | 1/4 | 82 | — | — |

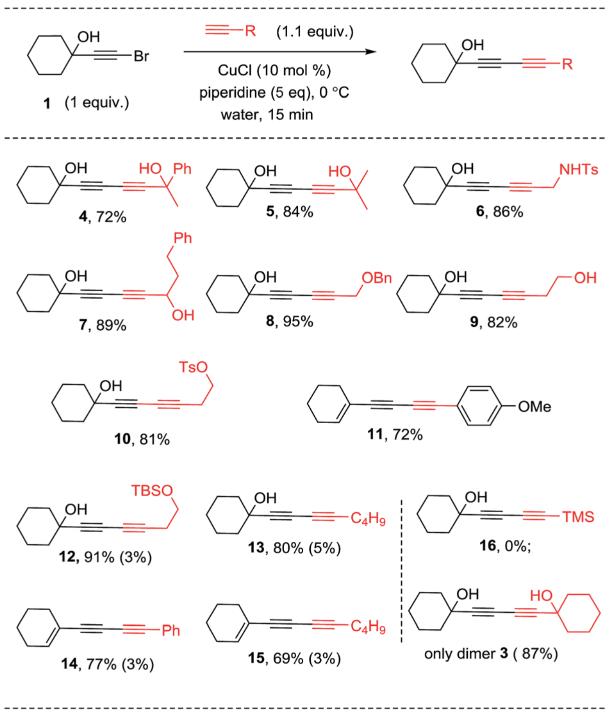
[a] Conditions: all the reactions were carried out with 0.2 mmol of **1** and 0.22 mmol of phenyl acetylene, either in degassed water or 1,2-DCE (2 mL/0.1 mmol of **1**). [b] Isolated yields after column chromatography. [c] 0 °C only. [d] 0 °C → RT.

formation of 65% of **2**, and 7% of **3**, along with 10% of unreacted bromoalcohol **1**.[13] In case of 3 equiv., of piperidine (entry 2), the reaction took only 15 min to yield 72% of cross diyne **2** and 5% of homodiyne **3**, without any left over starting bromide **1**. Surprisingly, 4 equivalents of piperidine afforded **2** as the sole product in 80% isolated yield (entry 3). Surprisingly, increasing amount of piperidine to 7 and 10 equivalents (Table 3A, entries 5 and 6) afforded **3** in comparable yields to 5 equiv., but there was a variable amount of homodimer **3** observed. In continuation, this study was also performed in 1,2-DCE. With 1 equivalent or less amount of piperidine (Table 3B, entries 1–3), the cross coupling was slow (3–5 h, at RT) and less efficient (37–62%) for **2**. In these cases, there was always a considerable amount (5–25%) of unreacted bromide **1** and formation of homo dimer **3** (up to 12–15%) was observed. On the other hand, 3 equivalents of piperidine (entry 4), gave 78% yield of **2** and ~2% of homo dimer **3** within 15 min. Similar to water, 4 equiv. of piperidine in 1,2-DCE (Table 3B, entry 5) resulted in 80% of **2** as the sole product in 15 min at 0 °C. The results and observations from Table 3A and B, clearly sets the lowest limit for the amount of piperidine as 5 equivalents for the quicker, selective, and efficient formation of heterodiynes, both in water as well as in organic solvents (1,2-DCE).

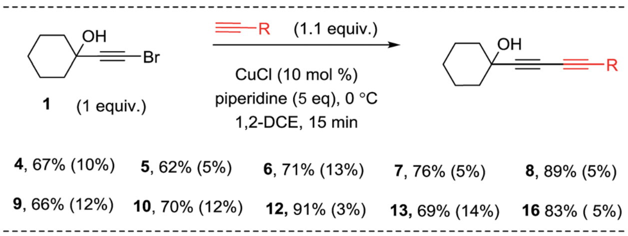
So the best conditions found for the Cadiot–Chodkiewicz cross coupling are water as the solvent, 0 °C as the temperature, and 5 equivalents of piperidine as the base. With an optimized reaction condition in hand, we next performed scope studies for various terminal alkynes and alkynylbromides for the synthesis of structurally divergent heterodiynes. Initially we screened diversely functionalized alkynes keeping the bromide **1** as the coupling partner. Many sensitive functional groups like primary, secondary, tertiary alcohols, amines, OTs and OBn, are compatible under the developed reaction conditions and gave excellent yields of corresponding heterodiynes **4–11**, within 15 min and without any traces of homo diynes. Similar alkyne substrates (functional groups) were reported to give very poor yields under classical Cadiot–Chodkiewicz coupling reaction conditions.[14] All these divergently functionalized diyne units can be useful synthons for materials possessing excellent electronic and optical properties. When highly non polar groups are present on alkynes, such as OTBS ether and long chain alkyls, 3–5% of homodimer **3** was typically observed though corresponding heterodiynes **12–15** were isolated in good yields (69–91%). But when highly hydrophobic TMS-acetylene was employed as an alkyne partner there was no formation of cross product **16**, homo product **3** was isolated instead in 87% yield. This may be due to the poor solubility of TMS-acetylene in water.

To compare the solvent effect *i.e.*, water *vs.* organic solvents, on reactivity and selectivity, we have also carried out the Cadiot–

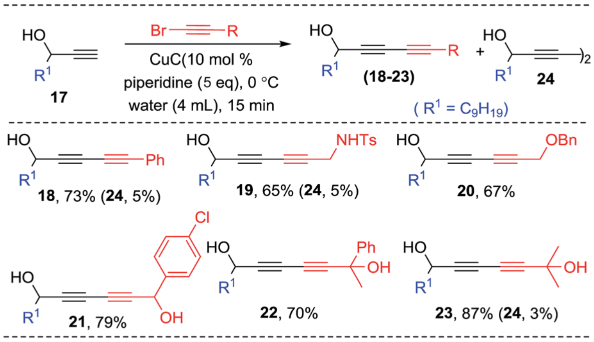
Chodkiewicz coupling of most of the above substrates in Scheme 2, in 1,2-DCE as shown in Scheme 3. Interestingly, all the substrates afforded good yields of corresponding cross diynes **4–10**, **12**, **13** & **16** but with relatively lesser selectivity, *i.e.* variable amounts (3–14%) of homo-coupled product **3** was always observed for all the substrates. Surprisingly and contrary to the outcome in water, coupling of TMS-acetylene with **1** gave excellent yield (83%) of cross diyne **16** and only 5% of homo diyne **3** was detected. These observations proved that water is the best solvent to perform the Cadiot–Chodkiewicz coupling reaction for a majority of substrates including long chain alkynes, with the exception of highly hydrophobic trialkylsilyl acetylenes (1,2-DCE would be a best solvent for them).



Scheme 2 Scope study for functionalized alkynes in water for the synthesis of structurally divergent heterodiynes. Conditions: all the reactions were carried out with 1 equiv. of **1** and 1.1 equiv. of alkynes, 0.1 equiv. of CuCl, 2 mL of degassed water for 0.1 mmol of **1** and 4 equiv. of degassed piperidine; [b] all the yields are after column chromatography; [c] numbers in paranthesis are isolated yields of homodimer **3**.



Scheme 3 Scope study for various alkynes in 1,2-DCE. Conditions: all the reactions were carried out with 1 equiv. of **1** and 1.1 equiv. of alkynes, 0.1 equiv. of CuCl, 2 mL of degassed 1,2-DCE for 0.1 mmol of **1** and 4 equiv. of degassed piperidine; [b] all the yields are after column chromatography; [c] numbers in paranthesis are isolated yields of homodimer **3**.

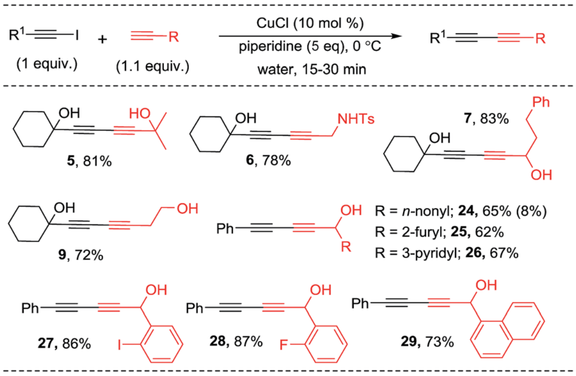


Scheme 4 Scope study for functionalized alkynyl bromides in water.

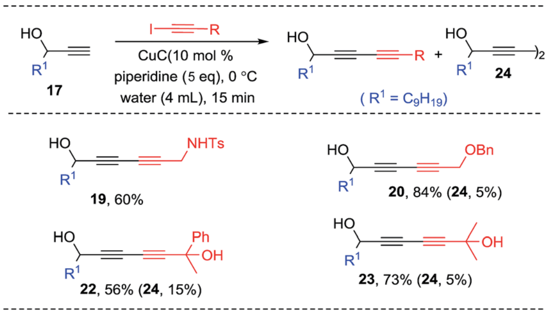
In continuation we have also studied the compatibility of variously functionalized alkynyl bromides with the optimized reaction conditions by employing the propargylic alcohol **17** as an alkyne partner (Scheme 4). All the substrates were found to undergo the coupling reaction smoothly in water and resulted in the formation of corresponding cross coupled diynes **18–23** in 65–87% yields along with 3–5% of homo coupling product **24**.

In the literature it is found that the bromoalkynes have been employed more frequently in the Cadiot–Chodkiewicz coupling reaction and give better yields than their corresponding iodo- and chloro-counter parts because of their milder reactivity. Hence, after studying the reactivity and substrate scope for various alkynyl bromides, we next turned our attention to observe the reactivity of various alkynyl iodides under our optimized reaction conditions.

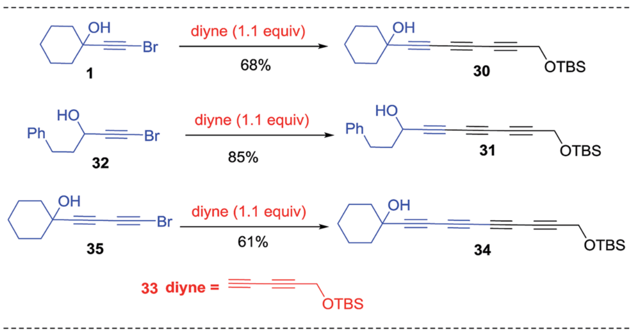
Structurally divergent terminal alkynes underwent smooth cross coupling reaction with both the iodocyclohexyl-propargylic alcohol and iodo-phenylacetylene to afford moderate to good yields of corresponding hetero-diynes **5–7**, **9** & **25–30** (Scheme 5). Next we performed a scope study for various functionalized iodoacetylenes employing **17** as an alkyne partner (Scheme 6). In all cases the reaction was smooth and afforded corresponding hetero-diynes **19**, **20**, **22**, & **23** in good yields along with variable amounts of homodiyne **24**. These



Scheme 5 Testing various alkynyl iodides in water.



Scheme 6 Scope study for various alkynyl iodides.



Scheme 7 Extension to triynes and tetraynes. Reaction conditions: CuCl (10 mol%); piperidine (5 eq.), 0 °C; water, 30 min.

experimental results and observations from Schemes 5 & 6, supports the fact that alkynyl iodides can also be employed as suitable partners during the Cadiot–Chodkiewicz cross coupling under our developed reaction conditions, as efficiently as their bromo-counterparts.

Finally, after finding a very good substrate scope for the newly developed, greener reaction conditions for the Cadiot–Chodkiewicz coupling, we aimed to extend it further for triynes and tetraynes as well (Scheme 7). As anticipated triynes **30** & **31** were efficiently (68% & 85%) and selectively prepared under standard conditions from the reaction between alkynyl bromides **1** & **32** and diyne **33**. The tetrayne **34** was also synthesized in moderate yield (61%) from two diyne units **33** & **35** and found to be stable under reaction conditions. Quite surprisingly there was no formation of homodimers.

## Conclusions

In conclusion, we have performed a systematic study on Cadiot–Chodkiewicz cross coupling reaction to develop greener, highly selective and efficient reaction conditions for the synthesis of unsymmetrical diynes. The most abundant, most economic and universal solvent water has been employed as the sole reaction medium in combination with 5 equivalents of piperidine base. These conditions offered operational simplicity, very less or no byproducts, use of green solvent water, and use of minimal base. The compatibility of these reaction conditions was tested against various sensitive functional groups, structurally diversified terminal alkynes as well as alkynyl bromides and iodides. The importance of the conditions has also been described by the efficient and selective synthesis of triynes and tetraynes. This study shows that the Cadiot–Chodkiewicz coupling can actually be a greener reaction, has broad scope and can be performed without the use of costly catalysts, highly basic conditions, in contrary to what has been shown so far in the literature.

## Experimental section

Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica plates using UV light and anisaldehyde or potassium permanganate stains for visualization. Column chromatography was performed on silica gel (60–120 mesh) using hexanes and ethyl acetate as eluents. NMR data were recorded on 400 and 500 MHz spectrometers. $^{13}$C and $^{1}$H chemical shifts in NMR spectra were referenced relative to signals of $CDCl_3$ ($\delta$ 7.263 ppm for $^{1}$H and 77.16 ppm for $^{13}$C). Chemical shifts $\delta$ and coupling constants $J$ are given in ppm (parts per million) and Hz (hertz), respectively. Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). HRMS were recorded by electron spray ionization (ESI) method on a Q-TOF Micro with lock spray source. Known compounds data have been compared with the reported data, and references were given appropriately. Characterization data for new compounds are given below. $^{1}$H and $^{13}$C (proton decoupled) NMR spectra for all new compounds are given in the ESI.† Reagents were purchased from chemical companies.

### General experimental procedure for synthesis of unsymmetrical diynes

To a solution of an alkyne (1 equiv.), and alkynyl bromide (1.1 equiv.) in freshly degassed amine (piperidine) (5 equiv.) and water or organic solvent like 1,2-DCE (4 mL/0.1 mmol) at 0 °C under nitrogen atmosphere, was added CuCl (0.1 equiv.), and the reaction mixture was stirred either at 0 °C or at room temperature for few minutes to several hours. Reaction mixture was diluted with EtOAc (10 mL/0.1 mmol), saturated with aq. $NH_4Cl$ (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude mixture by flash column chromatography gave the corresponding unsymmetrical diyne.

## Acknowledgements

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