E-Selective Radical Difunctionalization of Unactivated Alkynes: Preparation of Functionalized Allyl Alcohols from Aliphatic Alkynes

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Abstract: Radical difunctionalization of aliphatic alkynes provides direct access to valuable multi-substituted alkenes, but achieving a high level of chemo- and stereo-control remains a formidable challenge. Herein we report a novel photoredox neutral alkyne difunctionalization through functional group migration followed by radical-polar crossover and energy transfer-enabled stereoconvergent isomerization of alkenes. In this sequence, a hydroxyalkyl and an aryl group are incorporated concomitantly into an alkyne, leading to diversely functionalized *E*-allyl alcohols. The scope of alkynes is noteworthy, and the reaction tolerates aliphatic alkynes containing hydrogen donating C-H bonds which are prone to intramolecular hydrogen atom transfer. The protocol features broad functional group compatibility, high product diversity and exclusive chemo- and stereoselectivity, thus providing a practical strategy for the elusive radical difunctionalization of unactivated alkynes.

Direct transformation of unsaturated carbon-carbon bonds in alkenes or alkynes into valuable molecular skeletons is important, because it has high synthetic value and uses broadly available raw materials. In recent decades, research into radical-mediated difunctionalization of alkenes has seen significant progress[1-4], but radical difunctionalization of alkynes, which can generate diversely multi-substituted alkenes, has lagged far behind[5-8]. This can be ascribed to widely recognized kinetic and thermodynamic obstacles which include (Fig 1A): 1) radical addition to alkynes generating highly reactive vinyl radicals that usually are subject to undesired rapid cyclization or addition to other π systems[9-16]; 2) vinyl radicals engaging in fast hydrogen abstraction with rate coefficients of $>10^5 \ M^{-1} \ s^{-1}$ for intramolecular 1,5-hydrogen atom transfer (HAT)[17] and $\sim 10^6 \ M^{-1} \ s^{-1}$ for intermolecular HAT[18]. As a result, the currently available approaches are largely dependent on the conversion of activated alkynes, such as phenylacetylene derivatives in which vinyl radicals are stabilized by a p-π conjugate effect. Unactivated aliphatic alkynes lacking such p-π conjugation however remain challenging substrates. Moreover, free radical-mediated alkyne difunctionalization without transition-metal catalysis often leads to alkene products as *Z/E* mixtures[19-22], compromising the synthetic value of the method. Though a few reports achieve single stereoisomeric products, the most use of aryl alkynes limits product diversity and can not be applied to more common alkynes[23-28]. Therefore, strategic innovation to convert unactivated alkynes to functional alkenes with superior chemo- or stereoselectivity is

highly desirable but has not been achieved.

Fig. 1. A. Challenges in radical-mediated difunctionalization of alkynes; B. *E*-selective radical difunctionalization of unactivated alkynes.

Radical rearrangement has been shown to be a pre-eminent synthetic tactic for the transformation of unsaturated carbon-carbon bonds[29-34], and may support difunctionalization of unactivated alkynes. Taking advantage of radical rearrangement we report a proof-of-concept study, in which aliphatic alkynes can be transformed stereoselectively into valuable multisubstituted *E*-allyl alcohols (Fig 1B). This photoredox neutral cascade proceeds through sequential radical migration, radical-polar crossover and energy transfer (ET)-promoted stereoconvergent alkene isomerization. DFT calculations have been carried out to rationalize the unique selectivity of functional group migration beyond the alkenyl radical-induced 1,5-HAT that probably occurs with aliphatic alkynes.

Results and discussion

At the outset, difunctionalization of the aliphatic alkyne (**1a**) was investigated (Fig 2). This alkyne (**1a**) is one of the most challenging substrates for radical-mediated alkyne difunctionalization and has never been used in such transformations. The existing *O*-benzylic C-H bonds with relatively low bond dissociation energy (BDE = 79.8 kcal/ mol) could serve as hydrogen donor in a 1,5-HAT and could affect the functionalization of an alkenyl radical, leading to undesired hydrofunctionalization products. In fact, DFT calculations indicated that the alkenyl radical intermediate has a strong tendency (ΔG = -23 kcal/ mol) to abstract an H-atom from the benzylic site. The reaction of **1a**

with a sulfone (**2a**) using *fac*-Ir(ppy)$_3$ as photosensitizer and acetone/H$_2$O as co-solvent under green light (510 nm wavelength) irradiation led to a good yield of the allylic alcohol (**3a**) with exclusive *E*-configuration (*E/Z* > 20:1, entry 1). A brief survey of reaction parameters in terms of photocatalyst, solvent, additive and light source was carried out (for details, see the Supporting Information - SI). Replacement of the photocatalyst by other catalysts did not improve the reaction outcome (entries 2-6). Sodium acetate was used to neutralize the hydrobromic acid that was generated in the reaction, and a decreased yield was obtained in the absence of this base (entry 7). Control experiments showed that photocatalyst and light were crucial to the transformation (entries 8-9), and the hydroxyl group in **3a** was derived from water. The amount of water in the cosolvent appears to influence the reaction (entries 11-12). Reducing the reaction temperature slowed down the reaction rate and sharply decreased the yield (entry 13).

Entry	Variation	Yield (%)[a]	E/Z
1	none	78	>20:1
2	[Ir(dF(CF$_3$)$_2$ppy)$_2$(dtbbpy)]PF$_6$ as photocat.	0	-
3	[Ir(dtbbpy)(ppy)$_2$]PF$_6$ as photocat.	10	>20:1
4	Ru(bpy)$_3$Cl$_2 \cdot$6H$_2$O as photocat.	0	-
5	4CzIPN as photocat.	0	-
6	Eosin Y as photocat.	<5	>20:1
7	no base	44	>20:1
8	no photocat.	0	-
9	no light	0	-
10	no water	0	-
11	0.1 mL water	47	>20:1
12	1.0 mL water	35	3:1
13[b]	none	12	>20:1

Fig. 2. Optimized reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%) and NaOAc (0.1 mmol) in acetone/H$_2$O (2 mL/0.6 mL), irradiated with 30 W 510 nm green LED (5 cm away from the light) at rt under N$_2$ for 72 h. [a]Yields of isolated products are given. [b]0°C.

With the optimized reaction conditions in hand, the scope of unactivated alkynes was examined (Fig 3). The reaction has broad functional group compatibility and a plethora

of aliphatic alkynes proved to be suitable substrates, delivering synthetically useful yields with good stereoselectivity. The preparation of **3a** could be scaled up, giving a slightly decreased but acceptable yield. A diversity of susceptible groups, such as an unprotected alcohol (**3e**), iodide (**3f**), azide (**3j**), carboxylic acid (**3l, 3m**) or silane (**3n**), remained intact in the reaction. Notably, acetylene gas was also suitable for this reaction to afford the corresponding *E*-allylic alcohol (**3o**). A cyanoamide (**3q**) that could act as radical acceptor *via* 5-exo-dig cyclization did not interfere with the desired difunctionalization[35-36]. Though phenylsulfonyl[37-40] alkenylsulfonyl[41-42] and malonitrile[43-45]moieties all possess some migratory aptitude, the competitive migration of those groups did not occur in the cases of **3s-3v**, indicating that the migration of the benzothiazolyl group was faster. The reaction proceeded selectively at a terminal alkyne in the presence of an additional internal alkyne (**3x**). Alkyl carboxylate, phosphonate or sulfonate esters as substrates afforded the corresponding products (**3y-3ab**) with comparable yields. Substrates containing various heterocyclic fragments including piperidyl (**3ac**), benzofuryl (**3ad**), thienyl (**3ae**), quinolyl (**3af**), quinoxalinol (**3ag**), or isatoic anhydride (**3ah**) were also compatible with the reaction conditions. The *E*-configuration of the alkene in the product was unambiguously confirmed by the crystal structure of **3ai** (see SI). Using alcohols or aromatic amines as a nucleophilic solvent instead of water resulted in the corresponding allylic ethers (**3aj, 3ak**) or allylic amines (**3al-3an**). Remarkably, the method could be used to synthesize valuable cyclic compounds in one step. For instance, the reaction of alkynols under the current conditions led to 2H-pyran (**3ao**) or oxepene (**3ap**) by intramolecular cyclization. Moreover, the reaction of alkynoic acids gave rise to δ-pentenolide (**3aq**) and ε-caprolactone (**3ar**), following a reaction in which the carboxylic acid served as a nucleophile. In addition to electron-rich aliphatic alkynes, electron-deficient propionic acid was also amenable to the reaction, albeit with a lower yield. The conversion afforded the decarboxylative product (**3o**), the formal difunctionalization of acetylene.

The utility of this approach was further illustrated by the modification of natural products and drug derivatives (Fig 4). A portfolio of complex molecules based on diverse structural features, such as *N*-heteroaryl moieties (**4d, 4j, 4k**), lactones (**4a, 4i**), dichlorocyclopropane (**4e**), sulfonamide (**4k**), *α*-hydroxy acid (**4e**), and *α*-amino acid (**4l**), were readily converted to the corresponding products with excellent stereocontrol. The chiral centers adjacent to the carbonyl group are sensitive to strong basic or acidic conditions but remained intact under the mild reaction conditions (**4c, 4l**).

1 + **2a** → **3**

fac-Ir(ppy)₃, NaOAc, acetone/cosolvent, *hv*, rt

3a, 78% (61%)[a] E/Z > 20:1

3b, n = 4, 84%, E/Z > 20:1
3c, n = 8, 70%, E/Z > 20:1

3d, 75%, E/Z > 20:1

3e, 60%, E/Z > 20:1

3f, 45%, E/Z > 20:1

3g, 63%, E/Z > 20:1

3h, 65%, E/Z > 20:1

3i, 62%, E/Z > 20:1

3j, 70%, E/Z > 20:1

3k, 74%, E/Z > 20:1

3l, n = 3, 65%, E/Z > 20:1
3m, n = 4, 61%, E/Z > 20:1

3n, 40%, E/Z > 20:1

3o, 20%,[b] only E

3p, 62%, E/Z > 20:1

3q, 67%, E/Z > 20:1

3r, 50%, E/Z = 10:1

3s, 45%, E/Z = 6:1

3t, 60%, E/Z > 20:1

3u, 50%, E/Z = 10:1

3v, 67%, E/Z > 20:1

3w, 50%, E/Z > 20:1

3x, 70%, E/Z > 20:1

3y, 60%, E/Z > 20:1

3z, 77%, E/Z > 20:1

3aa, 70%, E/Z > 20:1

3ab, 73%, E/Z > 20:1

3ac, 60%, E/Z > 20:1

3ad, 68%, E/Z > 20:1

3ae, 75%, E/Z > 20:1

3af, 78%, E/Z > 20:1

3ag, 58%, E/Z > 20:1

3ah, 61%, E/Z > 20:1

3ai, 70%, E/Z > 20:1

3aj, 65%,[c] E/Z > 20:1

3ak, 60%,[d] E/Z > 20:1

3al, 45%,[e] E/Z > 20:1

3am, 50%,[e] E/Z > 20:1

3an, 56%,[e] E/Z > 20:1

3ao, 61%

3ap, 64%

3aq, 73%

3ar, 60%

3o, 35%, E/Z > 20:1

Fig. 3. Scope of aliphatic alkynes. Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%) and NaOAc (0.1 mmol) in acetone/H$_2$O (2 mL/0.6 mL), irradiated with 30 W 510 nm green LED (5 cm away from the light) at rt under N$_2$ for 56-72 h. [a]Scaled-up preparation with **1a** (4 mmol) and **2a** (2 mmol). [b]**2a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%) and NaOAc (0.1 mmol) in acetone/H$_2$O (2 mL/0.6 mL), irradiated with 50 W blue LED at rt with an acetylene balloon (1 atm) for 12 h. [c]KH$_2$PO$_4$ (0.4 mmol), MeCN/MeOH (2 mL/ 0.5 mL). [d]KH$_2$PO$_4$ (0.4 mmol), MeCN/EtOH (2 mL/0.5 mL). [e]Aromatic amine (0.4 mmol), 2,6-lutidine (0.4 mmol), MeCN (2 mL).

from Camphanic acid
4a, 71%, *E/Z* > 20:1

from Menthol
4b, 68%, *E/Z* > 20:1

from Naproxen
4c, 68%, *E/Z* > 20:1

from Oxaprozin
4d, 58%, *E/Z* > 20:1

from Ciprofibrate
4e, 61%, *E/Z* > 20:1

from Follestrol
4f, 60%, *E/Z* > 20:1

from Dehydrocholic acid
4g, 38%, *E/Z* > 20:1

from Fenofibric
4h, 61%, *E/Z* > 20:1

from Corey's lactone diol
4i, 50%, *E/Z* > 20:1

from Indomethacin
4j, 58%, *E/Z* > 20:1

from Celecoxib
4k, 42%, *E/Z* > 20:1

from Phenylalanie
4l, 62%, *E/Z* > 20:1

Fig. 4. Modification of complex structures of natural products and drug derivatives. Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%) and NaOAc (0.1 mmol) in acetone/ H$_2$O (2 mL/0.6 mL), irradiated with 30 W 510 nm green LED (5 cm away from the light) at rt under N$_2$ for 65-72 h.

The diversity of products from this reaction could be enriched by varying the readily accessible (hetero)aryl sulfones (**2**) (Fig 5). The electronic properties of substituents on benzothiazolyl group had little impact on the reaction outcomes, and products (**5a-5e**) were delivered in comparable yields. In addition, compounds with other heteroaryls such as benzoxazolyl (**5f**), benzofuryl (**5g**), benzothienyl (**5h**), thienyl (**5i**), thiazolyl (**5j**), and pyridyl (**5k**) could be incorporated into an alkyne, leading to the corresponding allylic alcohols in useful yields. Though the migration of aryl groups is much slower than that of heteroaryls and in fact failed on many occasions, cinnamyl alcohols (**5l-5o**) were readily obtained in this reaction *via* phenyl migration. Notably, the reaction with

alkynyl or alkenyl substituted sulfones resulted in a conjugated 1,3-enynyl alcohol (**5p**) and a 1,3-dienyl alcohol (**5q**) as a result of alkynyl or alkenyl migration. The alkyl substituent of sulfones was subsequently examined and it was found that both linear and cyclic alkyl moieties such as cyclopentyl, cyclohexyl and piperidyl could be introduced to the alkyne, forming 1,1-dialkyl-substituted tertiary allylic alcohols (**5r-5w**). The method is applicable to the preparation of secondary allylic alcohols (**5x-5ab**), and notably, the valuable deuterium-labeled allylic alcohol (**5ac**) could be readily produced using the appropriate deuterated sulfone reagent.

5a, 64%, *E/Z* > 20:1 **5b**, 60%, *E/Z* > 20:1 **5c**, 60%, *E/Z* > 20:1 **5d**, 60%, *E/Z* > 20:1 **5e**, 64%, *E/Z* > 20:1

5f, 70%, *E/Z* > 20:1 **5g**, 44%, *E/Z* > 20:1 **5h**, 40%, *E/Z* > 20:1 **5i**, 51%, *E/Z* > 20:1 **5j**, 40%, *E/Z* > 20:1

5k, 56%, *E/Z* > 20:1 **5l**, 67%[a], *E/Z* > 20:1 **5m**, 61%[a], *E/Z* > 20:1 **5n**, 70%[a], *E/Z* > 20:1 **5o**, 66%[a], *E/Z* > 20:1

5p, 40%[a], *E/Z* = 1:1 **5q**, 15%[a], *E/Z* > 20:1 **5r**, 47%, *E/Z* > 20:1 **5s**, 67%, *E/Z* > 20:1 **5t**, 65%, *E/Z* > 20:1

5u, 51%, *E/Z* > 20:1 **5v**, 52%, *E/Z* > 20:1 **5w**, 40%, *E/Z* = 17:1 **5x**, 66%, *E/Z* > 20:1 **5y**, 48%, *E/Z* = 13:1

5z, 45%, *E/Z* = 20:1 **5aa**, 35%, *E/Z* = 8:1 **5ab**, 63%, *E/Z* > 20:1 **5ac**, 62%, *E/Z* > 20:1

Fig. 5. Variation of bifunctional sulfone reagents. Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%) and NaOAc (0.1 mmol) in acetone/H$_2$O (2 mL/0.6 mL), irradiated with 30 W 510 nm green LED (5 cm away from the light) at rt under N$_2$ for 50-72 h. [a]K$_2$HPO$_4$ (0.4 mmol), irradiated with 456 nm Kessil LED light.

The products from this reaction could be employed as versatile intermediates, highlighting the synthetic value of the method (Fig 6). The benzothiazolyl group in **3a** serves as the precursor of carbonyl group, readily releasing a formyl and giving rise to the corresponding conjugated aldehyde (**6**) in a useful yield. The dehydration of **3a** resulted in the conformationally unified s-*cis* diene (**7**) that could serve in Diels-Alder reaction. Treatment of **3a** with diethylaminosulfur trifluoride (DAST) furnished the allylic fluoride (**8**), and with TMSN$_3$ afforded allylic azide (**9**). The benzyl group in **3a** was removed in the presence of Lewis acid, and the subsequent spontaneous cyclization led to a 2H-pyran (**10**). The epoxidation of alkenyl of **3a** smoothly generated the multi-functionalized oxirane (**11**).

Fig. 6. Product transformations.

A set of mechanistic experiments was carried out to elucidate the reaction pathways. The addition of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) entirely suppressed the formation of **3a** (Fig. 7A). The radical clock reaction of cyclopropylacetylene (**12**) with **2a** furnished the ring-opened product (**13**), indicating that radical pathways were involved in the reaction which was initiated by homolysis of the C-Br bond (**2a**) (Fig. 7B). The tautomerization of *Z*-**3a** to *E*-**3a** took place only in the presence of a photosensitizer under light irradiation. However, this process is irreversible and the conversion of *E*-**3a** to *Z*-**3a** failed in the presence or absence of a photosensitizer (Fig. 7C). The absorption peaks of *Z*-**3a** (325 nm) or *E*-**3a** (329 nm) did not overlap with the emission wavelength of green light (λmax = 510 nm), suggesting that the conversion of *Z*- to *E*-isomer was enabled by the energy transfer (EnT) from

the excited photosensitizer to substrate rather than by the direct light excitation of substrate[46-49]. Light on-off experiments showed that the reaction proceeded under light irradiation and stopped in its absence (Fig. 7D). This result is consistent with the quantum yield of the reaction ($\Phi < 0.6$ for details, see the SI), illustrating that the reaction is a light-dependent process. A Stern-Volmer analysis demonstrated that the luminescence emission of *fac*-Ir(ppy)$_3$ was efficiently quenched by **2a** but not by **1a** (Fig. 7E). EPR experiments displayed a conspicuous response signal when 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was added to the reaction as a radical trap (Fig. 7F)[24].

A. Radical trap experiment

B. Radical clock experiment

C. Tautomerization of Z/E isomers

Condition **A**: acetone, 30 W 510 nm green LED
Condition **B**: *fac*-Ir(ppy)$_3$, acetone, 30 W 510 nm green LED

D. Light on-off experiment

E. Stern-Volmer studies

F. EPR experiment

Fig. 7. Studies of the mechanism. **A.** Radical trap experiment. **B.** Radical clock experiment. **C.** Tautomerization of Z/E isomers. **D.** Light on-off experiment. **E.** Stern-Volmer studies. **F.** EPR experiment.

A plausible mechanism for the reaction is shown in Fig. 8. A single-electron transfer from the excited *fac*-Ir(ppy)$_3$ to **2a** generates an alkyl radical (**I**) that adds to the alkyne (**1a**) to form an alkenyl radical species (**II**). This radical is rapidly captured by the heteroaryl moiety, triggering the functional group migration. The competitive alkenyl radical-mediated 1,5-HAT is less favorable, and this was supported by DFT calculations (Fig. 9), and is not observed in the reaction. As is explicitly shown in Fig. 9, the 1,4-aryl migration proceeds with a lower energetic barrier than a 1,5-HAT (**TS1** *vs* **TS2**), leading to a more stable intermediate (**IV**), as opposed to **III**. The ensuing extrusion of SO$_2$ affords a radical (**V**) which is then single-electron oxidized by *in-situ* generated Ir^{IV} species to form the cation (**VI**) and regenerating the ground-state Ir^{III} catalyst. Subsequently, nucleophilic addition of H$_2$O to **VI** generates **Z-3a**. With the aid of photosensitizer, the energy transfer causes the conversion of **Z-3a** to the final product (**E-3a**) under light irradiation.

Conclusion

An ingenious photocatalytic protocol proceeding through sequential functional group migration, radical-polar crossover and stereoconvergent alkene isomerization has been exploited for the radical difunctionalization of unactivated alkynes. A hydroxyalkyl and a (hetero)aryl group can be incorporated into alkynes by this reaction, which stereoselectively furnishes densely functionalized *E*-allyl alcohols. The method can be applied to the modification of complex structures derived from natural products and drug molecules. Comprehensive experimental studies have been conducted to probe the reaction mechanism, and DFT calculations were carried out to rationalize the selectivity of functional group migration beyond an alkenyl radical-mediated 1,5-HAT. The protocol features broad substrate scope and high product diversity, thus opening up a new prospect for free radical-mediated difunctionalization of unactivated alkynes.

Fig. 8. Proposed reaction mechanism.

Fig. 9. DFT calculations.

Methods

General Procedures for difunctionalization of unactivated alkynes

1 (0.4 mmol), **2** (0.2 mmol), NaOAc (0.1 mmol), and *fac*-Ir(ppy)$_3$ (0.002 mmol) were loaded into a flask, which had been subjected 3 times to evacuation/flushing with N$_2$. Dry acetone (2.0 mL)/H$_2$O (0.6 mL) was added by syringe, and the mixture was irradiated by 30 W Green LEDs and stirred at rt until TLC showed that the starting material had been consumed. The mixture was quenched with H$_2$O and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to give the corresponding products.

1 (0.4 mmol), **2** (0.2 mmol), K$_2$HPO$_4$ (0.2 mmol), and *fac*-Ir(ppy)$_3$ (0.002 mmol) were loaded in a flask, which had been subjected 3 times to evacuation/flushing with N$_2$. Dry acetone (2.0 mL)/H$_2$O (0.5 mL) was added to the mixture by syringe, and the reaction was irradiated by 456 nm Kessil light and stirred at rt until TLC showed that the starting material had been consumed. The mixture was then quenched with H$_2$O and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to give the corresponding products.

References

1. Aoike, T & Akita, M. New Horizons of Photocatalytic Fluoromethylative Difunctionalization of Alkene. *Chem* **4**, 409-437 (2017).
2. Li, Z.-L., Fang, G.-C., Gu, Q. S. & Liu, X.-Y. Recent Advances in Copper-catalysed Radical-involved Asymmertric 1,2-Difunctionalization of Alkenes. *Chem. Soc. Rev.* **49**, 32-48 (2020).
3. Jiang, H. & Studer, A. Intermolecular Radical Carboamination of Alkenes. *Chem. Soc. Rev.* **49**, 1790-1811 (2020).
4. Wu, X., Wu, S & Zhu, C. Radical-mediated Difunctionalization of Unactivated Alkenes through Distal Migration of Functional Groups. *Tetrahedron Lett.* **59**, 1328-1336 (2018).
5. Wille, U. Radical Cascades Initiated by Intermolecular Radical Addition to Alkynes and Related Triple Bond Systems. *Chem. Rev.* **113**, 813-853 (2013).
6. Yao, H., Hu, W. & Zhang, W. Difunctionalization of Alkenes and Alkynes via Intermolecular Radical and Nucleophilic Additions. *Molecules* **26**, 105 (2021).
7. Zhang, Y., Cai, Z., Warratz, S., Ma, C. & Ackermann, L. Recent Advances in Electrooxidative Radical Transformations of Alkynes. *Sci. China. Chem.* **66**, 703-724 (2023).
8. Hu, C., Mena, J. & Alabugin, I. V. Design Principles of the use of Alkynes in Radical Cascades. *Nat. Rev. Chem.* **7**, 405-423 (2023).
9. Xuan, J. & Studer, A. Radical Cascade Cyclization of 1,n-Enynes and Diynes for the Synthesis of Carbocycles and Heterocycles. *Chem. Soc. Rev.* **46**, 4329-4346 (2017).
10. Stork, G. & Baine, N. H. Cyclization of Vinyl Radicals: A New Versatile Method for the Construction of Five- and Six-Membered Rings. *J. Am. Chem. Soc.* **104**, 2321-2323 (1982).
11. Beckwith, A. L. J. & O'Shea, D. M. Kinetics and Mechanism of Some Vinyl Radical Cyclisations. *Tetrahedron Lett.* **27**, 4525-4528 (1986).
12. Stork, G. & Mook, R. Vinyl Radical Cyclizations Mediated by the Addition of Stannyl Radicals to Triple Bonds. *J. Am. Chem. Soc.* **109**, 2829-2831 (1987).
13. Brumwell, J. E. & Simpkins, N, S. Radical Cyclisations of Dienes and Enynes using

Phosphorus- and Sulfur-Centred Radicals. *Tetrahedron* **50**, 13533-13552 (1994).

14. Pati, K., Gomes, G. P., Harris, T., Hughes, A., Phan, H., Banerjee, T., Hanson, K. & Alabugin, I. V. Traceless Directing Groups in Radical Cascades: From Oligoalkynes to Fused Helicenes without Tethered Initiators. *J. Am. Chem. Soc.* **137**, 1165-1180 (2015).

15. Mohamed, R. K., Mondal, S., Gold, B., Evoniuk, C. J., Banerjee, T., Hanson, K. & Alabugin, I. V. Alkenes as Alkyne Equivalents in Radical Cascades Terminated by Fragmentatins: Overcoming Stereoelectronic Restrictions on Ring Expansions for the Preparation of Expanded Polyaromatics. *J. Am. Chem. Soc.* **137**, 6335-6349 (2015).

16. Li, Y., Hu, M. & Li, J.-H. Silver-Catalyzed Intermolecular [3 + 2]/ [5 + 2] Annulation of N-Arylpropiolamides with Vinyl Acids: Facile Synthesis of Fused 2H-Benzo[b]azepin-2-ones. *ACS Catal.* **7**, 6757-6761 (2017).

17. Gilbert, B. C. & Parry, D. J. Fragmentation, Ring-opening, and Addition Reactions of Oxygen-conjugated Alkenyl Radicals Derived by Rapid 1,5-Hydrogen Shifts in Vinyl Radicals. An Electron Spin Resonance and Kinetic Investigation. *J. Chem. Soc., Perkin Trans. 2* 875-886 (1988).

18. Gilbert, B. C., McLay, N. R. & Parry, D. J. Intermolecular Hydrogen-Atom Abstraction by Vinyl Radicals Derived from Hydroxyalkyl Radicals and Alkynes: An Electron Spin Resonance Investigation. *J. Chem. Soc., Perkin Trans. 2* 329-336 (1987).

19. Xu, T., Cheung, C. W. & Hu, X. Iron-Catalyzed 1,2-Addition of Perfluoroalkyl Iodides to Alkynes and Alkenes. *Angew. Chem. Int. Ed.* **53**, 4910-4914 (2014).

20. Iqbal, N., Jung, J., Park, S. & Cho, E. J. Controlled Trifluoromethylation Reactions of Alkynes through Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **53**, 539-542 (2014).

21. Ouyang, Y., Xu, X.-H. & Qing, F.-L. Trifluoromethanesulfonic Anhydride as a Low-Cost and Versatile Trifluoromethylation Reagent. *Angew. Chem. Int. Ed.* **57**, 6926-6929 (2018).

22. Lü, S., Wang, Z., Gao, X., Chen, K & Zhu, S. 1,2-Difunctionalization of Acetylene Enabled by Light. *Angew. Chem. Int. Ed.* **62**, e202300268 (2023).

23. Iwasaki, M., Fujii, T., Nakajima, K. & Nishihara, Y. Iron-Induced Regio- and Stereoselective Addition of Sulfenyl Chlorides to Alkynes by a Radical Pathway. *Angew. Chem. Int. Ed.* **53**, 13880-13884 (2014).

24. Yu, M., Wang, H., Gao, Y., Bu, F., Cong, H. & Lei, A. Manganese-Catalyzed Chlorosulfonylation of Terminal Alkene and Alkyne via Convergent Paired Electrolysis. *Cell Rep. Phys. Sci.* **2**, 100476-100490 (2021).

25. Nie, X., Xu, T., Hong, Y., Zhang, H., Mao, C. & Liao, S. Introducing A New Class of Sulfonyl Fluoride Hubs via Radical Chloro-Fluorosulfonylation of Alkynes. *Angew. Chem. Int. Ed.* **60**, 22035-22042 (2021).

26. Lin, L., Yang, Z., Liu, J., Wang, J., Zheng, J., Li, J.-L., Zhang, X., Liu, X.-W., Jiang, H. & Li, J. Visible-Light-Induced Surfactant-Promoted Sulfonylation of Alkenes and Alkynes with Sulfonyl Chloride by the Formation of an EDA-Complex with NaI in Water at Room Temperature. *Green Chem.* **23**, 5467-5473 (2021).

27. Wang, Z., Zhang, Z., Zhao, W., Sivaguru, P., Zanoni, G., Wang, Y., Anderson, E. A. & Bi, X. Synthetic Exploration of Sulfinyl Radical Using Sulfinyl Sulfones. *Nat. Commun.* **12**, 5244-5254 (2021).

28. Suzuki, K., Sugihara, N., Nishimoto, Y. & Yasuda, M. Anti-Selective Borylstannylation of Alkynes with (o-Phenylenediaminato)borylstannanes by a Radical Mechanism. *Angew. Chem.*

Int. Ed. **61**, e202201883 (2022).

29. Wu, X & Zhu, C. Combination of Radical Functional Group Migration (FGM) and Hydrogen Atom Transfer (HAT). *Trends Chem.* **4**, 580-583 (2022).

30. Wu, X., Ma, Z., Feng, T & Zhu, C. Radical-Mediated Rearrangements: Past, Present, and Future. *Chem. Soc. Rev.* **50**, 11577-11613 (2021).

31. Wu, X & Zhu, C. Radical-Mediated Remote Functional Group Migration. *Acc. Chem. Res.* **53**, 1620-1636 (2020).

32. Li, W., Xu, W., Xie, J., Yu, S & Zhu, C. Distal Radical Migration Strategy: An Emerging Synthetic Means. *Chem. Soc. Rev.* **47**, 654-667 (2018).

33. Studer, A. & Bossart, M. Radical Aryl Migration Reactions. *Tetrahedron* **57**, 9649-9667 (2001).

34. Zhang, Y., Chen, J.-J. & Huang, H.-M. Radical Brook Rearrangements: Concept and Recent Developments. *Angew. Chem. Int. Ed.* **61**, e202205671 (2022).

35. Chen, D., Ji, M & Zhu, C. Intramolecular Nitration-Aminocarbonylation of Unactivated Olefins: Metal-Free Synthesis of γ-Lactams. *Chem. Commun.* **55**, 7796-7799 (2019).

36. Lu, J., Chen, D., Ji, M., Wu, X & Zhu, C. Synthesis of γ-Lactams via Trifluoromethylative Aminocarbonylation of Unactivated Olefins. *Tetrahedron Lett.* **61**, 151479-151482 (2020).

37. Kong, W., Casimiro, M., Merino, E. & Nevado, C. Copper-catalyzed one-pot trifluoromethylation/aryl migration/desulfonylation and C(sp^3)-N bond formation of conjugated tosyl amides. *J. Am. Chem. Soc.* **135**, 14480-14483 (2013).

38. Kong, W., Merino, E & Nevado, C. Arylphosphonylation and Arylazidation of Activated Alkenes. *Angew. Chem. Int. Ed.* **53**, 5078-5082 (2014).

39. Douglas, J. J., Albright, H., Sevrin, M. J. Cole, K. P. & Stephenson, C. R. J. A visible-light-mediated radical smiles rearrangement and its application to the synthesis of a difluoro-substituted spirocyclic ORL-1 antagonist. *Angew. Chem. Int. Ed.* **54**, 14898-14902 (2015).

40. Wang, Z.-S., Chen, Y.-B., Zhang, H.-W., Sun, Z., Zhu, C & Ye, L.-W. Ynamide Smiles Rearrangement Triggered by Visible-Light-Mediated Regioselective Ketyl-Ynamide Coupling: Rapid Access to Functionalized Indoles and Isoquinolines. *J. Am. Chem. Soc.* **142**, 3636-3644 (2020).

41. Wei, Y., Zhong, H., Wu, X. & Zhu, C. Alkene Difunctionalization Triggered by a Stabilized Allenyl Radical: Concomitant Installation of Two Unsaturated C-C Bonds. *Angew. Chem. Int. Ed.* **60**, 20215-20219 (2021).

42. Yu, J., Zhang, H., Wu, X & Zhu, C. Intermolecular Radical Fluoroalkylative Olefination of Unactivated Alkenes. *CCS Chem.* **4**, 1190-1198 (2022).

43. Chang, C., Zhang, H., Wu, X. & Zhu, C. Radical trifunctionalization of hexenenitrile via remote cyano migration. *Chem. Commun.* **58**, 1005-1008 (2022).

44. Guo, K., Gu, C., Li, Y., Xie, X., Zhang, H., Chen, K & Zhu, Y. Photoredox Catalyzed Trifluoromethyl Radical-Triggered Trifluctionalization of 5-Hexenennitriles via Cyano Migration. *Adv. Syn. Catal.* **364**, 1388-1393 (2022).

45. Wang, J., Wang, Y., Li, J., Wei, Z., Feng, J & Du, D. Organocatalytic Radical Relay Trifunctionalization of Unactivated Alkenes by a Combination of Cyano Migration and Alkylacylation. *Chem. Commun.* **59**, 5395-5398 (2023).

46. Singh, K., Staig, S. J. & Weaver, J. Facile synthesis of Z-alkenes via uphill catalysis. *J. Am. Chem. Soc.* **136**, 5275-5278 (2014).

47. Fabry, D. C., Ronge, M. A. & Rueping, M. Immobilization and continuous recycling of

photoredox catalysts in ionic liquids for applications in batch reactions and flow systems: catalytic alkene isomerization by using visible light. *Chem. Eur. J.* **21**, 5350-5354 (2015).

48. Singh, A., Fennell, C. J. & Weaver, J. D. Photocatalyst size controls electron and energy transfer: selectable E/Z isomer synthesis via C-F alkenylation. *Chem. Sci.* **7**, 6796-6802 (2016).

49. Molloy, J. J., Metternich, J. B., Daniliuc, C. G., Watson, A. J. B. & Gilmour, R. Contra-thermodynamic, photocatalytic E→Z isomerization of styrenyl boron species: vectors to facilitate exploration of 2D chemical space. *Angew. Chem. Int. Ed.* **57**, 3168-3172 (2018).

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Author contributions

CZ conceived the idea and designed the experiments. JW performed most of the laboratory experiments. XW performed DFT calculations. CZ helped with analysis of the data. XW and XZ prepared some of starting materials. JW and CZ wrote the manuscript. CZ supervised the project.

Competing interests

The authors declare no competing interests.