Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202202421
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

A Cascade Sonogashira Cross-Coupling-Substitution-Elimination Reaction for the Synthesis of Linear Conjugated Dienynes

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Abstract: The engagement in tandem of well-known organic reactions such as the Pd-catalyzed Sonogashira cross-coupling reaction, nucleophilic substitution and elimination reactions, enables the synthesis of otherwise difficult to obtain linear dienynes, in moderate to high yields. This retrosynthetic approach opens new ways to prepare highly conjugated alkenes and alkynes. Furthermore, ionic liquids are suitable solvents to perform the cascade reaction and recycle the metal catalysts.

Introduction

Conjugated enynes attract considerable attention owing to their occurrence in various natural products and molecules of pharmaceutical interest.[1–6] For example, the enyne compounds calicheamicins, esperamicins and dynemycins show antibiotical activity and are considered antitumoral agents, while norcapillene, thiarubrine and falcarindol also show prominent biological activities.[7] Besides, enynes are also useful intermediates to prepare aromatic rings, heterocycles, allenes, and related structures.[8,9] The versatility of 1,3-enynes allows to prepare propargyl cyclopropanes,[10] allenes,[11,12] and to perform [2+2] cycloadditions.[13]

Figure 1 shows that various methods have been developed in the past few decades for the synthesis of enynes, including: a cross-coupling reaction of 1-alkynes with vinyl iodides catalyzed by CuI/*N*,*N*-dimethylglycine to afford conjugated enynes in a palladium- and phosphine-free catalytic system for the Sonogashira-type coupling reaction (Figure 1a);[14] the coupling reaction of vicinal-diiodoalkenes with conjugated carboxylic esters catalyzed by nonstoichiometric PdHAP (Figure 1b);[15] the cross-coupling reaction of alkynylmagnesium reagents under iron catalysis by the acceleration effect of lithium salts (Figure 1c);[16] a single-step synthesis of enyne derivatives through Pd-

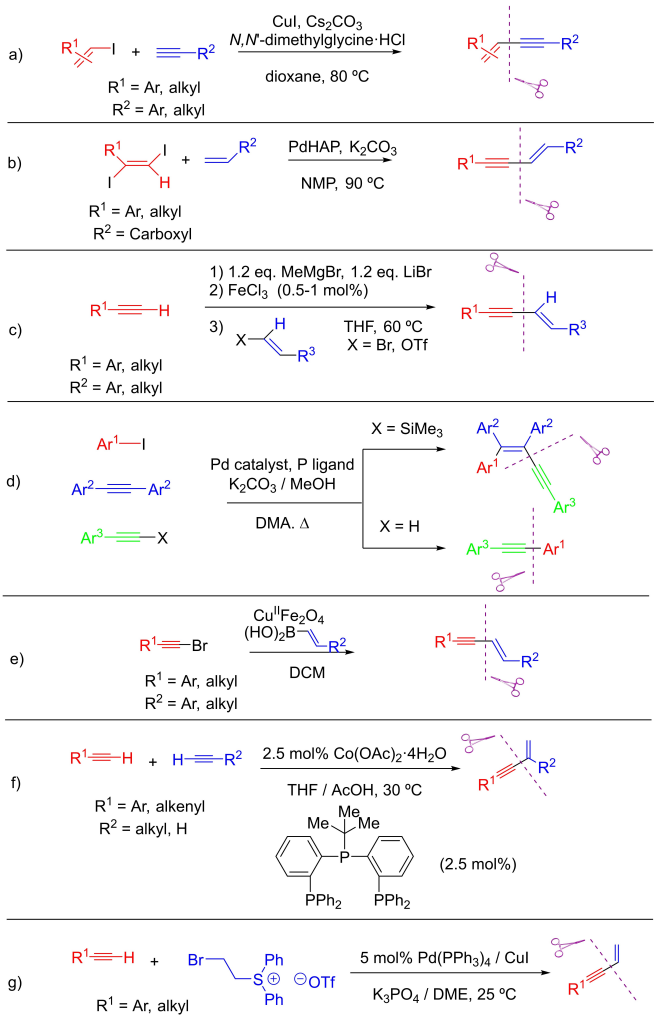

Figure 1. Some procedures reported in the literature to prepare 1,3-enynes by coupling reaction of different unsaturated units.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202202421

catalyzed arylalkynylation of aryl iodides, internal alkynes, and alkynylsilanes (Figure 1d);[17] an efficient Csp–Csp^2 coupling reaction of alkynyl bromides and alkenyl boronic acids catalyzed by $CuFe_2O_4$ nanoparticles (Figure 1e);[18] a $Co(OAc)_2$/triphos catalyst system for the selective cross-dimerization reaction between aryl or alkenyl alkynes and aliphatic alkynes (Figure 1f);[19] and a recent vinylation reaction of terminal alkynes with bromosulfonium triflate compounds catalyzed by palladium and copper (Figure 1g);[20] among others.[21] However, to the best of our knowledge, these methods involve the coupling of two unsaturated units or, when aiming to synthesize terminal enynes, expensive, dangerous and non-easily available acetylene gas (Figure 1f), except for the last example (Figure 1g).

Cascade reactions allow the efficient synthesis of organic molecules that otherwise will not find suitable precursors for their preparation, since the cascade reaction offers a different synthetic pathway by circumventing the isolation of unstable intermediates.[22,23] In this way, new retrosynthetic plans can be designed. As we have seen above, and even considering some recent examples published with Sonogashira couplings in cascade reactions,[24–28] it is difficult to find in the literature a synthesis of dienynes by cross-coupling reactions of terminal enynes, since the latter are unstable molecules.[1] This is the reason why dienynes are generally prepared from monoalkenes and alkynes. Here, we show that the enyne moiety can be easily generated by elimination of a halide atom after a first Pd-catalyzed Sonogashira cross-coupling reaction between aryl iodides and homopropargyl halides, with the same amine base employed for the cross-coupling reaction. On this wise, optimization of the reagents needed for the three transformations required, i.e. cross-coupling, nucleophilic substitution and elimination reactions, is made, avoiding isolation of intermediates and driving to an efficient synthesis of the final conjugated system.

Figure 2 shows the synthetic strategy proposed in this work, which consists in a one-pot Sonogashira coupling, nucleophilic substitution and elimination reaction sequence, in order to obtain conjugated enynes with the very same catalytic system of the cross-coupling reaction during the three steps. The novelty of this process is based on the combination of the three reactions involved, thus the elimination step does not occur without the previous Sonogashira coupling[29–31] and takes place using the same base in catalytic amounts. Moreover, the synthesis does not involve the assembly of two different unsaturated units. The enynes obtained can be either terminal or internal, depending on the starting product structure, and they are formed in good yields from simple iodobenzene derivatives and alkynes. A study of the mechanism will show the role of both catalysts, Pd and amine, in each step of the reaction sequence.

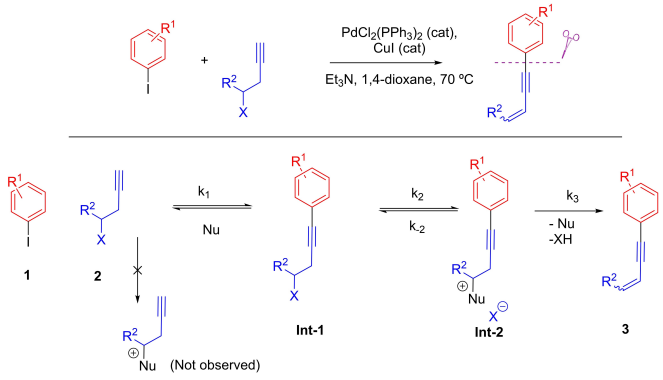


Figure 2. Sonogashira cross-coupling-nucleophilic substitution-elimination cascade reaction and mechanism proposed in this work.

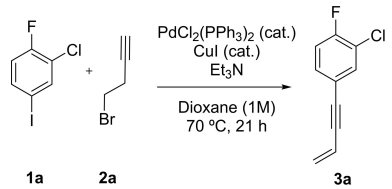
Ionic liquids are suitable and recoverable solvents for different organic reactions,[32] including Sonogashira cross-coupling reactions,[33–36] and allow the easy reuse of catalytic metal species after reaction. We will also show here that our synthetic methodology is compatible with the use of ionic liquid solvents, with the advantage of the reusability of the catalytic system.

Results and Discussion

Optimization and scope of the Sonogashira coupling/nucleophilic substitution/β-elimination cascade reaction

Table 1 shows that 3-chloro-4-fluoroiodobenzene (**1a**) reacts with 3-bromo-1-butyne (**2a**) in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and triethylamine, to give enyne **3a** in good yields (67% yield, 71% conversion), after *in situ* elimination of HBr. The formation of **3a** is the final step of a cascade reaction involving, in principle, a Sonogashira coupling, the nucleophilic substitution of the bromide atom by amine, and a

Table 1. Reaction optimization conditions for the cascade synthesis of 1,3-enynes.



1a 2a 3a

Test	Catalysts [eq]	[Butyne] [eq]	Sonogashira v_0 [%/min]	Global v_0 [%/min]	Yield [%]
1	[Pd]: 0.0057 [Cu]: 0.0114 [Et_3N]: 5	1.5	8.2734	2.1182	>99
2	[Pd]: 0.0057 [Cu]: 0.0114 [Et_3N]: 2	1.5	6.5513	1.2924	92
3	[Pd]: 0.0057 [Cu]: 0.0114 [Et_3N]: 2	1.01	5.224	1.2788	94
4	[Pd]: 0.0114 [Cu]: 0.0228 [Et_3N]: 2	1.5	0.5961	0.0853	25

final β-elimination of the amine, to form the corresponding conjugated alkene. The absence of elimination products in the starting homopropargylic halide **2a** suggests a good engagement between the Sonogashira coupling and the elimination step reactions. In other words, it seems that the elimination product only appears after the Sonogashira coupling.

Table 1 also shows the results with different amounts of catalysts, reagent **2a** and base, and the best conditions found were 0.57 mol% Pd, 1.1 mol% CuI, 5 eq. Et_3N and 1.5 eq. of **2a**, which allowed to obtain >98% of product **3a** with an initial reaction rate (v_0) of 2.1 min^{-1} (see Supporting Information, Table S1 for a complete optimization of the reaction conditions). Different amines were effective for the reaction (see Table S2) and 1,4-dioxane was the best solvent tested under these reaction conditions (Table S3).

Figure 3 shows that a diversity of 1,3-enynes can be prepared in reasonable to excellent yields under the optimized reaction conditions. It is also possible to use triflate (**2b**) or even chloride compounds, but in lower yields (**2c**). Furthermore, this methodology is also compatible with substituents in the terminal alkene position (**3u** and **3v**), also with linear iodoalkenes (**3w**) and 1-iodonaphtalene (**3t**). Other substituents usually present in organic molecules, such as halides (**3i** and **3p**), ether (**3b** and **3n**), ester (**3c**), amine (**3f** and **3q**), amide (**3g**), nitro (**3k** and **3o**), and ketone (**3l**) functionalities, are tolerated in the aromatic ring. Hydroxyl substituents in *para*-(**3m**) gave low yields, and substitution in the *ortho*-position (**3s**) produces the in situ cyclization.

Kinetic studies and energetic parameters

The experimental kinetic rate equations for both the Sonogashira step and for the global reaction sequence were calculated (equations 1 and 2, see Table S1 and Figures S2–S5 for complete calculations).

Sonogashira

$$v = k_1[\mathbf{1a}]^{1.12}[\mathbf{2a}]^{-0.16}[Et_3N]^{1.23}[Pd + Cu]^{2.41} \quad (1)$$

Global

$$v = k_{global}[\mathbf{1a}]^{0.70}[\mathbf{2a}]^{-0.70}[Et_3N]^{1.28}[Pd + Cu]^{1.87} \quad (2)$$

Equations (1) and (2) show that the Sonogashira coupling partially controls the reaction rate, but the following steps have some influence, as assessed by the negative action of the homopropargyl bromide in the global reaction rate. This negative order for **2a** comes from the triggering of undesired by-reactions, such as eliminations, that decrease the reaction rate at higher concentrations of **2a**. Nevertheless, the cascade reaction works well under the optimized reaction conditions.

Figure 4 shows the Hammett plot for the Sonogashira reaction, with different *para*-substituted iodobenzenes, which shows a slope $\rho = +1.5(1)$. The positive value for ρ indicates that the reaction is favored by electron withdrawing groups in the aromatic ring, which is consistent with the typical mechanism of Pd-catalyzed cross-coupling reaction, where the oxidative addition of the iodoaromatic to Pd is the rate-determining step. Besides, electron withdrawing groups in the aromatic ring also facilitates the later β-elimination step, which explains why a $\rho = +2.9(2)$ is obtained for the global process.

A screening of different amines was then carried out. Figure 5 shows a plot representing the initial rate of the reaction *vs.* the nucleophilicity of the amine, assessed by the pKa value of the conjugated acid (Table S2). It can be seen that, in general, the more nucleophilic the base is, the better catalytic activity for the elimination step shows. Poor nucleophilic bases, like Troeger's base or pyridine, are not able to substitute the halogen and perform the elimination, thus obtaining the Sonogashira coupling intermediate as the only final product. According to the optimization results shown above, the amount of base necessary to achieve the cascade sequence (entries 1 to 4 in Table S1) can be catalytic, because only 0.07 eq. of base are necessary to catalyze the elimination reaction when starting from the isolated Sonogashira intermediate. However, the 32% yield obtained with 1.07 equivalents of base means 4 catalytic cycles (7% of base), and given that the order of reaction for the amine is ~1.2, lower amine amounts severely decrease the global reaction rate.

Figure 6 shows that the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the Sonogashira-elimination cascade reaction of iodobenzene **1a** with alkyne **2a**, calculated experimentally with the Eyring-Polanyi equation, indicate that the major contribution of the Sonogashira coupling and the amine-assisted elimination reaction for the cascade reaction is enthalpic. This result is in good agreement with the bimolecular nature of the different reactions.

Mechanistic studies on the elimination step

At this point, since the Sonogashira coupling and amine nucleophilic substitution are well-known processes, the elimination step was studied in detail. Different elimination mechanisms can be operative under our reaction conditions, as shown in Figure 7. The elimination of quaternary amines giving an olefin product is a classic scheme for a Hoffman elimination mechanism, which is an E_2 elimination with stereoelectronic requirements. In this case, the leaving group (LG) and the H atom have to be antiperiplanar, leaving in a concerted way.[26,27] Thus, the main factor which determines the outcome of the Hoffman elimination is the steric hindrance in the E_2 transition state,[26] and the expected major product obtained would be ethylene, not observed here. Another factor that is involved in the orientation of the Hoffman products is the acidity of the β hydrogen, and it is obvious than the β hydrogen in intermediate **Int-1**, whose carbanionic conjugated base can resonate throughout the alkyne and the phenyl group, is more acidic than the primary β′ hydrogen. This could explain why product **3a** is observed over ethylene, but it is hard to think that the

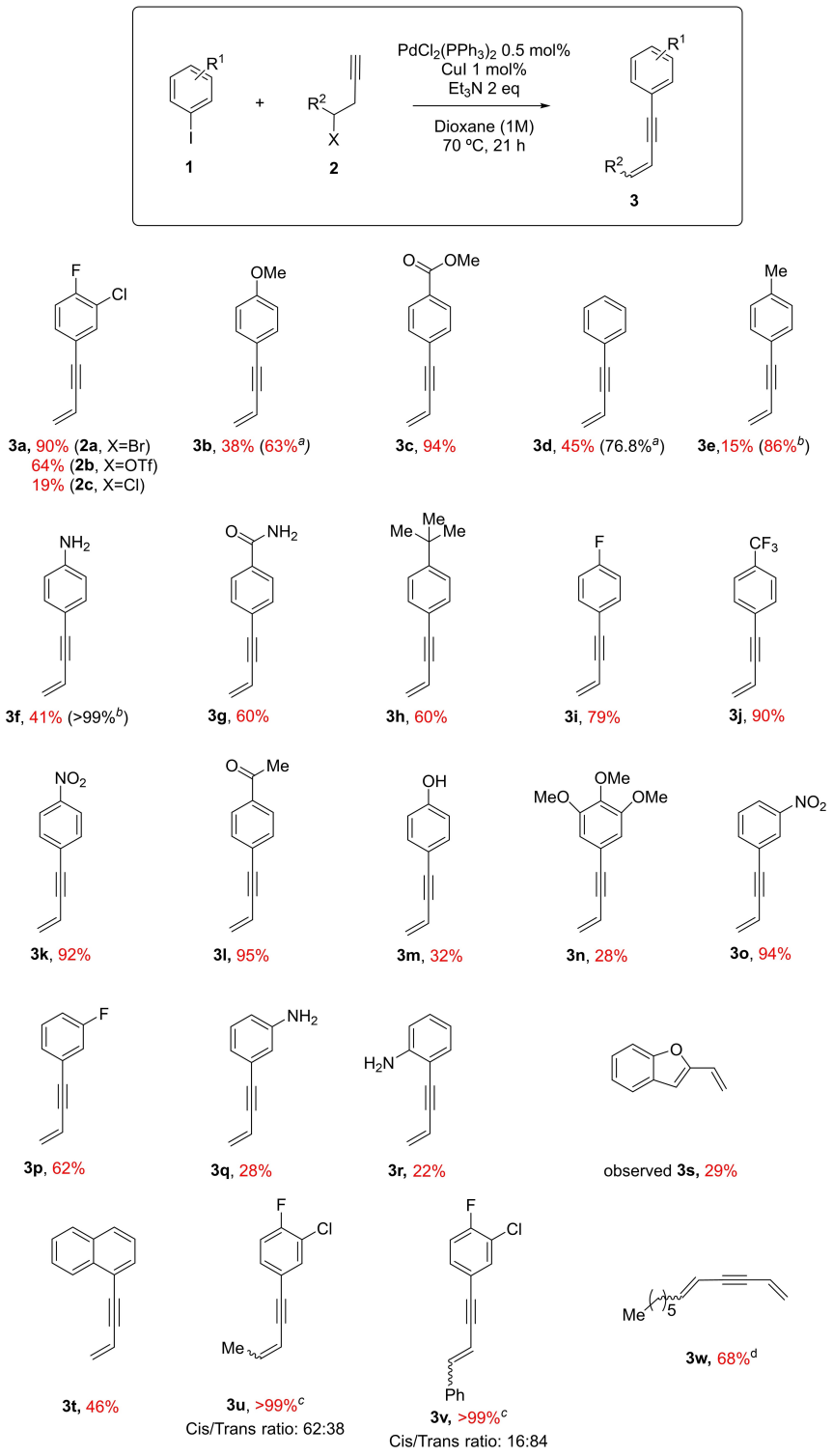


Figure 3. Scope for the Sonogashira-substitution-elimination cascade reaction with different iodobenzenes (**1**) and alkynes (**2**). Yields calculated by GC and NMR. [a] 1.1 mol% $PdCl_2(PPh_3)_2$, 2.2 mol% CuI, 2.5 eq. Et_3N. [b] 2.5 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI, 3 eq. Et_3N, 75 °C. [c] Yield referred to the bromo butyne derivative. 1 eq. bromo-butyne derivative, 10 eq. 3-chloro-4-fluoroiodobenzene **1a**, 5.5 mol% $PdCl_2(PPh_3)_2$, 11 mol% CuI, 20 eq. Et_3N, 70 °C. [d] 1.7 mol% $PdCl_2(PPh_3)_2$, 3.4 mol% CuI, 3.6 eq. Et_3N, 75 °C, 42 h.

acidity of the hydrogen atoms, alone, justifies that ethylene is never observed throughout the scope of molecules studied. Indeed, the acidity factor does not explain why when $R^1 = Me$ (**3v**), the *cis*: *trans* ratio observed is 62:38, since both products practically present the same acidity in the β hydrogen. Therefore, the steric factor here must definitely have influence. The

Substituent	σ
p-H	0
p-OMe	-0.27
p-COOMe	0.45
p-NH_2	-0.66
p-Me	-0.17
p-$COONH_2$	0.36
p-F, *m*-Cl	0.43
p-*t*-butyl	-0.15
3,4,5-OMe	-0.03
m-NO_2	0.71
m-F	0.34
m-NH_2	-0.16

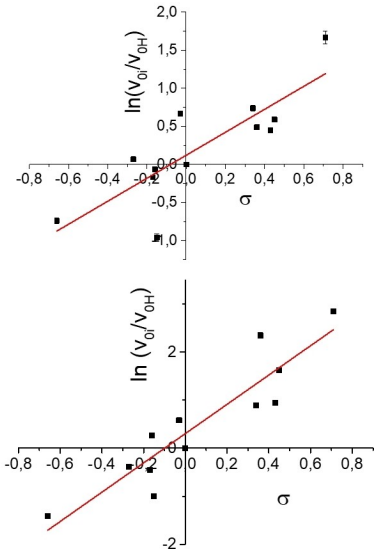


Figure 4. Left) Table of functional groups as substituents in the aromatic ring of compound **1**, with their substituent constants for Hammett's representation. Right top) Hammett representation for Sonogashira reaction. The reaction constant ρ (slope) calculated is +1.5(1). Right bottom) Hammett representation for the global reaction. The reaction constant ρ (slope) calculated is +2.9(2).

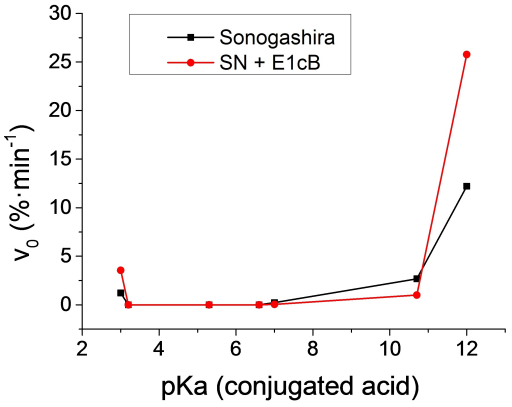


Figure 5. Correlation of the initial reaction rate vs. pKa of the conjugated acid of the amine for both the Sonogashira (black line) and nucleofilic substitution and elimination reactions (red line, see Table S2 for the values of the different amines). For SN + E1cB initial rates, experiments were carried out from isolated **Int-1** as the starting material without 4-bromo-1-butyne (with Pd and CuI catalyst, 1 eq. of amine, dioxane (1 M) as a solvent and 70 °C reaction temperature).

Hoffmann elimination gives stereospecifically *trans* isomers as major products, which is not the case here, thus according to the observed *cis*:*trans* mixture, it is safe to conclude that the elimination step is not a classic Hoffman elimination.

In contrast to the E_2 mechanism, the E_1 mechanism depicts the H atom leaving first and then the LG. Indeed, the E_1cB mechanism (elimination unimolecular conjugate base) nicely explains the experimental observations. In the E_1cB, the H atom leaves first, and only after that, the LG (two-step process).[28] For this to happen, a base has to abstract a relatively acidic proton to generate a stabilized anion. The lone pair of electrons on the anion moves to the neighboring atom, thus expelling the LG and forming the new double or triple bond.

Figure 8 shows that three limiting cases can be distinguished in the E_1cB elimination: (1) A fast and reversible first step, with a second slow and rate-determining step: The carbanion returns to starting material faster than it forms product ($(E_1cB)_{rev}$). (2) Step 1 is the slow and rate-determining step, and formation of product is faster than returning from the carbanion to starting material: Step 1 is essentially irreversible ($(E_1cB)_{irrev}$). (3) Step 1 is rapid and also irreversible, and the carbanion goes slowly to product: This case occurs only with the most stable carbanions ($(E_1cB)_{anion}$).[28]

In order to unveil which elimination mechanism exactly takes place, the following experiments were performed. First, the reaction was carried out in methanol and deuterated methanol as solvents. A protic solvent should give some product deuterated in the β position (Figures S5–S6) if the first step of the E_1cB is reversible and faster than the last step. However, the NMR analysis did not display any significant difference in the product signals between the experiments with MeOH or MeOD, thus suggesting that fast reversibility in the first step of the elimination process does not occur. This result discards the $(E_1cB)_{rev}$ mechanism (Figure S6). Besides, the NMR analysis did not show any evidence of anion formation, which also leads to discard the $(E_1cB)_{anion}$ mechanism. Thus, the $(E_1cB)_{irrev}$ mechanism seems the most plausible to explain the elimination reaction and also explains why the undesired elimination of ethylene can be circumvented. Besides, stronger amine bases should enhance the rate of the $(E_1cB)_{irrev}$ reaction,[29] and indeed, Figure 5 above shows that this is what happens.

Plausible mechanism: good engagement of the individual reactions

Figure 9 shows the plausible mechanism of the cross-coupled - amine-induced $(E_1cB)_{irrev}$ mechanism, experimentally supported by the above results. The cascade reaction is triggered by the base (marked in blue), which is the key actor in all the steps. While the individual reactions admit a rather broad range of bases, such as amines and basic salts, the cascade reaction can only be (synergistically) performed with the choice of certain amines having enough base and nucleophilic character. For instance, the reaction stops at **Int-1** when using 5 eq. of K_2CO_3 as a base, confirming that this intermediate does not experiment direct elimination in the presence of a base to give products **3**.

Cascade cross-coupling-elimination in a reusable catalytic system

Ionic liquids are typically constituted by ionically bonded organic molecules of high polarity, immiscible in water and with some acidity.[31] In order to obtain the enyne compounds in a more sustainable and reusable system, we have performed

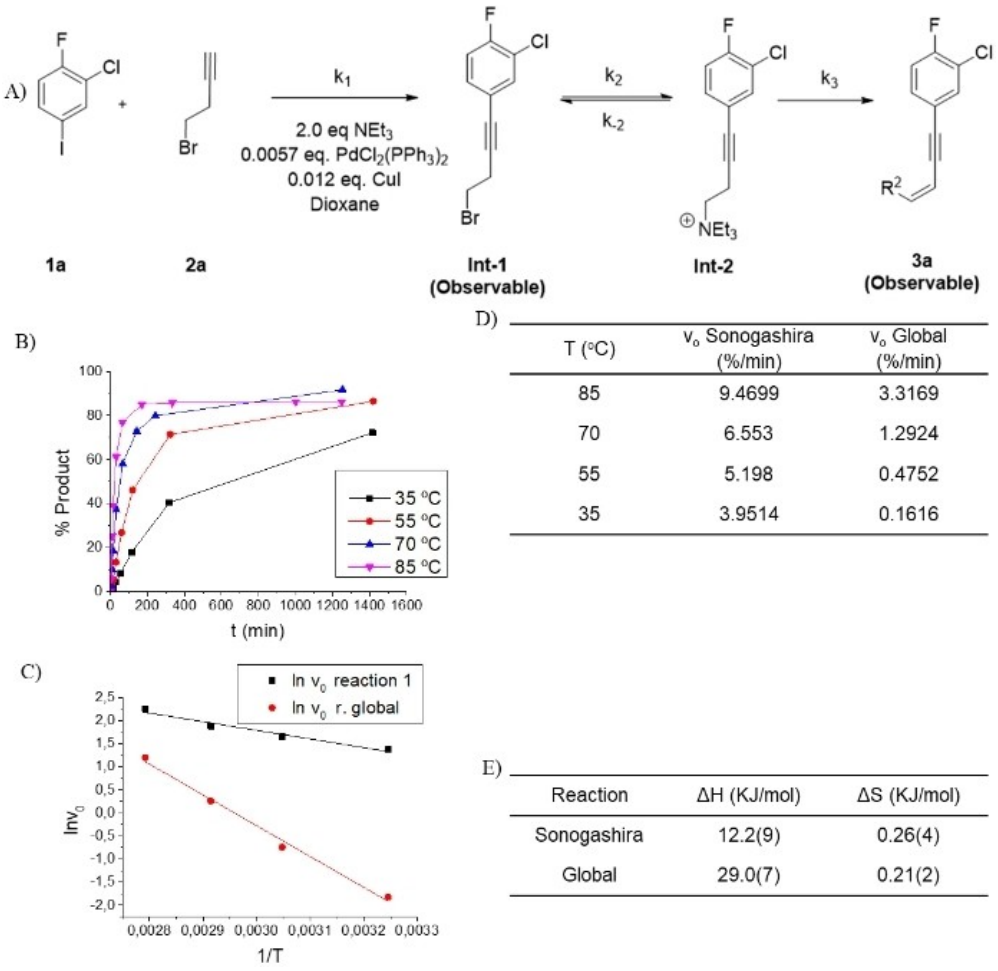


Figure 6. A) Reaction scheme. B) Kinetic plot of product formation (global reaction) at different temperatures. C) Table with the initial rates obtained for each temperature. D) Activation energy (E_a) for both Sonogashira and elimination processes, using Arrhenius's linear regression and the initial rate kinetic expression. E) Transition state enthalpy and entropy values for the Sonogashira-elimination cascade reaction with **1a** and **2a** obtained at the reaction temperatures indicated in B).

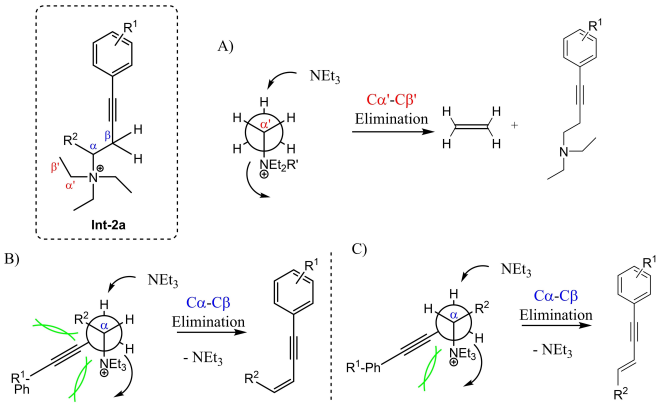


Figure 7. Newman projections of the intermediate and the base showing steric impediments (in green) for the Hoffman elimination. A) E_2 Hoffman elimination in Cα′–Cβ′ giving ethylene, without noticeable steric impediments in the *anti* transition state conformation. B) E_2 Hoffman elimination in Cα–Cβ giving the *cis* enyne product and amine, with two important steric impediments in the *anti* transition state conformation. C) E_2 Hoffman elimination in Cα–Cβ giving the *trans* enyne product and amine, with an important steric impediment in the *anti* transition state conformation.

the cascade reaction in ionic liquids. In our group, we have previously optimized other catalytic reactions in ionic liquids,[32,33] including cascade processes.[33] Here, we tested different ionic liquids, and it was found that [bmim][PF_6], [bmim][BF_4] and [bmim][OTf] are all suitable for the reaction, to give yields of **3a** >90% (Figure S7). The ionic liquids with Cl^- as a counteranion (entries 3 and 6 in Figure S7) where discarded because they formed the Cl-substituted Sonogashira intermediate, after substitution of the Br by the Cl atom, hampering the elimination step.

Figure 10 shows the results for the different cascade reactions performed in the ionic liquid medium, which show moderate yields for most of the reactants used. However, Figure 11 shows that the ionic liquid could be recycled up to 4 times without losing reactivity, which may justify its use despite the moderate final yields.[34,35]

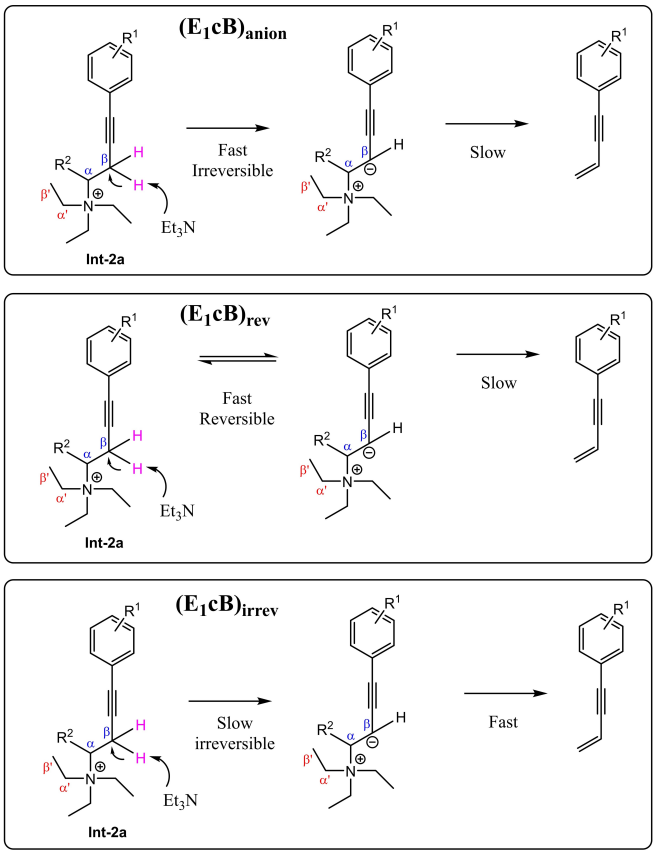


Figure 8. The three different potential mechanisms for the proposed E_1cB elimination process that takes place in the cascade reaction. Hydrogen atoms depicted in pink colour are indistinguishable.

Conclusion

A new methodology to obtain dienynes and trienes by cascade reactions is described here. The cascade process involves a Sonogashira coupling, a fast nucleophilic substitution and an E_1cB irreversible reaction, which circumvents a plethora of undesired reactions (starting halide elimination, ethylene formation,…) and paves the way to obtain terminal and internal conjugated dienynes from simple starting materials. Moreover, this cascade reaction is compatible with sustainable and recyclable ionic liquid solvents.

Experimental Section

General: Reagents were obtained from commercial sources (Merck-Aldrich) and used without further purification otherwise indicated. Glassware was dried in an oven at 100 °C before use. Reactions were typically performed in 6.0 mL reactors equipped with a magnetic stirrer and closed with a plastic cap having a rubber septum part to sample out, and placed in steel heaters. All the products obtained were characterized by GC connected to a FID detector, GC-MS, IR, ^{1}H, ^{13}C NMR, and DEPT. When available, the characterization given in the literature was used for comparison. Gas chromatographic analyses were performed in an instrument equipped with a 25 m capillary column of 5% phenylmethylsilicone. Dodecane was used as an external standard. GC-MS analyses were performed on a spectrometer equipped with the same column as the GC and operated under the same conditions. Preparative chromatography and TLC were performed over SiO_2. ^{1}H, ^{13}C NMR, and DEPT were recorded in a 400 MHz instrument using $CDCl_3$ as a solvent, containing TMS as an internal standard. IR spectra of the compounds were recorded on a spectrophotometer by impregnating the windows with an ether solution of the compound and letting to evaporate before analysis.

General reaction procedure for the synthesis of enynes by Sonogashira-elimination cascade reaction: Iodobenzene derivatives (**1a**–**1w**) (1 mmol) and the corresponding alkyne (140.8 µL, 1.5 mmol) were added to a 6 mL reaction flask containing 1 mL of anhydrous dioxane and a magnetic stirrer. Bis(triphenylphosphine)palladium(II) dichloride (4.0 mg, 0.0057 mmol) and copper iodide (2.2 mg, 0.011 mmol) were added to the reaction mixture, followed by the addition of triethylamine (280 µL, 2 mmol). The reaction flask is placed at a steel heater previously set at 70 °C, with a stirring rate of 500 rpm. The reaction mixture was collected, washed with dioxane, concentrated under reduced pressure, and treated three times with diethyl ether, filtrated, and concentrated under reduced pressure. Products were purified by preparative chromatography using hexane as an eluent for compounds **3a**, **3b**, **3f**, and **3h**, and hexane: ethyl acetate (9.5:0.5) for compounds **3c**, and **3i**. Compounds **3d**, **3e**, **3j**, **3k** and **3l** were directly collected without further purification after the work-up, but modifying the reaction conditions in order to maximize the product yield.

Kinetic measurements: After the addition of the amine in the Sonogashira reaction, the reaction mixture is stirred at 500 rpm for 30 seconds, the zero sample is quickly taken, and the reaction mixture is placed in a steel heater already set at the desired temperature (70 °C for the general procedure), considered this moment as the initial time for the reaction. Samples are taken following this procedure: 25 µL of the reaction mixture is placed in a 2 mL chromatography vial containing 1 mL of an ether:dodecane (1000:1) solution. The precipitate is filtered with a syringe filter of 0.22 µm of pore size.

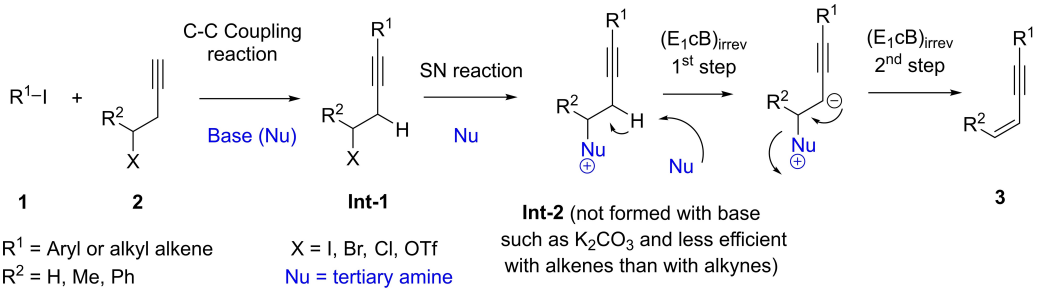


Figure 9. Reaction mechanism proposed for the cross-coupled - amine-induced $(E_1cB)_{irrev}$ reaction, where the role of the base can be seen.

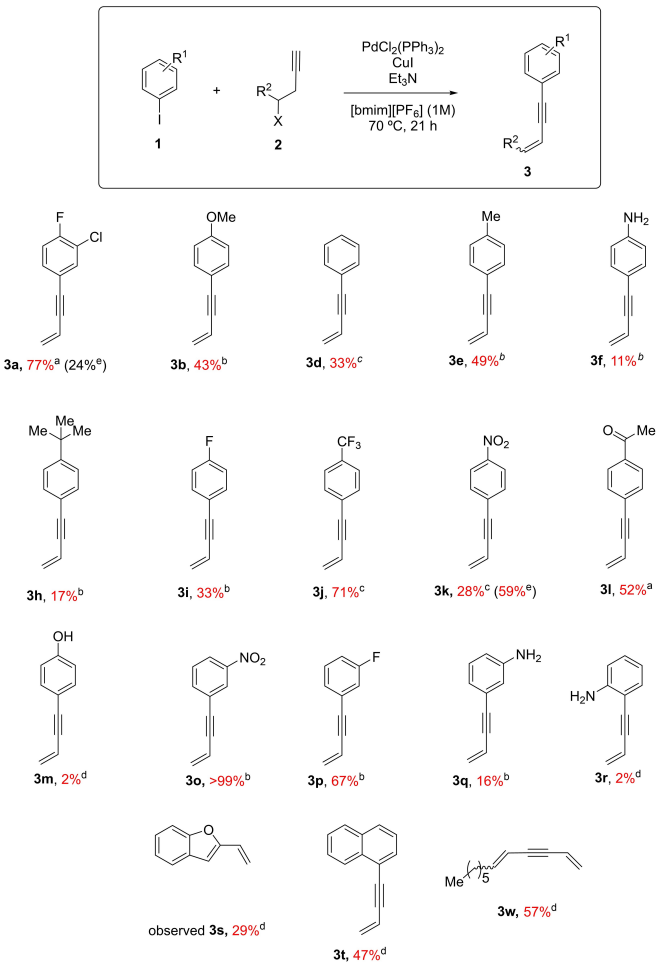


Figure 10. Scope for the Sonogashira-amine-induced elimination cascade reaction with different iodobenzenes (**1**) and alkynes (**2**) in [bmim][PF_6] ionic liquid. Yields are calculated by GC and NMR. [a] 0.5 mol% $PdCl_2(PPh_3)_2$, 1 mol% CuI, 4 eq. Et_3N. [b] 1.1 mol% $PdCl_2(PPh_3)_2$, 2.2 mol% CuI, 4 eq. Et_3N. [c] 0.5 mol% $PdCl_2(PPh_3)_2$, 1 mol% CuI, 2 eq. Et_3N. [d] 1.7 mol% $PdCl_2(PPh_3)_2$, 3.4 mol% CuI, 4 eq. Et_3N. [e] Performed under microwave conditions: 0.5 mol% $PdCl_2(PPh_3)_2$, 1 mol% CuI, 4 eq. Et_3N, 90 min.

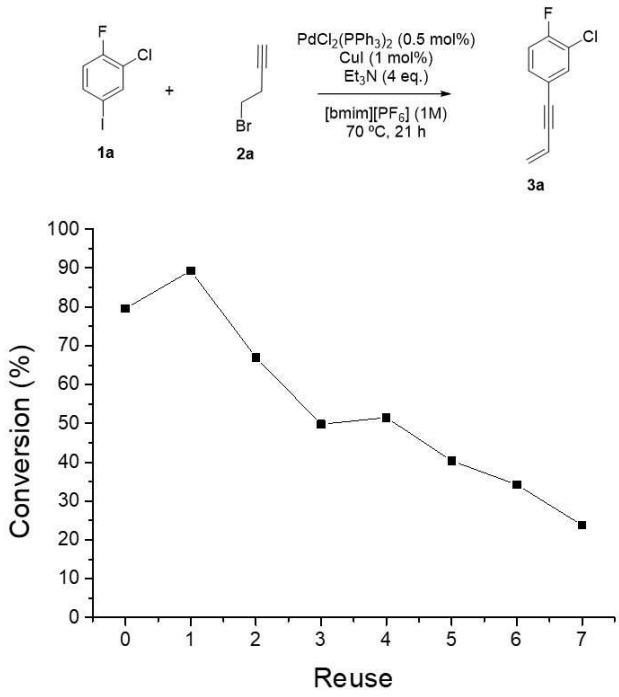


Figure 11. Reuses of the [bmim][PF_6] ionic liquid. Conversion of 3-chloro-4-fluoroiodobenzene **1a** with each reuse. Reuse 0 stands for the first use.

Synthesis of 4-(4-bromobut-1-yn-1-yl)-2-chloro-1-fluorobenzene (Int-1): 3-Chloro-4-fluoroiodobenzene **1a** (2.55 mL, 20 mmol) and 4-bromobut-1-yne **2a** (2.1 mL, 22 mmol) were added to a 50 mL reaction flask containing 12 mL of anhydrous dioxane and a magnetic stirrer. Bis(triphenylphosphine)palladium(II) dichloride (80 mg, 0.5 mol%) and copper iodide (40 mg, 1 mol%) were added to the reaction mixture, followed by the addition of potassium carbonate (5.5 g, 2 eq.). The reaction flask is placed at a steel heater previously set at 70 °C, with a stirring rate of 500 rpm during 22 h. The reaction mixture was extracted with DCM and concentrated under reduced pressure. Products were purified by preparative chromatography using a gradient from hexane to hexane: ethyl acetate (90:10) as the eluent.

Synthesis of but-3-yn-1-yl trifluoromethanesulfonate (2b): 3-Butyn-1-ol (760 µL, 10 mmol) and pyridine (800 µL, 10 mmol) are added to 7 mL of dichloromethane (DCM). This solution is added to a 25 mL round flask containing triflic anhydride (1.68 mL, 10 mmol) and 6 mL of DCM at 0 °C. The solution is stirred at 0 °C for 1 h under nitrogen atmosphere. The reaction mixture is extracted three times with water, dried with sodium sulfate, and finally the solvent is removed on rotary evaporator.

Synthesis of homopropargylic bromides: The synthesis of different homopropargylic bromides was carried out with the corresponding alcohols, using carbon tetrabromide and triphenylphosphine, according to an already described procedure[27] with some modifications, as follows:

Synthesis of 4-bromo-1-pentyne (2d): 4-Pentyn-2-ol (252.4 mg, 3 mmol) and carbon tetrabromide (1.094, 3.3 mmol) are placed in a 10 mL round flask with 2 mL of DCM. The reaction mixture is cooled down to 0 °C and triphenylphosphine (866 mg, 3.3 mmol) is slowly added over 30 min under vigorous stirring (900 rpm). Upon addition of the phosphine, the colorless solution turned a pale brown color and was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure to a brown oil and quickly added to stirring hexane (2 mL). The white precipitate was filtered three times, and the remaining solution was concentrated yielding 4-bromo-1-pentyne as a colorless oil (87%).

Synthesis of (1-bromobut-3-yn-1-yl)benzene (2e): 1-Phenylbut-3-yn-1-ol (192 mg, 1.31 mmol) and carbon tetrabromide (479 mg, 1.44 mmol) are placed in a 10 mL round flask with 2 mL of DCM. The reaction mixture is cooled down to 0 °C and triphenylphosphine (379 mg, 1.44 mmol) is slowly added over 30 min under vigorous stirring (900 rpm). Upon addition of the phosphine, the colorless solution turned a pale brown color and was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure to a brown oil and quickly added to stirring hexane (2 mL). The white precipitate was filtered three times, and the remaining solution was concentrated yielding 4-bromo-1-pentyne as a yellowish brown oil (72%).

General reaction procedure for the synthesis of enynes by Sonogashira-elimination cascade reaction with ionic liquids: Iodobenzene derivatives (**1a–1w**, 1 mmol) and the corresponding

alkyne (140.8 μL, 1.5 mmol) were added to a 6 mL reaction flask containing 1 mL of ionic liquid and a magnetic stirrer. Bis(triphenylphosphine)palladium(II) dichloride (0.5 mol%) and copper iodide (1 mol%) were added to the reaction mixture, followed by the addition of triethylamine (4 eq.).The reaction flask was placed at a steel heater previously set at 70 °C, with a stirring rate of 750 rpm. The reaction mixture was extracted three times with diethyl ether, and concentrated under reduced pressure. Products yield were obtained by GC comparing with the previous ones obtained in anhydrous dioxane.

Acknowledgements

This work was supported by the MICINN (Spain) (Project PID2020-115100GB–I00). The work has also been funded by Generalitat Valenciana, Grupos Emergentes (GV/2021/138). A. L.-T. thanks the MICINN for the concession of the FPI grant PRE2020-093338 (through SEV-2016-0683-20-3). J. O.-M. acknowledges the Juan de la Cierva program for the concession of a contract (IJC2018-036514-I). M. B. thanks ITQ for the concession of a contract.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: cascade reaction · cross-coupling · dienynes · elimination · ionic liquids · substitution

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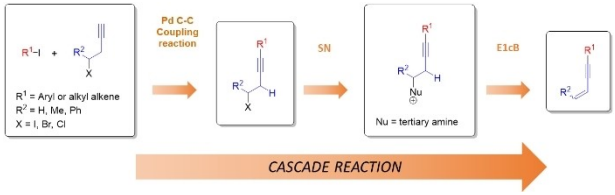
Manuscript received: August 4, 2022
Accepted manuscript online: September 22, 2022
Version of record online: ■■, ■■■

RESEARCH ARTICLE



A Sonogashira cross-coupling, nucleophilic substitution and elimination cascade reaction allows the synthesis of otherwise difficult to obtain linear dienynes, in moderate to high yields. Ionic liquids are suitable recyclable solvents for the reaction. This synthetic strategy opens new ways to prepare highly conjugated alkenes and alkynes.

A. Lumbreras-Teijeiro, M. Bacic, Dr. J. Oliver-Meseguer, Dr. A. Leyva-Pérez**

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A Cascade Sonogashira Cross-Coupling-Substitution-Elimination Reaction for the Synthesis of Linear Conjugated Dienynes