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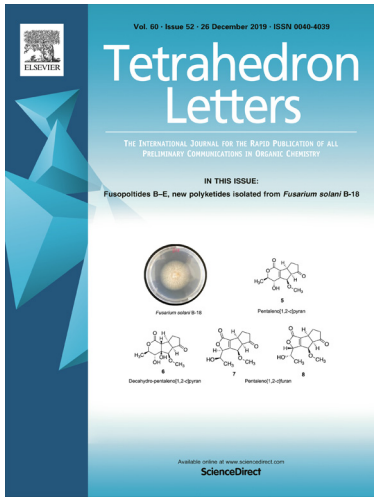

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Conversion of Alkynes into 1,2-Diketones using HFIP as Sacrificial Hydrogen Donor and DMSO as Dihydroxylating Agent

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ABSTRACT

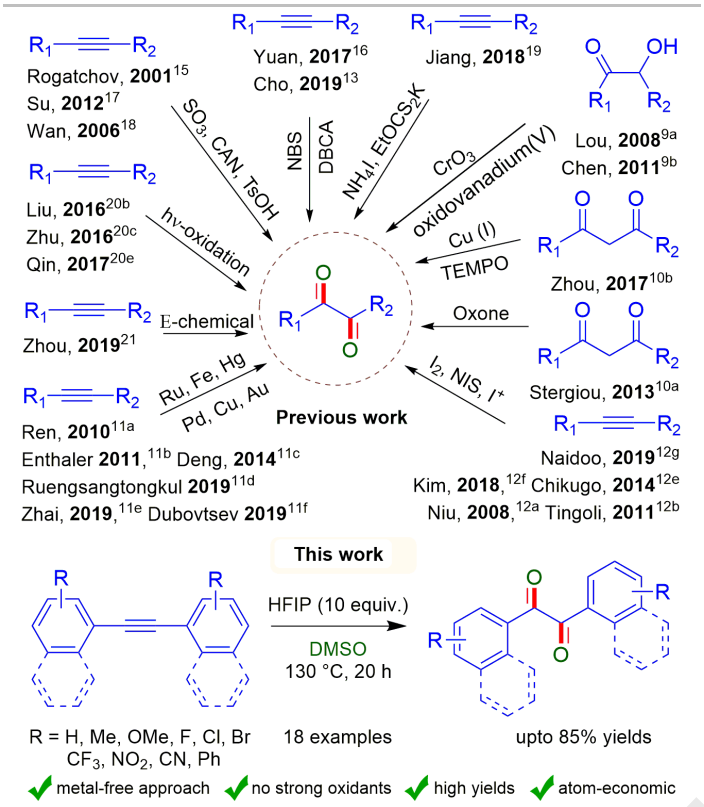
A metal-free and hypervalent iodine free conversion of internal alkynes into 1,2-diketo compounds has been described. The efficacy of the present protocol rely on the use of HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol) as reducing agent of alkynes and DMSO as dihydroxylating agent of olefins to acquire the desired chemical transformations. The obtained 1,2-diketones were further transformed into useful derivatives.

Introduction

The development of efficient protocols towards the synthesis of biologically important intermediates under metal-free conditions has been a topic of interest in industries as well as academia.[1-3] In this sense, chemists around the globe are regularly working on formulating new synthetic strategies to meet the expectations of industries to synthesize these important intermediates. It is evident from the literature that 1,2-diketo compounds play major role in synthesizing broad range of biologically and medicinally important *N*-heterocyclic moieties.[3a-e] In addition, 1,2-diketo compounds found their value as useful precursors for the synthesis of chiral 1,2-diols,[4] *N*-heterocyclic carbenes[5] and α-diimine ligands.[6] These 1,2-diketo compounds, in particular benzils can also be found as naturally occurring Scandione and Calophione A.[7] Benzils are also known for their pharmaceutical activities such as antitumor, antimicrobial, cytotoxic and carboxylesterase inhibition.[8] The well-known synthetic routes to 1,2-diketo compounds includes the oxidation of α-hydroxy ketones,[9] α,β C-C bond cleavage of 1,3-diketones[10] and oxidation of alkynes using metal-catalyzed[11] or metal-free approach.[11-21] Oxidation of alkynes using wide range of iodine species[12] such as I_2, $PhI(OAc)_2$ and NIS as well as in presence of strong oxidants such as dibromoisocyanuric acid,[13] oxone,[14] sulfur trioxide[15] and NBS[16] have received large attention of the synthetic chemist. In addition to above mentioned strategies the photo-oxidation[20] and electrochemical transformation[21] of alkynes came into the lime light to achieve this synthetic transformations. It has been largely accepted that, iodine sources are most suitable for this conversion because of their Lewis acid properties with which they can co-ordinate to alkyne moiety. Synthetic chemists are still investigating a suitable alternate for iodine source for accompanying 1,2-diketo compounds from alkynes (Scheme 1). In view of this, we were successful in exploring HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol) as a befitting replacement for iodine sources in obtaining 1,2-diketo compounds from alkynes. HFIP which is generally known as solvent and in rare cases it was shown that HFIP can act as reducing equivalent to pursue wide range of chemical transformations.[3e,22] The hydrogen bonding interactions of HFIP to assist substrates to undergo chemical alterations makes it versatile organic solvent in synthetic organic chemistry as well as in biochemistry.[23] The chemistry of HFIP mediated reactions have been developed over the past decade to obtain large number of chemical transformations. In this context, we were fascinated to use this unique organic compound to acquire 1,2-diketo compounds from their corresponding internal alkynes in presence DMSO as an oxidant. In addition, obtained 1,2-diketo compounds were subjected to further chemical modifications to achieve quinoxalines and highly substituted carbocyclic derivatives.

We started our proceedings by synthesizing internal alkynes using previously reported methods.[24-25] With an objective of formulating an efficient protocol towards the synthesis of 1,2-diketo compounds from their alkyne precursors in absence of iodine source, we have started experimenting by taking diphenylacetylene (**1a**) as model substrate (Table 1). The reaction of diphenylacetylene (**1a**) was performed in the presence of 30 mol% KI in DMSO at 120 °C for 24 h, which leads to the formation of benzil (**2a**) in 48% yield (Table 1, entry 1). It was found that catalytic amount of iodine sources are capable of giving the desired product **2a** in moderate yields. Next, we focused on the screening of alternate sources for

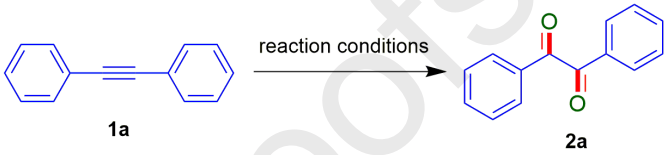
iodi ed thiourea, niacin and 1,10-phenanthroline as potential reagents for the conversion of diphenylacetylene (**1a**) into benzil (**2a**) (Entries 2-5).



Scheme 1. Comparison between previous methods and our report towards synthesis of 1,2-diketo compounds.

Interestingly, all of the screened reagents gave relatively lower yields and maximum yield was observed in case of 30 mol% niacin in DMSO at 120 °C for 48 h (Entry 4). It was observed that these organocatalyst were also efficient enough to bring about the desired chemical transformations but in lower yields. Next, we carried out the reaction of diphenylacetylene (**1a**) in the presence of 30 mol% KI and 5 equiv. HFIP in DMSO at 120 °C for 36 h (Entry 6). Surprisingly, the yield was increased from 48% to 62%, which showed the efficacy of the reaction conditions when a combination of KI and HFIP was used. The reaction yield was further increased to 70% when the reaction was carried out at 130 °C (Entry 7). It was evident from entries 6 and 7 that, HFIP is playing certain role in obtaining the desired product **2a**. To know the role of HFIP, we performed reaction of diphenylacetylene (**1a**) in the presence of 5 equiv. HFIP in DMSO at 120 °C for 36 h, which leading to the formation of benzil (**2a**) in 65% yield (Entry 8). Further, the reaction was carried out with 10 equiv. of HFIP in DMSO at 120 °C for 36 h, which ends up in giving 76% yield (Entry 9). Gratifyingly, maximum reaction yield was obtained on changing the reaction temperature from 120 °C to 130 °C under the identical reaction conditions (Entry 10). The reaction of diphenylacetylene (**1a**) in presence of 10 equiv. HFIP in DMSO at 130 °C for 20 h gave an excellent yield of 82% (Entry 10). To evaluate the role of fluorinated alcohol, we have carried out the reaction of diphenylacetylene (**1a**) in presence of 10 equiv. TFE (2,2,2-Trifluoroethanol) in DMSO at 130 °C for 20 h (Entry 11). Surprisingly, the reaction conditions gave neglesible yield of product **2a**, which assures the necessity of HFIP as hydrogen donor. Further modifications in reaction time and reaction temperature does not result in improved yield of the when the reaction was carried out with different amount of HFIP (Entries 14-15). At last, we were intended to screen the effect of different solvents on the reaction kinetics. For pursuing this purpose, we have screened DMF, DMA, Dioxane and Toluene as solvents along with 10 equiv. HFIP at 130 °C for 20 h (Entries 16-19). Unsatisfactory results were observed when the reaction was carried out in absence of DMSO. To evaluate the role of inert atmospheric conditions, a reaction was carried out using **1a** as substrate under standard reaction conditions in presence of N_2 atmosphere. The reaction conditions responded with an unsatisfactory yield of 21%.[26]

Table 1. Screening of reaction conditions for the synthesis of benzil (**2a**).[a]



Entry	Reaction Conditions (Equiv.)	Solvent	T/t (°C/h)	% Yield 2a[b]
1	KI (0.3)	DMSO	120/36	48
2	KO^{t}Bu (0.5)	DMSO	120/40	<5
3	Thiourea (0.3)	DMSO	120/40	<10[c]
4	Niacin (0.3)	DMSO	120/48	25[c]
5	1,10-Phen (0.3)	DMSO	120/36	20[c]
6	KI (0.3)/ HFIP (5)	DMSO	120/36	62
7	KI (0.3)/ HFIP (5)	DMSO	130/36	70
8	HFIP (5)	DMSO	120/36	65
9	HFIP (10)	DMSO	120/36	76
10	**HFIP (10)**	**DMSO**	**130/20**	**82**
11	TFE (10)	DMSO	130/20	<10[c]
12	HFIP (10)	DMSO	140/20	74
13	HFIP (10)	DMSO	130/30	72
14	HFIP (5)	DMSO	130/20	69
15	HFIP (15)	DMSO	130/20	80
16	HFIP (10)	DMF	130/20	58
17	HFIP (10)	DMA	130/20	42
18	HFIP (10)	Dioxane	130/20	31
19	HFIP (10)	Toluene	130/20	25
20	HFIP (10)	DMSO	130/20	21[d]

[a] All reactions were performed using 1.0 mmol **1a** and Solvent (2 mL) in a sealed tube.

[b] Isolated yields.

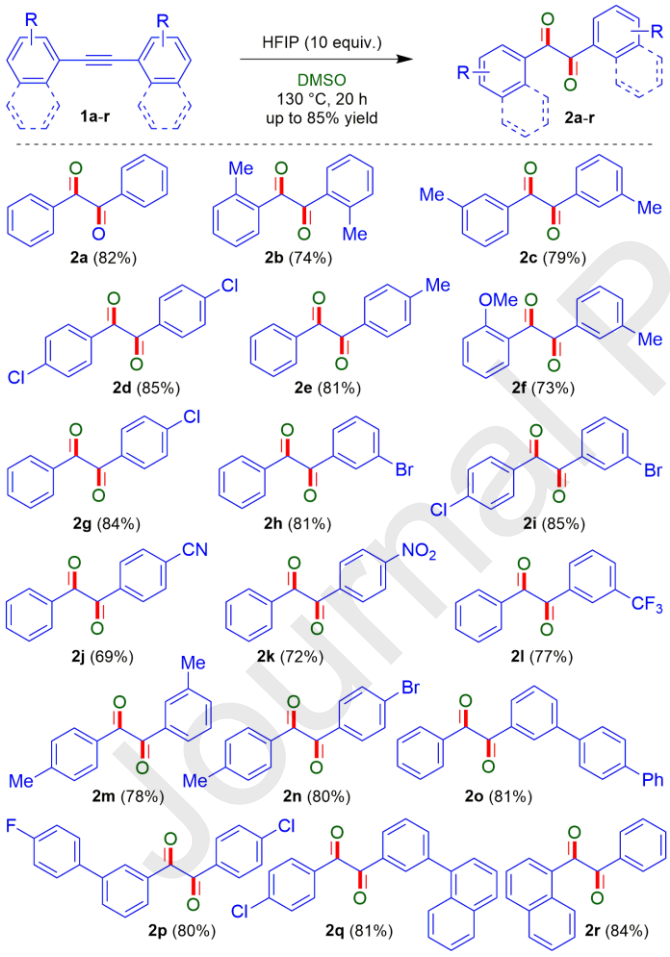
[c] Only 25% conversion into product was observed and remaining SM is recovered.

[d] Reaction was carried out under N_2 atmosphere in a round bottom flask.

After performing an extensive screening of the reaction conditions using diphenylacetylene (**1a**) as model substrate, we envisage highest yield of 82%, when the reaction

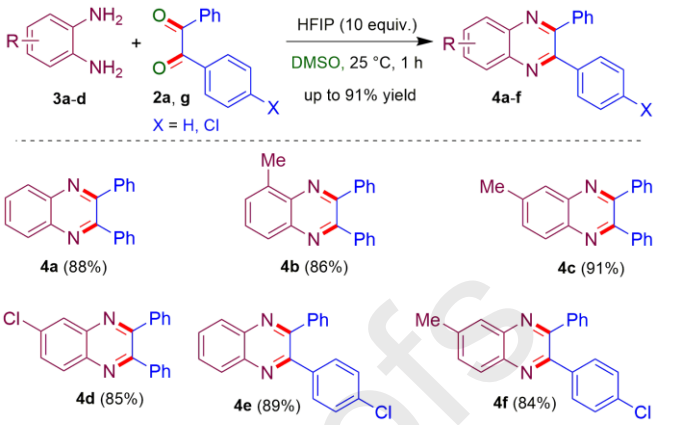
was es (Table 1, entry 10).

With these optimized reaction conditions in hand, we explored wide range of diarylacetylenes **1a-r** consisting of electron donating and electron withdrawing functional groups (Scheme 2). Under the developed reaction conditions, functional groups such as methyl, methoxy, fluoro, chloro, bromo, cyano, nitro and trifluoromethyl were well tolerated to deliver the desired 1,2-diketones **2a-n** in yields ranging from 73-85%. Symmetrical as well as unsymmetrical internal alkynes were reacted satisfactorily to obtain the desired products in moderate to good yields. Under these reaction conditions, diarylacetylenes containing bulkier biphenyl and naphthyl groups were also reacted to deliver the desired products **2o-r** in up to 78% yield. Surprisingly, under the developed reaction conditions aliphatic internal alkynes and terminal aryl alkynes does not participate to furnish the desired products rather starting materials were observed in case of aliphatic internal alkynes and unidentified products were formed in case of terminal alkynes. The reason can be attributed to the reactivity of aliphatic internal alkynes towards HFIP is negligible in comparison to iodine sources.



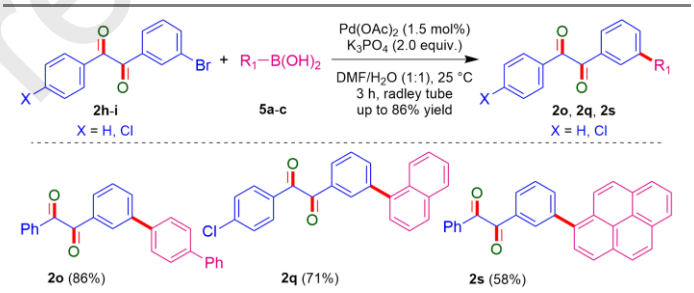
Scheme 2. Scope of HFIP-mediated synthesis of 1,2-diketones.

Next, we indented to explore the applications of these 1,2-diketones in synthesizing structurally useful *N*-heterocycles.[3e] To fulfill this purpose, we have chosen wide range of *o*-phenylenediamines **3a-d** and 1,2-diketones **2a**, **2g** as substrates for synthesizing broad range of 2,3-diaryl quinoxalines **4a-f** *via* one-pot two step protocol. After obtaining 1,2-diketones **2a**, **2g** as primary products, we added *o*-phenylenediamines **3a-d**, and stir the reaction mixture at 25 °C for 1 h to obtain 2,3-diaryl quinoxalines reacted well with good functional group tolerance to deliver desired products in up to 91% yield (Scheme 3).



Scheme 3. Synthesis of quinoxalines from *o*-phenylenediamines and 1,2-diketones.

After accomplishing the synthesis of quinoxalines, we focused on carrying out palladium-catalyzed Suzuki-Miyaura cross-coupling reactions[25] with halogen-substituted 1,2-diketones which leads to higher aromatic rings of 1,2-diketones. We have chosen 1,2-diketones **2h** and **2i** along with aryl boronic acids **5a-c** as model substrates for synthesizing higher analogous 1,2-diketones **2o**, **q**, **s** in good to excellent yields (Scheme 4).

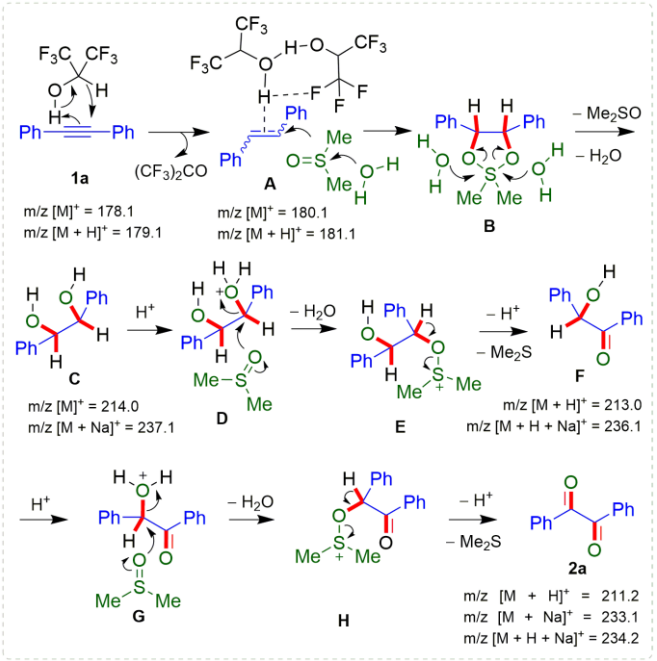


Scheme 4. Synthesis of higher analogous 1,2-diketones.

Having developed the synthetic methods and broad application, we aimed on establishing the plausible reaction mechanism for this described chemical transformation. To gain further insight into the reaction mechanism, we carried out the reaction of diphenylacetylene (**1a**) under standard reaction conditions. The course of the reaction was examined and analyzed by liquid chromatography-mass spectrometry (LC-MS) after an interval of every 5 h.

Based on the spectroscopic data, it was observed that the intermediates **A**, **C** and **F** could be formed during the course of the reaction (details of mass spectra are given in Figure 1, SI). A plausible reaction mechanism was proposed based on the above experimental results and literature evidences.[12g,27] According to proposed mechanism and spectroscopic observation, diphenylacetylene (**1a**) may be reduced to stilbene (**A**) ($[M]^+$ = 180.1, $[M + H]^+$ = 181.1) in presence of HFIP. Next, HFIP assisted dihydroxylation of stilbene (**A**) may take place under the influence of DMSO to form an intermediate **B**. Hydrolysis of the intermediate **B** leads to the formation of 1,2-diol intermediate **C** ($[M]^+$ = 214.1, $[M + Na]^+$ = 237.1), which on oxidation by DMSO gives the benzoin (**F**) ($[M]^+$ = 213.0, $[M + H + Na]^+$ = 236.1). Subsequently, benzoin (**F**) undergoes further oxidation in presence DMSO leading to the formation of benzil (**2a**) ([M

+ H … **1f**, (Scheme 5).



Scheme 5. The postulated mechanism for HFIP-mediated synthesis of 1,2-diketones.

In conclusion, we have proposed a metal-free and iodine free protocol to accomplish 1,2-diketones from their corresponding internal alkynes. The reaction conditions were realized using HFIP as a reducing agent in the presence DMSO as solvent as well as oxidant. The rarely explored protocol towards HFIP mediated reduction of alkynes and DMSO mediated dihydroxylation of olefins were described. The reaction conditions were executed on a broad range of internal alkynes to obtain 1,2-diketones in moderate to good yields. In addition, we have also carried out the further transformations of 1,2-diketones into structurally important 2,3-diaryl quinoxalines and the higher analog of 1,2-diketones. A plausible reaction mechanism was drawn based on mass-spectroscopic investigations.

Acknowledgments

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Supplementary Material

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

Experimental Section

1h-r were prepared using previously reported methods[24-25] and all other 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 carried in an oven-dried glassware with magnetic stirring. The reactions were performed in pressure tube purchased from Sigma-Aldrich glassware. 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 LC-MS are recorded in APCI method in acetonitrile solvent. ^{1}H (^{13}C) NMR spectra were recorded at 600 (150) 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 1,2-Diketones 2a-r using Diarylacetylenes 1a-r: A 10 mL reaction vial was charged with internal alkynes **1a-r** (1.0 mmol), HFIP (10.0 mmol) and DMSO (2 mL)**.** The reaction vial was then sealed and heated at 130 ℃ for 20 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 9:1), 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 = 9:1 as an eluent to obtain the desired 1,2-diketones **2a-r** in high isolated yields.

Benzil (2a)[10b]: **Yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 101-102 ℃ (Lit[10b] 100-101 ℃); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.96 (d, ^{3}J = 7.6 Hz, 4H; 3-H), 7.64 (t, ^{3}J = 7.2 Hz, 2H; 5-H), 7.50 (t, ^{3}J = 7.6 Hz, 4H; 4-H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 193.41 (C-1), 133.73 (C-5), 131.85 (C-2), 128.74 (C-4), 127.87 (C-3) ppm; **HRMS** (EI-QTOF, $[M + H]^+$): calculated for $C_{14}H_{11}O$: 211.0759; found: 211.0747.

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26. It was observed during the reaction process that HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol) is getting evaporated and the reaction vial become dry. It is believed that, the necessity of sealed tube arises because of lower boiling point of HFIP (b.p 58.2 ℃) and not because of DMSO (b.p. 189 ℃) solvent. It is also believed that N_2 atmosphere is not facilitating the reaction of HFIP as a hydrogen donor.
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- DMSO as Dihydroxylating Agent.
- Conversion of internal Alkynes into 1,2-Diketones.
- A metal-free and hypervalent iodine free phenomenon.
- Broad substrate scope with high yields of the products.

Conversion of Alkynes into 1,2-Diketones using HFIP as Sacrificial Hydrogen Donor and DMSO as Dihydroxylating Agent

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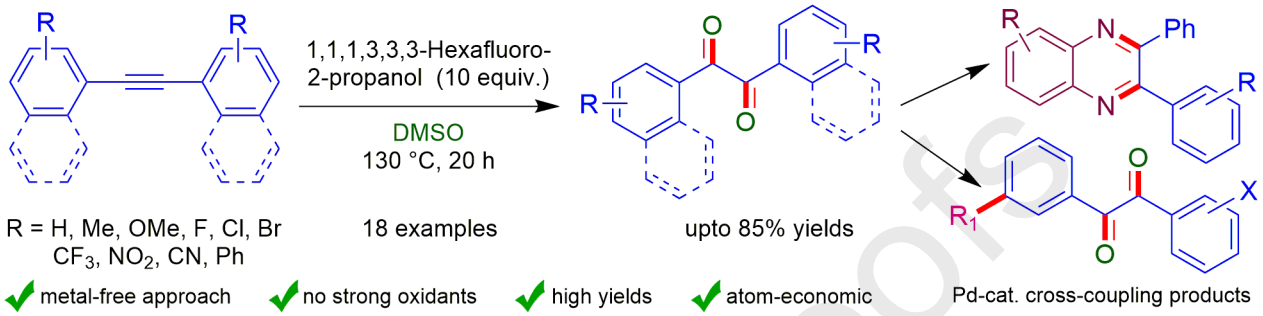

R = H, Me, OMe, F, Cl, Br
CF_3, NO_2, CN, Ph

18 examples

upto 85% yields

Pd-cat. cross-coupling products

✔ metal-free approach ✔ no strong oxidants ✔ high yields ✔ atom-economic