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Nonafluorobutanesulfonyl Azide as a Shelf-Stable Highly Reactive Oxidant for the Copper-Catalyzed Synthesis of 1,3-Diynes from Terminal Alkynes

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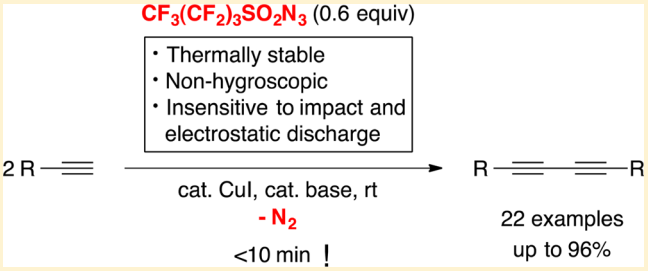
Supporting Information

ABSTRACT: Nonafluorobutanesulfonyl azide is a highly efficient reagent for the copper-catalyzed coupling of terminal alkynes to give symmetrical and unsymmetrical 1,3-diynes in good to excellent yields and with good functional group compatibility. The reaction is extremely fast (<10 min), even at low temperature (−78 °C), and requires substoichiometric amounts of a simple copper(I) or copper(II) salt (2−5 mol %) and an organic base (0.6 mol %). A possible mechanistic pathway is briefly discussed on the basis of model DFT theoretical calculations. The quantitative assessment of the safety of use and shelf stability of nonafluorobutanesulfonyl azide has confirmed that this reagent is a superior and safe alternative to other electrophilic azide reagents in use today.



INTRODUCTION

The synthesis of conjugated diynes and polyynes has recently experienced a renaissance due to their importance as building blocks for the preparation of natural products, pharmaceuticals, and advanced materials with interesting optoelectronic properties.[1] The oxidative coupling of terminal alkynes has become the standard method for the preparation of these essential π-conjugated structural motifs. Alkyne homocoupling to give 1,3-diynes was first discovered by Glaser[2] in 1869, employing stoichiometric copper(I) salts in the presence of a base under aerobic conditions, and was later improved by Hay,[3] and Campbell and Eglinton[4] using catalytic amounts of copper salts or complexes with appropriate nitrogen bases (as ligands or solvents) in the presence of dioxygen, the so-called Glaser−Hay coupling. More recent research on the Glaser−Hay coupling reaction has mainly focused on modifications of Glaser's original conditions to improve its efficiency,[5] introducing other catalytic systems based on Pd/Cu,[6] Co,[7] a combination of Cu and Ag,[8] Fe,[9] or Ni[5d,k,10] salts, and more recently, Au.[11] The Pd-catalyzed version has developed into a powerful synthetic tool due to its mildness and efficiency, but palladium reagents are expensive and require air-sensitive and expensive phosphine ligands and copper cocatalysts. The copper-catalyzed homocoupling remains attractive because copper salts are economical, easy to handle, and relatively environmentally friendly, but this method also has drawbacks. The requirement of stoichiometric amounts of copper salts to achieve acceptable rates and yields, excess oxidants, high temperature, excess bases, cocatalysts, relatively long reaction times (2−48 h), and the low to moderate yields generally obtained for coupling aliphatic alkynes are the major shortcomings.

In our recent work on the copper-catalyzed synthesis of *N*,*N*′-disulfonylamidines from sulfonamides and terminal alkynes using the shelf-stable nonafluorobutanesulfonyl azide (NfN_3),[12] we observed the formation of varying amounts of 1,3-diynes when attempting to perform the reaction in a one-pot fashion by mixing all the reagents together with the copper catalyst. This formal oxidative homocoupling of the starting terminal alkyne was the dominant process under some of the conditions tested in those studies. Surprised by the high rate observed for this coupling, we decided to further explore and optimize the reaction in order to obtain the 1,3-diynes in synthetically useful yields. We describe below our experimental results on this novel oxidative coupling of terminal alkynes promoted by NfN_3, its application to the preparation of symmetrical and nonsymmetrical 1,3-diynes, a theoretical investigation of the possible mechanistic pathway of this process, and a quantitative assessment of the safety of use and shelf stability of NfN_3.

RESULTS AND DISCUSSION

We selected phenyl acetylene as a model alkyne and studied its reaction with NfN_3 in an open flask under different experimental conditions (Table 1). No reaction took place by stirring both compounds together, with or without catalytic CuI

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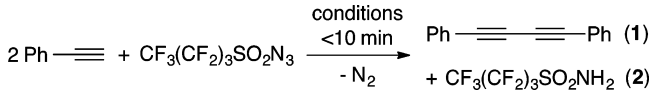
Table 1. Development of the Oxidative Coupling of Terminal Alkynes Promoted by NfN_3[a]



entry	cat. (mol %)	base (equiv)	solvent	temp	yield[b] (%)
1			THF	r.t.	n.r.[c]
2	CuI (5)		THF	r.t.	n.r.
3		Et_3N	THF	r.t.	n.r.[d]
4	CuI (5)	Et_3N (1.2)	THF	r.t.	93
5	CuI (5)	Et_3N (1.2)	MeCN	r.t.	64
6	CuI (5)	Et_3N (1.2)	MeOH	r.t.	62
7	CuI (5)	Et_3N (1.2)	$CHCl_3$	r.t.	88
8	CuI (5)	2,6-lutidine (1.2)	$CHCl_3$	r.t.	92
9	CuCl (5)	2,6-lutidine (1.2)	$CHCl_3$	r.t.	90
10	CuBr (5)	Et_3N (1.2)	THF	r.t.	82
11	CuBr (5)	DBU (1.2)	$CHCl_3$	r.t.	85
12	CuI (5)	DBU (1.2)	$CHCl_3$	r.t.	96
13	$Cu(OTf)_2$ (5)	DBU (1.2)	$CHCl_3$	r.t.	87
14	CuI (3)	DBU (1.2)	$CHCl_3$	r.t.	92
15	CuI (2)	DBU (1.2)	$CHCl_3$	r.t.	90
16	CuI (1)	DBU (1.2)	$CHCl_3$	r.t.	72
17[e]	CuI (2)	DBU (0.6)	$CHCl_3$	r.t.	90
18	CuI (2)	DBU (0.3)	$CHCl_3$	r.t.	78
19	CuI (2)	DBU (0.2)	$CHCl_3$	r.t.	69
20[e]	CuI (2)	DBU (0.6)	$CHCl_3$	−78 °C	80

[a]Unless otherwise stated, 1.2 equiv of NfN_3 was used. [b]Isolated yield after purification by column chromatography. [c]No reaction. [d]The alkyne remained unreacted under these conditions, and NfN_3 reacted with the tertiary amine to give *N,N*-diethyl-*N*′-((perfluorobutyl)sulfonyl)formimidamide together with other unidentified minor products.[13] [e]Only 0.6 equiv of NfN_3 was used.

(5 mol %), in THF at room temperature for 12 h (entries 1 and 2). The alkyne also remained unreacted after addition of Et_3N (1.2 equiv) to an equimolar mixture of alkyne and NfN_3 under the same experimental conditions, but in the absence of the metal catalyst (entry 3). In these experiments, most of NfN_3 apparently remained unreacted, as readily evidenced by the characteristic pungent odor of this reagent. In contrast, when the alkyne (1.0 equiv), NfN_3 (1.2 equiv), CuI (5 mol %), and Et_3N (1.2 equiv) were all mixed together in THF (the order of addition of reagents is of no consequence, although, for practical reasons, the final dropwise addition of NfN_3 is recommended), a fast (<5 min) and exothermic reaction occurred, accompanied by strong gas evolution (N_2) to afford 1,4-diphenylbuta-1,3-diyne (**1**) in very high yield along with nonafluorobutanesulfonamide (**2**) (entry 4). Other organic solvents (entries 5−7), including hydroxylic ones (entry 6), were successfully employed in this reaction with variable yields. The use of $CHCl_3$ (entry 7) was particularly appealing since it facilitated purification of the product diyne by allowing a simple removal of insoluble **2** by filtration through a small pad of silica, which also removed most of the inorganic catalyst. The reaction was also very tolerant to changes in the nature of the base and the copper catalyst. Thus, aromatic bases (2,6-lutidine: entries 8 and 9), or amidines (DBU: entries 11−20), and copper(I) salts such as CuCl (entry 9) and CuBr (entries 10 and 11), or copper(II) salts such as $Cu(OTf)_2$ (entry 13), could be used with similarly good yields. The amount of added copper catalyst (entries 14−16) and base (entries 17−19) could be significantly reduced at the expense of the product yield, although, even under the most economical conditions (entry 16: 1 mol % CuI; entry 19: 0.2 equiv DBU), moderately good yields were still obtained (72% or 69%, respectively). The amount of NfN_3 could be reduced to 0.6 equiv with no significant change in yield (entry 17), but further reduction of the equivalents of base (entries 18 and 19) or oxidant (data not shown) significantly lowered the yield, as could be anticipated from the atom balance of the reaction shown in the scheme of Table 1. Remarkably, the reaction could be performed at very low temperatures (entry 20: −78 °C) with almost equal rate and efficiency.

Under the optimized reaction conditions, to a mixture of alkyne (1.0 equiv), catalytic CuI (5 mol %), and DBU (0.6 equiv) in $CHCl_3$ was added NfN_3 (0.6 equiv) dropwise at room temperature in an open flask (*strong gas evolution!*). As indicated above, the process is rather exothermic, and we recommend cooling the reaction to 0−4 °C when ≥2.0 mmol of alkyne is employed. Using this procedure, a series of differently substituted terminal alkynes were efficiently transformed into the corresponding 1,4-disubstituted-1,3-diynes in good to excellent yields (78−93%) and in short reaction times (<10 min) (Scheme 1).

Aromatic, aliphatic, and silyl-substituted alkynes were all smoothly homocoupled in good to very high yields. The procedure was readily extended to the preparation of unsymmetrical diynes by heterocoupling of a terminal alkyne **A** with an excess (4 equiv) of a different terminal alkyne **B** using the same optimized conditions (Scheme 2). In this case, separation of the target heterodiyne (**AB**) from the major homodiyne product (**BB**), which is concomitantly formed under these conditions, can be readily performed by column chromatography when the less polar alkyne is selected as **B** (see the Experimental Section). The reaction was compatible with the presence of ether groups (**4**, **7**), tertiary amines (**5**), aryl halides (**6**, **15**, **16**, **18**, **20**), free hydroxyl groups (**9**, **10**, **15**−**21**, **23**), and imides (**14**) in the substrate.

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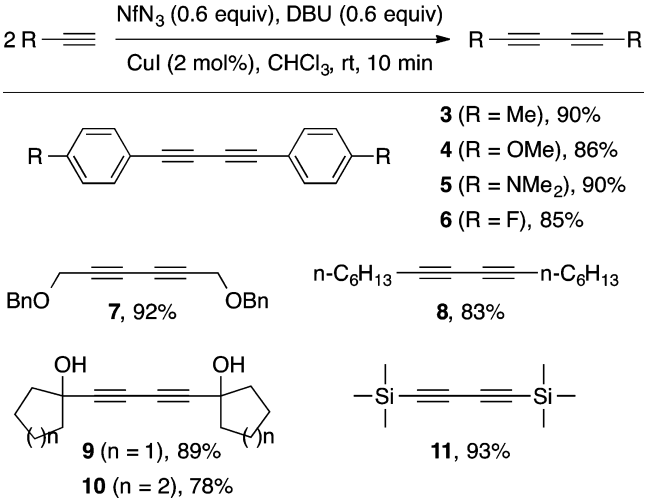
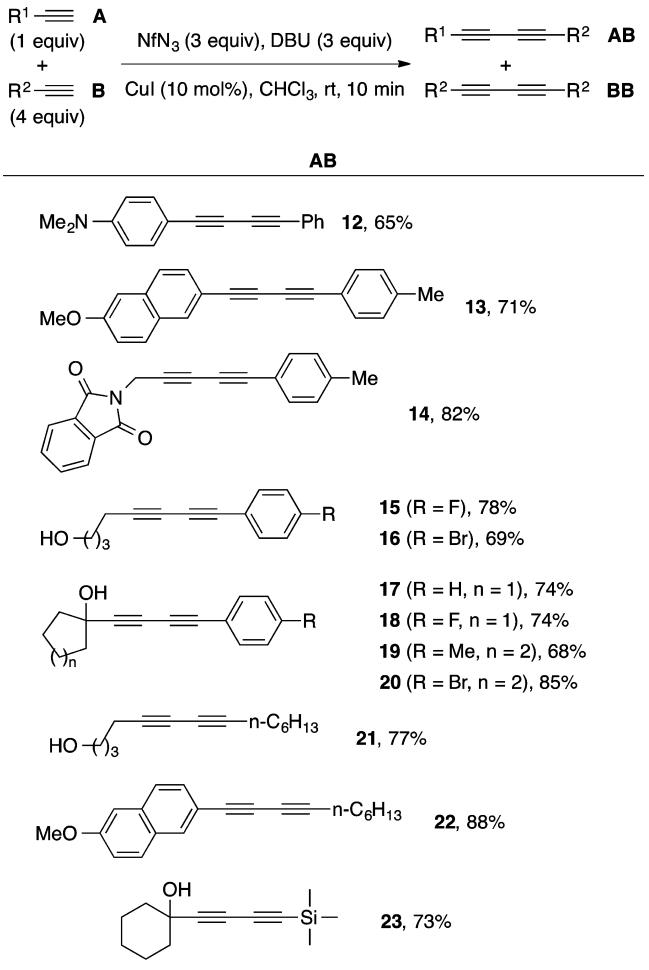
Scheme 1. Synthesis of Symmetrical 1,3-Diynes

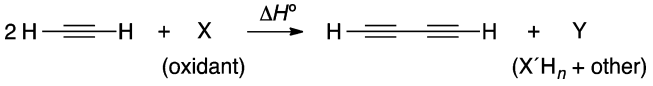


Scheme 2. Synthesis of Unsymmetrical 1,3-Diynes



Theoretical Studies. In an attempt to understand the exceptional efficiency of NfN_3 in promoting the copper-catalyzed coupling of terminal alkynes as compared to common oxidants generally employed in this transformations, we have calculated the reaction enthalpies of a series of model simplified processes (Table 2). For this, we have selected the DFT B3LYP/dgdzvp method that has been shown[14] to give good agreement with experimental bond lengths and reaction enthalpies of iodine compounds, which are involved in some of the model reactions included in Table 2.

Table 2. Theoretical Reaction Enthalpies ($\Delta H°$, 298 K) Calculated at the DFT B3LYP/dgdzvp Level for the Homocoupling of Acetylene Promoted by a Series of Common Oxidants, Including Trifluoromethanesulfonyl Azide (TfN_3) and NfN_3[a]



entry	X (oxidant)	Y (reduced products)	$\Delta H°$ (kcal mol^{-1})
1		H_2	−6.18
2	I_2	2 HI	−7.68
3	BQ	HQ	−27.28
4	NIS	NHS + HI	−33.74
5	$PhI(OAc)_2$	PhI + 2AcOH	−60.88
6	MeOOH	MeOH + H_2O	−66.43
7	1/2 O_2	H_2O	−68.32
8	TfN_3	$TfNH_2$ + N_2	−78.38
9	NfN_3	$NfNH_2$ + N_2	−77.92

[a]NIS: *N*-iodosuccinimide; NHS: succinimide; BQ: benzoquinone; HQ: hydroquinone.

The theoretical results clearly show that (i) acetylene homocoupling in the absence of an oxidant, with formation of dihydrogen, is an exoergic process (entry 1); and (ii) perfluoroalkanesulfonyl azides provide the strongest enthalpic driving force (ca. ≥10 kcal mol^{-1} more exothermic than the next best oxidant: O_2) for this coupling when compared to other oxidants used (cf. entries 2−7 and 8−9), thus explaining the strong exothermic behavior experimentally observed.

The generally accepted mechanism of the Glaser reaction was proposed by Bohlmann and co-workers in 1964.[15] Thus, the coordination of Cu(I) ions to the alkyne triple bond activates it to deprotonation, giving a dinuclear Cu(II)−acetylide complex in the presence of an oxidant that then collapses to the oxidatively coupled product. However, the strong exothermicity and high rate of the NfN_3-promoted coupling as compared to a typical Glaser−Hay reaction reveal that both processes should be mechanistically distinct. We have carried out additional DFT calculations (B3LYP/6-31G(d)/LANL2DZ), in order to get insight into the possible reaction mechanism of this alkyne dimerization. Trifluoromethanesulfonyl azide (**I**), propyne, and Me_3N were used as simplified model reagents. We considered alkynyl−Cu(I) complex **II** (Scheme 3) as the starting point, since these intermediates are readily formed by reaction of Cu(I) salts and alkynes in the presence of base. Initially, coordination of the sulfonyl azide and Me_3N to intermediate **II** was considered. Extrusion of N_2 from coordinated azide was calculated to have a relatively high activation energy (18.8 kcal mol^{-1}), which is hardly compatible with the observed fast reaction rate at low temperature (see the Supporting Information for details). For this reason, this pathway can be disregarded. Alternatively, 1,3-cycloaddition of azide **I** with alkynyl−Cu complex **II** is a faster process (ΔG_a = 10.1 kcal mol^{-1}, Scheme 3). This elementary step has been previously proposed for the formation of triazoles and imidines involving methylsulfonyl azide.[16] In contrast to this previously reported computational result, the activation energy is significantly lower in our case. Although transition state TS_{II-III} suggests the occurrence of a [3 + 3] cycloaddition involving the alkyne carbons and Cu, intrinsic reaction coordinate (IRC)

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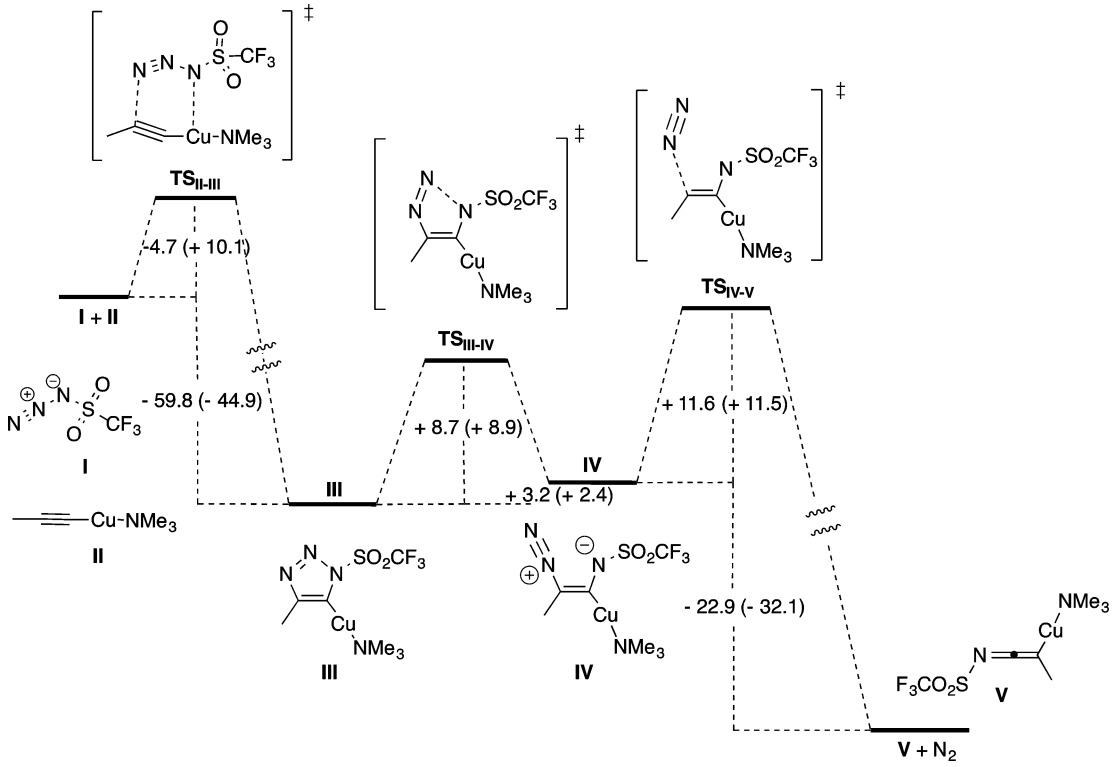
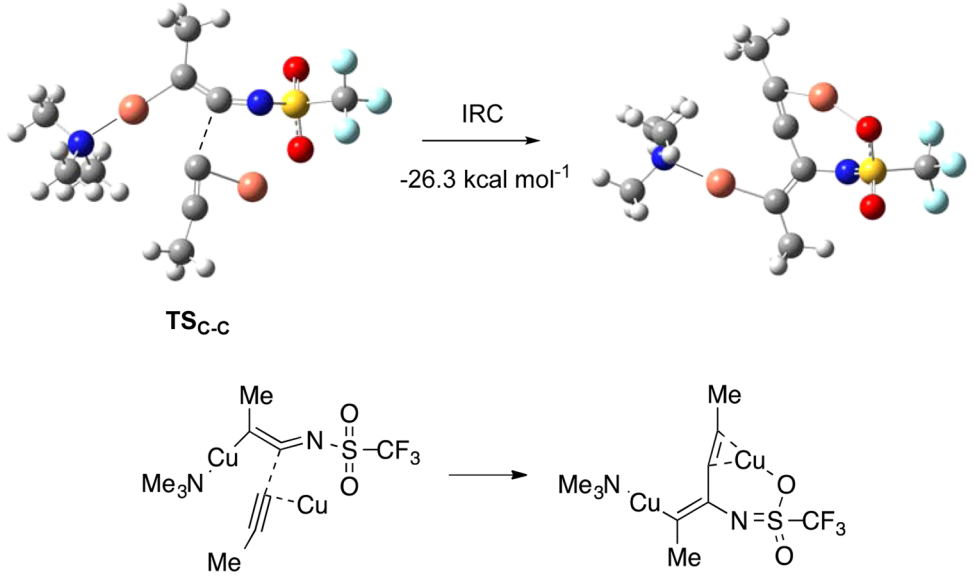
Scheme 3. Calculated Reaction Profile for the Initial Steps of the Alkyne Activation and the Role of NfN_3 at B3LYP/6-31G(d) (C,H,N,O,S,F) LANL2DZ (Cu) Level[a]



[a]Δ(E + ZPE) values in kcal mol^{-1} (ΔG values in brackets).

Scheme 4. Plausible Mechanism for the Formation of the C−C Bond by Reaction of V and an Alkynyl−Cu Intermediate[a]



[a]B3LYP/6-31G(d) (C,H,N,O,S,F) LANL2DZ (Cu) level. Δ(E + ZPE) value in kcal mol^{-1} (grey: C; white: H; dark blue: N; pink: Cu; yellow: S; red: O; light blue: F).

studies lead to the formation of the five-membered ring complex **III** in a strongly exoergic process (−55.0 kcal mol^{-1}). This is also in contrast to the result obtained for methylsulfonyl azide and pyridine as ligand, which affords a six-membered cupracycle previous to ring contraction to a similar triazol derivative.[16] Triazolyl complex **III** subsequently experiences a slightly endoergic ring opening process (+2.4 kcal mol^{-1}) with a relatively low activation barrier (8.9 kcal mol^{-1}), leading to complex **IV**. Elimination of N_2 from this intermediate takes place through TS_{IV-V}, which lies 11.5 kcal mol^{-1} above the reagent. Interestingly, after a partial IRC calculation, minimization led to intermediate **V**, in which 1,2-migration of Cu has taken place along the reaction coordinate. This type of complex has been proposed as intermediate in the Cu-catalyzed

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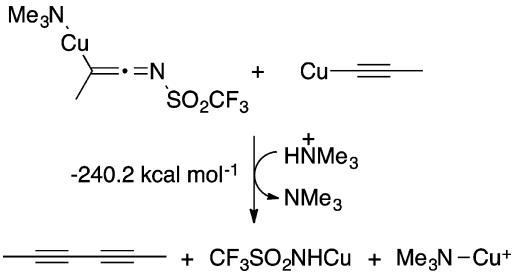
formation of amidines from sulfonyl azides and alkynes in the presence of secondary amines.[16] We searched for several possible pathways that could explain the formation of diynes from **V**, since formation of this intermediate is highly probable following the above-mentioned pathway, which is very favorable thermodynamically and involves low activation barriers. After a high number of trials, we were able to locate a transition state involving C−C coupling for which association of **V** and an alkynyl−Cu(I) have to previously occur. This transition state is only 16.3 kcal mol^{-1} above the reagents. Partial IRC calculation leads to the structure shown in Scheme 4, which is not a stationary point. This complex is 26.3 kcal mol^{-1} more stable than the transition state, and shows complete C−C bond formation. Therefore, this transition state ($\mathbf{TS_{C-C}}$) actually corresponds to a productive reaction. Dissociation of the final diyne from Cu will be probably assisted by coordination of amine and protonation of the N ligand, an overall process that has been calculated to be strongly favorable, as shown in Scheme 5.

Scheme 5. Overall Transformation of V and an Alkynyl−Cu Intermediate into the Final Products[a]



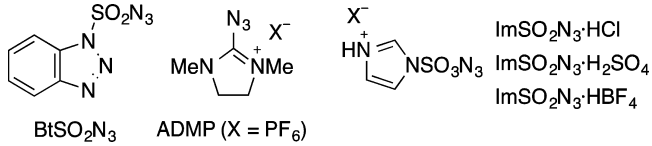
[a]B3LYP/6-31G(d) (C,H,N,O,S,F) LANL2DZ (Cu) level. Δ(*E* + ZPE) value in kcal mol^{-1}.

In summary, although other possible pathways cannot be discarded, we have found a plausible mechanism that accounts for the observed reactivity. The formation of the C−C bond would be the rate-limiting step, and the activation energy we have found constitutes an upper limit for the process.

Assessment of the Safety of Use and Shelf Stability of NfN_3. The growing number of applications of NfN_3 in synthetic organic chemistry (as a diazo-transfer reagent, 1,3-dipole in cycloaddition-started multicomponent reactions, or as a nitrenenoid precursor in CH amination reactions),[12,17] outperforming its more costly and hazardous lower homologue triflyl azide (TfN_3), calls for a rational assessment of its safety of use and shelf stability. To this end, the sensitivity of neat NfN_3 toward heat, impact, and electrostatic discharge (ESD) has been quantified (Table 3 and the Supporting Information).[18]

The thermal stability was assessed by differential scanning calorimetry (DSC) using two different heating rates (10.0 or 20.0 °C min^{-1}) in hermetic aluminum pans with either sealed or pierced lids. The DSC curve (see the Supporting Information) at 10 °C min^{-1} in a pierced lid pan (atmospheric pressure) showed that NfN_3 melts at −22 °C and boils at 100 °C without decomposition. In a hermetically sealed pan, a small exotherm of only 0.100 kcal g^{-1} was observed with an extrapolated onset temperature of 140.8 °C. The exotherm was 0.107 kcal g^{-1} with an onset temperature of 152.0 °C when the heating rate was 20.0 °C min^{-1}. Both energy values are well below those of conventional energetic materials (>0.24 kcal g^{-1}). An ignition temperature assay was also carried out by heating two 0.5 g samples in open glass tubes at a 5 °C min^{-1} heating rate from room temperature to 450 °C. Boiling of the samples was observed at 100 °C, with formation of white fumes above 144 °C. An energetic decomposition with gas evolution (N_2), but without detonation, was seen at 152 °C, with deposition of an unidentified white solid residue at the walls of the tube, which remained to the end of the experiment. Thus, no potential thermal hazards were detected for NfN_3 at or below its boiling point. The shock sensitiveness was determined with a BAM drop hammer following a 30-trial Bruceton method, which gave a minimum impact energy of at least 25.5 J, which is comparable to that of TNT (30 J) considered as not sensitive to impact. The compound proved to be also insensitive toward electrostatic discharge (tested at up to 30 000 V, i.e., 3.4 J, for 10 repetitions). Regarding its shelf stability, we have safely stored 40 g batches of the neat reagent in closed vials at −25 °C for 12 months without any observed decomposition. These stability and safety parameters compare very favorably with those recently described for related azide

Table 3. Sensitivity and Thermal Stability Data for Sulfonyl Azide Reagents



	sensitivity			DSC		
compd.	impact (J)	friction (N)	ESD (J)	T_{eo} (°C)[a]	T_p (°C)[b]	Δ*H* (kcal/g)
NfN_3	>25.5	[c]	>3.4	140.82[d,e]	163.66[d,e]	0.100[d,e]
				152.02[d,f]	174.00[d,f]	0.107[d,f]
$BtSO_2N_3$[g]	[h]	[h]	[h]	>95	[h]	[h]
ADMP[i]	>25	>360	[h]	>200[j]	[h]	[h]
$ImSO_2N_3·HCl$[k]	6	240	0.50	102	[h]	[h]
$ImSO_2N_3·H_2SO_4$[k]	40	240	0.30	131	[h]	[h]
$ImSO_2N_3·HBF_4$[k]	40	240	0.50	146	[h]	[h]

[a]Extrapolated onset temperature. [b]Peak temperature. [c]Not applicable because the compound is a liquid under standard conditions. [d]In hermetically sealed aluminum pan. At atmospheric pressure (in aluminum pan with pierced lid), the compound evaporates at 100 °C without decomposition. [e]At 10 °C/min. [f]At 20 °C/min. [g]Reference 19. [h]Not reported. [i]Reference 20. [j]In open aluminum pan. [k]Reference 21.

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reagents (Table 3). Contrary to NfN_3, these reagents have been reported to be hygroscopic and sensitive to moisture, which poses an explosion hazard due to inadvertent formation of hydrazoic acid. The nonhazardous nature of NfN_3, its high shelf stability, low sensitivity to hydrolysis, good reaction yields, and easy-to-purify reaction mixtures make it a clearly superior alternative to other electrophilic azide reagents in use today.

CONCLUSION

We have shown that nonafluorobutanesulfonyl azide (NfN_3) promotes the copper-catalyzed coupling of terminal alkynes in the presence of an organic base to give symmetrical and unsymmetrical 1,3-diynes in high yields and with good functional group compatibility. The very fast coupling rates observed, even at low temperature, and the high exothermic character of the reaction point to a distinct mechanism as compared with typical Glaser−Hay couplings. A possible mechanistic pathway via an intermediate ketenimine has been discussed on the basis of model DFT calculations. Given the increasing importance of NfN_3 as an efficient and versatile reagent in organic synthesis, a quantitative assessment of its safety of use and shelf stability has confirmed it to be a superior and safe alternative to other electrophilic azide reagents in use today. The novel procedure for the oxidative coupling of terminal alkynes here described could prove to be of wide interest for the efficient synthesis of molecules and materials based on the 1,3-diyne motif.

EXPERIMENTAL SECTION

General Methods. All melting points were measured with a micromelting apparatus. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. The chromatograms were viewed under UV light and/or by treatment with a solution of ammonium molybdate (50 g) and cerium(IV) sulfate (1 g) in 5% aqueous H_2SO_4 (1 L) (Hanessian stain), followed by charring on a hot plate. Flash column chromatography was performed with silica gel, grade 60, 230−400 mesh. ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively, using $CDCl_3$ or CD_3COCD_3 as solvents. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual peaks of the deuterated NMR solvent used. Accurate mass values were determined on a mass spectrometer equipped with an electrospray or APCI ion source and a TOF detector. All reactions were carried out with magnetic stirring in loosely capped 15 mL reaction vials or open 25 mL round-bottom flasks. All solvents were of HPLC grade and were used as provided. All starting materials and reagents are commercially available and were used as received, with the exception of nonafluorobutanesulfonyl azide (NfN_3), which was prepared from nonafluorobutanesulfonyl fluoride and sodium azide following literature procedures.[22]

Typical Experimental Procedure for the Synthesis of Symmetrical 1,3-Diynes. To a solution of the corresponding alkyne (1.0 mmol) in $CHCl_3$ (4 mL) were added CuI (9.5 mg, 0.05 mmol), DBU (0.045 mL, 0.3 mmol), and, finally, perfluorobutanesulfonyl azide dropwise (195 mg, 0.6 mmol) (***Caution!*** *Exothermic reaction with strong gas evolution*). After stirring the mixture at room temperature for 10 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were separated, dried over Na_2SO_4, and concentrated at reduced pressure, and the crude product was purified by column chromatography on silica gel (using a hexane/EtOAc mixture as eluent) to afford the corresponding 1,3-diyne. Alternatively, the reaction mixture was filtered through a small pad of silica gel eluting with $CHCl_3$ to remove the metal catalyst and most of sulfonamide **2**. Evaporation of the filtrate at reduced pressure removed residual **2** by sublimation to afford the crude product that could be further purified by column chromatography as above.

Typical Experimental Procedure for the Synthesis of Unsymmetrical 1,3-Diynes. To a solution of alkyne **A** (0.3 mmol, 1 equiv) and alkyne **B** (1.2 mmol, 4 equiv) in $CHCl_3$ (4 mL) were added CuI (14 mg, 0.075 mmol), DBU (0.276 mL, 1.8 mmol), and, finally, perfluorobutanesulfonyl azide dropwise (586 mg, 1.8 mmol) (***Caution!*** *Exothermic reaction with strong gas evolution*). After stirring the mixture at room temperature for 10 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were separated, dried over Na_2SO_4, and concentrated at reduced pressure, and the crude product was purified by column chromatography over silica gel. In all cases described in Scheme 2, the less polar symmetrical alkyne (**BB**) was eluted first from the column with hexane/EtOAc 9:1 (v/v) and then the corresponding unsymmetrical 1,3-diyne (**AB**) using hexane/EtOAc 4:1 (v/v). Alternatively, the simplified workup procedure indicated for the symmetrical diynes could be followed.

*1,4-Diphenylbuta-1,3-diyne (**1**).* Yield: 90% (91 mg); colorless solid; R_f = 0.35 (hexane). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.38 (m, 6 H), 7.52−7.55 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.0, 81.7, 121.9, 128.6, 129.4, 132.6.

*1,4-Di-p-tolylbuta-1,3-diyne (**3**).* Yield: 90% (104 mg); colorless solid; R_f = 0.41 (hexane). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 6 H), 7.15 (d, J = 8.0 Hz, 4 H), 7.42 (d, J = 8.0 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 73.6, 81.7, 118.9, 129.4, 132.5, 139.6.

*1,4-Bis(4-methoxyphenyl)buta-1,3-diyne (**4**).* Yield: 86% (113 mg); yellow solid; R_f = 0.33 (hexane/EtOAc 9:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6 H), 6.85 (d, J = 8.8 Hz, 4 H), 7.46 (d, J = 8.8 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 73.1, 81.4, 114.1, 114.3, 134.2, 160.4.

*1,4-Bis(p-N,N-dimethylaminophenylethynyl)buta-1,3-diyne (**5**).* Yield: 90% (130 mg); dark powder; R_f = 0.32 (hexane/EtOAc 5:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[6d] ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (s, 12 H), 6.61 (d, J = 8.7 Hz, 4 H), 7.39 (d, J = 8.7 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 72.8, 82.5, 108.8, 111.8, 133.8, 150.5; HRMS (ESI) calcd for $C_{20}H_{21}N_2$ ([M + H$^+$]) 289.1705, found m/z 289.1703.

*1,4-Bis(4-fluorophenyl)buta-1,3-diyne (**6**).* Yield: 85% (101 mg); white solid; R_f = 0.52 (hexane/EtOAc 9:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (t, J = 8.7 Hz, 4 H), 7.51 (dd, J = 8.9, 5.4 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.7, 80.6, 116.1 (d, J = 22.3 Hz), 118.1 (d, J = 3.5 Hz), 134.71 (d, J = 8.6 Hz), 163.2 (d, J = 251.6 Hz).

*1,6-Bis(benzyloxy)hexa-2,4-diyne (**7**).* Yield: 92% (134 mg); orange oil; R_f = 0.49 (hexane/EtOAc 9:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[10d] ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 4 H), 4.54 (s, 4 H), 7.23−7.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.7, 70.7, 71.9, 75.5, 128.1, 128.3, 128.6, 137.2.

*Hexadeca-7,9-diyne (**8**).* Yield: 83% (91 mg); yellow oil; R_f = 0.41 (hexane). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 6 H), 1.23−1.42 (m, 8 H), 1.46−1.55 (m, 4 H), 2.23 (t, J = 7.0 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.3, 22.7, 28.5, 28.7, 31.56, 65.4, 77.6.

*1,1′-(Buta-1,3-diyne-1,4-diyl)bis(cyclopentan-1-ol) (**9**).* Yield: 89% (97 mg); colorless solid; R_f = 0.42 (hexane/EtOAc 5:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, CD_3COCD_3) δ 1.69−1.90 (m, 16 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 24.0, 42.9, 67.2, 74.4, 84.8.

*1,1′-(Buta-1,3-diyne-1,4-diyl)bis(cyclohexan-1-ol) (**10**).* Yield: 78% (96 mg); colorless solid; R_f = 0.39 (hexane/EtOAc 5:1). ^1H NMR and ^{13}C NMR were in agreement with those reported in the literature.[5l] ^1H NMR (300 MHz, (CD_3COCD_3) δ 1.25−1.34 (m, 4 H), 1.46−1.72

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(m, 120 H), 1.81−1.87 (m, 4 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 23.6, 26.0, 40.4, 68.2, 68.5, 84.8.

*1,4-Bis(trimethylsilyl)buta-1,3-diyne (**11**).* Yield: 93% (90 mg); colorless solid; R_f = 0.58 (hexane). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[23] ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.18 (s, 18 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ −0.36, 86.1, 88.1.

*N,N-Dimethyl-4-(phenylbuta-1,3-diyn-1-yl)aniline (**12**).* Yield: 65% (48 mg); brown solid; mp 112−114 °C (lit.[24] 113 °C); R_f = 0.32 (hexane/EtOAc 15:1). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 6 H), 6.55 (d, J = 8.8 Hz, 2 H), 7.26−7.28 (m, 3 H), 7.35 (d, J = 8.8 Hz, 2 H), 7.44−7.47 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.2, 72.2, 74.9, 80.9, 83.6, 108.0, 111.8, 122.6, 128.5, 128.9, 132.5, 134.0, 150.7; HRMS (ESI) calcd for $C_{18}H_{16}N$ ([M + H$^+$]) 246.1286, found 246.1295.

*2-Methoxy-6-(p-tolylbuta-1,3-diyn-1-yl)naphthalene (**13**).* Yield: 71% (63 mg); brown solid; mp 113−115 °C (lit.[25] 92−95 °C); R_f = 0.52 (hexane/EtOAc 9:1). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 3.93 (s, 3 H), 7.10−7.19 (m, 4 H), 7.43 (t, J = 7.3 Hz, 2 H), 7.51 (dd, J = 8.5, 1.5 Hz, 1 H), 7.69 (t, J = 7.3 Hz, 2 H), 7.99 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 55.5, 73.2, 73.9, 81.9, 82.2, 106.0, 116.8, 119.0, 119.8, 127.1, 128.5, 129.3, 129.4, 129.6, 132.6, 132.9, 134.7, 139.7, 158.9; HRMS (ESI) calcd for $C_{22}H_{17}O$ ([M + H$^+$]) 297.1274, found 297.1284.

*2-(5-(p-Tolyl)penta-2,4-diyn-1-yl)isoindoline-1,3-dione (**14**).* Yield: 82% (74 mg); brown solid; mp 126−128 °C; R_f = 0.28 (hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.61 (s, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.75 (dd, J = 5.5, 3.0 Hz, 2 H), 7.90 (dd, J = 5.5, 3.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 28.1, 68.3, 72.9, 75.8, 78.0, 118.3, 123.8, 129.3, 132.1, 132.7, 134.4, 139.9, 167.0; HRMS (ESI) calcd for $C_{20}H_{14}NO_2$ ([M + H$^+$]) 300.1019, found 300.1029.

*8-(4-Fluorophenyl)octa-5,7-diyn-1-ol (**15**).* Yield: 78% (51 mg); white solid; mp 69−71 °C; R_f = 0.22 (hexane/EtOAc 9:1). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 1 H), 1.65−1.76 (m, 4 H), 2.41 (t, J = 6.5 Hz, 2 H), 3.69 (t, J = 6.1 Hz, 2 H), 6.99 (t, J = 8.8 Hz, 2 H), 7.45 (dd, J = 8.9, 5.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 24.7, 31.9, 62.4, 65.5, 74.0, 74.2, 84.4, 115.9 (d, J = 22.3 Hz), 118.3 (d, J = 3.5 Hz), 134.6 (d, J = 8.5 Hz), 163.0 (d, J = 250.8 Hz); HRMS (ESI) calcd for $C_{14}H_{12}F$ ([M + H$^+$]) 199.0918, found 199.0911.

*8-(4-Bromophenyl)octa-5,7-diyn-1-ol (**16**).* Yield: 69% (57 mg); pale yellow oil; R_f = 0.26 (hexane/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (br s, 1 H), 1.62−1.74 (m, 4 H), 2.41 (t, J = 6.6 Hz, 2 H), 3.69 (t, J = 6.0 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.44 (t, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.7, 31.9, 62.4, 65.5, 73.9, 75.6, 85.1, 121.2, 123.4, 131.8, 134.0. HRMS (ESI) calcd for $C_{14}H_{12}Br$ ([M + H$^+$]) 277.0223, found 277.0230.

*1-(Phenylbuta-1,3-diyn-1-yl)cyclopentanol (**17**).* Yield: 74% (47 mg); orange solid; mp 88−90 °C; R_f = 0.22 (hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−2.07 (m, 8 H), 7.29−7.33 (m, 3 H), 7.47−7.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 42.6, 68.1, 73.4, 75.1, 79.0, 86.1, 121.82, 128.6, 129.3, 132.6; HRMS (ESI) calcd for $C_{15}H_{13}$ ([M + Na$^+$]) 233.0937, found 233.0933.

*1-((4-Fluorophenyl)buta-1,3-diyn-1-yl)cyclopentanol (**18**).* Yield: 74% (51 mg); white solid; mp 90−92 °C; R_f = 0.25 (hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71−2.09 (m, 8 H), 7.04 (t, J = 8.8 Hz, 2 H), 7.51 (dd, J = 8.8, 5.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 42.5, 67.5, 73.7, 74.9, 80.6, 83.4, 116.1 (d, J = 22.3 Hz), 118.0 (d, J = 3.4 Hz), 134.7 (d, J = 8.5 Hz), 163.2 (d, J = 251.6 Hz); HRMS (ESI, negative mode) calcd for $C_{15}H_{12}FO$ ([M − H$^+$]) 227.0878, found 227.0882.

*1-(p-Tolylbuta-1,3-diyn-1-yl)cyclohexanol (**19**).* Yield: 68% (49 mg); white solid; mp 58−60 °C; R_f = 0.41 (hexane/EtOAc 5:1). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26−1.32 (m, 1 H), 1.56−1.74 (m, 7 H), 1.91−1.99 (m, 2 H), 2.07 (br s, 1 H), 2.35 (s, 3 H), 7.12 (d, J = 7.9 Hz, 2 H), 7.38 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 23.3, 25.2, 40.0, 69.2, 69.5, 72.9, 78.9, 85.6, 118.6, 129.3, 132.6, 139.7; HRMS (ESI) calcd for $C_{17}H_{17}$ ([M + Na$^+$]) 261.1250, found 261.1243.

*1-((4-Bromophenyl)buta-1,3-diyn-1-yl)cyclohexanol (**20**).* Yield: 85% (77 mg); white solid; mp 97−99 °C; R_f = 0.25 (hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25−2.10 (m, 11 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.45 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.2, 39.8, 68.9, 69.5, 70.6, 74.7, 87.0, 120.7, 123.8, 131.9, 134.0; HRMS (APCI, negative mode) calcd for $C_{16}H_{14}BrO$ ([M − H$^+$]) 301.0223, found 301.0216.

*Tetradeca-5,7-diyn-1-ol (**21**).* Yield: 77% (48 mg); yellow oil; R_f = 0.36 (hexane/EtOAc 3:1). ^{1}H NMR and ^{13}C NMR were in agreement with those reported in the literature.[26,28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3 H), 1.25−1.68 (m, 12 H), 1.86 (br s, 1 H), 2.20−2.30 (m, 4 H), 3.64 (t, J = 6.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.4, 19.6, 22.9, 25.0, 28.7, 28.9, 31.7, 32.0, 62.7, 65.5, 66.1, 77.3, 78.2; HRMS (APCI) calcd for $C_{14}H_{23}O$ ([M + H$^+$]) 207.1743, found 207.1749.

*2-(Deca-1,3-diyn-1-yl)-6-methoxynaphthalene (**22**).* Yield: 88% (77 mg); yellow oil; R_f = 0.56 (hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3 H), 1.26−1.50 (m, 6 H), 1.54−1.64 (m, 2 H), 3.91 (s, 3 H), 7.09 (d, J = 2.4 Hz, 1 H), 7.15 (dd, J = 9.2, 2.5 Hz, 1 H), 7.45−7.48 (m, 1 H), 7.66 (t, J = 8.6 Hz, 2 H), 7.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.8, 22.7, 28.4, 28.7, 31.5, 55.5, 65.4, 74.2, 75.5, 84.9, 105.9, 116.9, 119.7, 127.0, 128.4, 129.5, 132.7, 134.5, 158.7; HRMS (APCI) calcd for $C_{21}H_{23}O$ ([M + H$^+$]) 291.1743, found 291.1749.

*1-((Trimethylsilyl)buta-1,3-diyn-1-yl)cyclohexanol (**23**).* Yield: 73% (48 mg); white solid; mp 107−109 °C (lit.[29] 108−109 °C); R_f = 0.44 (hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9 H), 1.21−1.62 (m, 8 H), 1.88−1.93 (m, 2 H), 2.17 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.32, 23.2, 25.1, 39.7, 69.3, 81.5, 87.4, 87.5.

Computational Methods. Calculations were performed with Gaussian 03 at the DFT level.[30] The geometries of all complexes here reported were optimized using the B3LYP hybrid functional.[31] Optimizations were carried out using the standard 6-31G(d) basis set for C, H, N, O, S, and F, or the dgdzvp basis set for the case of the model compounds in Table 2. The LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt and employs a split-valence (double-ζ) basis set, was used for Cu and I.[32] Harmonic frequencies were calculated at the same level to characterize the stationary points and to determine the zero-point energies (ZPEs). The starting approximate geometries for the transition states (TSs) were graphically located. Intrinsic reaction coordinate (IRC) studies were performed to confirm the relation of the transition states with the corresponding minima.

■ ASSOCIATED CONTENT

Supporting Information

DFT calculation results, stability and safety assay of NfN_3, and images of ^{1}H and ^{13}C NMR spectra of the isolated reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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