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Transition-Metal-Free Variant of Glaser- and Cadiot-Chodkiewicz-Type Coupling: Benign Access to Diverse 1,3-Diynes and Related Molecules

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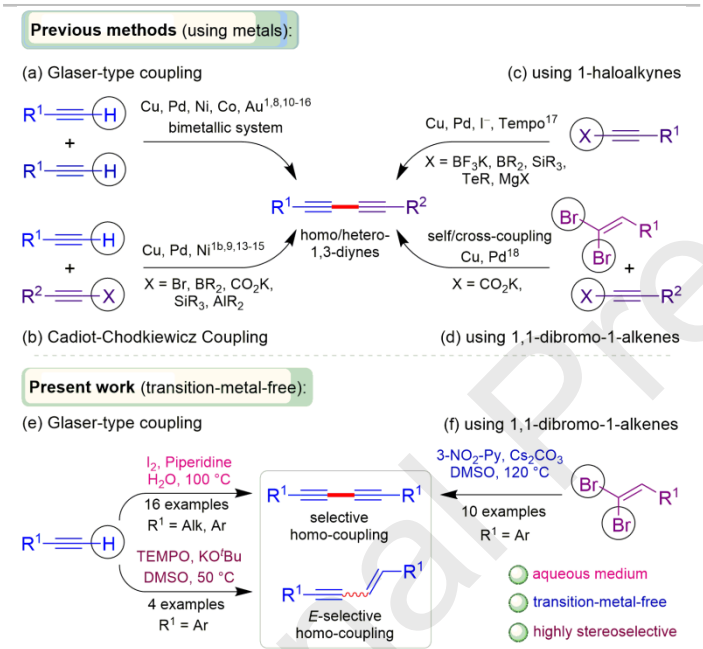
ABSTRACT

Efficient and transition-metal-free transformations towards the synthesis of 1,3-diynes have been described from their corresponding terminal acetylenes or 1,1-dibromo-1-alkenes. The efficiency of molecular iodine as catalyst in aqueous medium, driven the transformation to afford 1,3-diynes in moderate to good yields. The developed reaction conditions revealed appreciable functional group tolerance in aqueous medium. Further, the scope of the transition-metal-free approach for the synthesis of 1,3-enynes has been investigated using terminal alkynes as easy available precursors.

Introduction

The conjugated 1,3-diynes and poly-ynes are witnessed as well-perceived molecular architecture because of their on-growing recognitions in multidisciplinary fields of research.[1] These moieties are well-understood as decisive constituent of talented bio-molecules, such as natural products and pharmaceuticals.[2] The complex compounds embodied with 1,3-diynes have found wide attentions as anti-inflammatory, anti-fungal, anti-HIV, anti-bacterial and anti-cancer agents.[2] Moreover, their application has been greatly acknowledged in material science towards engineering of advanced optoelectronic materials,[3] polymers,[4] supramolecular materials[5] and "high-tech" smart materials, such as liquid crystals, electrically conductive and high strength fibers.[6] In addition, the conjugated 1,3-diyne moieties are revealed as fruitful precursors for the synthesis of pivotal heterocyclic scaffolds and organometallic compounds.[7] Hence, development of novel and diverse tools for their preparation remain as peering assignment in the area of C-C bond forming reactions.[1]

These molecules are traditionally synthesized by Glaser-type (Scheme 1a)[8] and Cadiot-Chodkiewicz (Scheme 1b)[1b, 9] coupling reactions in the presence of Cu-salts as promoters. However, these methods rely on the use of stoichiometric Cu-sources, toxic and rigid organic bases, high reaction temperature and excess of alkynes. Referring the noteworthy earliest reports,[8-9] the urge towards evolving more practical, eco-friendly and cost effective reaction conditions have acquired a renewed concern in the area of catalytic oxidative coupling to form C(sp)-C(sp) bonds. Therefore, the extensive revival of the original conditions based on metal-catalysts and ligands have secured a landmark contribution towards the development of a spectrum of efficient methods in homogeneous catalysis (Scheme 1a,b).[1,10]



Scheme 1. Overview of previous and present reports.

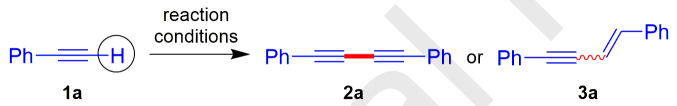
Among the remarkable modifications on catalytic systems, the reactions using Pd-salts are endorsed as most facile approaches in homogeneous catalysis for the homo-coupling of terminal alkynes. These reactions are well-executed and shown to be effective due to the need of low-catalyst loading and mild conditions.[10d, 11] However, the merits of the well-documented Pd-catalyzed homo-coupling processes suffer from barriers such as poor selectivity, high cost of reagents, use of sensitive and environmentally-unfriendly phosphine ligands and amine reagents. Therefore, considering the economic and environmental perspective, the versatility of both homo- and hetero-coupling processes are well-investigated under heterogeneous catalysis.[12] In this regards, the heterogeneous systems based on Cu,[10g-h, 13] Pd,[11, 14] Ni[15] and Au[10t, 16] are studied extensively to facilitate high selectivity in product formation. Admitting the leading breakthrough realized by several researchers over past 148 years that shares an ample platform for the useful applications of these protocols; nevertheless, few reported methods accord with the similar hurdles such as use of metal/bimetallic catalysts, toxic reagents, ligands, complex reaction conditions and the use of excess alkynes. On the other hand, the typical substrates 1-haloalkynes those used in Cadiot-Chodkiewicz coupling (Scheme 1b) and in their self-coupling reactions (Scheme 1c) are traditionally prepared under highly basic conditions and are normally unstable.[17] These limitations lead to the narrow practical applications in large scale synthesis of conjugated 1,3-diynes. Improvements of the methods using surrogates of 1-haloalkyne precursors are not well-explored so far. Recently, 1,1-dibromo-1-alkenes are effectively employed

as substrates instead of 1-haloalkynes for the synthesis of conjugated 1,3-diynes (Scheme 1d).[18] These reactions are investigated using metal-catalyst under harsh reaction conditions. Thus, the rising concern towards novel and eco-friendly surrogate approaches for C(sp)-C(sp) cross-coupling reactions that avoids use of metals and toxic reagents remains important.

Recently, the transition-metal-free transformations are envisioned as most powerful tools and have emerged considerable attention due to their uniqueness in terms of high atom-economy and low waste disposal.[19] A number of synthetic strategies are devised for C-C and C-heteroatom bond formations to serve effective preparation of complex molecules and the success of these methods rely on high selectivity and well investigated functional group tolerance under relatively mild conditions.[19] The transition-metal-free approaches towards the synthesis of 1,3-diynes from terminal alkynes are rarely investigated and the reported methods have not completely explored the synthetic utility of reaction conditions.[19d-e] The transition-metal-free protocols are restricted by the usage of expensive reagents or the use of strong bases.[19d] Here, we represent two distinct transition-metal-free approaches for the synthesis of 1,3-diynes based on (i) transition-metal-free oxidative coupling of terminal alkynes (Scheme 1e) and (ii) organocatalytic oxidative dimerization of 1,1-dibromo-1-alkenes (Scheme 1f).

We commenced with the experiments by investigating the homo-coupling reaction of phenylacetylene (**1a**) (Table 1). To our delight, after having a short optimization, the desired homo-coupling product 1,4-diphenylbuta-1,3-diyne (**2a**) was formed in highest yield of 93%, when using 30 mol% of molecular iodine as catalyst and 3.0 equiv. of piperidine as base in water at 100 °C (Table 1, Entry 18). To identify these suitable conditions, we have subsequently screened the effect of various catalysts, oxidants, bases and solvents. Initially, TBAI was investigated as a catalyst for this transformation. It was observed that when phenylacetylene (**1a**) was reacted using catalytic amounts of TBAI and in presence of 2.5 equiv. TBHP; the corresponding terminal iodinated product has been formed in 31% yield under solvent free conditions at ambient temperature after 12 h (Table 1, Entry 1).

Table 1. Screening of reaction conditions for the transition-metal-free Glaser-type coupling of phenyl acetylene (**1a**).[a]



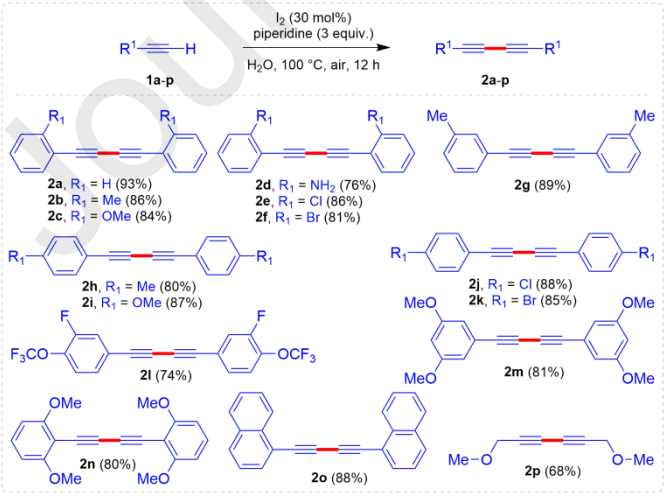
1a **2a** **3a**

Entry	Catalyst (mol%)	Oxidant/Base (Equiv.), Solvent, Temperature	2a % yield[b]	3a % yield[b]
1	TBAI (30)	TBHP (2.5), neat, 25 °C	0[c]	0[c]
2	TBAI (30)	TBHP (2.5), DMSO, 100 °C	33	0
3	TBAI (30)	TBHP (2.5), DMF, 100 °C	37	0
4	PIDA (30)	TBHP (2.5), DMSO, 100 °C	0[d]	0[d]
5	NIS (30)	TBHP (2.5), DMSO, 100 °C	23	0
6	KI (30)	TBHP (2.5), DMSO, 100 °C	35	0
7	I_2 (30)	TBHP (2.5), DMSO, 100 °C	51	0
8	I_2 (30)	K_2CO_3 (2.5), DMSO, 100 °C	<5	0
9	I_2 (30)	*n*-BuLi (2.5), THF, 25 °C	19	0
10	I_2 (30)	LiHMDS (2.5), THF, 25 °C	26	0
11	I_2 (30)	KO^{t}Bu (2.5), DMSO, 100 °C	11	0
12	TEMPO (5)	KO^{t}Bu (0.2), DMSO, 50 °C	0	79
13	I_2 (30)	DABCO (2.5), DMSO, 100 °C	<5	0

14	I_2 (30)	Et_3N (3), DMSO, 100 °C	17	0
15	I_2 (30)	Morpholine (3), DMSO, 100 °C	67	0
16	I_2 (30)	Piperidine (2.5), DMSO, 100 °C	55	0
17	I_2 (30)	Morpholine (3), H_2O, 100 °C	81	0
18	**I_2 (30)**	**Piperidine (3), H_2O, 100 °C**	**93**	**0**
19	I_2 (30)	Piperidine (3), H_2O, 50 °C	<5	0
20	I_2 (15)	Piperidine (3), H_2O, 100 °C	61	0

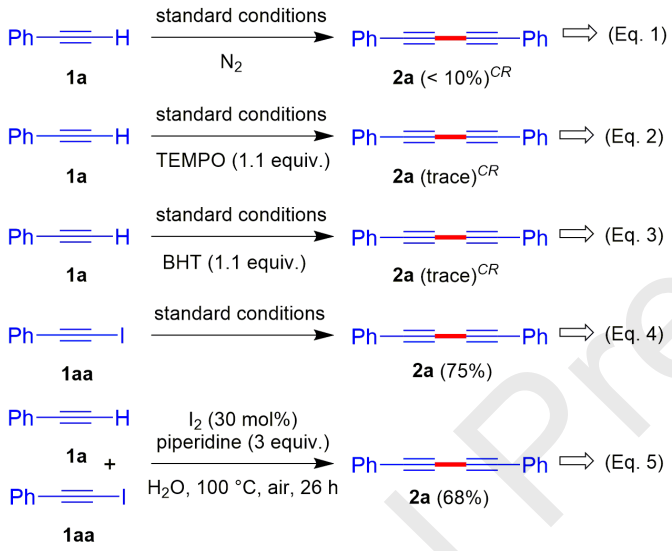
[a] All reactions were performed using 1.0 mmol **1a** in 2 mL solvent for 12 h. [b] Isolated yields. [c] Terminal iodinated product was isolated in 31% yield. [d] 1,2-diiodo product was isolated in 22% yield.

Interestingly, the similar reaction delivered the homocoupling product 1,3-diyne **2a** in low yield, when the transformations were carried out in presence of DMSO and DMF as solvents at 100 °C (Table 1, Entries 2-3). Next, various iodine-based reagents like PIDA (phenyliodine(III) diacetate), NIS (*N*-iodosuccinimide), KI and I_2 were examined as catalysts. It was realized that using PIDA the transformation did not lead to the desired product **2a**, rather the reaction favoured the formation of 1,2-diiodo derivative in 22% yield (Table 1, Entry 4). Among the other catalysts tested, NIS and KI revealed low efficiencies under the reaction conditions towards formation of the product **2a** (Table 1, Entries 5-6). Moreover, 30 mol% molecular iodine as catalyst in presence of 2.5 equiv. TBHP as oxidant in DMSO at 100 °C delivered the product **2a** in 51% yield (Table 1, Entry 7). Inspired by these results, we further attempted to screen the conditions using molecular iodine as catalyst. Several organic and inorganic bases were investigated for this transformation (Table 1, Entries 8-11 and 13-15). Among the tested bases, inorganic bases like K_2CO_3, *n*-BuLi, LiHMDS and KO^{t}Bu were inefficient towards the conversion of **1a** into **2a** (Table 1, Entries 8-11). Surprisingly, when the reaction was performed using catalytic amounts of KO^{t}Bu in presence of TEMPO, the formation of 1,3-enyne **3a** in 79% yield was observed (Table 1, Entry 12) On the other hand, DABCO and triethylamine as bases furnished low yields of the product **2a** (Table 1, Entries 13-14). Interestingly, morpholine and piperidine as bases showed the considerable efficacies towards the successful conversion of **1a** into **2a** with 67% and 55% yields respectively in DMSO at 100 °C (Table 1, Entries 15-16). Surprisingly, when DMSO was replaced with H_2O as solvent, both morpholine and piperidine mediated reactions accomplished the transformation with 81% and 93% yield of the product **2a** respectively (Table 1, Entries 17-18). It was also realized that reducing the reaction temperature and catalyst amounts, the yield of the reaction decreased drastically (Table 1, Entries 19-20). Hence, the reaction using 30 mol% of molecular iodine and 3.0 equiv. of piperidine in H_2O at 100 °C for 12 h was considered as optimal conditions towards the formation of 1,4-diphenylbuta-1,3-diyne (**2a**) (Table 1, Entry 18).



Scheme 2. Substrate scope of terminal alkynes towards the synthesis of 1,3-diynes **2**.

After attaining the best reaction conditions to obtain 1,3-diynes **2**, the transformations of a broad range of terminal alkynes **1** bearing different synthetically useful functional groups were examined under the standard conditions (Scheme 2). In general, all the investigated starting materials were successfully reacted under the developed conditions and the corresponding products **2** were obtained in high yields. Terminal alkynes with mono- and di- functional groups on the aromatic ring such as methyl ($-CH_3$), methoxy ($-OCH_3$), amino ($-NH_2$), chloro (–Cl), bromo (–Br), fluoro (–F) and trifluromethoxy ($-OCF_3$) at various positions were well tolerated under the reaction conditions and leading to the corresponding products **2b**-**n** in high yields despite the electronic nature and substitution pattern. Terminal alkynes embedded with naphthyl ring also delivered the product **2o** in good yield using the developed method. Interestingly, it was investigated that the scope of the protocol could be successfully extended to terminal alkyne with alkyl substituent with moderate isolated yield of the product **2p**.



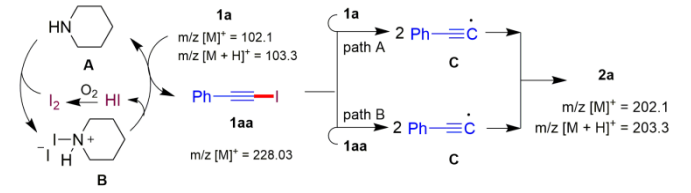
Scheme 3. Control experiments to establish the plausible reaction mechanism.

Next, we determined to establish a plausibe reaction mechanism for this transition-metal-free approach. In this regard, we have carried out several control experiments to depict the plausible reaction mechanism. To begin with, the reaction of **1a** was carried out using standard reaction conditions under N_2 atmosphere. The reaction conditions gave an unsatisfactory result with less than 10% isolated yield of **2a** from a complex reaction mixture (Scheme 3, Eq. 1). It is thus believed that the reaction conditions require sufficient amounts of aerial oxygen towards completion of the transformation. Then, we carried out the reaction of **1a** using standard reaction conditions under the influence of radical scavengers like TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and BHT (butylated hydroxytoluene) (Scheme 3, Eq. 2 and Eq. 3). To our disappointment, we found the trace amount of product **2a** in both the above mentioned cases. From the obtained results, it was concluded that the mechanism follows a radical pathway to afford the desired product **2a**. To further realize about the mechanistic pathway, we have performed the reaction of terminal iodinated acetylene **1aa** under standard reaction conditions. Surprisingly, the reaction conditions were successful towards the formation of 1,3-diyne **2a** in 75% yield (Scheme 3, Eq. 4). Simultaneously, we have also carried out the reaction of terminal iodinated acetylene **1aa** with phenylacetylene (**1a**) under the standard reaction conditions, which is leading to the formation of 1,3-diyne **2a** in 68% yield (Scheme 3, Eq. 5).

Finally, to have better understanding about the plausible reaction mechanism, we were influenced to carry out the reaction of phenylacetylene (**1a**) ($[M]^+ = 102.1$, $[M + H]^+ = 103.1$) under standard reaction conditions. The course of the reaction was inspected and analyzed by gas chromatography-mass spectrometry (GC-MS) after an interval of 3 h, 6 h and 9 h. The mass-spectroscopic data disclosed that the mechanism could proceed *via* the

formation of intermediate **1aa** ([M]$^+$ = 228.03) to obtain the desired product **2a** ([M]$^+$ = 202.1, [M + H]$^+$ = 203.3) (details of mass spectra are given in Figure 1, SI).

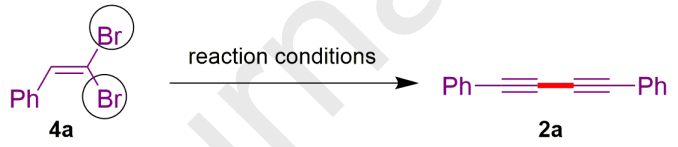
Having these informations from the above experiments and literature evidences, we were able to propose a plausible mechanism (Scheme 4).[10l, 20] According to the proposed mechanism, iodopiperidinium iodide (**B**) can be *in situ* formed from iodine and piperidine (**A**).[20a] The intermediate **B** further acts as an iodinating agent to deliver intermediate **1aa** from **1a**. It is believed that after obtaining the intermediate **1aa**, the reaction may proceed in two pathways. According to path A; the intermediate **1aa** adds on to another molecule of phenylacetylene (**1a**) *via* radical pathway resulting in product **2a**. In accordance to the path B; the intermediate **1aa** *via* self-dimerization of phenylacetylene radical leading to the formation of desired product **2a**. It is presumed that molecular iodine can be regenerated from hydrogen iodide in presence of aerial oxygen.[20b]



Scheme 4. Plausible mechanism for 1,3-diyne **2** formation.

After establishing Glaser-coupling reaction for the synthesis of 1,3-diynes under iodine-mediated protocol, we envisioned to establish the transition-metal-free variant for the synthesis of conjugated 1,3-diynes using 1,1-dibromo-1-alkenes **4** as starting materials. In this regards, we have strived the optimization of the reaction conditions towards the formation of 1,4-diphenylbuta-1,3-diyne (**2a**) using (2,2-dibromovinyl)benzene (**4a**) as starting material.

Table 2. Screening of reaction conditions for the transition-metal-free coupling of 2,2-dibromovinyl)benzene (**4a**).[a]



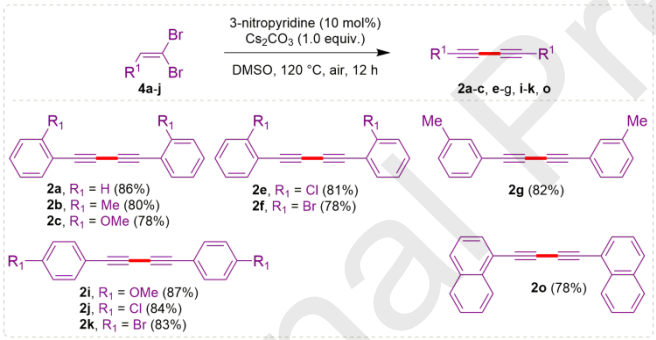
Entry	Catalyst (mol%)	Base (Equiv.), Solvent, Temperature	2a % yield[b]
1	I_2 (10)	Piperidine (3.0), H_2O, 100 °C	0
2	TEMPO (10)	Cs_2CO_3 (3.0), DMSO, 100 °C	63
3	TEMPO (10)	NaO^{t}Bu, (3.0), DMSO, 100 °C	57
4	Thiourea (10)	Cs_2CO_3 (3.0), DMSO, 120 °C	51
5	Niacin (10)	Cs_2CO_3 (3.0), DMSO, 120 °C	55
6	3-nitropyridine (10)	Cs_2CO_3 (3.0), DMSO, 120 °C	69
7	**3-nitropyridine (10)**	**Cs_2CO_3 (1.0), DMSO, 120 °C**	**86**
8	3-nitropyridine (10)	Cs_2CO_3 (0.5), DMSO, 120 °C	47
9	3-nitropyridine (10)	Cs_2CO_3 (1.0), MeCN, 120 °C	23

10	3-nitropyridine (10)	Cs_2CO_3 (1.0), diglyme, 120 °C	49
11	3-nitropyridine (10)	Cs_2CO_3 (1.0), DMSO, 70 °C	Trace

[a] All reactions were performed using 1.0 mmol **4a** in 2 mL solvent for 12 h.
[b] Isolated yields.

Initial reaction conditions using 10 mol% I_2 in presence of 3.0 equiv. of piperidine in water at 100 °C were inactive to deliver the product **2a** (Table 2, Entry 1). Surprisingly, when 10 mol% TEMPO was used as catalyst in addition with 3.0 equiv. of Cs_2CO_3 or 3.0 equiv. of NaO^{t}Bu in DMSO at 100°C, the formation of product **2a** was observed in 63% and 57% yield respectively (Table 2, Entries 2-3). Replacing TEMPO with thiourea or niacin as catalyst, the product **2a** was obtained with similar yields under identical reaction conditions (Table 2, Entries 4-5). Further investigation revealed that catalytic amounts of 3-nitropyridine in presence of base showed maximum efficacy towards this transformation (Table 2, Entries 6-7). Among the tested bases, 1.0 equiv. of Cs_2CO_3 accomplished the transformation with 86% yield of the product **2a** (Table 2, Entry 7). It was also described that with decreasing amounts of base, changing the solvent and reaction temperature leading to the unsuccessful transformation (Table 2, Entries 8-11). Hence, the reaction using 10 mol% of 3-nitropyridine and 1.0 equiv. of Cs_2CO_3 in DMSO at 120 °C for 12 h was considered as optimal conditions towards the formation of 1,4-diphenylbuta-1,3-diyne (**2a**) (Table 2, Entry 7).

Further, the scope of (2,2-dibromovinyl)arenes **4** was explored towards the preparation of 1,3-diynes **2**. It was observed that the (2,2-dibromovinyl)arenes **4** containing both electron donating and electron withdrawing substituents on aromatic rings in various positions leading to the formation of the corresponding 1,3-diynes **2a**-**c**, **e**-**g**, **i**-**k**, **o** in good yields. However, the transformation remains inactive using the corresponding (2,2-dibromovinyl)alkenes as the substrates (Scheme 5).

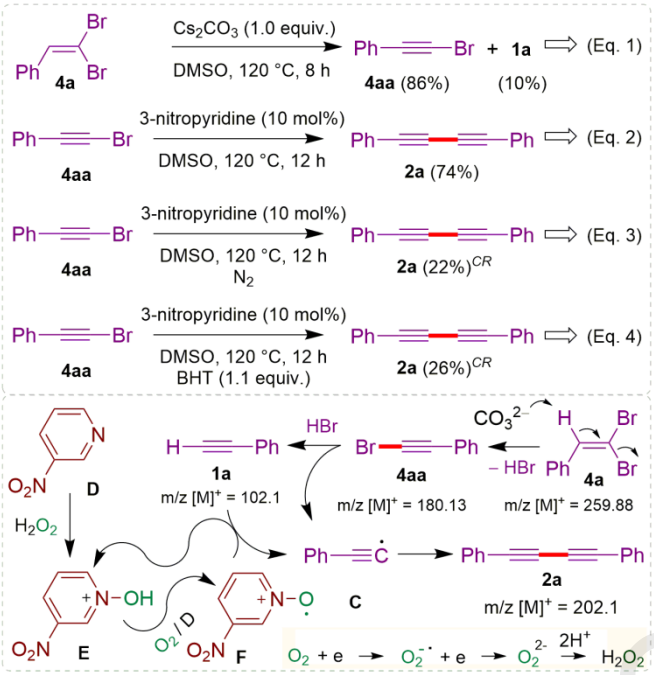


Scheme 5. Scope of 1,3-diyne **2** from (2,2-dibromovinyl)arenes **4**.

Subsequently, to know the mechanistic insights, we were wilful of carrying out the control experiments. To begin with, the reaction of **4a** was performed in the presence of 1.0 equiv. of Cs_2CO_3 in DMSO at 120 °C for 8 h. The reaction conditions gave the terminal brominated acetylene **4aa** in 86% and phenylacetylene (**1a**) in 10% isolated yield (Scheme 6, Eq. 1). Then, the intermediate **4aa** was subjected to a reaction with 10 mol% 3-nitropyridine in DMSO at 120 °C for 12 h. Delightfully, the reaction conditions gave **2a** in 74% isolated yield (Scheme 6, Eq. 2). Similarly, to know the role of aerial oxygen, we were encouraged to carry out the reaction of intermediate **4aa** under above mentioned conditions in the presence of N_2 atmosphere. The reaction conditions were found inefficient and provided the product **2a** in only 22% yield (Scheme 6, Eq. 3). At last to inquire about the radical pathways, a reaction of **4aa** was performed with 10 mol% of 3-nitropyridine in DMSO at 120 °C for 12 h in the presence of 1.1 equiv BHT as radical scavenger. To our realization, the reaction conditions offered desired product **2a** with an unsatisfactory yield of 26% (Scheme 6, Eq. 4).

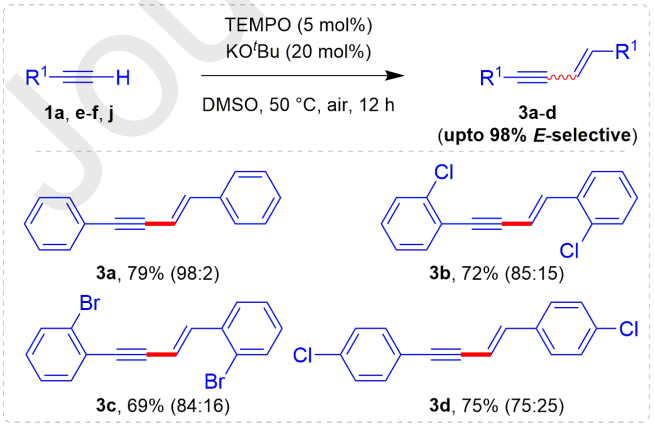
Finally, to realize the feasible reaction mechanism, we were guided to carry out the reaction of 2,2-dibromovinyl)benzene (**4a**) ($[M]^+$ = 259.88) under the standard reaction conditions. The course of the reaction was monitored and studied by gas chromatography-mass spectrometry (GC-MS) after an interval of 40 min, 2 h, 4 h, 6 h, 8 h and 10 h. The mass-spectroscopic data revealed that the mechanism could progress *via* the formation of

intermediate **4aa** ([M]$^+$ = 180.13), **1a** ([M]$^+$ = 102.1) to obtain the desired product **2a** ([M]$^+$ = 202.1) (details of mass spectra are given in Figure 2, SI).



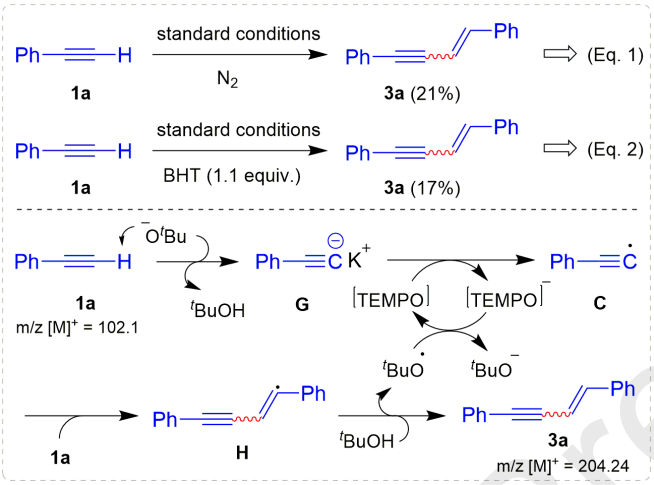
Scheme 6. Control experiments and plausible mechanism for formation of 1,3-diyne **2** from (2,2-dibromovinyl)arenes **4**.

With this much information, we proceeded to propose a plausible mechanism based on the experimental and literature evidences (Scheme 6).[21-23] According to the proposed mechanism, the base mediated dehydrohalogenation of **4a** takes place to deliver the terminal brominated acetylene **4aa**.[21] During the reaction monitoring, it was observed that the phenylacetylene (**1a**) was also forming in lower concentration. Hence, we put up two pathways to generate phenylacetylene radical **C** either from intermediate **4aa** or **1a** under 3-nitropyridine-*N*-oxide **F** catalyzed protocol. It is reported that the intermediate **F** can be generated from 3-nitropyridine by *in situ* generated H_2O_2 under aerobic conditions.[22-23] Finally, the intermediate **C** involves in self-dimerization to obtain the desired product **2a**.



Scheme 7. Scope of 1,3-enyne **3** from aryl acetylenes **1**.

More surprisingly during our screening experiments (Table 1), we have observed that when, phenylacetylene (**1a**) was reacted in presence of catalytic amounts of TEMPO and KO^{t}Bu, the unexpected formation of 1,3-enyne product **3a** was observed with higher *E*-selectivity (Table 1, Entry 12).[24] This serendipitous finding was scrutinized and obtained the suitable optimal conditions (The additional optimization of reaction conditions are provided in SI). The maximum yield of 1,3-enyne **3a** was obtained when the reaction of **1a** was carried out in presence of 5 mol% TEMPO and 20 mol% KO^{t}Bu in DMSO at 50 °C for 12 h. To explore these serendipitous findings, we have investigated the brief substrate scope of this approach (Scheme 7). It has been described that the terminal aryl acetylenes **1**, despite the electronic nature of the substituents in various positions were well tolerated to deliver the corresponding products **3a**-**d** in high yields ranging from 69-79% (Scheme 7).



Scheme 8. Control experiments and plausible mechanism for formation of 1,3-enyne **3** from aryl acetylenes **1**.

We were fascinated in establishing the plausible reaction mechanism for this unexpected finding. In pursuing this objective, we have carried out few control experiments. The reaction of **1a** was carried out under the standard reaction conditions in the presence of N_2 atmosphere to obtain the product **3a** in 21% yield (Scheme 8, Eq. 1). Next, we performed the reaction of **1a** under standard reaction conditions in presence of 1.1 equiv. BHT. The reaction conditions gave a disappointing yield of **3a** in 17% (Scheme 8, Eq. 2). Hence, from above performed reactions we could assume that the reaction may proceed *via* radical pathway in the presence of aerobic conditions. Additionally, we have carried out the reaction of **1a** under the standard reaction conditions and the course of the reaction was examined and analyzed by gas chromatography-mass spectrometry (GC-MS) after an interval of 1 h, 3 h, 6 h and 9 h (details of mass spectra are given in Figure 3, SI). From GC-MS data we could not identify the formation of any intermediate, but we could monitor the disappearance of starting material **1a** ([M]$^+$ = 102.1) and increase in percentage of product **3a** (([M]$^+$ = 204.24) formation at regular intervals. With this much information we decided to describe the plausible mechanism. The fact may be explained as the generation of potassium acetylide **G** in the presence of KO^{t}Bu. The intermediate **G** undergoes single electron transfer in presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) to form the phenylacetylene radical **C**.[25] The generated intermediate **C** adds on to another molecule of **1a** *via anti*-approach leading to the formation of 1,3-enyne radical **H**. Finally, subsequent protonation of **H** from *tert*-butanol to obtain the desired 1,3-enyne **3a**. It is presumed that TEMPO anion could transfer an electron to *tert*-butoxide radical and results in TEMPO radical and *tert*-butoxide anion respectively (Scheme 8).

In summary, we have developed the benign transition-metal-free approach towards the synthesis of 1,3-diyne from their corresponding terminal acetylenes or 1,1-dibromo-1-alkenes under iodine or 3-nitropyridine catalyzed reaction conditions respectively. The described strategies holds good for wide range of substrates bearing different functional groups. Additionally, we also have investigated a mild approach towards the synthesis of *E*-

selective 1,3-enyne under transition-metal-free reaction conditions. The proposed mechanism were validated by using relevant control experiments and mass-spectroscopic investigations.

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Supplementary Material

A detailed supporting information is available which includes the purity and source of the reagents, copies of GC–MS for investigation of the reaction mechanism, experimental procedures, ^{1}H NMR and ^{13}C NMR of the final products. Supplementary material for this article can be found in online version, at doi……...

Experimental Section

General Method: All starting materials were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media) and were used without further purification unless otherwise indicated. All reactions were performed in a 10 mL reaction vial with magnetic stirring. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on TLC plates purchase from Merck. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Products were purified by column chromatography on silica gel, 100-200 mesh. Melting points were determined in open capillary tubes on EZ-Melt automated melting point apparatus and are uncorrected. All the compounds were fully characterized by ^{1}H and ^{13}C NMR and further confirmed by EI-HRMS analysis. All HRMS are recoreded in EI-QTOF method and GC-MS are recorded in EI method in methanol solvent. ^{1}H (^{13}C) NMR spectra were recorded at 600 (150) MHz, 500 (125) MHz and 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26/77.28 ($CDCl_3$) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad).

General experimental procedure for the synthesis of 1,3-diynes 2a-p using terminal acetylenes 1a-p: A 10 mL reaction vial was charged with a terminal acetylenes **1a**-**p** (1.0 mmol), piperidine (3.0 mmol), H_2O (1 mL) and 30 mol% molecular iodine**.** The reaction vial was then heated at 100 °C for 12 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 9.5:0.5), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate (9.5:0.5) as an eluent to obtain the desired products **2a**-**p** in high yields.

1,4-diphenylbuta-1,3-diyne (2a)[17h]: White solid, R_f = 0.75 (SiO_2, Hexane/EtOAc = 9.5:0.5); **m.p** = 84-85 °C (Lit[17h] 86-87 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.54-7.51 (dd, ^{3}J = 7.8 Hz, 4H; 1-H, 5-H), 7.37-7.31 (m, 6H; 2-H, 3-H and 4-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 132.59 (C-1 and C-5), 129.3 (C-2, C-4), 128.53 (C-3), 121.88 (C-6), 81.64 (C-7), 74.4 (C-8) ppm; **HRMS** (EI, $[M + H]^+$): calculated for $C_{16}H_{11}$: 203.0860; found: 203.0858.

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Graphical Abstract

Transition-Metal-Free Variant of Glaser- and Cadiot-Chodkiewicz-Type Coupling: Benign Access to Diverse 1,3-Diynes and Related Molecules

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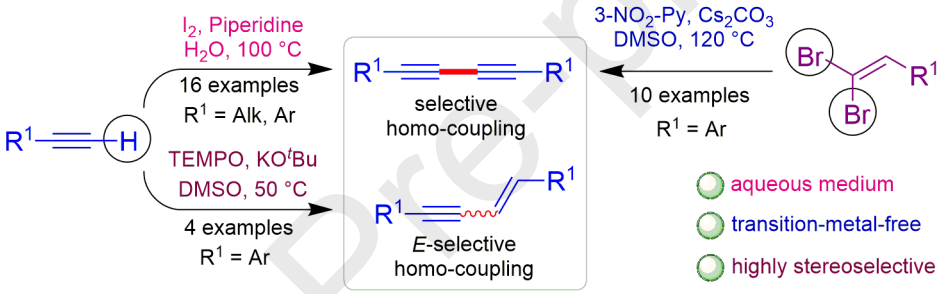

Declaration of Interest Statement

Transition-Metal-Free Variant of Glaser- and Cadiot-Chodkiewicz-Type Coupling: Benign Access to Diverse 1,3-Diynes and Related Molecules

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Authors have NO conflict of interest to declare on the above cited manuscript.

- Transition-metal-free approach towards Glaser- and Cadiot-Chodkiewicz-type Coupling.
- Regioselective synthesis of 1,3-diynes and 1,3-enynes.
- Chemical transformations were possible in aqueous medium.
- Organocatalyzed chemical transformations.
- Broad substrate scope with high yields of the products.