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One-pot transition metal-free synthesis of alkynes and enynes

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SUMMARY

Alkynes are key motifs in chemistry, serving as precursors in many organic reactions toward the synthesis of bioactive compounds, polymers and new materials. Methods to synthesize terminal alkynes with extension of the carbon skeleton involve harsh and/or dangerous reagents. Further derivatization of terminal alkynes to diaryl alkynes largely relies on the popular Sonogashira coupling. This cross-coupling uses expensive Pd catalysts, phosphine ligand, and toxic Cu co-catalysts. Herein is introduced a one-pot approach to diaryl alkynes under transition metal-free conditions from feedstock chemicals (toluenes and methyl benzoates). This approach is also applicable to the preparation of conjugated 1,3-enynes in a single flask. The disclosed methods are expected to be complementary to the state-of-the-art by streamlining the synthesis of alkynes, reducing the costs of production of these valuable building blocks, and increasing the sustainability of the synthesis of alkynes.

Keywords: Alkynes, diaryl acetylenes, enynes, elimination reactions, toluene deprotonation, cation-pi interactions, silyl amide bases, cesium, petroleum feedstocks

INTRODUCTION

Alkynes are among the most synthetically valuable building blocks,[1] finding use in a myriad of applications including materials science,[2-4] liquid crystals,[5] and conducting polymers[6] among others. They have found ample use in drug discovery for pursuing diverse therapeutic targets,[7] are recognized as privileged scaffolds, and found in 6 of the top 200 selling small molecule medications in 2022.[8]

Among alkynes, 1,2-diaryl alkynes are present in biologically active substances[9] exhibiting a range of activities, including antiproliferative agents,[10] anti-inflammatory cyclooxygenase-2 inhibitors,[11] follicle-stimulating hormone receptor antagonists,[12] anxiolytic neurokinin NK-1 and NK-2 receptor modulators[13] and metabotropic glutamate receptor antagonist with anxiolytic activity.[14,15] There are several FDA approved or fast-tracked 1,2-diaryl alkyne-based medications, including Trazarotene,[16] Olverembatinib[17] Ponatinib[18], Futibatinib,[19] and Eganelisib[20].

While members of the class of 1,2-diaryl alkynes are known to exhibit diverse biological activities,[7] their highest value stems from their applications in synthesis. 1,2-Diaryl alkynes are valued precursors in many annulation reactions,[21-29] including the Larock indole synthesis,[30,31] Fürstner's Pt-catalyzed benzofuran synthesis,[32] C–H functionalization strategies such as Fagnou's indole synthesis,[33] and recently the Nobel Prize winning azide-alkyne cycloaddition reaction.[34]

THE BIGGER PICTURE

Diaryl alkynes and enynes are foundational building-blocks in synthetic chemistry, finding applications in many annulation reactions, polymer syntheses and the preparation of materials. The state-of-the-art methods to prepare them are laborious multi-step processes that rely on harsh reagents (Corey-Fuches), cryogenic temperatures, dangerous precursors (Bestmann-Ohira) and/or precious metal catalysts (Sonogashira). One-pot approaches to the *transition metal-free* synthesis of diaryl alkynes and enynes can have a dramatic impact on synthetic chemistry.

Herein, diaryl alkynes are prepared from petroleum feedstocks Ar–CH_3 and Ar'CO_2Me under basic conditions. Enynes are generated in one pot from allyl benzenes and methyl benzoates. Compared to existing name reactions, both syntheses are more sustainable, more economical, and more synthetically efficient.

The synthesis of 1,2-diaryl alkynes from non-alkyne precursors is known, but methods to make them are cumbersome and suffer in terms of efficiency and sustainability. By far, the most common method to prepare 1,2-diaryl alkynes is the palladium/copper co-catalyzed Sonogashira reaction of terminal alkynes (Figure 1A).[35] Despite the immense popularity of the classic Sonogashira cross-coupling, it leaves room for improvement, including the high cost of Pd catalyst and many phosphine ligands, the toxicity of copper salts, and difficulties in separating Pd and phosphine ligand-derived byproducts from active pharmaceutical ingredients (APIs).[36,37]

The substrates for the Sonogashira cross-coupling reactions are terminal alkynes, which are synthesized by two popular strategies. The first is formation of the $C\equiv C$ bond from isolated reagents, like the Corey-Fuchs[38,39] (Figure 1B) or Bestmann–Ohira reaction (Figure 1C).[40] Downsides of the Corey-Fuchs are the harsh reagents (*n*-BuLi or LDA) and two step procedure (often with purification of the 1,1-dibromoalkene intermediate). Preparation of the Bestmann–Ohira reagent is done *in-situ* with azides. While warnings about explosive azides in the preparation of the Bestmann-Ohira reagent have been described, attempts have been made to employ less dangerous azide transfer reagents.[41]

The second class of terminal alkyne syntheses employ elimination processes.[42-46] Synthesis of alkynes from methyl ketones by deprotonation to form the enolate, enolate capture using an electrophile followed by an elimination under basic conditions (Figure 1D). Sample electrophiles include $ClP(O)(OMe)_2$, $PhN(Tf)_2$, and Nf–F (Nf = $SO_2CF_2CF_2CF_2CF_3$).[47-51] These reactions are functional group interconversions and do not extend the carbon framework.

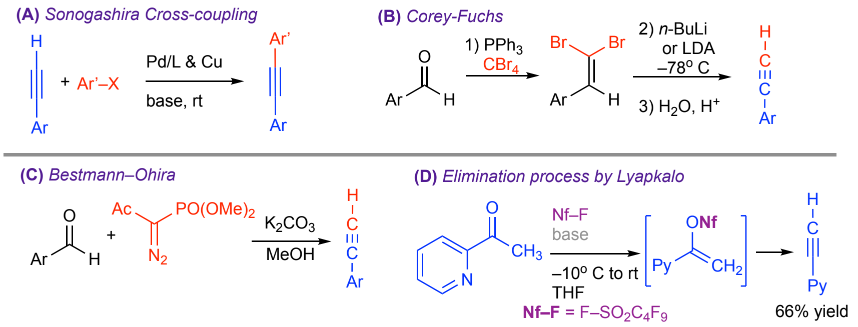


Figure 1. Methods to synthesize alkynes.
(A) Sonogashira Cross-coupling reaction
(B) Corey-Fuchs reaction
(C) Bestmann-Ohira reaction
(D) Elimination process by Lyapkalo

One pot methods for the synthesis of alkynes have also been introduced. For example, the Bestmann–Ohira reagent can be used to make 1,2-diaryl alkynes directly from benzophenones (Figure 2A). Otera's group introduced a method to make 1,2-diaryl alkynes that involves a double elimination strategy beginning from benzylic sulfones (Figure 2B).[52] Deprotonation of the benzylic sulfone at –78 °C with *n*-BuLi, addition of aldehydes and trapping the resultant alkoxides with an electrophile, like TMS-Cl, is followed by elimination with 10 equiv KO^tBu or 5 equiv LDA.[52,53] This method has broad scope, but uses excessive amounts of base, employs cryogenic temperatures that are difficult to achieve on scale and has not gained the traction of the two-step methods in Figure 1A–D. Recently, Liu and co-workers reported the development of a modular synthesis of alkynes through reaction of esters with lithiated gem-diborylalkanes and aryl trifimides [4-CF_3-C_6F_4-N($Tf)_2$] (Figure 2C). This method is excellent for the synthesis of a host of ^{13}C labelled alkynes. Applications on scale, however, would be costly and limited by the need to synthesize the lithiated (bis-Bpin) nucleophiles and the triflating agent, which are not commercially available.[54] Finally, in 2015 we introduced the first catalytic method to make all three bonds of the alkyne from isolated materials (Figure 2D).[55] The reaction entails the sulfenate anion ($PhSO^{\ominus}$) catalyzed coupling of benzyl chlorides with benzaldehydes in the presence of KO^{t}Bu. This procedure has not attracted significant use, because it requires slow addition of benzyl chloride and a sulfoxide pre-catalyst that is not commercially available.

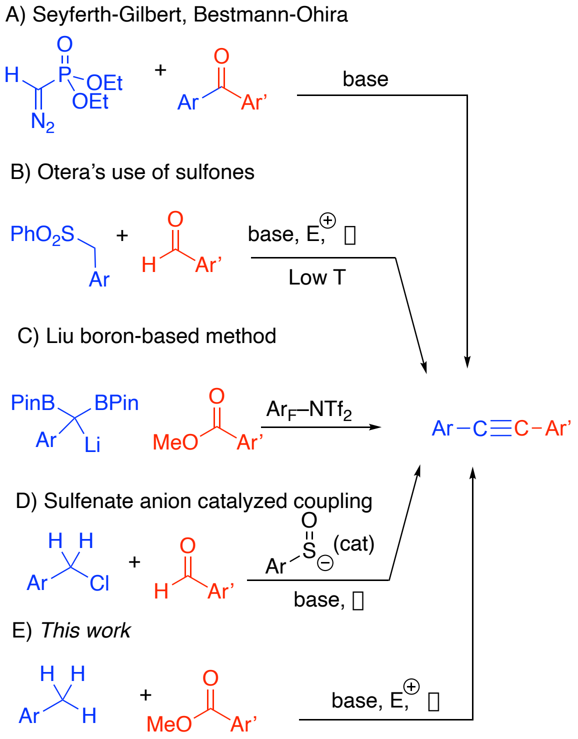


Figure 2. One-pot alkyne (a-d) syntheses. A new approach to alkynes from petroleum feedstocks (this work, e)

Our team has a long-standing interest in employing weakly acidic pro-nucleophiles under basic conditions in C–C bond-forming reactions.[56-66] Many others have made important contributions to this area as well.[67] Our work culminated in the demonstration that $MN(SiMe_3)_2$ (M=Li, Na, K) bases could reversibly deprotonate even *toluene and its derivatives*,[68,69] despite their high pK_a values (43 in DMSO[70]). The capacity of metal silylamide bases to deprotonate toluene derivatives was partially attributed to the formation of cation-pi interactions.[68] We subsequently developed an amino benzylation of aldehydes from toluenes[69] and an indole synthesis based on reversible deprotonation of 2-fluoro toluenes.[71] A key finding of these works was the beneficial impact of Cs^+ salts, which led to a dramatic increase in yields. We hypothesized that the Cs^+ salts react with $MN(SiMe_3)_2$ (M = Na, Li) to produce $CsN(SiMe_3)_2$ or related species. We demonstrated that non-enolizable esters are viable electrophiles for mono-addition of benzyl organometallics derived from toluenes. The ketone intermediate is deprotonated faster than it undergoes a second benzyl addition, giving an enolate that yields ketone upon workup (Figure 3). A similar reaction was subsequently published by the Gandhi group.[72] Guan and co-workers nicely demonstrated that LDA (H−N*i*Pr_2 pKa=36 in THF[73]) could mediate the benzylic aroylation of toluene and $ArCONiPr_2$, to give 2-aryl acetophenones in good yields.[74]

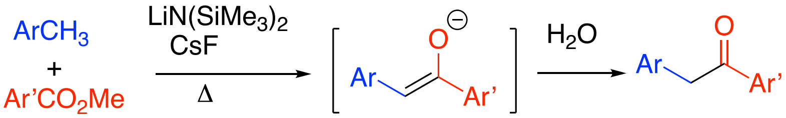


Figure 3. Aroylation of toluenes with $LiN(SiMe_3)_2$, CsF.

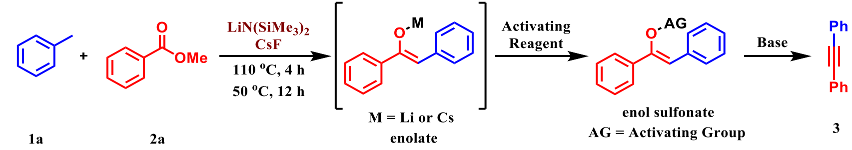
We rationalized that the enolate intermediate in Figure 3 could be a precursor to 1,2-diaryl alkynes, providing a one-pot synthesis of these valuable building blocks. Herein we present the achievement of a one-pot synthesis of 1,2-diaryl alkynes from readily available methyl benzoates and toluene derivatives under basic conditions with the help of perfluorobutanesulfonyl fluoride (Nf–F) or TBS–Cl. The advantage of this one-pot approach to 1,2-diaryl alkynes over the existing methods in Figure 1 are 1) increased synthetic efficiency, 2) reduction in the harshness of reagents, 3) avoidance of cryogenic temperatures, and 4) circumvention of transition metals, costly ligands, and the need to remove these materials from the desired products. This approach is also applied to a one-pot synthesis of enynes.

RESULTS

Building on the discovery that $LiN(SiMe_3)_2$/CsF is effective in the deprotonation of the benzylic position of toluene derivatives in the aroylation (Figure 3), we aimed to trap the enolate intermediate (Table 1) to set up an E2 elimination to form 1,2-diaryl alkynes (**3**). The procedure involves first heating the Cs^+ salt with $LiN(SiMe_3)_2$ at 110 °C with the toluene derivative, most likely to generate either $CsN(SiMe_3)_2$ or mixed metal amides such as $CsLi[N(SiMe_3)_2]_2$.[75] Next, the methyl benzoate is added at 50 °C, trapping the benzylic organometallic by forming the C–C bond. Because the concentration of the benzylic organometallic is likely very low, the ketone is deprotonated by the silyl amide base to form the enolate (identified by ^1H and ^{13}C NMR), which is trapped by the activating agent.[76] We first tested silyl groups as activating agents. We envisioned the possibility that the trimethylsilyl group of the silyl amide base might migrate to the enolate oxygen to form a silyl enol ether, but no product was detected (entry 1). Using TMS–Cl, TES–Cl or TBDPS–Cl in the presence of NEt_3 or NaI also failed to provide more than trace products (entries 2–4), highlighting the challenging nature of the activation-elimination steps. The silyl group *tert*-butyldimethylsilyl (TBS) is more resistant to the basic conditions than TMS–Cl or TES–Cl and generated 42% isolated yield when 3 equiv $LiN(SiMe_3)_2$ was used (entry 5). A higher yield of alkyne **3**, 84%, was obtained with 4.9 equiv $LiN(SiMe_3)_2$ (entry 6), suggesting that the elimination of the *tert*-butyldimethylsilyl ether is initiated by the silyl amide base.

As a complementary approach, we envisioned facilitating the E2 reaction by using a more active leaving group. Several electrophiles have been used to convert ketones to alkynes, including $ClP(O)(OMe)_2$, $PhN(Tf)_2$, and Nf–F (Nf = $SO_2CF_2CF_2CF_2CF_3$).[47-50] Use of isolated vinyl triflate is exemplified by the work of Mori, where the enol triflate was generated at –80 °C with LDA.[51] Such conditions, however, are inconvenient and incompatible with the development of practical methods. We tested different electrophiles, including Ts–Cl, Ts_2O and Ts–F, which were added to the *in-situ* formed enolate at 0 °C (see Table S1). We observed the formation of the activated enolate from tosyl anhydride and tosyl fluoride. Unfortunately, the conversion from the activated sulfonate ester to the desired product was low, possibly due to the attack of the silyl amide base at sulfur. Inspired by Lyapkalo's synthesis of terminal alkynes (Figure 1D), we used perfluorobutanesulfonyl fluoride (Nf–F) to trap the enolate. As outlined in Reissig's review,[77] Nf–F is less costly than other sulfonating agents. A 90% yield of Nf sulfonate ester was detected by ^{1}H NMR but the yield of alkyne was only 50% (entry 7). To improve the elimination of Nf–$O^{\ominus}$, different bases and loadings were examined. Increasing the silyl amide loading and removing or changing the cesium additive did not increase product formation (entries 8–9, with other conditions listed in ESI Table S1). Adding NEt_3 to the sulfonated enolate did not facilitate the elimination (entry 10), whereas the addition of DBU, increased the yield of product to 94% (entry 11). We then investigated the role of DBU in the reaction by lowering the loading of silyl amide base from 3 to 2 equiv (entry 12). No significant decrease in product yield was observed. The result suggests that 2 equiv of $LiN(SiMe_3)_2$ is sufficient to form the enolate and one equiv of DBU is required for the elimination. Thus, two sets of optimized conditions using Nf–F and TBS–Cl were carried forward to explore the substrate scope.

Table 1. Reaction optimization



Entry	Base (equiv)	Additive (equiv)	Activating Reagent (equiv)	Other Reagents (equiv)	**3** IY (%)
1	$LiN(SiMe_3)_2$ (3)	CsF (2)	-	-	NP
2	$LiN(SiMe_3)_2$ (3)	CsF (2)	TMS–Cl (1.3)	NEt_3 (1.5) NaI (1.4)	NP
3	$LiN(SiMe_3)_2$ (3)	CsF (2)	TES–Cl (1.6)	-	Trace
4	$LiN(SiMe_3)_2$ (3)	CsF (2)	TBDPS–Cl (1.3)	NEt_3 (1.5) NaI (1.4)	NP
5	$LiN(SiMe_3)_2$ (3)	CsF (2)	TBS–Cl (1.6)	-	42
6	$LiN(SiMe_3)_2$ (4.9)	CsF (2.6)	TBS–Cl (1.05)	-	84
7	$LiN(SiMe_3)_2$ (3)	CsF (2)	Nf–F (1.6)	-	50

8	$LiN(SiMe_3)_2$ (3)	-	Nf–F (1.6)	-	NP
9	$LiN(SiMe_3)_2$ (5)	CsF (2)	Nf–F (1.6)	-	28
10	$LiN(SiMe_3)_2$ (3)	CsF (2)	Nf–F (1.6)	NEt_3 (1)	Trace
11	$LiN(SiMe_3)_2$ (3)	CsF (2)	Nf–F (1.6)	DBU (1)	94
12	$LiN(SiMe_3)_2$ (2)	CsF (1.3)	Nf–F (1.6)	DBU (1)	91

[a] Reactions conducted under nitrogen on 0.1 mmol scale.

[b] Assay yield determined by GC integration with *n*-tetradecane as an internal standard.

With the optimized conditions in hand, we explored the 1,2-diaryl alkyne synthesis using the Nf–F and TBS–Cl activators. We examined the scope using toluene with a wide range of methyl benzoate derivatives (Figure 4). In all cases, use of Nf–F gave higher yields than with TBS–Cl. Thus, only the results with Nf–F are outlined in the text, with the yields with TBS–Cl presented in Figure 4 for comparison and highlighted in teal. Methyl benzoate had excellent conversion efficiency under the standard reaction conditions with Nf–F and provided the desired product **3aa** in 94% isolated yield. Methyl benzoate derivatives containing various alkyl substituents, such as 3-Me, 4-^{t}Bu, 4-^{i}Pr, and 3,5-$(CH_3)_2$, provided the corresponding target products **3ab**–**3ae** in 76–90% yields. Methyl benzoates containing electron-donating substituents, such as 2-OMe, 4-OMe, and 4-OPh, gave the alkyne products **3af**, **3ag**, and **3ah** in 48%, 78%, and 90% yields, respectively. Esters bearing electron-withdrawing groups, such as 3-NMe_2, 3-OPh, 3-OMe, 3-OCF_3, 3-CF_3, and 3,5-$(OMe)_2$, provided the corresponding products **3ai**–**3an** in 75–92% yields. Various halogenated methyl benzoates, such as 4-F, 4-Cl, 4-Br, 2-Cl, had good to excellent reactivity and provided the target products **3ao**–**3at** in 65–90% yields. Surprisingly, a methyl benzoate containing a 4-cyano group, which is susceptible to nucleophilic attack by silyl amide bases, provided the target product **3au** in 62% yield. Methyl 4-phenylbenzoate, reacted with toluene to yield the product **3av** in 86% yield. π-Extended ester **1w** generated **3aw** in 80% yield. Various ester derivatives containing heterocycles, such as pyridine, quinoline, 1,3-dioxolan and N-methylpyrrole were suitable substrates and furnished the alkyne products **3ax**–**3azb** in 40–76% yields. Finally, diynes are important precursors to a variety of polycyclic aromatic hydrocarbons and have a wide range of applications in organic synthesis and materials. Use of dimethyl isophthalate provided the desired diyne product **3azc** in 80% yield.

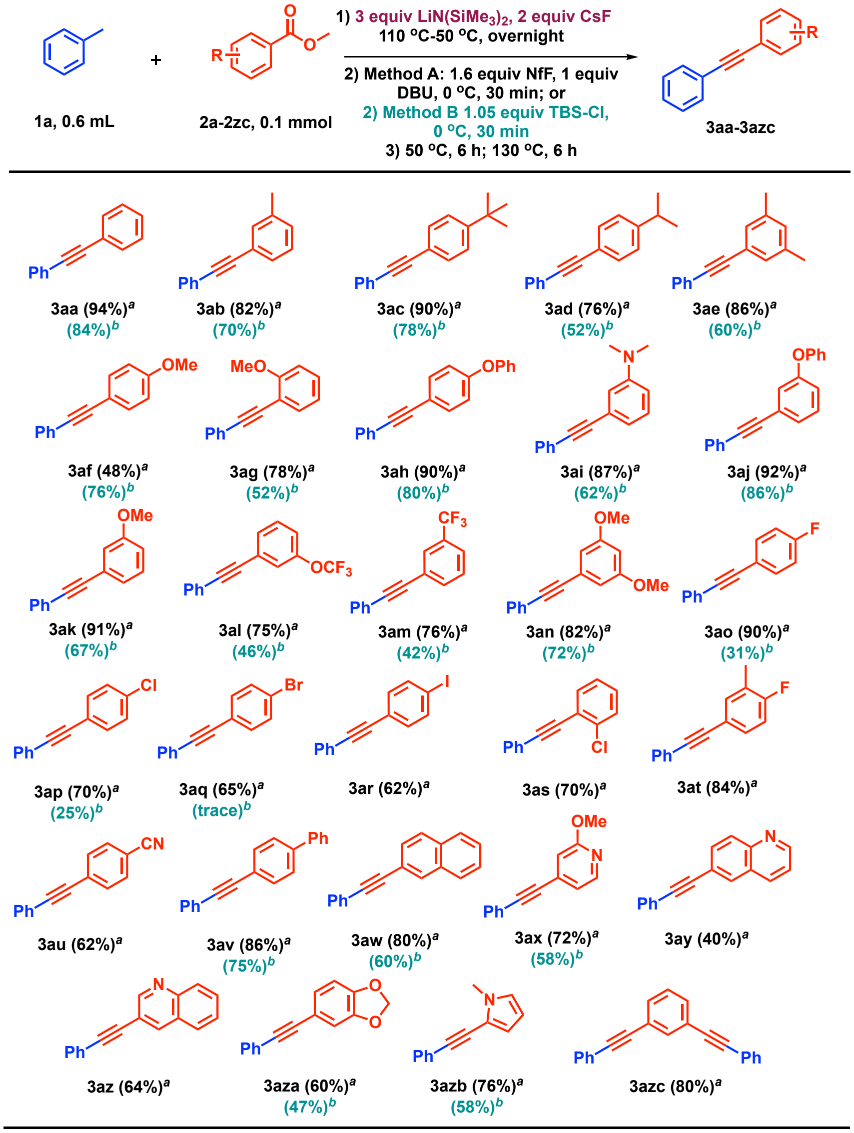


Figure 4. Substrate Scope of Methyl Benzoates (Yields with TBS–Cl in Teil)

[a]Reactions conducted under argon on 0.1 mmol scale with 0.6 mL toluene, 3 equiv LiN(SiMe$_3$)$_2$, 2 equiv CsF, at 110 °C, for 4 h, then cooling to 50 °C, addition of **2a** (0.1 mmol) and stirring for 4 h; cooling to 0 °C, addition of 1.6 equiv Nf–F and 1 equiv DBU for 30 min then heating at 50 °C for 6 h and 130 °C for 6 h.

[b]Reactions conducted under argon on 0.1 mmol scale, 0.6 mL toluene, 3 equiv LiN(SiMe$_3$)$_2$, 2 equiv CsF, 110 °C for 4 h, then addition of 2 (0.1 mmol) at 50 °C for 4 h; addition of 1.05 equiv TBS-Cl at 50 °C for 6 h then heating to 130 °C for 6 h.

Next, a series of toluene derivatives were investigated for compatibility with the standard method employing Nf–F (Figure 4). Polymethyl substituted toluene derivatives, such as p-xylene, m-xylene, o-xylene and mesitylene, showed good reactivity, providing 75–90% isolated yields (**3ba**, **3ab**, **3ca** and **3ae**). Electron-withdrawing groups on the toluene, such as 3-OMe, 3-OMe-4-Me and 3-CF$_3$, generated target products **3ak**, **3da**, and **3am** in 64–88% yields. Under the standard conditions substrates bearing halogens, provided the target products with poor yields. Therefore, we reoptimized to ensure compatibility with these substrates. The modified conditions involved 0.5 mL 2-MeTHF, 3 equiv of $LiN(SiMe_3)_2$ and 2 equiv of CsF at 110 °C for 4 h, while other conditions remain unchanged. Under the revised conditions, the yields of such substrates were significantly improved, giving the desired products **3ea–3ha, 3as and 3ap-3aq** in 62–90% yields. Similarly, we were intrigued to know how the increased acidity of benzylic methyl groups on pyridine and quinoline heterocyclic substrates would impact our method. In the event, 3 equiv of these substrates sufficed, providing the corresponding products **3ia–3la**, **3ax–3ay**, **3ma**, **3if–3kf**, **3mf** and **3jv** in 62–89% yields. It is noteworthy these substrates required additional Nf–F (3 equiv) for maximum yields (see Figure 4 footnote *d*).

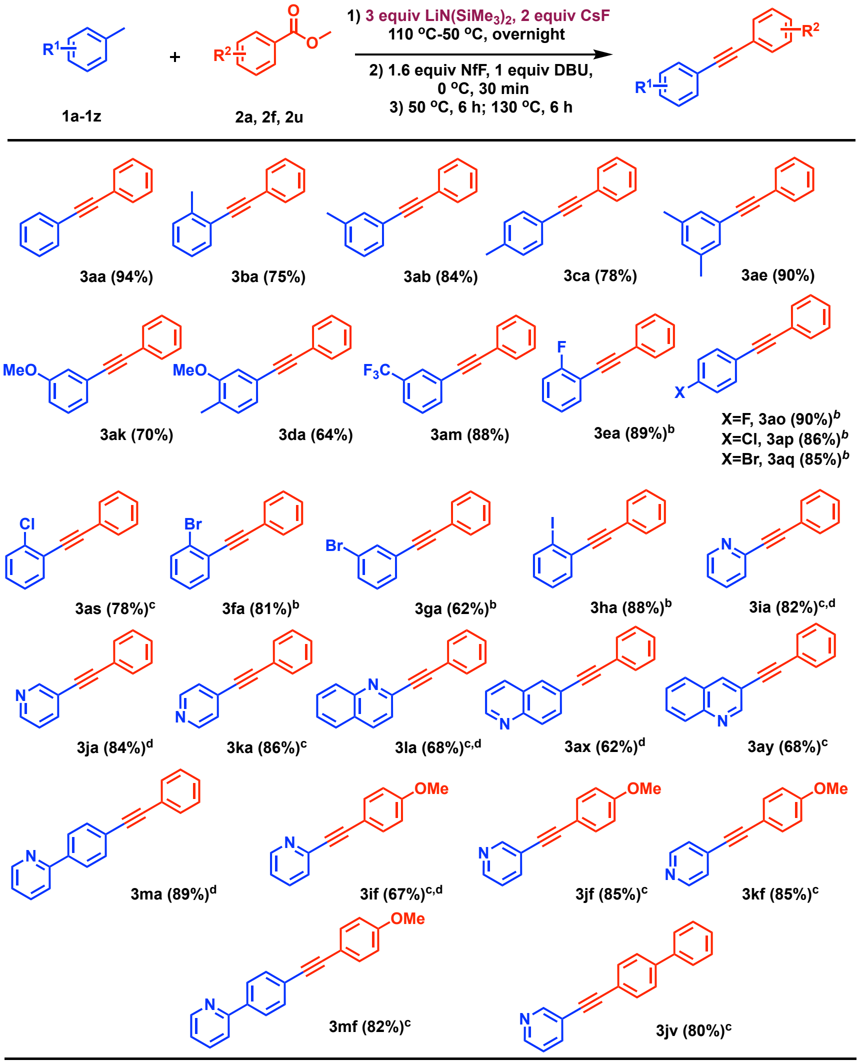
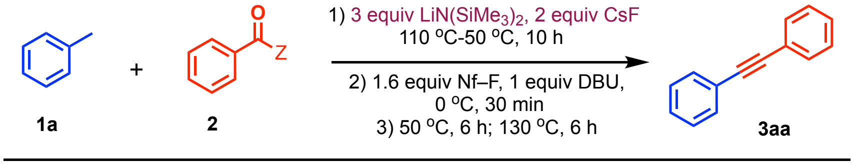


Figure 4. Substrate Scope of Toluene Derivatives

[a] Reactions conducted under argon on 0.1 mmol scale, 0.6 mL toluene, 3 equiv $LiN(SiMe_3)_2$, 2 equiv CsF, 110 °C, and 4 h, then add **2a** (0.1 mmol), 50 °C, and 4 h; add 1.6 equiv Nf-F and 1 equiv DBU, 0 °C, 30 min; 50 °C, 6 h; 130 °C, 6 h.

[b] 0.3 mL toluene derivative in 0.5 mL 2Me-THF.
[c] 3 equiv toluene derivative in 0.5 mL 2Me-THF.
[d] 3 equiv Nf-F.

To expand the substrates scope and the method generality, we explored various esters and amides (Figure 5). Ethyl benzoate also reacted smoothly, providing the desired product **3aa** in 90% yield. For esters with greater steric protection about the carbonyl group, such as *tert*-butyl benzoate, the target product was obtained in yield 71%. The phenyl ester, however, exhibited 28%, likely due to its increased reactivity. For amide substrates, the *N*,*N*-dimethyl benzamide was not compatible with our standard conditions. Interestingly, the Weinreb amide derived from benzoic acid was an excellent substrate and firnished the target product with 88% yield.



Z = OEt, 90% yield
Z = O^{t}Bu, 71% yield
Z = OPh, 28% yield
Z = NMe$_2$, trace
Z = N(OMe)Me, 88% yield

Figure 5. Synthesis of alkynes using various esters and amides.

[a] Reactions conducted under argon on 0.1 mmol scale, 0.6 mL toluene, 3 equiv LiN(SiMe$_3$)$_2$, 2 equiv CsF, 110 °C, and 4 h, then add **2** (0.1 mmol), 50 °C, and 4 h; add 1.6 equiv Nf-F and 1 equiv DBU, 0 °C, 30 min; 50 °C, 6 h; 130 °C, 6 h.

We next examined the scalability of a series of substrates (Figure 6). A 7 mmol scale reaction with the model substrates toluene (**1a**) and methyl benzoate (**2a**) gave a 92% isolated yield of 3aa (1.15 g, Figure 6A) with no palladium, ligands or copper added. Likewise, in the case of **3ao** containing a 4-F group the product was formed in 88% yield (1.21 g, Figure 6B). Pyridines are among the most useful heterocycles in medicinal chemistry. Here, because 4-methylpyridine is valuable, the reaction was conducted with 3 equiv of the heterocycle in 2-MeTHF (35 mL). The pyridyl-containing alkyne **3ka** was obtained on a 7.0 mmol scale reaction in 80% yield (1.0 g, Figure 6C).

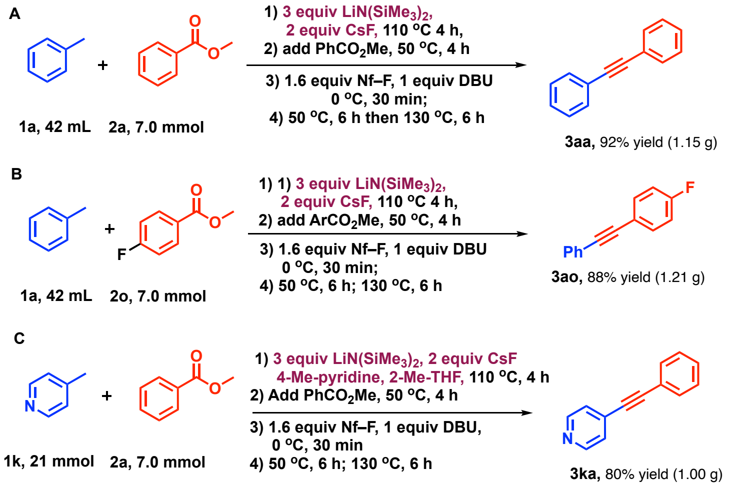


Figure 6. Scale up reactions to 7.0 mmol for the synthesis of 3aa, 3ao, and 3ka (for additional details see the ESI)

We next performed a few additional reactions to demonstrate the applicability of our method to isotopically labelled compounds and tandem reactions. Given the low cost of toluene-d$_8$, it is an excellent substrate for preparing diphenylacetylene-d$_5$ (Figure 7A). Thus, use of toluene-d$_8$ under the standard conditions provided diphenylacetylene-d$_5$ (**3aa-d$_5$**) in 85% yield. We envisioned that use of methyl 2-mercaptobenzoate in the alkyne synthesis would afford an alkyne that would undergo cyclization to provide benzothiophene (Figure 7B). Use of 4-methylpyridine as the pro-nucleophile under standard conditions resulted in only 30% AY when Nf–F was used as the activating group. Switching to Cl–P(O)Ph$_2$, however, provided the benzothiophene in 98% yield.

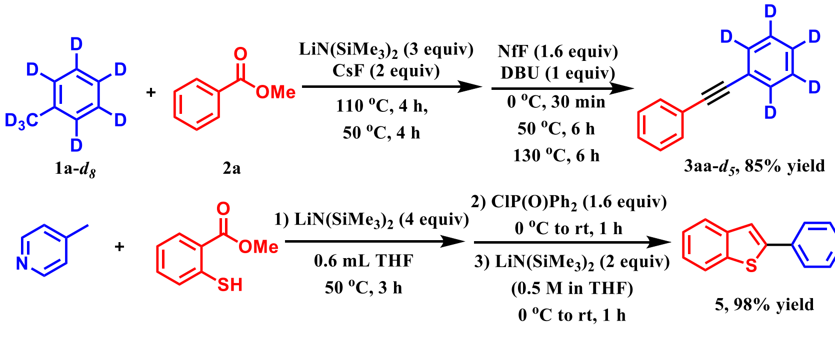


Figure 7. Reaction with Toluene-d$_8$ and tandem reaction to prepare benzothiofuran. (for additional details see the ESI)

We were curious of we could extend our method to synthesize alkynes to a one-pot synthesis of enynes, which have broad utility in synthesis. We previously demonstrated the deprotonation of allyl benzene with silylamide bases and arylation at the benzylic position under Pd-catalysis.[78] Schneider's team subsequently demonstrated the deprotonation of allyl benzenes and addition of the terminal allyl anion to imines to provide efficient access to allylic amines,[79] which was followed by the amino allylation of aldehydes.[80] Therefore, we employed allylbenzene and methyl benzoate under our alkyne-forming conditions. As shown in Figure 8, allyl benzene provided the product **4aa** in 86% isolated yield. Allylbenzene derivatives containing substituents, such as Me, ^{t}Bu, Ph, F and Cl, provided the desired products **4ba**–**4ia** in 48–82% yields. This method represents the most efficient method for the synthesis of these valuable unsaturated compounds under transition metal free conditions.

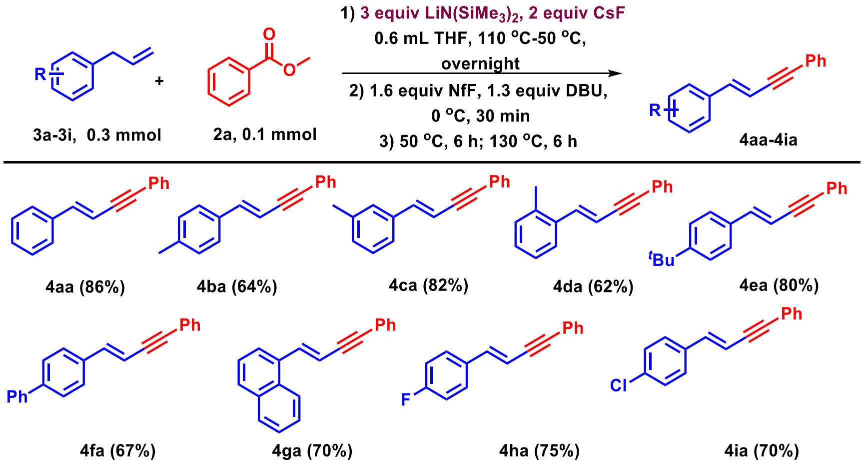


Figure 8. Scope of allyl benzenes in the synthesis of enynes

^{a}Reactions conducted under argon on 0.1 mmol scale, 0.3 mmol allylbenzene (**3**), 0.6 mL THF, 3 equiv $LiN(SiMe_3)_2$, 2 equiv CsF with heating to 110 °C for 4 h, then addition of **2a** (0.1 mmol) at 50 °C and stirring for 4 h and addition 1.6 equiv Nf-F and 1 equiv DBU at 0 °C for 30 min then heating at 50 °C for 6 h and 130 °C for 6 h.

To gain insight into this alkyne formation, we set out to isolate and identify intermediates and examine their reactivity (Figure 9). We expected toluene to undergo reversible deprotonation and react with methyl 4-fluorobenzoate, generating the enolate that is captured upon addition of Nf–F to form intermediate **C**. In the event, we were able to isolate intermediate **C** in 90% yield (Figure 9A). The geometry of this intermediate was determined to be syn based on NOE experiments (See ESI, Figures S114–116 for details). Intermediate **C** was treated with $LiN(SiMe_3)_2$/CsF, affording the alkyne **3ao** in only 30% yield (Figure 9B). In contrast, when intermediate **C** was treated with DBU the alkyne product was formed in 95% (Figure 9C). These results indicate that both DBU and $LiN(SiMe_3)_2$/CsF can complete the elimination process of **C**, but the efficiency of DBU is much higher. This result is consistent with the observation in the optimization, where use of DBU as additive afforded higher yields than excess $LiN(SiMe_3)_2$ (Table 1, entries 11 and 12 vs. 7). The decreased yields with excess $LiN(SiMe_3)_2$ is proposed to be due to attack of the base at the sulfur center of the sulfonated enolate, cleaving the O–S bond and ultimately forming 2-phenylethanones. Indeed, the 2-phenylethanone was recovered in 60% yield in Figure 9B.

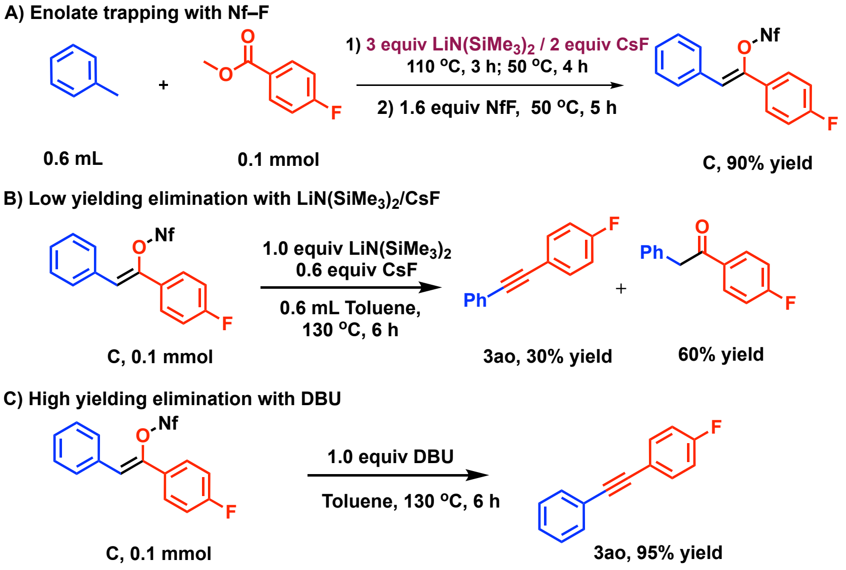


Figure 9. Isolation and reactivity of intermediates

Based on the results above, we propose a mechanism of this tandem reaction (Figure 10). As noted earlier, activation of the $\mathrm{LiN(SiMe_3)_2}$/CsF likely generates $\mathrm{CsN(SiMe_3)_2}$ and may form the dimer $\mathrm{LiCs[N(SiMe_3)_2]_2}$. The newly formed base reversibly deprotonates the toluene benzylic $\mathrm{C(sp^3)}$–H bond, presumably through a cation-p interaction. The benzylic organometallic reacts with methyl benzoate **2** to generate the ketone. The ketone is rapidly deprotonated by the $\mathrm{MN(SiMe_3)_2}$ base, to afford the enolate **B**. Trapping enolate **B** with Nf–F provides intermediate **C**. Finally, addition of DBU to **C** initiates the elimination process with formation of alkyne **3a**.

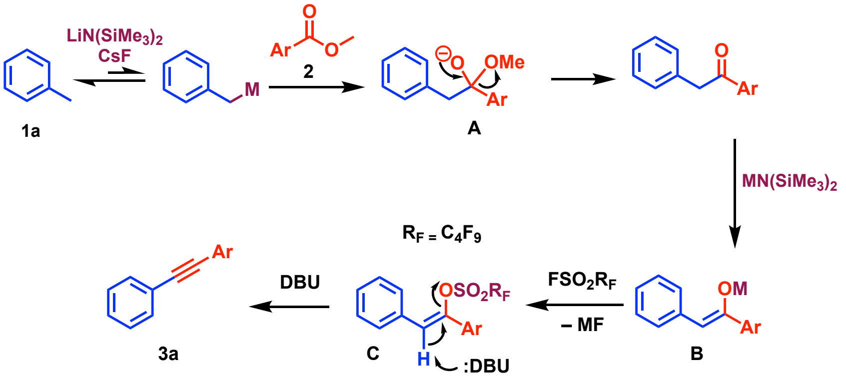


Figure 10. Possible mechanism

In summary, alkynes are among the most valuable unsaturated building-blocks in organic chemistry because of their wide-reaching applications in the pharmaceutical sciences, photonics, optoelectronics, and molecular electronics. Here, we developed a simple, convenient, and economical method that employs petroleum feedstocks toluenes and methyl benzoates under basic conditions to form C–C bonds and generate enolate intermediates. Trapping with either TBS–Cl or Nf–F is followed by elimination to furnish alkynes (48 examples, 48–94% yields). Initial results indicate that this method can be extended to the one-pot synthesis of enynes (9 examples, 48–86% yields). Compared to the state-of-the-art methods for the synthesis of alkynes, this method is complementary with high synthetic efficiency (one-pot vs. 2–3 steps), uses of readily available petroleum feedstock coupling partners, economical, does not require cryogenic temperatures and avoids the use of palladium catalysts, expensive ligands, and toxic copper salts. In cases where terminal alkynes are not available, we anticipate that this method to prepare 1,2-diaryl alkynes and enynes will be competitive with all alternatives.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contacts

Further information and requests for resources should be directed to and will be fulfilled by the lead contacts, Jianyou Mao (ias_jymao@njtech.edu.cn) and Patrick J. Walsh (pwalsh@sas.upenn.edu).

Materials availability

All reagents in this study are commercially available or can be easily prepared as indicated in the supplemental information.

Data and code availability

All the data supporting the findings of this study are presented within the article and supplemental information. See Tables 1 and S1 for optimization of the alkyne syntheses. Supplementary Figures 1-93 for NMR spectroscopic data of alkynes, and Supplementary Figures 94-111 NMR spectroscopic data of enynes. All other data are available from the authors upon reasonable request.

Methods

General procedure for the synthesis of alkynes using Nf–F. An oven-dried 10 mL microwave vial with a stir bar was charged with $LiN(SiMe_3)_2$ (50.2 mg, 0.30 mmol, 3.0 equiv), CsF (30.4 mg, 0.20 mmol, 2.0 equiv) and toluene derivative (0.6 mL) under a nitrogen atmosphere in the glove box. The reaction vial was capped and removed from the glove box, and heated at 110 °C for 4 h in an oil bath. After cooling to room temperature, methyl benzoate derivative (0.10 mmol, 1.0 equiv) was added to the reaction via syringe with nitrogen purged through a needle connected on a Schlenk line. The vial was heated at 50 °C for 4 h in an oil bath. The reaction was cooled to 0 °C in an ice bath, and then 1,8-diazabicyclo(5.4.0)undec-7-ene (15 µL, 0.1 mmol, 1.0 equiv.) and perfluoro-1-butanesulfonyl fluoride (29 µL, 0.16 mmol, 1.6 equiv.) were added in sequence at 0 °C under a Schlenk line system with nitrogen flow. The reaction was allowed to stir for 30 min at 0 °C and then heated to 50 °C for 6 h. The reaction was then heated to 130 °C for 6 h. The reaction was cooled to room temperature and was quenched with two drops of water, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional 5 mL of ethyl acetate and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General procedure for the synthesis of enynes. An oven-dried 10 mL microwave vial with a stir bar was charged with $LiN(SiMe_3)_2$ (50.5 mg, 0.30 mmol, 3.0 equiv), CsF (30.4 mg, 0.20 mmol, 2.0 equiv), allylbenzene derivative (0.3 mmol, 3.0 equiv.) and THF (0.5 mL) under a nitrogen atmosphere in the glove box. The reaction vial was capped and removed from the glove box, and heated at 110 °C for 4 h in an oil bath. After cooling to room temperature, methyl benzoate (12.8 µL, 0.10 mmol, 1.0 equiv) were added to the reaction via syringe with nitrogen purged through a needle connected on a Schlenk line. The vial was heated at 50 °C for 4 h in an oil bath. The reaction was cooled to 0 °C in an ice bath, and then 1,8-diazabicyclo(5.4.0)undec-7-ene (15 µL, 0.1 mmol, 1.0 equiv.) and perfluoro-1-butanesulfonyl fluoride (54 µL, 0.16 mmol, 3.0 equiv.) were added in sequence at 0 °C under a Schlenk line system with nitrogen flow. The reaction was allowed to stir for 30 min at 0 °C and then heated to 50 °C for 6 h. The reaction was then heated to 130 °C for 6 h. The reaction was cooled to room temperature and was quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional 5 mL of ethyl acetate and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

SUPPLEMENTAL INFORMATION

Document S1. Supplemental experimental procedures, Supplementary Figures 1–116, and Table S1

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AUTHOR CONTRIBUTIONS

The research was conceived and directed by J.M. and P.J.W. The experiments were performed by Y.G. and Y.W. (equal contribution) with help from NP and DX. The manuscript was written by Y.G., Y.W., JM and PJW. All authors have approved the final draft of this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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(Please note that each numbered entry may contain only one reference, i.e., no parts a, b, c, etc.)

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