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N-Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts – Evidence for Alkynyl Transfer via Direct Substitution at Acetylenic Carbon

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ABSTRACT

Alkynylation of aldehydes with alkynyl(aryl)iodonium salts catalyzed by an *N*-heterocyclic carbene (NHC) has been developed. The application of the organocatalyst and the hypervalent iodine group-transfer reagent allowed for metal-free C–H functionalization and C–C bond formation. The reaction proceeds under mild conditions, at –40 ºC and in the presence of an amine base, providing access to an array of heteroaryl-propargyl ketones containing various substituents in good to excellent yields. The mechanism of the reaction was investigated by means of both experiments and density functional theory calculations. ^{13}C-labeling and computations determined

that the key alkynyl transfer step occurs via an unusual direct substitution at an acetylenic carbon, wherein an iodine-based leaving group is exchanged by a Breslow intermediate nucleophile. Moreover, kinetic studies revealed that the turnover-limiting step of the catalytic cycle is the generation of the Breslow intermediate, whereas the subsequent C–C bond-formation is a fast process. These results are fully reproduced and rationalized by the calculated full free energy profile of the reaction, showing that the largest energy span is located between the protonated form of NHC catalyst and the transition state for the carbene attack on the aldehyde substrate.

Keywords: NHC organocatalysis, ynones, hypervalent iodine, alkynylation, mechanistic studies

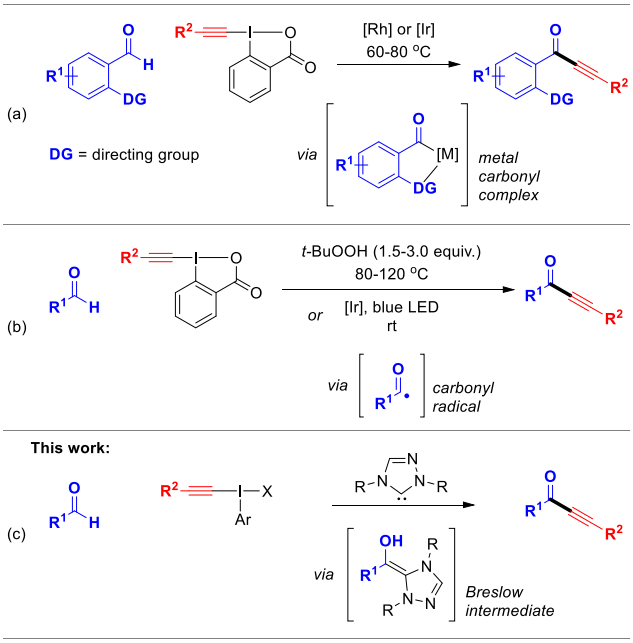
INTRODUCTION

Over the last two decades, the organocatalysis with *N*-heterocyclic carbenes (NHCs) has established a strong position in synthetic organic chemistry. Its success stems primarily from enabling a smooth access to a group of versatile nucleophilic species, such as Breslow intermediate (acyl anion equivalent), homoenolate, acylazolium enolate, and other, via the umpolung of abundant carbonyl substrates. The coupling of these nucleophiles with a plethora of electrophiles has allowed for the development of numerous highly useful synthetic methods.[1] In the recent years, the applicability of NHC catalysis is being further expanded by employing novel unconventional electrophilic partners, which provide a direct entry to important structural motiffs.[2] One class of such electrophilic reagents that has recently opened new opportunities in NHC organocatalysis are hypervalent iodine compounds. Due to the ability of iodine atom to undergo a very energetically favorable reduction from +III to +I oxidation state, accompanied by a simultaneous bond formation involving its ligands (resembling a reductive elimination at a metal center), the hypervalent iodine species are superior electrophilic atom- and group-transfer reagents.[3] At the same time, they lack the toxicity and high price of transition metal catalysts, making them a good alternative from the environmental and economical viewpoints.[4] The group transfer reagents based on hypervalent iodine have been used in a number of organocatalyzed reactions,[5] but there is so far only a handful examples of NHC-promoted processes utilizing these unique electrophilic coupling partners.[6]

Ynones, or propargyl ketones, are a prominent class of organic compounds. First, the ynone motif is present in several biologically active molecules.[7] Even more importantly, the combined reactivities of the triple bond and the carbonyl group give rise to numerous reactions, wherein ynones serve as precursors for the preparation of a diverse array of molecular scaffolds.[8,9] The high

synthetic utility of ynones is proven by their application as key intermediates in multiple total syntheses.[10]

Ynones have traditionally been synthesized by one of three methods: (1) the reaction of metal acetylides with acyl chlorides or other carboxylic derivatives; (2) the oxidation of propargylic position in alkynes or of propargylic alcohols; and (3) a carbonylative cross-coupling.[8f,11] An interesting alternative to these standard approaches that has recently gained attention is the direct alkynylation of the C–H bond in aldehydes (Scheme 1).[12] Such strategy possesses the advantage of providing propargyl ketones in a single synthetic step from abundant and stable starting materials. The first example employing this concept was reported by Zhou and co-workers in 2015, who described a rhodium- and iridium-catalyzed alkynyl transfer from ethynylbenziodoxolone (EBX) to aromatic aldehydes (Scheme 1a).[13] The reaction proceeds via the incipient directing group-assisted activation of the formyl C–H to form a metal carbonyl complex. The second existing approach to effect the alkynylation of aldehydes relies on the homolytic cleavage of the C–H bond. The groups of Wei, Yu, and Li described independently the synthesis of ynones in the presence of *tert*-butyl hydroperoxide as a radical initiator (Scheme 1b).[14] Despite the robustness and simplicity of these methods, their considerable disadvantage is the high reaction temperature required, imposing constraints on the scope. To alleviate the above drawback, Glorius and co-workers employed photoredox catalysis to generate radicals from aldehydes (Scheme 1b).[15] By the application of iridium complex, the alkynylation of a variety of aldehydes with EBX could be carried out at room temperature.



Scheme 1. Synthesis of Ynones via Direct C–H Alkynylation of Aldehydes.

Building on the seminal work by Gaunt on the NHC-catalyzed arylation of aldehydes,[6a] as well as on our own studies on the vinylation of aldehydes,[6b] we envisioned that the formation of a Breslow intermediate by the action of an NHC catalyst on aldehyde substrate may constitute an alternative mean to activate the formyl C–H bond allowing for the subsequent alkynyl group transfer. Herein, we present our work on the development of a novel NHC-catalyzed direct C–H alkynylation of aldehydes outlined in Scheme 1c. Importantly, the reaction makes use of alkynyl(aryl)iodonium salts as the alkynyl group donor, in contrast to all of the previously reported methods that employ EBX reagents (Schemes 1a and 1b).[16] While alkynyl(aryl)iodonium salts have been widely applied for the direct alkynylation of heteroatom nucleophiles and enolates of 1,3-dicarbonyl compounds,[17,18] their use for transferring alkynyl moiety to less trivial carbon nucleophiles have usually required transition metal catalysis.[19] On the contrary, the application of NHC organocatalyst gives rise to an efficient metal-free C–C bond formation involving an acyl anion equivalent. In addition to the synthetic studies, we perform a thorough mechanistic

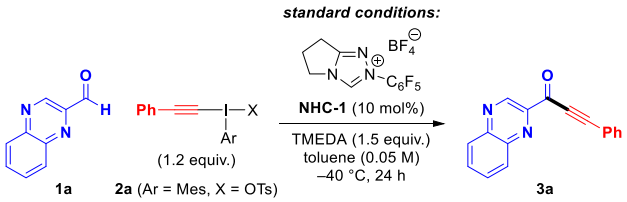
investigations of this new transformation by the combination of experimental and computational approaches. In particular, we identify the turnover-limiting step of the catalytic cycle and elucidate that the transfer of alkynyl moiety from the iodonium salt to the Breslow intermediate follows an unusual pathway of a direct substitution at an acetylenic carbon atom.

RESULTS AND DISSCUSSION

Synthetic studies. First, we investigated the effect of a number of reaction parameters on a model coupling between 2-quinoxalinecarbaldehyde **1a** and phenylethynyl(aryl)iodonium salts containing different auxiliary aryl groups and counter-ions (Table 1). The established optimal conditions consist of *N*-pentafluorophenyl-triazolium carbene precursor **NHC-1**, tetramethylethylenediamine (TMEDA) as the base, and toluene at –40 ºC, affording ynone **3a** in 86% yield (entry 1). The structure of the iodonium salt was found to be crucial for the selective and efficient alkynyl group transfer.[20] Mesityl was identified as the superior auxiliary aryl group, securing the formation of product in high yield (entry 1). Less sterically hindered, including singly *ortho*-substituted, aryls lead to a loss of the selectivity of the transfer, and to the formation of a bisaryl ketone side-product (entries 2–4). The presence of two *ortho* substituents in 2,6-dimethylphen-1-yl suppresses the side aryl-transfer, but the desired ynone is furnished is a lower yield than for the mesityl-containing salt **2a** (entry 5 vs. 1). A significant effect of the counter-ion was also observed. The best result was obtained with a tosylate salt (entry 1), whereas iodonium trifluoromethanosulfonate and trifluoroacetate display only a moderate reactivity (entries 6–7), and a tetrafluoroborate salt is quite ineffective (entry 8). Finally, we tested EBX reagent **4**, but it provides only traces of product under these conditions (entry 9). Importantly, the optimal

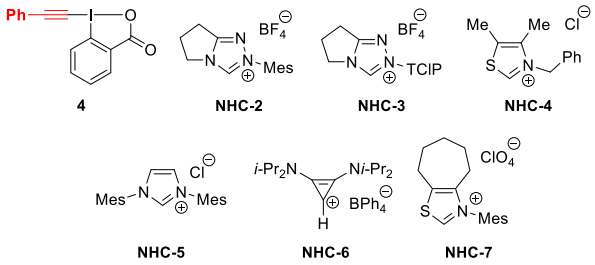
alkynyl(mesityl)iodonium tolsylates of type **2a** are stable and easy to handle, and they can be very conveniently prepared by the method reported by Stang.[21]

Table 1. Effect of Reaction Parameters[a]



entry	deviation from the standard conditions	yield (%)[b]
1	-	86
2	Ar = Ph **(2b)**, instead of Ar = Mes	38 (16)[c]
3	Ar = *o*–anisyl **(2c)**, instead of Ar = Mes	17 (11)[c]
4	Ar = *o*–tolyl **(2d)**, instead of Ar = Mes	73 (20)[c]
5	Ar = 2,6-dimethylphen-1-yl **(2e)**, instead Ar = Mes	67
6	X = OTf **(2f)**, instead of X = OTs	64
7	X = CF_3COO **(2g)**, instead of X = OTs	66
8	X = BF_4 **(2h)**, instead of X = OTs	24
9	Ph-EBX **(4)**, instead of **2a**	4
10	**NHC-2**, instead of **NHC-1**	50
11	**NHC-3**, instead of **NHC-1**	58
12	**NHC-4**, instead of **NHC-1**	11
13	**NHC-5**, instead of **NHC-1**	<1
14	**NHC-6**, instead of **NHC-1**	<1
15	**NHC-7**, instead of **NHC-1**	19
16	5 mol% of **NHC-1**	64
17	no **NHC-1**	<1

18	0 °C, instead of –40 °C	66
19	r.t., instead of –40 °C	47
20	Et_3N, instead of TMEDA	66
21	Et_3N (3.0 equiv.), instead of TMEDA	50
22	DMAP, instead of TMEDA	32
23	DABCO, instead of TMEDA	80
24	K_3PO_4, instead of TMEDA	8
25	DCE, instead of toluene	62[d]
26	CH_2Cl_2, instead of toluene	51
27	MeCN, instead of toluene	50

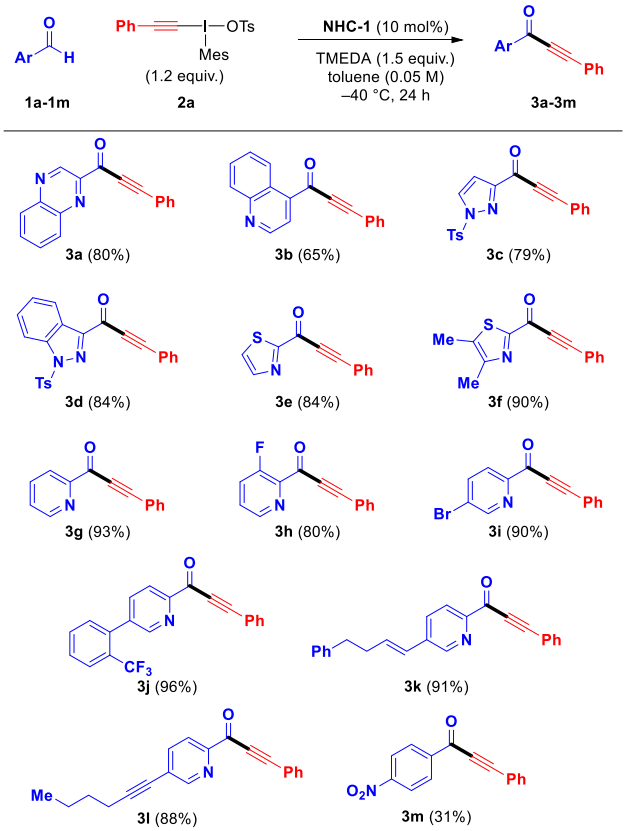


[a]All data are the average of two experiments. [b]Determined through analysis by ^{1}H NMR spectroscopy. [c]The formation of bisaryl ketone side-product was observed, its yield is given in parenthesis. [d]At –35 °C. Mes = 2,4,6-trimethylphen-1-yl; OTs = *p*-tolenesulfonate; OTf = trifluoromethanesulfonate; TClP = 2,4,6-trichlorophen-1-yl; DCE = 1,2-dichloroethane.

As far as the other reaction parameters are concerned, we found that the different types of NHCs commonly used in organocatalysis (entries 10–15) are inferior to the commercially available **NHC-1**, bearing an electron deficient pentafluorophenyl group. Lowering of the catalyst loading from 10 to 5 mol% decreases the yield to a moderate level (entry 16) and no product formation is observed in the absence of catalyst (entry 17). Elevated temperatures have an adverse effect on the reaction (entries 18–19). Application of other organic amine bases results in moderate to good yields (entries 20–23), while inorganic bases are ineffective in this transformation (*e.g.*, entry 24).

The good performance of TMEDA cannot be attributed to just providing a double number of amine groups, as an increased amount of triethylamine did not lead to an improved yield, quite the contrary (entry 21). Interestingly, more polar solvents (entries 25-27) that completely solubilize the reactants are not as efficient as toluene, which affords a heterogenous reaction mixture.

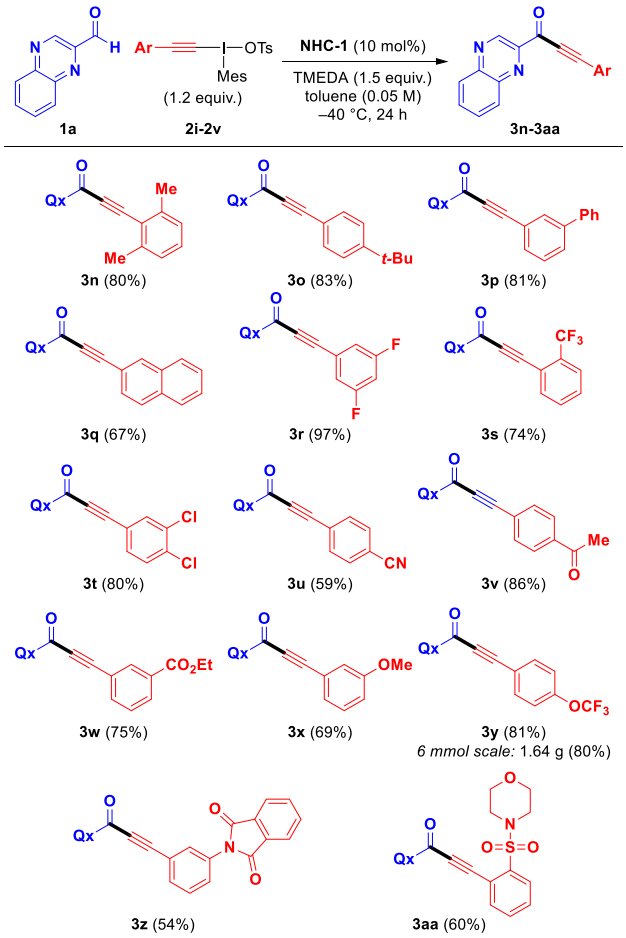
Having established the optimal conditions for the NHC-catalyzed alkynylation of aldehydes, we proceeded to evaluate the scope and limitations of this reaction. An array of heteroaromatic aldehydes could be efficiently alkynylated (Scheme 2). In particular, arylpropargyl ketones containing heterocyclic six-membered rings with nitrogen, such as quinoxaline (**3a**), quinoline (**3b**), and pyridine (**3g**–**3l**), as well as five-membered rings, *e.g.*, pyrazole (**3c**–**3d**) and thiazole (**3e**–**3f**), were synthesized in good to excellent yields. The ability to incorporate these moieties is highly advantageous, as they are prevalent in therapeutically important molecules.[22] A number of functional groups is tolerated under the reaction conditions, including aryl bromide (**3i**), double (**3k**), and triple (**3l**) bonds, providing useful handles for further functionalization and built-up of the molecular complexity. The method is also compatible with fluorinated substituents (**3h** and **3j**), which adds to its value for the synthesis of pharmaceutically relevant compounds.[23] On the downside, benzaldehydes are poor substrates and only the one containing a strongly electron-withdrawing nitro group afforded the desired product in an admissible yield (**3m**). Also, aliphatic aldehydes and enals were found to be incompetent starting materials.[24]



Scheme 2. Scope with Regard to the Aldehyde

Next, we examined the scope with regard to the alkynyliodonium salt. The method could be applied to transfer a range of arylethynyl groups, containing a multitude of substituents (Scheme 3). All the alkyl-substituted (**3n**, **3o**), aryl-substituted (**3p**), as well as extended (**3q**) aryl systems can be incorporated into the product. The reaction proceeds equally well for arylethynyl moieties bearing both electron-withdrawing and electron-donating groups. Thus, regardless of the substituent position, ynones containing halogens (**3r** and **3t**), trifluromethyl (**3s**), cyano (**3u**), ketone (**3v**), ester (**3w**), and ether (**3x**–**3y**) functionalities were synthesized in good to excellent yields. Notably, we also prepared propargyl ketones with a phtalamide-masked amine (**3z**) and a sulfonamide (**3aa**), demonstrating a broad functional group tolerance of the developed

methodology. Unfortunately, when iodonium salts containing alkylethynyl and silylethynyl groups were tested, the desired products were formed in low yields under these conditions.[24]

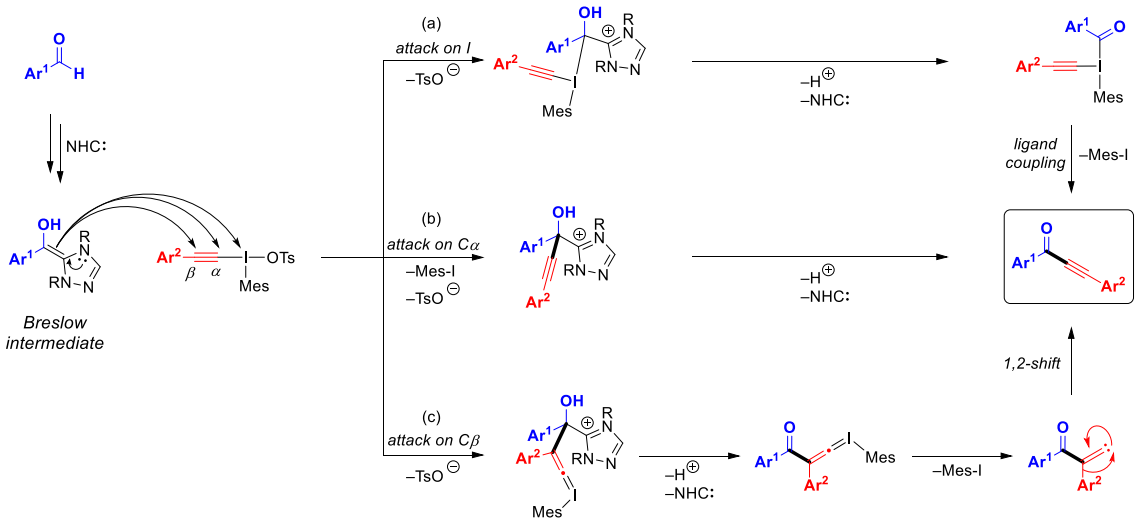


Scheme 3. Scope with Regard to the Alkynyliodonium Salt (Qx = quinoxalin-2-yl)

Finally, to validate the synthetic utility of the developed procedure, we have applied it to synthesize compound **3y** on a gram scale, which was obtained without any appreciable loss in the yield (80%, 1.64 g of product).

Experimental mechanistic studies. The hypervalent iodine compounds bearing an alkynyl group contain three distinct electrophilic centers: the iodine atom, the α-carbon of the triple bond, and the β-carbon of the triple bond. Therefore, the reactions involving such reagents may in principle

follow three general mechanistic pathways, outlined in Scheme 4 for the particular case of the NHC-catalyzed alkynylation of aldehydes with alkynyliodonium salts.

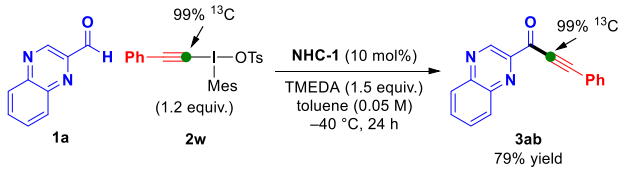


Scheme 4. Outline of Possible General Mechanisms

In the first scenario the nucleophile, Breslow intermediate, is incorporated into the coordination sphere of iodine (Scheme 4a). After the expulsion of NHC catalyst, the key C–C bond-formation takes place via a reductive ligand coupling, affording the ynone product. This type of mechanism is common for related aryl transfer reactions with diaryliodonium salts, as revealed by several computational investigations, but it has never been implicated for an alkynylation with hypervalent iodine reagents.[25] The second possibility is a direct substitution at the α-acetylenic carbon, *i.e.*, the displacement of iodine acting as a leaving group by the attacking nucleophile (Scheme 4b). Such a mechanistic route has so far been shown to operate only in a single instance of alkynyl transfer from hypervalent iodine species, namely for the alkynylation of thiols with EBX reagents.[26,27] Nevertheless, it has been demonstrated that this pathway is not the exclusive mechanism in that case, and depending on the substituents present in the starting materials it may contribute to a larger or a lesser extent to the formation of product.[26b] In the final alternative, the nucleophile attacks at the β-carbon of the triple bond in a Michael-type conjugate addition (Scheme 4c). The

resulting iodonium ylide, after a prior elimination of NHC, undergoes a fragmentation producing a vinylidene carbene intermediate. Subsequently, the vinylidene carbene rearranges to the final product by a 1,2-shift of the aryl substituent. It is generally accepted that the majority of alkynylations with hypervalent iodine reagents follow this last mechanism, as there exists strong experimental evidence supporting it. In particular, first, in multiple cases the iodonium ylide could be trapped by protonation, yielding isolable vinyliodonium derivatives.[28] Secondly, in the absence of any substituents prone to migration, the emergence of products originating from the insertion of the vinylidene carbene into C–H bonds has been observed.[18k,29] Finally, the acetylenic carbons have been shown to swap their positions during the reactions with ^{13}C-labeled alkynyliodonium starting materials, in line with the 1,2-shift step.[26b,29a,30]

The fact that alkylethynyliodonium salts are not effective in the NHC-catalyzed reaction (*vide supra*) suggested that it may follow the most common pathway staring with the nucleophilic attack on the β-carbon (Scheme 4c), since the alkyl substituents are not likely to undergo the 1,2-migartion. On the other hand, we did not observe any products originating from the insertion of the vinylidene carbene into the C–H bonds of the alkyl chains, either. Therefore, in order to obtain a more direct proof distinguishing between the different possible mechanisms, we carried out the alkynylation of aldehyde **1a** using iodonium salt **2w** that was labeled with ^{13}C at the α-carbon (Scheme 5). The resulting product **3ab** was generated in an unchanged yield compared to its unlabeled counterpart (*cf*. **3a** in Scheme 2) and it contained the ^{13}C label exclusively incorporated at the acetylenic carbon adjacent to the carbonyl group. Such an outcome allows to unambiguously eliminate the attack of Breslow intermediate on the β-carbon of the alkynyliodonium salt (Scheme 4c) as the valid pathway of the investigated reaction.



Scheme 5. NHC-Catalyzed Alkynaltion of Aldehyde **1a** with Alkynyliodonium Salt **2w** Labelled with ^{13}C at the α-Carbon.

Stimulated by the result of above experiment, demonstrating that the developed reaction does not follow the most prevalent mechanism for alkynylations with hypervalent iodine compounds, we decided to perform more thorough investigations of this interesting process. To obtain insight into its course, we carried out kinetics investigations. First, the progress of the reaction under the optimized conditions was monitored over time (Figure 1a). The analysis of the decay of the starting material shows that the reaction displays overall second order in the concentrations of the substrates, as the linear dependence of reciprocal substrate concentration vs. time was observed (Figure 1b).[31]

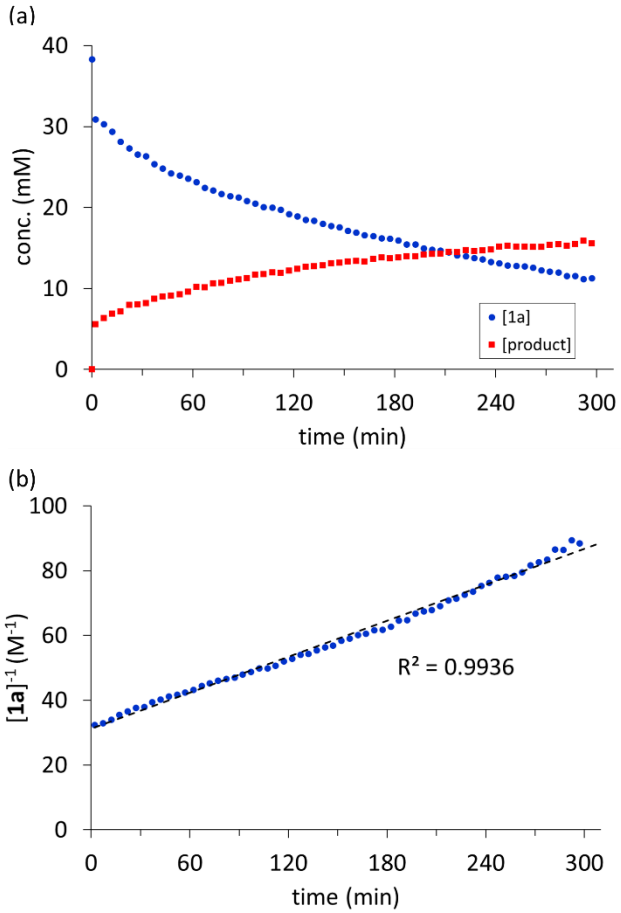


Figure 1. (A) Time-course of the NHC-Catalyzed Alkynylation of Aldehyde **1a** with Alkynyliodonium salt **2a** in d_8-Toluene at –40 °C.[a,b] (B) Corresponding Plot of Reciprocal Substrate Concentration vs. Time.

[a]The concentrations were determined by ^{1}H NMR spectroscopy relative to internal standard. [b]The initial leap in the concentrations is due to a temporary heating of the sample during the addition of the initiating reagent (TMEDA).

In order to ascribe the orders to the concentrations of specific reagents, we conducted an initial rate study. Our first attempts to follow the initial rates under the optimized conditions were unsuccessful, as highly erratic and irreproducible time curves were being obtained. We were able to trace this problem to the heterogeneity of the reaction mixture, and, thus, upon switching the

solvent from d_8-toluene to $CDCl_3$, which solubilizes all the reactants at the reaction temperature of –40 °C, better quality data could be acquired. However, due to the technical difficulties of measuring the reaction kinetics at so low temperature, in particular the problem to start the reaction cleanly at –40 °C using NMR as the measurement method, the alignment of the data points is still far from perfect (see the Supporting Information for the experimental details and the data handling procedure). Anyhow, despite the very preliminary character of these kinetic studies and considerable uncertainties of the obtained orders, we believe that we were able to grasp the general kinetic characteristics of the transformation.

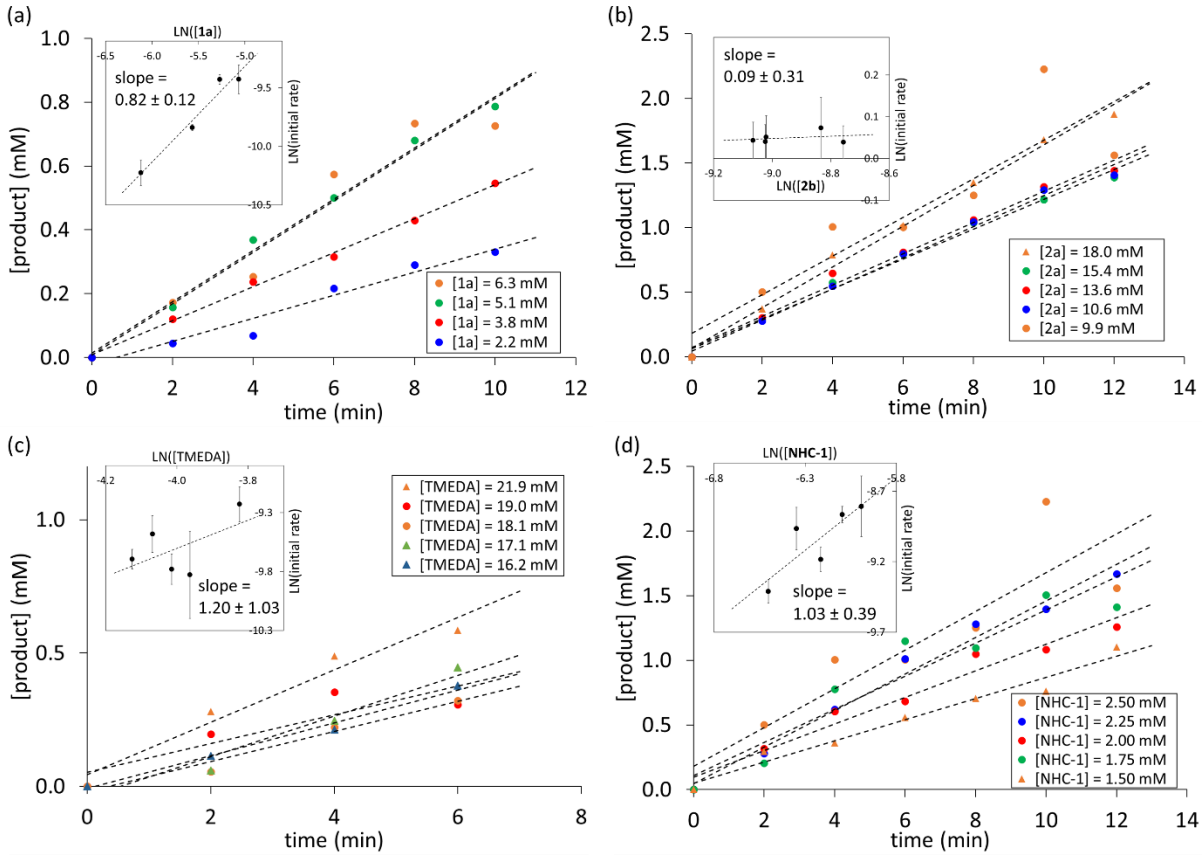


Figure 2. Initial Rate Measurements for the NHC-Catalyzed Alkynylation of Aldehyde **1a** with Alkynyliodonium Salt **2a** in $CDCl_3$ at –40 °C, with Varied Concentration of (a) **1a**, (b) **2a**, (c) TMEDA, and (d) **NHC-1**. The Insets Show the Corresponding LN-LN Plots.[a]

[a] Product concentration was determined by ^{1}H NMR spectroscopy relative to internal standard.

Figure 2 presents the initial rate plots measured with varied concentrations of the respective reagents and the catalyst precursor. The analysis of this data results in an experimental rate law, wherein the reaction is first order in the concentrations of **1a**, TMEDA, and **NHC-1**, whereas zeroth order in the concentration of **2a** (eq 1). This is in agreement with the overall second order in the substrates (*i.e.*, **1a** and TMEDA), determined from the reaction monitored over a longer period (Figure 1; the concentration of **NHC-1** is constant with conversion, hence its influence on the rate does not appear in that experiment).

$$rate = k[\mathbf{1a}][\text{TMEDA}][\mathbf{NHC\text{-}1}] \quad (1)$$

The presence of the aldehyde and the NHC precatalyst concentrations in rate law (1) directly implies that the formation of Breslow intermediate is the turnover-limiting step of the catalytic cycle. In turn, since the concentration of the alkynyliodonium salt does not impact the rate, the subsequent key C–C bond formation must be a fast step, demonstrating a very high mutual affinity between the alkynyliodonium salt and the Breslow intermediate. Taking this into account, the appearance of the concentration of TMEDA in the rate law indicates its involvement also during the generation of the Breslow intermediate, in addition to the deprotonation needed to expel NHC toward the end of the mechanism (Scheme 4).

Computational studies. To gain insight into the details of the catalytic cycle and complement the mechanistic picture obtained in the previous section, we performed a computational density functional theory (DFT) investigation. The alkynylation of 2-pyridinecarboxaldehyde (**1g**) with

(mesityl)(phenylethynyl)iodonium tosylate (**2a**) using precatalyst **NHC-1** was employed as a model reaction in the calculations. The computations were carried out at B3LYP-D3BJ/Def2-QZVP//B3LYP-D3BJ/6-31+G(d,p) (LANL2DZ(d) for I) level of theory with the modelling of toluene solvation using SMD method for both the geometry optimizations and the final energy calculations (see the Supporting Information for the full computational details).[32] Figure 3 shows the free energy profile for the mechanism established by the calculations.

The initial formation of the Breslow intermediate was found to occur according to the standard mechanism implicated for the NHC-catalyzed processes.[1c] Thus, the reaction begins by a facile deprotonation of catalyst precursor **NHC-1** with TMEDA via transition state **TS1**. The resulting free carbene **A** is higher in energy by 2.4 kcal/mol compared to its protonated form. In the following step, the NHC attacks aldehyde **1g**, generating alkoxide species **B**. The overall barrier for this transformation is calculated to be 16.7 kcal/mol relative to **NHC-1**. In the next step, **B** undergoes a barrierless protonation at oxygen by the salt of TMEDA, yielding the corresponding alcohol **C**. Finally, Breslow intermediate **D** is furnished upon the deprotonation of **C** at the carbon atom by TMEDA via a low-barrier **TS3**. Overall, the formation of the Breslow intermediate is exergonic by 2.1 kcal/mol relative to the catalyst precursor. The highest energy span along the way, amounting to 16.7 kcal/mol, is located between **NHC-1** and **TS2**. Importantly, within this part of the energy diagram all three species, whose concentrations are present in the experimental rate-law (1), are involved, that is: the catalyst precursor, the aldehyde substrate, and TMEDA. The subsequent stepwise proton-shuttling (**B** → **D**) is facile and does not contribute to the reaction rate.

Although, the computations did not reveal any involvement of the second amine group of TMEDA in any of the transition states, in $TMEDAH^{+}BF_4^{-}$ salt, the lone electron pair of the second nitrogen is pointing toward the proton (with a 2.58 Å separation), providing some stabilization (on

the order of 1 kcal/mol, judging from the energies of other conformations of this salt lacking such interaction). Thus, the presence of this interaction leads to the lowering of the energy of intermediate **A**, in turn lowering the rate-determining barrier. This effect is most likely responsible for the better performance of TMEDA compared to simple amines, such as Et_3N, in promoting the reaction.

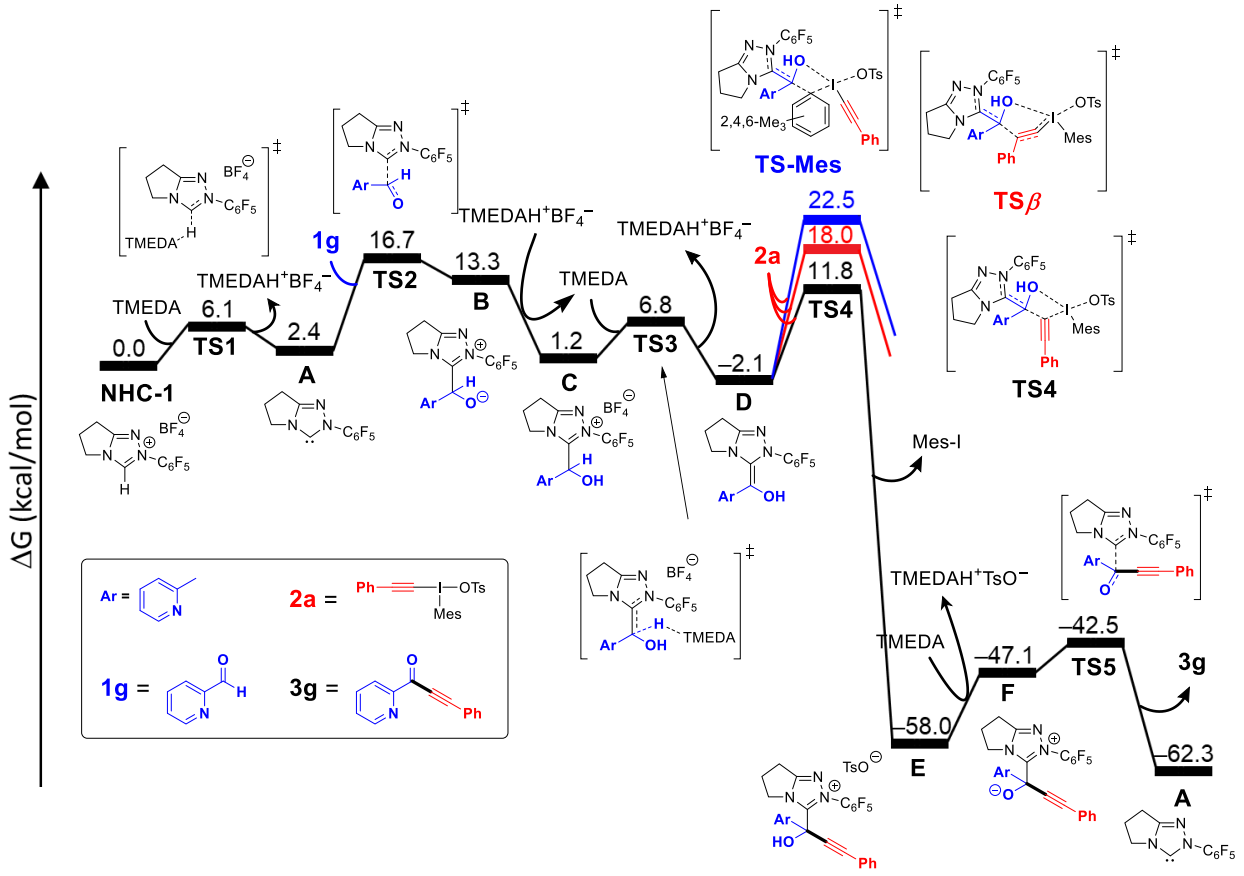


Figure 3. Free Energy Profile for the Alkynylation of Aldehyde **1g** with Alkynyliodonium Salt **2a** Using Precatalyst **NHC-1** in Toluene, Calculated at B3LYP-D3BJ/Def2-QZVP(SMD)//B3LYP-D3BJ/6-31+G(d,p)(SMD) Level of Theory.

Next, we examined the possible options for the reaction of Breslow intermediate **D** with alkynyliodonium salt **2a**. It was quickly established that the direct coordination of **D** to the iodine

center is not feasible, as it does not result in a stable structure that constitutes a minimum on the energy surface. Therefore, the mechanism involving the inner-sphere reductive ligand coupling (Scheme 4a) can be discarded. On the other hand, we were capable of finding the plausible transition states, **TS4** and **TSβ**, for the other two alternative pathways, *i.e.*, the direct substitution at the α-carbon (Scheme 4b) and the Michael-type addition to the β-carbon (Scheme 4c), respectively. The former one is calculated to be clearly energetically favorable over the latter (by 6.2 kcal/mol), thus, it constitutes the actual pathway of the C–C bond-formation. The transfer of the alkynyl group via **TS4** is found to be a very exergonic, thus, irreversible process (by 55.9 kcal/mol). This is due to the accompanying reduction of iodine from +III to +I oxidation state and the loss of hypervalency. For completeness, we calculated the transition state for the transfer of the mesityl group in **2a** (**TS-Mes**), instead of the alkynyl group. Such course of the reaction would require crossing a very high barrier of 24.6 kcal/mol, explaining the excellent performance of the mesityl substituent as the auxiliary non-transferable aryl group in the alkynyl(aryl)iodonium salts.

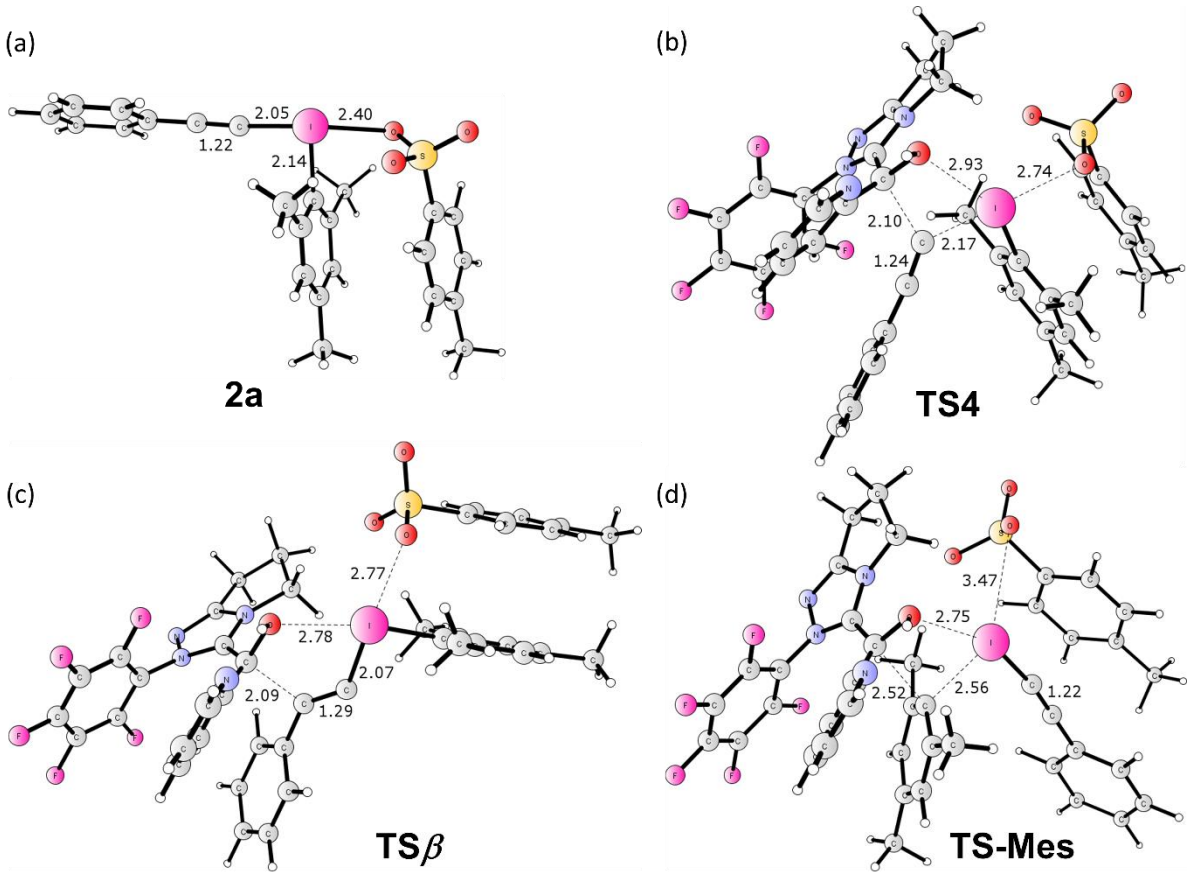


Figure 4. Optimized Structures of (a) Alkynyliodonium Salt **2a**, (b) **TS4**, (c) **TS*β***, and (d) **TS-Mes** (Distances Are Given in Å).

The optimized structures of transition states **TS4**, **TS*β***, and **TS-Mes**, as well as of alkynyliodonium salt **2a**, are depicted in Figure 4. In all three transition states the ligand participating in the new C–C bond formation occupies the hypervalent position. Hence, in the case of **TS4** and **TS*β*** (Figure 4b and 4c, respectively), the arrangement of ligands around the iodine center is the same as in the parent salt (Figure 4a), while in **TS-Mes** the phenylethynyl and mesityl groups are swapped (Figure 4d). Such opposite orientation of the ligands is probably the most significant contributor to the high barrier associated with **TS-Mes**, as the calculated energy of the isomer of **2a** having the mesityl group in the hypervalent position and the alkynyl group in the equatorial position is higher by as much as 10.0 kcal/mol compared to the energy of **2a**. As far as

the energy difference between **TS4** and **TSβ** is concerned, it most likely originates from distorting the conjugation between the forming double C–C bond and the phenyl substituent, which due to steric reasons must rotate nearly perpendicularly, in the latter transition state. On the other hand, in **TS4**, the phenyl ring can align itself in way allowing for a complete π-conjugation over the triple bond to both the breaking C–I bond and the newly forming C–C bond, providing stabilization. Importantly, in all the transition states, the hydroxyl group of Breslow intermediate is interacting with the iodine center. This is somewhat similar to the case of alkynylation of thiols with EBX, wherein the thiolate nucleophile has been shown to simultaneously interact with the alkynyl group and iodine in a three-center transition state structure.[26] However, we could also locate other, higher in energy, conformations of the TSs lacking this interaction, hence it is not absolutely required, but it renders the C–C bond formation more facile.

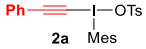
The catalytic cycle is closed by a barrierless deprotonation of intermediate **E**, followed by **TS5**, which releases the final product **3g** and regenerates free NHC **A**. Importantly, as **A** is not the most stable form of the catalyst, it is converted to the more favorable off-cycle resting state **NHC-1**. Overall, the total thermodynamics of the reaction is calculated to –59.9 kcal/mol.

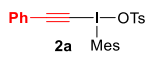
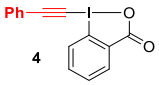
The mechanistic picture emerging from the calculations is in a full agreement with the results of experimental studies described in the previous section. First, the lowest energy pathway established for the C–C bond formation, *i.e.*, the direct substitution at α-acetylenic carbon via **TS4**, explains the direct transfer of the ^{13}C-label between iodonium salt **2w** and product **3ab** without swapping (Scheme 5). Secondly, the computed free energy profile is in line with the experimental rate-law (1). It correctly predicts that only the NHC precatalyst, the aldehyde, and TMEDA are involved in the turnover-limiting step, constituted by the largest energy span between **NHC-1** and **TS2** (overall 16.7 kcal/mol).[33] The height of this turnover-limiting barrier is also quantitatively

consistent with the experimental rate of the reaction at –40 °C. Conversely, the iodonium salt enters the free energy profile within a lower barrier, later in the catalytic cycle (13.9 kcal/mol, **D** to **TS4**), thus, its concentration does not influence the overall rate.

To better understand the characteristics and limitations of the developed transformation, we re-calculated the key stationary points in the free-energy profile for other substrates, in particular those that did not provide satisfactory results (Table 2). Hence, as far as propionaldehyde (**1n**) and benzaldehyde (**1o**) are concerned (entries 1 and 2), although the Breslow intermediates derived from them could readily react with iodonium salt **2a** (8.9 kcal/mol and 14.9 kcal/mol barriers, respectively), the preceding barriers for their formation (20.3 kcal/mol and 19.3 kcal/mol, respectively) are considerably higher than that calculated for 2-pyridinecarboxaldehyde **1g** (16.7 kcal/mol; Figure 3). Thus, the electron-poor aldehyde substrates are required to efficiently furnish the corresponding Breslow intermediates. We evaluated computationally also the barrier for the alkynyl group transfer for Ph-EBX reagent (**4**, entry 3). It was found to be appreciably higher compared to the one obtained in the case of the iodonium salt **2a** (13.9 kcal/mol; Figure 3). We believe that this is due to the considerable basicity of the carboxylate moiety in EBX, which lowers the leaving group ability of iodine, rendering the alkynyl transfer more challenging.

Table 2. Relative Free-Energies of Key Stationary Points for the Reactions Involving Other Substrates, Calculated at B3LYP-D3BJ/Def2-QZVP(SMD)//B3LYP-D3BJ/6-31+G(d,p)(SMD) Level of Theory.

Entry	Aldehyde	Alkynyliodonium Reagent	**NHC-1** (initial state)	**TS2**	**D**	**TS4**
1			0.0	20.3	6.2	15.1

2	 1o	 2a	0.0	19.3	3.3	18.2
3	 1g	 4	0.0	16.7	–2.1	21.2

CONCLUSIONS

In summary, we have developed an NHC-catalyzed direct C–H alkynylation of aldehydes using alkynyliodonium salts as alkynyl donors, expanding the scope of the NHC organocatalysis. The proper choice the auxiliary aryl substituent secured the selective transfer of the alkynyl substituent from iodine, providing a facile entry to a variety of ynones in good to excellent yields. In particular, the method is well-suited for the synthesis of compounds bearing pharmaceutically relevant heterocyclic scaffolds. Due to the mild reaction conditions, in terms of both the reaction temperature and the use of a weak amine base, a range of fragile functional groups is tolerated. Specifically, alkenes, alkynes, nitriles, ketones, esters, and amides can be incorporated into the products. Finally, the application of the organocatalyst in the combination with a hypervalent iodine reagent, allowed for a completely metal-free C–H functionalization, rendering the developed reaction a green alternative for the preparation of propargylic ketones from abundant aldehyde starting materials.

The mechanism of the reaction has been thoroughly studied by both experimental and computational methods. The ^{13}C-labbeling and DFT calculations have shown that the alkynyl group transfer proceeds via a direct substitution of iodine by the Breslow intermediate occurring at α-acetylenic carbon, and not by the prevalent pathway involving the initial attack of nucleophile at the *β*-position. This constitutes the second reported example of such a course of the alkynylation reaction with a hypervalent iodine reagent and the first wherein it is the clearly preferred, exclusive mechanistic pathway. Therefore, the finding may implicate that analogous mechanisms can be

more common than previously thought. Additionally, the kinetic studies, corroborated by the computed free energy profile, have identified the formation of Breslow intermediate to be the turnover-limiting step of the catalytic cycle. This demonstrates that the subsequent C–C bond-forming reaction between the Breslow intermediate and the alkynyliodonium salt is a very facile, low-barrier process. Above result opens opportunities for the application of alkynyliodonium salts as efficient alkynyl-transfer reagents for other non-trivial nucleophilic species, including catalytically generated ones, in the future.

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Notes

The authors declare no conflict of interest.

ASSOCIATED CONTENT

Supporting Information:

Experimental procedures, compound characterization data, NMR spectra of compounds **2w** and **3a**–**3ab**, list of unsuccessful substrates, details of kinetic investigations, computational details,

free-energy profile for the reaction in $CHCl_3$, calculated energies and energy corrections, optimized structures and Cartesian coordinates of stationary points (PDF).

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REFERENCES

1. (a) Moore, J. L.; Rovis, T. Lewis Base Catalysts 6: Carbene Catalysts. *Top. Curr. Chem.* **2010**, *291*, 77-144; (b) Bugaut, X.; Glorius, F. Organocatalytic Umpolung: *N*-heterocyclic Carbenes and Beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by *N*-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307-9387; (d) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in *N*-heterocyclic Carbene (NHC)-Catalysed Benzoin Reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 444-461.

2. Biju, A. T.; Kuhl, N.; Glorius, F. Extending NHC-Catalysis: Coupling Aldehydes with Unconventional Reaction Partners. *Acc. Chem. Res.* **2011**, *44*, 1182-1195.

3. (a) Zhdankin, V. V. *Hypervalent iodine chemistry: preparation, structure, and synthetic applications of polyvalent iodine compounds*; Wiley: Chichester, 2013; (b) *Top. Curr. Chem.*, Vol. 373; Wirth, T. Ed.; Springer: Switzerland, 2016; (c) Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016**, *116*, 3328-3435; (d) Hyatt, I. F. D.; Dave, L.; David, N.; Kaur, K.; Medard, M.; Mowdawalla,

C. Hypervalent Iodine Reactions Utilized in Carbon–Carbon Bond Formations. *Org. Biomol. Chem.* **2019**, *17*, 7822-7848.

4. Yusubov, M. S.; Zhdankin, V. V. Hypervalent Iodine Reagents and Green Chemistry. *Curr. Org. Synth.* **2012**, *9*, 247-272.

5. Ghosh, M. K.; Rajkiewicz, A. A.; Kalek, M. Organocatalytic Group Transfer Reactions with Hypervalent Iodine Reagents. *Synthesis* **2019**, *51*, 359-370.

6. (a) Toh, Q. Y.; McNally, A.; Vera, S.; Erdmann, N.; Gaunt, M. J. Organocatalytic C–H Bond Arylation of Aldehydes to Bis-Heteroaryl Ketones. *J. Am. Chem. Soc.* **2013**, *135*, 3772-3775; (b) Rajkiewicz, A. A.; Kalek, M. *N*-Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate α,β-Unsaturated Ketones. *Org. Lett.* **2018**, *20*, 1906-1909; (c) Gelat, F.; Patra, A.; Pannecoucke, X.; Biju, A. T.; Poisson, T.; Besset, T. *N*-Heterocyclic Carbene-Catalyzed Synthesis of α-Trifluoromethyl Esters. *Org. Lett.* **2018**, *20*, 3897-3901; (d) Yang, W.; Ma, D.; Zhou, Y.; Dong, X.; Lin, Z.; Sun, J. NHC-Catalyzed Electrophilic Trifluoromethylation: Efficient Synthesis of γ-Trifluoromethyl α,β-Unsaturated Esters. *Angew. Chem. Int. Ed.* **2018**, *57*, 12097-12101.

7. (a) Fawcett, C. H.; Firn, R. D.; Spencer, D. M. Wyerone Increase in Leaves of Broad Bean (*Vicia faba L.*) after Infection by *Botrytis fabae*. *Physiol. Pl. Path.* **1971**, *1*, 163-166; (b) Kundu, N. G.; Das, B.; Spears, C. P.; Majumdar, A.; Kang, S. I. Synthesis and Biological Activities of Novel 5-(2-Acylethynyl)uracils. *J. Med. Chem.* **1990**, *33*, 1975-1979; (c) Kundu, N. G.; Mahanty, J. S.; Spears, C. P. Unusual Cytotoxicities of 5-(Acylethynyl)-1-(2-hydroxyethoxy)methyluracils. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1497-1502; (d) Quesnelle, C. A.; Gill, P.; Dodier, M.; St. Laurent, D.; Serrano-Wu, M.; Marinier, A.; Martel, A.;

Mazzucco, C. E.; Stickle, T. M.; Barrett, J. F.; Vyas, D. M.; Balasubramanian, B. N. Sordaricin Antifungal Agents. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 519-524; (e) Kuklev, D. V.; Domb, A. J.; Dembitsky, V. M. Bioactive Acetylenic Metabolites. *Phytomedicine* **2013**, *20*, 1145-1159.

8. Recent reviews: (a) Bagley, M. C.; Glover, C.; Merritt, E. A. The Bohlmann-Rahtz Pyridine Synthesis: from Discovery to Applications. *Synlett* **2007**, 2459-2482; (b) Arai, T.; Ikematsu, Y.; Suemitsu, Y. Nickel-Catalyzed Multicomponent Coupling Reaction Using Ynones. *Pure Appl. Chem.* **2010**, *82*, 1485-1490; (c) Sengee, M.; Sydnes, L. K. Specific Conjugate Addition to α,β-Acetylenic Aetones. *Pure Appl. Chem.* **2011**, *83*, 587-596; (d) Fraile, A.; Parra, A.; Tortosa, M.; Alemán, J. Organocatalytic Transformations of Alkynals, Alkynones, Propriolates, and Related Electron-Deficient Alkynes. *Tetrahedron* **2014**, *70*, 9145-9173; (e) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. Sequential Addition and Cyclization Processes of Ynones and α,β-Ynoates Containing Proximate Nucleophiles. *Synthesis* **2014**, *46*, 687-721; (f) Whittaker, R. E.; Dermenci, A.; Dong, G. Synthesis of Ynones and Recent Application in Transition-Metal-Catalyzed Reactions. *Synthesis* **2016**, *48*, 161-183.

9. Selected examples: (a) Kel'i, A. V.; Gevorgyan, V. Efficient Synthesis of 2-Mono- and 2,5-Disubstituted Furans via the CuI-Catalyzed Cycloisomerization of Alkynyl Ketones. *J. Org. Chem.* **2002**, *67*, 95-98; (b) Silva, F.; Sawicki, M.; Gouverneur, V. Enantioselective Organocatalytic Aldol Reaction of Ynones and Its Synthetic Applications. *Org. Lett.* **2006**, *8*, 5417-5419; (c) D'Souza, D. M.; Müller, T. J. J. Catalytic Alkynone Generation by Sonogashira Reaction and Its Application in Three-Component Pyrimidine Synthesis. *Nat. Protoc.* **2008**, *3*, 1660-1665; (d) Willy, B.; Dallos, T.; Rominger, F.; Schönhaber, J.; Müller, T. J. J. Three-Component Synthesis of Cryofluorescent 2,4-Disubstituted 3*H*-1,5-Benzodiazepines –

Conformational Control of Emission Properties. *Eur. J. Org. Chem.* **2008**, 4796-4805; (e) Zhao, T.; Xu, B. Palladium-Catalyzed Tandem Amination Reaction for the Synthesis of 4-Quinolones. *Org. Lett.* **2010**, *12*, 212-215; (f) Zora, M.; Kivrak, A. Synthesis of Pyrazoles via CuI-Mediated Electrophilic Cyclizations of α,β-Alkynic Hydrazones. *J. Org. Chem.* **2011**, *76*, 9379-9390; (g) Zhou, J.; Zhang, G.-L.; Zou, J.-P.; Zhang, W. Synthesis of Phosphonylated and Thiolated Indenones by Manganese(III)-Mediated Addition of Phosphorus- and Sulfur-Centered Radicals to 1,3-Diarylpropynones. *Eur. J. Org. Chem.* **2011**, 3412-3415; (h) Xu, B.-H.; Kehr, G.; Fröhlich, R.; Wibbeling, B.; Schirmer, B.; Grimme, S.; Erker, G. Reaction of Frustrated Lewis Pairs with Conjugated Ynones-Selective Hydrogenation of the Carbon–Carbon Triple Bond. *Angew. Chem. Int. Ed.* **2011**, *50*, 7183-7186; (i) Khong, S.; Kwon, O. One-Pot Phosphine-Catalyzed Syntheses of Quinolines. *J. Org. Chem.* **2012**, *77*, 8257-8267; (j) Neumann, K. T.; Laursen, S. R.; Lindhardt, A. T.; Bang-Andersen, B.; Skrydstrup, T. Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Bromides Using Near Stoichiometric Carbon Monoxide. *Org. Lett.* **2014**, *16*, 2216-2219; (k) Peng, S.; Wang, Z.; Zhang, L.; Zhang, X.; Huang, Y. Streamlined Asymmetric α-Difunctionalization of Ynones. *Nat. Commun.* **2018**, *9*, 375; (l) Li, J.; Yang, F.; Ma, Y.-T.; Ji, K. Gold(III)-Catalyzed Intermolecular Oxidation-Cyclization of Ynones: Access to 4-Substituted Chroman-3-ones. *Adv. Synth. Catal.* **2019**, *361*, 2148-2153.

10. (a) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. Stereoselective Total Synthesis of (−)-Borrelidin. *Angew. Chem. Int. Ed.* **2004**, *43*, 3947-3951; (b) Forsyth, C. J.; Xu, J.; Nguyen, S. T.; Samdal, I. A.; Briggs, L. R.; Rundberget, T.; Sandvik, M.; Miles, C. O. Antibodies with Broad Specificity to Azaspiracids by Use of Synthetic Haptens. *J. Am. Chem. Soc.* **2006**, *128*, 15114-15116; (c) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. Total Synthesis

and Revised Structure of Biyouyanagin A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4708-4711; (d) Tietze, L. F.; Singidi, R. R.; Gericke, K. M.; Böckemeier, H.; Laatsch, H. Isolation, Enantioselective Total Synthesis and Structure Determination of the Anthrapyran Metabolite SS 43405-e. *Eur. J. Org. Chem.* **2007**, 5875-5878.

11. Chinchilla, R.; Nájera, C. Chemicals from Alkynes with Palladium Catalysts. *Chem. Rev.* **2014**, *114*, 1783-1826.

12. For an alternative alkynylation of aldehydes, proceeding via an oxidative C–C bond cleavage, see: Wang, Z.; Li, L.; Huang, Y. A General Synthesis of Ynones from Aldehydes via Oxidative C−C bond Cleavage under Aerobic Conditions. *J. Am. Chem. Soc.* **2014**, *136*, 12233-12236.

13. Ai, W.; Wu, Y.; Tang, H.; Yang, X.; Yang, Y.; Li, Y.; Zhou, B. Rh(III)- or Ir(III)-Catalyzed Ynone Synthesis from Aldehydes via Chelation-Assisted C–H Bond Activation. *Chem. Commun.* **2015**, *51*, 7871-7874.

14. (a) Liu, X.; Yu, L.; Luo, M.; Zhu, J.; Wei, W. Radical-Induced Metal-Free Alkynylation of Aldehydes by Direct C–H Activation. *Chem. Eur. J.* **2015**, *21*, 8745-8749; (b) Zhang, R.-Y.; Xi, L.-Y.; Zhang, L.; Chen, S.-Y.; Yu, X.-Q. Metal-Free Synthesis of Ynones via Direct C–H Alkynylation of Aldehydes with Ethynylbenziodoxolones. *Tetrahedron* **2015**, *71*, 6176-6182; (c) Ouyang, X.-H.; Song, R.-J.; Wang, C.-Y.; Yang, Y.; Li, J.-H. Metal-Free Carbonyl C(sp^2)–H Oxidative Alkynylation of Aldehydes Using Hypervalent Iodine Reagents Leading to Ynones. *Chem. Commun.* **2015**, *51*, 14497-14500.

15. Mukherjee, S.; Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Glorius, F. Alkynylation of C (O)–H Bonds Enabled by Photoredox-Mediated Hydrogen-Atom Transfer. *Angew. Chem. Int. Ed.* **2017**, *56*, 14723-14726.

16. For reviews on the application of EBX reagents in alkynyl transfer reactions, see: (a) Brand, J. P.; Fernández González, D.; Nicolai, S.; Waser, J. Benziodoxole-Based Hypervalent Iodine Reagents for Atom-Transfer Reactions. *Chem. Commun.* **2011**, *47*, 102-115; (b) Fernández González, D.; Brand, J. P.; Mondière, R.; Waser, J. Ethynylbenziodoxolones (EBX) as Reagents for the Ethynylation of Stabilized Enolates. *Adv. Synth. Catal.* **2013**, *355*, 1631-1639; (c) Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. Cyclic Hypervalent Iodine Reagents for Atom-Transfer Reactions: Beyond Trifluoromethylation. *Angew. Chem. Int. Ed.* **2016**, *55*, 4436-4454; (d) Hari, D. P.; Caramenti, P.; Waser, J. Cyclic Hypervalent Iodine Reagents: Enabling Tools for Bond Disconnection via Reactivity Umpolung. *Acc. Chem. Res.* **2018**, *51*, 3212-3225.

17. Reviews: (a) Zhdankin, V. V.; Stang, P. J. Alkynyliodonium Salts in Organic Synthesis. *Tetrahedron* **1998**, *54*, 10927-10966; (b) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. Iodonium Salts in Organic Synthesis. *Arkivoc* **2011**, 370-409; (c) Brand, J. P.; Waser, J. Electrophilic Alkynylation: The Dark Side of Acetylene Chemistry. *Chem. Soc. Rev.* **2012**, *41*, 4165-4179.

18. Selected examples: (a) Lodaya, J. S.; Koser, G. F. Alkynyliodonium Salts as Alkynylating Reagents: Direct Conversion of Alkynylphenyliodonium Tosylates to Dialkyl Alkynylphosphonates with Trialkyl Phosphites. *J. Org. Chem.* **1990**, *55*, 1513-1516; (b) Tykwinski, R. R.; Williamson, B. L.; Fischer, D. R.; Stang, P. J.; Arif, A. M. A New Synthesis

of Alkynyl Sulfones and Single Crystal X-ray Structure of *p*-(Tolylsulfonyl)ethyne. *J. Org. Chem.* **1993**, *58*, 5235-5237; (c) Liu, Z.; Chen, Z. Hypervalent Iodine in Synthesis. 10. An Efficient Route to *S*-Alkynyl *O*,*O*-Dialkyl phosphorodithioates. *J. Org. Chem.* **1993**, *58*, 1924-1925; (d) Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y. A Convenient Synthesis of New 1-Alkynyl-1*H*-benzotriazoles by Reaction of Alkynyl(phenyl)iodonium Salts with Benzotriazole Ion. *Heterocycles* **2000**, *52*, 303-312; (e) Witulski, B.; Alayrac, C. A Highly Efficient and Flexible Synthesis of Substituted Carbazoles by Rhodium-Catalyzed Inter- and Intramolecular Alkyne Cyclotrimerizations. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281-3284; (f) Beringer, F. M.; Galton, S. A. Acetylenic and Ethylenic Iodonium Salts and Their Reactions with a Carbanion. *J. Org. Chem.* **1965**, *30*, 1930-1934; (g) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y. Synthesis of Ethynyl(phenyl)iodonium Tetrafluoroborate. A New Reagent for Ethynylation of 1,3-Dicarbonyl Compounds. *J. Chem. Soc., Chem. Commun.* **1990**, 118-119; (h) Kitamura, T.; Fukuoka, T.; Zheng, L.; Fujimoto, T.; Taniguchi, H.; Fujiwara, Y. Reaction of Alkynyl(phenyl)(*p*-phenylene)bisiodonium Ditriflates with Nucleophiles. High Reactivity of the Alkynyl Component. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2649-2654; (i) Dhara, A.; Weinmann, J.; Krause, A.-M.; Beuerle, F. Apical Functionalization of Tribenzotriquinacenes. *Chem. Eur. J.* **2016**, *22*, 12473-12478; (j) Companys, S.; Peixoto, P. A.; Bosset, C.; Chassaing, S.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S. Asymmetric Alkynylation of β-Ketoesters and Naphthols Promoted by New Chiral Biphenylic Iodanes. *Chem. Eur. J.* **2017**, *23*, 13309-13313; a single example of C-nucleophile other than enolates of 1,3-dicarbonyls: (k) Finkbeiner, P.; Weckenmann, N. M.; Nachtsheim, B. J. Alkynyliodonium Salt Mediated Alkynylation of Azlactones: Fast Access to Cα-Tetrasubstituted α-Amino Acid Derivatives. *Org. Lett.* **2014**, *16*, 1326-1329;

19. Selected examples: (a) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. Palladium-Catalysed Cross-Coupling Reactions of Aryl-, Alkenyl- and Alkynyl-Iodonium Salts and Iodanes with Terminal Alkynes in Aqueous Medium. *Chem. Commun.* **1996**, 835-836; (b) Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Yoon, S.-K.; Son, H.-J. Palladium-Catalyzed Carbonylative Cross-Coupling of Organoboranes with Hypervalent Iodonium Salts: Synthesis of Aromatic Ketones. *Synth. Commun.* **1998**, *28*, 1481-1489; (c) Yu, C.-M.; Kweon, J.-H.; Ho, P.-S.; Kang, S.-C.; Lee, G. Y. Copper-Catalyzed Cross- and Carbonylative Coupling Reactions of Alkynyliodonium Salts with Organoboronic Acids and Organostannanes. *Synlett* **2005**, 2631-2634; (d) Zhu, M.; Song, Y.; Cao, Y. A Fast and Convenient Heck Reaction in Water under Microwave Irradiation. *Synthesis* **2007**, 853-856; (e) Guo, J.; Lin, L.; Liu, Y.; Li, X.; Liu, X.; Feng, X. Nickel(II)-Catalyzed Enantioselective α-Vinylation of β-Keto Amides/Esters with Hypervalent Iodine Salts. *Org. Lett.* **2016**, *18*, 5540-5543.

20. Stuart, D. R. Aryl Transfer Selectivity in Metal-Free Reactions of Unsymmetrical Diaryliodonium Salts. *Chem. Eur. J.* **2017**, *23*, 15852-15863.

21. Kitamura, T.; Stang, P. J. Improved Synthesis of Alkynylphenyliodonium Arylsulfonates (RCCIPh·OSO2Ar). *J. Org. Chem.* **1988**, *53*, 4105-4106.

22. (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859; (b) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. Modern Advances in Heterocyclic Chemistry in Drug Discovery. *Org. Biomol. Chem.* **2016**, *14*, 6611-6637.

23. (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315-8359; (b) Huchet, Q. A.;

Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery. *J. Med. Chem.* **2015**, *58*, 9041-9060; (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422-518.

24. See the Supporting Information for a list of unsuccessful substrates.

25. (a) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. α-Arylation by Rearrangement: On the Reaction of Enolates with Diaryliodonium Salts. *Chem. Eur. J.* **2010**, *16*, 8251-8254; (b) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. Arylation with Unsymmetrical Diaryliodonium Salts: A Chemoselectivity Study. *Chem. Eur. J.* **2013**, *19*, 10334-10342; (c) Stridfeldt, E.; Lindstedt, E.; Reitti, M.; Blid, J.; Norrby, P.-O.; Olofsson, B. Competing Pathways in *O*-Arylations with Diaryliodonium Salts: Mechanistic Insights. *Chem. Eur. J.* **2017**, *23*, 13249-13258; (d) Ghosh, M. K.; Rzymkowski, J.; Kalek, M. Transition-Metal-Free Aryl–Aryl Cross-Coupling: C−H Arylation of 2-Naphthols with Diaryliodonium Salts. *Chem. Eur. J.* **2019**, *25*, 9619-9623.

26. (a) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 16563-16573; (b) Wodrich, M. D.; Caramenti, P., Waser, J. Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition? *Org. Lett.* **2016**, *18*, 60-63.

27. The direct substitution at the α-acetylenic carbon has also been determined by computations to be the favored reaction pathway during a related addition of nucleophilic carbon radicals to EBX reagents, see: Le Vaillant, F.; Wodrich, M. D.; Waser, J. Room Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: A Divergent Mechanism Compared to Alkynylation. *Chem. Sci.* **2017**, *8*, 1790-1800.

28. (a) Kitamura, T.; Stang, P. J. Generation, Trapping and Fate of Alkylidenecarbene-Iodonium Ylides from the Addition of NaN_3 to Alkynylphenyliodonium Tosylates. *Tetrahedron Lett.* **1988**, *29*, 1887-1889; (b) Ochiai, M.; Oshima, K.; Masaki, Y. Nucleophilic Vinylic Substitutions of (*Z*)-(β-(Phenylsulfonyl)-alkenyl)iodonium Tetrafluoroborates with Tetra-butyl-ammonium Halides: Retention of Configuration. *Tetrahedron Lett.* **1991**, *32*, 7711-7714; (c) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. Generation of [β-(Phenylsulfonyl)alkylidene]carbenes from Hypervalent Alkenyl- and Alkynyliodonium Tetrafluoroborates and Synthesis of 1-(Phenylsulfonyl)cyclopentenes. *J. Am. Chem. Soc.* **1991**, *113*, 3135-3142; (d) Ochiai, M.; Kitagawa, Y.; Yamamoto, S. Generation and Reaction of Monocarbonyliodonium Ylides: Ester Exchange of (*Z*)-(β-Acetoxyvinyl)iodonium Salts with Lithium Ethoxide and Synthesis of α,β-Epoxy Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 11598-11604.

29. (a) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. Tandem Michael-Carbene Insertion Reactions of Alkynyliodonium Salts. Extremely Efficient Cyclopentene Annulations. *J. Am. Chem. Soc.* **1986**, *108*, 8281-8283; (b) Tykwinski, R. R.; Whiteford, J. A.; Stang, P. J. Alkylidenecarbene Insertions into Aromatic C–H Bonds in Solution. *J. Chem.*

Soc., Chem. Commun. **1993**, 1800-1801; (c) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. A New Method for the Synthesis of Cyclopentenones via the Tandem Michael Addition-Carbene Insertion Reaction of β-Ketoethynyl(phenyl)iodonium Salts. *J. Am. Chem. Soc.* **1994**, *116*, 93-98; (d) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. Alkynyliodonium Salts in Organic Synthesis. Development of a Unified Strategy for the Syntheses of (−)-Agelastatin A and (−)-Agelastatin B. *J. Org. Chem.* **2002**, *67*, 7096-7109.

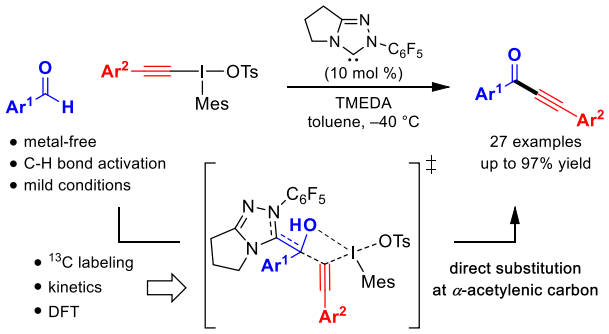
30. Fernández González, D.; Brand, J. P.; Waser, J. Ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX): An Exceptional Reagent for the Ethynylation of Keto, Cyano, and Nitro Esters. *Chem. Eur. J.* **2010**, *16*, 9457-9461.

31. The data points did not show linear dependence in the coordinate systems corresponding to the 1st and 3rd overall orders. See the Supporting Information for details.

32. We have also calculated the full mechanism in $CHCl_3$, the solvent that was used in the initial rate studies. The overall mechanistic picture and conclusions are identical to these obtained for the calculations in toluene. See the Supporting Information for details.

33. The computed free energy profile predicts that the conjugated acid of TMEDA will inhibit the reaction, as it is expelled within the largest energy span. This should in turn result in the lower than the observed second order during the time-course experiment (Figure 1). However, under the experimental conditions (toluene, –40 °C) the salts of TMEDA are insoluble, hence, their concentrations remain constant, lacking the impact on the kinetics of the reaction.

SYNOPSIS


(10 mol %)
TMEDA
toluene, –40 °C
27 examples
up to 97% yield
• metal-free
• C-H bond activation
• mild conditions
• ^{13}C labeling
• kinetics
• DFT
direct substitution
at α-acetylenic carbon