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Review article

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Design principles of the use of alkynes in radical cascades

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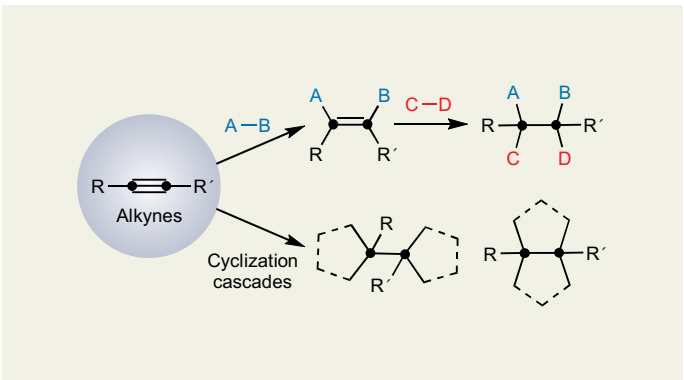
Abstract

One of the simplest organic functional groups, the alkyne, offers a broad canvas for the design of cascade transformations in which up to three new bonds can be added to each of the two sterically unencumbered, energy-rich carbon atoms. However, kinetic protection provided by strong π-orbital overlap makes the design of new alkyne transformations a stereoelectronic puzzle, especially on multifunctional substrates. This Review describes the electronic properties contributing to the unique utility of alkynes in radical cascades. We describe how to control the selectivity of alkyne activation by various methods, from dynamic covalent chemistry with kinetic self-sorting to disappearing directing groups. Additionally, we demonstrate how the selection of reactive intermediates directly influences the propagation and termination of the cascade. Diverging from a common departure point, a carefully planned reaction route can allow access to a variety of products.



Sections

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Introduction

Alkynes are among the simplest organic chemistry functional groups: it takes only two carbons and two hydrogens to make C_2H_2, the parent alkyne. However, the two carbon atoms harbour a surprising potential for electron complexity, as illustrated by the continuing saga of C_2 (acetylene stripped of its hydrogens), an intriguing molecule in which the number of bonds between the two carbons can range from two to four, depending on how the chemical bonding is analysed[1,2]. Although C_2H_2 is far less exotic and controversial than C_2, alkynes still have many interesting and useful electronic features associated with the presence of two types of bond (σ and π)[3]. Furthermore, the orthogonality of the two alkyne π-systems allows them to be involved in chemical transformations independent of one another — a useful property for selective cascade transformations in which multiple new bonds are formed, and complex products are derived from simple starting materials[4–13] (Fig. 1a).

The utility of alkynes as a platform for both the design of reactions and in the discovery of modes of reactivity results from their relatively high energy and electronic peculiarities. The high energy stored in an alkyne can be illustrated by the fact that the thermodynamic cost of making a triple bond (~65 kcal mol^{-1}) is much higher than for making a double bond (28 kcal mol^{-1}) or cyclopropane (~30 kcal mol^{-1})[14] (Fig. 1b). This feature makes many reactions involving alkynes highly exergonic. The alkyne moiety can be compared to a tightly wound spring, its high energy waiting to be released to provide a driving force for reaction. However, harnessing this reactivity is impossible without mastering stereoelectronic control of alkyne activation.

Paradoxically, the high energy stored between two alkyne carbons (>60 kcal mol^{-1}; ref. 14) is paired with relative kinetic stability, originating from their strong π-overlap at the short C–C distance[15]. Only once this stereoelectronic puzzle is solved can it unlock useful transformations. For instance, the parent anionic 5-endo-dig cyclization of an alkyne has a higher barrier than the >30 kcal mol^{-1} less exergonic 5-endo-trig cyclization of an alkene (Fig. 1c). This relatively low reactivity can be translated into high selectivity, whereas thermodynamic instability can be used to make reactions irreversible. Not surprisingly, alkynes are closely associated with 'click chemistry'[16–20], for which high selectivity and full conversions are desired. In addition, alkynes are 'carbon-rich'[14] and can be used for the preparation of heterocycles[21–28] and carbon-rich nanomaterials in an atom-economical manner[29–31].

Despite their simplicity, alkynes are not a completely blank canvas of reactivity — they are primed to be quite electrophilic by the relatively high electronegativity of *sp*-hybridized carbons[3]. For these reasons, generation of the same archetypal reactive intermediates (such as cations, radicals and anions) from similarly substituted alkenes and alkynes comes with distinctly different thermodynamic preferences (Fig. 1e). Therefore, alkynes prefer more electron-rich reacting partners and can be thought of as having 'electrophilic' functionality. In fact, alkyne carbon atoms are in the same oxidation state as those in the $-CH_2C(O)-$ moiety and can be introduced into carbonyl reaction pathways without the need for external redox agents[32]. Hence, alkynes provide a convenient and energetically favourable entry to carbonyl chemistry because they can be converted into enols and enamines through exergonic nucleophilic additions (Fig. 1d). In essence, alkynes can be energy-rich surrogates for other groups and can unlock reactions that would be otherwise thermodynamically uphill.

The fundamental features of alkyne reactivity impose unique substituent effects on their stability and reactivity towards nucleophiles, electrophiles and radicals (Fig. 1f). The same factors define the properties of the reactive intermediates derived from alkynes: vinyl anions formed from alkyne reactions with nucleophiles are rather stable (−34 kcal mol^{-1} for hydride addition) whereas vinyl cations (+9 kcal mol^{-1} for protonation) formed in the reactions with electrophiles are quite unstable. The instability of vinyl cations limits their synthetic utility, while the greater stability of vinyl anions can be a disadvantage for cascade reactions as it can create thermodynamic traps by increasing the barriers for subsequent steps in domino transformations. From that point of view, vinyl radicals possess an attractive combination of properties for cascade design: their formation has neither the prohibitive thermodynamic penalty of vinyl cations nor the deactivating unproductive stabilization of vinyl anions. In other words, vinyl radicals are easy enough to make but also reactive, penetrating readily even through the aromatic 'armour'[33].

The goal of this Review is to highlight the fundamental reasons for the role of alkynes in radical cascade transformations. Radical processes have unique advantages for cascade transformations — unlike anions, cations and complexes with transition metal catalysts, the translocation of a radical centre in a domino sequence of reactions does not require physical transport of an accompanying group (for example, the counterion or the catalyst)[34,35]. The focus of this article will be the unique opportunities provided by the inherent structural, energetic and stereoelectronic features of a carbon–carbon triple bond for the controlled design of cascade reactions.

Stereoelectronics of alkyne reactions

The structural simplicity of alkynes provides an interesting contrast to their stereoelectronic complexity. This complexity originates from the presence of two mutually orthogonal π-bonds. One can think of alkynes as 'two functional groups in one package'[3], each of which can be selectively activated in a sequence of transformations.

This complexity is reflected by the fact that stereoelectronic factors in intramolecular alkyne reactions, such as cyclizations, have been surprisingly controversial. In the classic 1976 paper, Baldwin suggested dramatically different guidelines for the cyclizations of sp^2 (trig) and *sp* (dig) systems, based on the notion that nucleophilic and radical additions to alkynes follow an unusual acute trajectory[36]. More recent experimental and computational data, summarized in 2011 by Alabugin and Gilmore[37], showed that the basic stereoelectronic guidelines for alkenes and alkynes are similar, opposed Baldwin's original predictions, and reinforced Beckwith's alternative guidelines for radical reactions[38]. Because an obtuse, Burgi–Dunitz-like trajectory is favoured for radical attack at both alkynes and alkenes, both functionalities generally prefer exo cyclizations (Fig. 2a). The stereoelectronic preferences embodied in the new rules, as mentioned above, are favourable for the design of alkyne cascades. Indeed, radical exo-dig cyclizations turned out to be more suitable in cascade transformations to extended polyaromatics than their endo-dig counterparts. For the all-exo cascades of **1** illustrated in Fig. 2a, the average yield is ~90% per step. By contrast, the radical cascade propagated by endo-dig cyclization is inefficient, as illustrated by <10% yield of the 6-endo-dig product **4** in[39] Fig. 2a. The design of endo-cyclizations of alkynes is much more difficult. Efficient radical 5-endo-dig cyclizations remains scarce and, for a long time, the only example of such a process was the cyclization of a silyl radical (**6**) reported by Studer and co-workers[40]. The first example of an efficient carbon radical 5-endo-dig cyclization (**10**) by the Alabugin group was initiated by a tosyl radical, where the 5-endo transition state is additionally stabilized by S=O···H hydrogen bonding[41]. One way to satisfy stereoelectronic requirements is by changing the alkyne LUMO

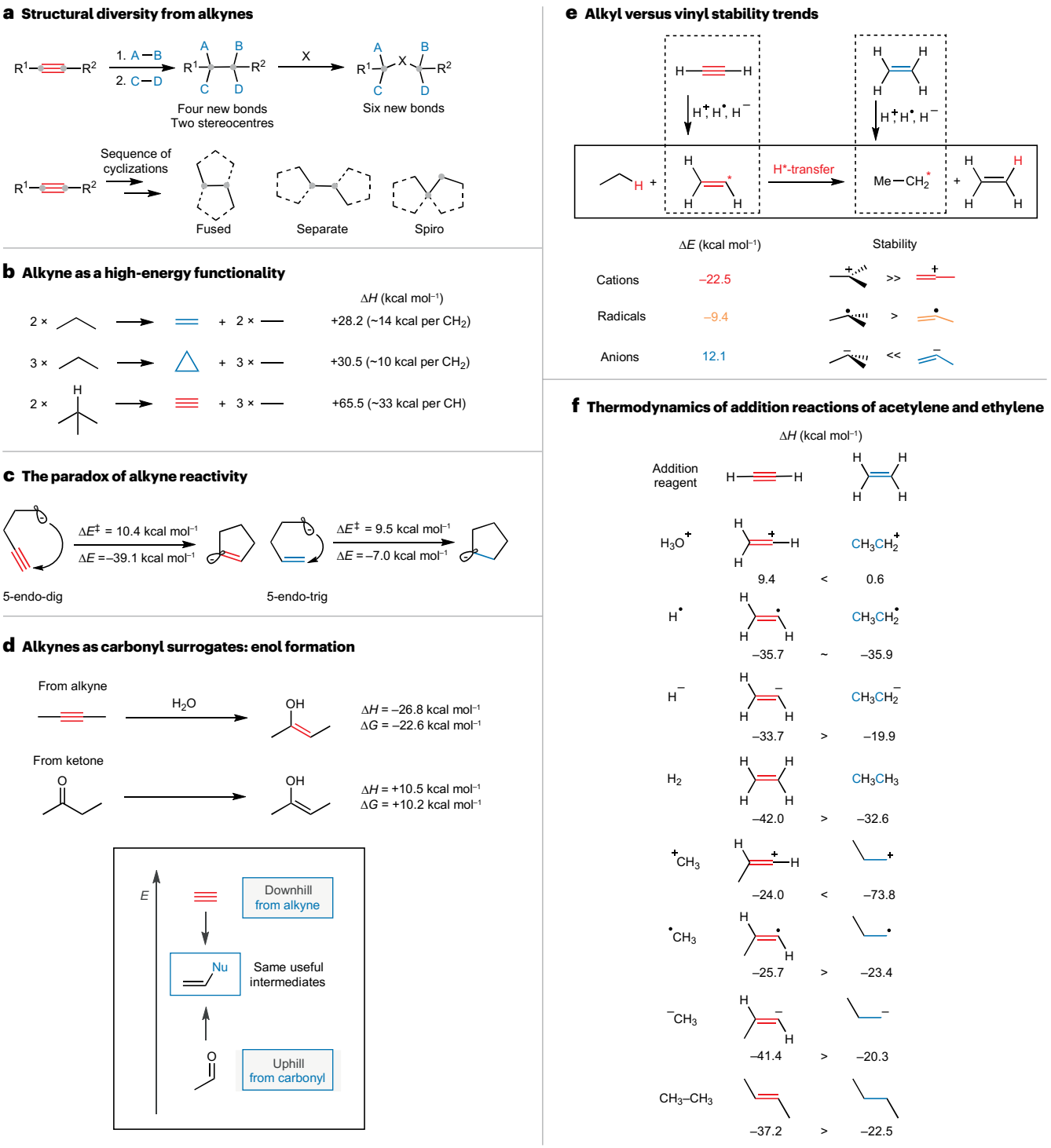


Fig. 1 | Unique characteristics of alkynes. a, Structural diversity from alkynes. Up to six new bonds and different types of cycle can be formed from an alkyne. **b**, Alkyne as a high-energy functionality. Energies in kcal mol^{-1} at MP2/6-311++G(d,p) level. **c**, The paradox of alkyne reactivity. Energies are given in in kcal mol^{-1} at the M05-2X/6-31+G(d,p) level. **d**, Alkynes as carbonyl surrogates. Energies are given in in kcal mol^{-1} at the M06-2X/6-31+G(d,p) level. **e**, Alkyl versus vinyl stability. Energies are given in in kcal mol^{-1} at the G2 level of theory. Vinyl cations are strongly disfavoured compared to the alkyl cation (>20 kcal mol^{-1}). The vinyl radicals are disfavoured compared to the alkyl radical (-10 kcal mol^{-1}). The vinyl anion is favoured compared to alkyl anion (12 kcal mol^{-1}). **f**, Thermodynamics of addition reactions of acetylene and ethylene. Energies are given in in kcal mol^{-1} at the B3LYP/6-31+G(d,p) level.

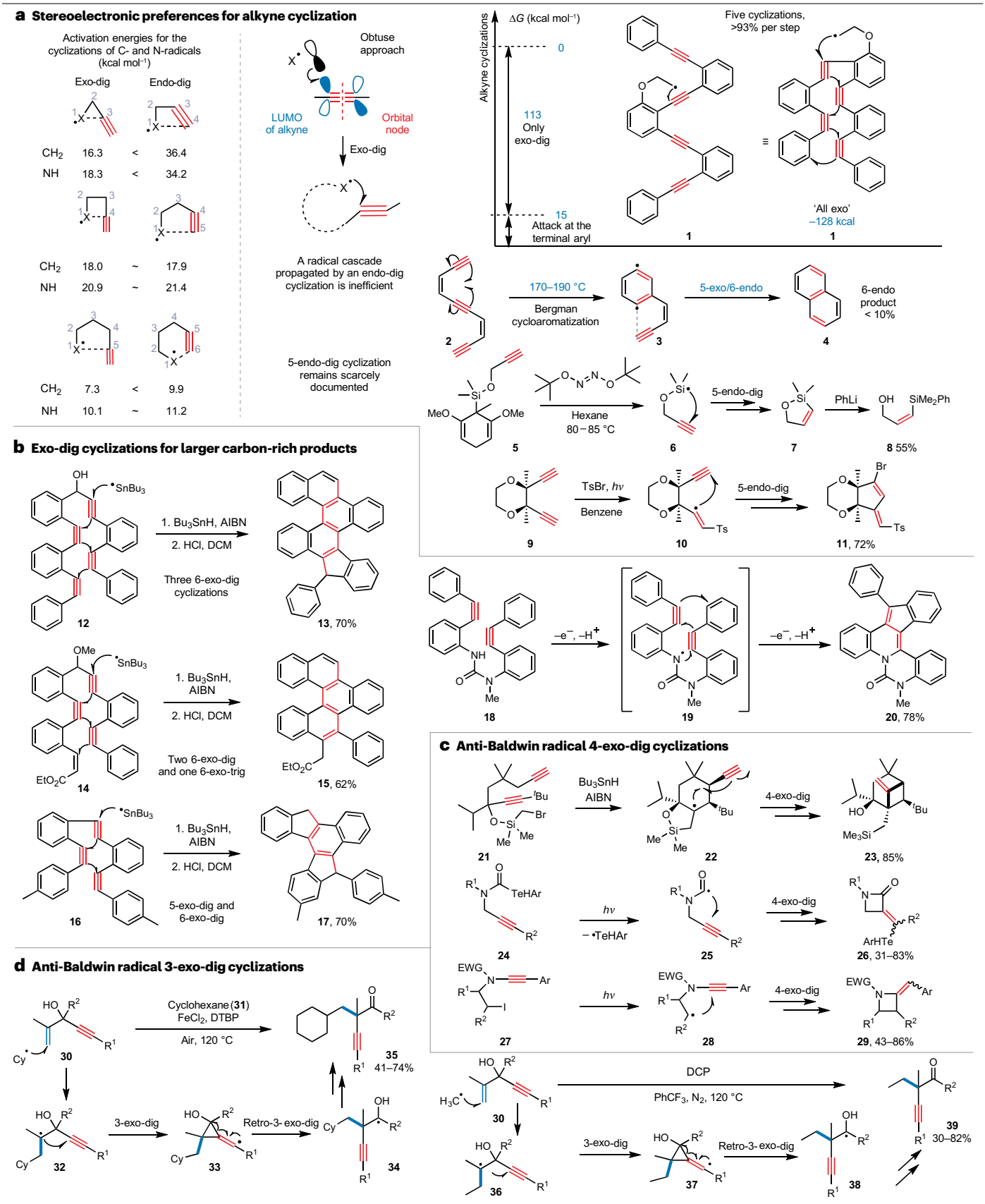

a Stereoelectronic preferences for alkyne cyclization
Activation energies for the cyclizations of C- and N-radicals (kcal mol⁻¹)
Exo-dig
Endo-dig
CH2 16.3 < 36.4
NH 18.3 < 34.2
CH2 18.0 ~ 17.9
NH 20.9 ~ 21.4
CH2 7.3 < 9.9
NH 10.1 ~ 11.2
Obtuse approach
LUMO of alkyne
Orbital node
Exo-dig
A radical cascade propagated by an endo-dig cyclization is inefficient
5-endo-dig cyclization remains scarcely documented
ΔG (kcal mol⁻¹)
Alkyne cyclizations
0
113
Only exo-dig
15
Attack at the terminal aryl
Five cyclizations, >93% per step
1
'All exo'
–128 kcal
1
2
170–190 °C
Bergman cycloaromatization
3
5-exo/6-endo
4
6-endo product < 10%
5
Hexane
80–85 °C
6
5-endo-dig
7
PhLi
8 55%
9
TsBr, hν
Benzene
10
5-endo-dig
11, 72%
b Exo-dig cyclizations for larger carbon-rich products
12
1. Bu3SnH, AIBN
2. HCl, DCM
Three 6-exo-dig cyclizations
13, 70%
14
1. Bu3SnH, AIBN
2. HCl, DCM
Two 6-exo-dig and one 6-exo-trig
15, 62%
16
1. Bu3SnH, AIBN
2. HCl, DCM
5-exo-dig and 6-exo-dig
17, 70%
18
–e⁻, –H⁺
19
–e⁻, –H⁺
20, 78%
c Anti-Baldwin radical 4-exo-dig cyclizations
21
Bu3SnH AIBN
22
4-exo-dig
23, 85%
24
hν
– •TeHAr
25
4-exo-dig
26, 31–83%
27
hν
28
4-exo-dig
29, 43–86%
d Anti-Baldwin radical 3-exo-dig cyclizations
30
Cyclohexane (31)
FeCl2, DTBP
Air, 120 °C
35
41–74%
32
3-exo-dig
33
Retro-3- exo-dig
34
30
DCP
PhCF3, N2, 120 °C
36
3-exo-dig
37
Retro-3- exo-dig
38
39
30–82%

Fig. 2 | Stereoelectronic preferences of alkyne reactions. a, Use of the stereoelectronic preferences for alkyne cyclizations. Energies are given in kcal mol^{-1} at the B3LYP/6-31+G(d,p) level. **b**, Use of alkynes for annealing aromatic systems into larger carbon-rich products. **c**, Anti-Baldwin radical 4-exo-dig cyclization. **d**, Anti-Baldwin 3-exo-dig cyclizations. AIBN, azobisisobutyronitrile; Cy, cyclohexyl; DCM, dichloromethane; DCP, dicumyl peroxide; DTBP, di-*tert*-butyl peroxide; EWG, electron-withdrawing group; LUMO, lowest unoccupied molecular orbital; Ts, toluenesulfonyl.

(lowest unoccupied molecular orbital) symmetry. This can be achieved by coordination of the alkyne to an external Lewis acid ('LUMO umpolung')[42] in electrophile-promoted nucleophilic cyclizations, which are discussed elsewhere[42].

Together with the high carbon content, the efficiency of exo-dig cyclization makes oligoalkynes excellent precursors to the carbon-rich polyaromatic ribbons (Fig. 2b). Independent of the initiation sequence and the number of participating alkyne units, these multistep sequences reliably produce polyaromatic products in yields of 62% to 78%. This high efficiency is associated with the selective intermolecular attack of the Sn radical at the central alkyne. This selectivity ensures that all alkyne units participate in a sequence of exo-dig cyclizations. To achieve this selectivity, traceless directing groups have been used at the propargylic positions of skipped oligoalkynes **12** (ref. 43). With this approach, fused [5]helicenes (**13**) can be synthesized after three 6-exo-dig cyclization in ~70% yield at the gram scale. By replacing the final alkyne with an alkene, as in **14**, this cascade can be interrupted before the formation of a five-membered ring. This is a result of the penultimate alkyl radical being insufficiently reactive to attack the terminal aromatic ring. Therefore, the use of enynes enables access to a defect-free hexagonal framework via a sequence of 6-exo-dig cyclizations terminated by a 6-exo-trig step[44]. A topologically analogous electrochemical cascade demonstrated the utility of selective deprotonation of radical-cations for initiating an efficient synthesis of *N*-heteroaromatics (**20**)[45].

Although they are relatively rare, 3- and 4-exo cyclizations have begun to find synthetic application. Although such processes may be uphill in energy, this is not a problem for the cascade processes, in which a mildly endothermic step can be coupled with subsequent strong exothermic reactions to drive the overall sequence forward. 4-exo-dig cyclizations, one of the least explored cyclization modes and unfavourable according to the Baldwin rules, often have lower energy barriers than the alternative 5-endo-dig cyclization. This is because of the stereoelectronic advantage for the obtuse angle of radical attack at the π-bond[37]. The higher strain of the formation of the smaller ring can partially offset the 4-exo-dig stereoelectronic preference in favour of more stable 5-endo-dig products. However, the extra help needed for the 5-endo-dig to prevail over 4-exo-dig only reemphasizes the intrinsic preference for exo-dig cyclizations in alkyne cascades. The first example of radical 4-exo-dig cyclization that forms an unsubstituted vinyl radical intermediate before generating bicyclo[3.1.1]heptane **23** was reported by Malacria's group[46]. Kambe et al. reported the synthesis of α-alkylidene-β-lactam **26** with 4-exo-dig closure of the carbamoyl radical **25** (ref. 47). More recently, an efficient and general synthesis of azetidines by radical 4-exo-dig cyclization of ynamides (**28**) was described[48] (Fig. 2c).

Owing to the same stereoelectronic factors, the 3-exo-dig cyclization has a lower barrier than 4-endo-dig cyclization. The ring opening of 3-exo-dig products is also fast because they are often less stable than the acyclic reactants, and ring opening proceeds through the same low transition state as ring closure. A method for alkynylation of olefins (**30**) was developed via a 3-exo-dig cyclization followed by ring opening of the 3-exo-dig product[49,50] (Fig. 2d).

But what about intermolecular radical reactions of alkynes, especially in the presence of other functional groups? This question will be addressed in the following section because it has important consequences for chemo- and regioselective alkyne activation in structurally and functionally complex substrates.

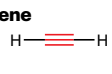
Alkynes versus alkenes

Alkynes are full of paradoxes. To start with, alkynes have a seemingly conflicting disconnection between kinetics and thermodynamics. On one hand, alkynes have high-energy functionalities and many of their reactions are more exergonic than the analogous reactions with alkenes (Fig. 1). Furthermore, alkynes are, on average, less sterically protected than alkenes because they can accommodate fewer substituents. In addition, the presence of two π-bonds can alleviate some of the stereoelectronic restrictions, especially for 'endo'-cyclizations. However, despite their high energy, alkynes possess substantial kinetic stability and often react more slowly than alkenes. From this point of view, selective activation of alkynes, in the presence of alkenes and other functionalities, presents an interesting challenge. Development in this field has provided valuable insights regarding reaction control and the complex interplay between kinetics and thermodynamics on chemoselectivity.

Acetylene has a lower highest occupied molecular orbital (HOMO) and a higher LUMO than does ethylene, which parallels the higher ionization energy and the less negative electron affinity of acetylene[51] (Fig. 3a). The rate constants of intermolecular radical addition to alkenes and alkynes demonstrate that addition to alkenes is faster for a wide range of radicals[52–55]. This preference depends on the nature of the radical — the k_{alkene}/k_{alkyne} ratios vary from 1.7 to 36 for the examples shown in Fig. 3b. The smaller rate difference observed for the sterically hindered 'Bu-substituted variants and a relatively bulky Et_3Si radical indicates that alkynes are more sterically forgiving than alkenes (Fig. 3b). However, even in this case, intermolecular addition to the alkene is faster, indicating that steric factors cannot override intrinsic electronic differences. The large difference of k_{alkene}/k_{alkyne} ratios observed for electrophilic radicals (36 for $\cdot CF_3$) versus nucleophilic radicals (3.5 for $\cdot$c-C_6H_{11}) stems from the electron-deficient nature of *sp*-hybridized carbons.

High-level ab initio calculations of the barriers, enthalpies and rate constants for methyl radical addition to simple alkenes and alkynes have found that addition to alkenes is kinetically favoured over addition to alkynes, despite a larger exothermicity in alkyne addition[56]. At the W1h//QCISD/6-31G(d) level, the exothermicities favour addition to the ethyne and propyne by 1.2 and 1.5 kcal mol^{-1} even though the corresponding Arrhenius activation energies are ~2.0 kcal mol^{-1} lower for the addition to alkenes (ethene and propene). Such 'contra-thermodynamic behaviour' has been attributed to the greater deformation energies associated with the addition to an alkyne and the much larger alkyne singlet–triplet gap. As reported by Radom et al., this difference in the singlet–triplet gap is the greatest contributor to the activation barrier according to the Shaik–Pross curve-crossing model of chemical reactivity[56]. From a simpler but equally accurate perspective, this is also a consequence of alkynes having a much stronger π-bond than alkenes, which dominates the reaction kinetics.

a Acetylene versus ethylene

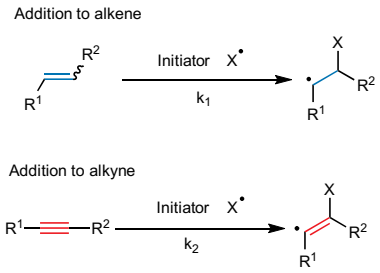


NBO charge on H and C (eV):	0.22; –0.22	0.17; –0.34
HOMO (eV):	–8.07	–7.55
LUMO (eV):	0.40	–0.22
IP (eV)	11.28	10.49
EA (eV)	–1.44	–1.77
Singlet/triplet gap, kcal mol^{-1}	135	107

Calculated kinetic and thermodynamic parameters for methyl radical addition to ethyne and propyne

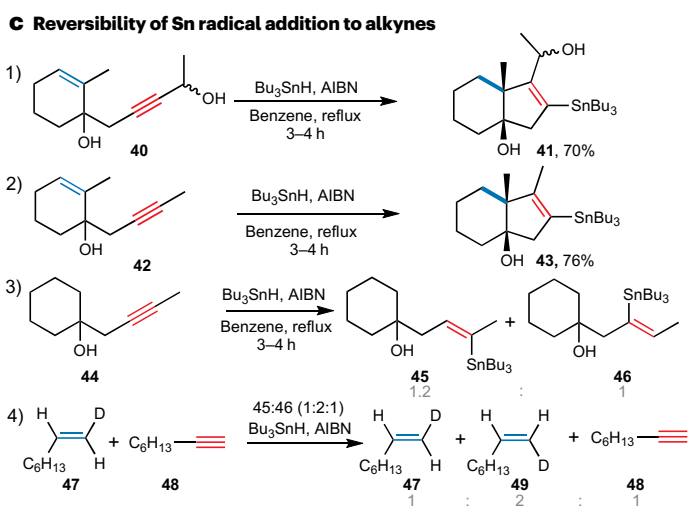
Reaction	$\Delta H^{\ddagger}_0$ (kcal mol^{-1})	ΔH_0 (kcal mol^{-1})
$^{\bullet}CH_3$ + $H_2C{=}CH_2$	9.1	–21.6
$^{\bullet}CH_3$ + $HC{\equiv}CH$	11.3	–22.8
$^{\bullet}CH_3$ + $H_2C{=}CHCH_3$	8.7	–21.7
$^{\bullet}CH_3$ + $HC{\equiv}C{-}CH_3$	11.0	–23.2

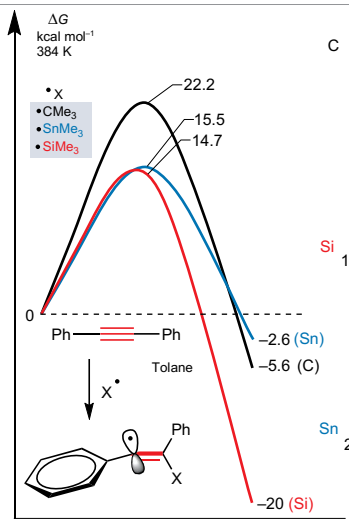
b Radical addition to alkenes and alkynes

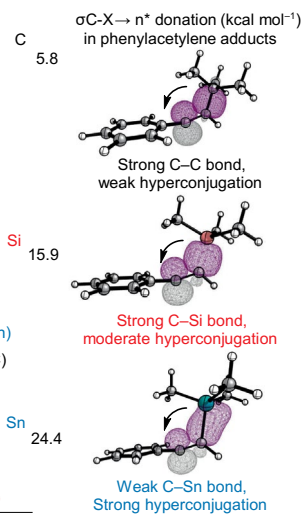


R^1	R^2	X	k_1/k_2	T(K)
Ph	H	$^{\bullet}SiEt_3$	2.2	300
^{t}Bu	H	$^{\bullet}SiEt_3$	1.7	300
H	CF_3	$^{\bullet}CF_3$	2.0	457
Ph	H	$^{\bullet}CF_3$	36	338
Ph	H	$^{\bullet}$c-C_6H_{11}	3.5	293
CO_2CH_3	H	$^{\bullet}$c-C_6H_{11}	3.0	293
CO_2CH_3	CO_2CH_3	$^{\bullet}C(CH_3)_3$	2.5	293
H	H	$^{\bullet}CH_3$	2.5	298
H	CH_3	$^{\bullet}CH_3$	3.0	298
p-MeOPh	H	p-$ClC_6H_4S^{\bullet}$	27.7	296
Ph	H	p-$ClC_6H_4S^{\bullet}$	24.5	296
p-ClPh	H	p-$ClC_6H_4S^{\bullet}$	19.5	296

c Reversibility of Sn radical addition to alkynes

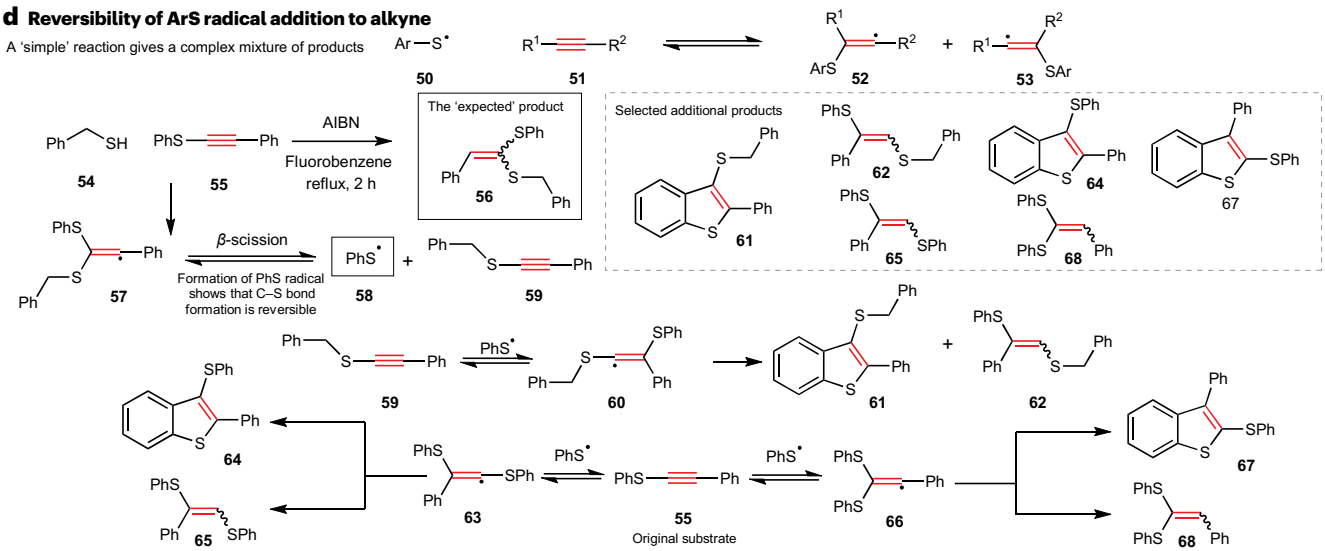






d Reversibility of ArS radical addition to alkyne

A 'simple' reaction gives a complex mixture of products



e Reversibility of sulfonyl radical addition to alkyne

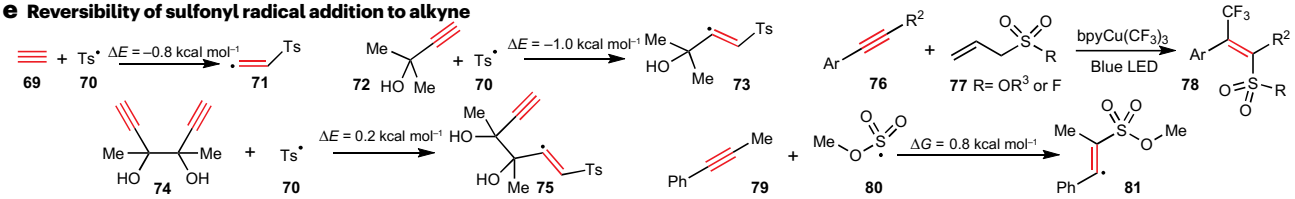


Fig. 3 | Alkynes versus alkenes and the reversibility of radical additions to alkynes. a, Acetylene versus ethylene. **b**, Radical addition to alkenes and alkynes. W1h//QCISD/6-31G(d). **c**, Reversibility of Sn radical addition to alkyne. **d**, Reversibility of ArS addition to alkyne. **e**, Reversibility of sulfonyl radical addition to alkyne. B3LYP/6-31G**(ref. 41); M06-L/LANL2DZ(Cu)-6-311G**(ref. 79). AIBN, azobisisobutyronitrile; bpy, 2,2′-bipyridine; EA, electron affinity; HOMO, highest occupied molecular orbital; IP, ionization potential; LUMO, lowest unoccupied molecular orbital; NBO, natural bond orbital; *T*, temperature; Ts, toluenesulfonyl.

However, even though formation of vinyl radicals by intermolecular radical addition to alkynes is slower than formation of alkyl radicals from alkenes, vinyl radicals are more reactive than the alkyl radicals[57–59]. For example, 5-exo cyclizations of vinyl radicals are >1,000 times faster than cyclizations of analogous alkyl radicals[60]. Vinyl radicals are also much more electrophilic than alkyl radicals — an additional advantage in reactions with electron rich targets[15]. The electron affinity of vinyl radical is rather large (15.5 kcal mol^{-1}), whereas the ethyl radical has a negative electron affinity of −6.4 kcal mol^{-1}, meaning that the ethyl anion is unbound.

Selectivity in alkyne cascades

Precise control of selectivity in radical cascades is essential but challenging, especially when several reactive functionalities are present. Designing a radical cascade in a controllable manner with precise chemo- and regioselective alkyne activation requires different strategies under different circumstances.

Reversible intermolecular addition

When the intermolecular radical addition is reversible, the radical acceptor may survive until the productive step occurs, which potentially offers precise control of selectivity in a radical cascade. In this section, we discuss the reversibility of radical additions to alkynes and illustrate how to utilize this behaviour for the design of radical cascades.

Why are radical additions to alkynes reversible? From the relative rates of alkyne and alkene reactions, one would expect that intermolecular radical addition to non-conjugated enynes would favour reaction at the alkene. However, the classic work of Stork revealed the opposite chemoselectivity[61]. As shown in Fig. 3c, the reaction of acetylenic diol **40** with tributyltin hydride and azobisisobutyronitrile (AIBN) afforded a 70% yield of the 5-exo-trig product **41**, formed via the intermolecular attack at the alkyne. The modified precursor **42**, lacking the propargyl alcohol, follows the same reaction path to give the cyclized product **43** in 76% yield. The propargyl alcohol is therefore not necessary for the chemoselective alkyne activation. Without the alkene, the Sn radical attacks both sites of the alkyne moiety, transforming the alkyne (**44**) into a mixture of regioisomeric alkenes (**45** and **46**). Additionally, the exposure of a 1:1 mixture of (*E*)-1-D-oct-1-ene (**47**) and 1-octyne (**48**) in the presence of Bu_3SnH and AIBN returned the alkene isomerized into a mixture of *E* and *Z* isomers. These experiments reveal that addition to the alkene remains undetected during the activation of the alkyne and that the Bu_3Sn radical adds quickly and reversibly to both the alkynes and the alkenes. It is the reversibility of the 'invisible' radical addition that is responsible for the selective formation of the observed cyclic product.

These early pioneering studies paved the way for many radical cascades of alkynes that are much more selective than one would expect[62–72]. To properly analyse a broader variety of the newer data, we will briefly discuss the origin of reversibility for the radical additions.

The reversibility of radical addition to alkynes may seem to contradict our earlier discussion regarding the exothermicity of alkyne addition reactions. However, unlike hydrogenation and hydration, where two σ-bonds are formed, radical addition forms only one σ-bond. Hence, the outcome is more sensitive to the properties of the newly formed σ-bond.

Additions to both alkynes and alkenes are only exothermic when the newly formed σ-bond is stronger than the broken π-bond. In other words, if only one weak σ-bond is formed while a strong π-bond is broken, such as vinyl radical formation from an alkyne, the thermodynamics can be finely balanced — uphill or downhill, depending on the interplay of several factors. In this context, reversibility is generally observed in the formation of vinyl radicals from alkynes in reactions with large polarizable heteroatomic partners. If the new σ-bond is weak, which is typical for a relatively large soft radical X (Fig. 3c), its strength can be similar to that of the broken π-bond. In this case, the addition step is nearly thermoneutral and reversible. Hence, the paradox of higher endothermicity of radical additions to alkynes, compared to the other addition reactions in Fig. 3c where two new σ-bonds are formed, is explained by the incomplete compensation for breaking the strong alkyne π-bond and forming only one sp^2-X (X = Sn, Si, C) σ-bond.

From this point of view, the special role of Sn radical addition in initiating reversible alkyne activation (part of the 'tyranny of tin' phenomenon[73,74]) can be illustrated by the comparison of addition of Sn-, Si- and C-centred radicals of comparable steric bulk to diphenyl acetylene (tolane)[75]. While the addition of the $SnMe_3$ radical to tolane (ΔG = −2.6 kcal mol^{-1}) is close to thermoneutral, the additions of the CMe_3 radical (−5.6 kcal mol^{-1}) and, especially, the $SiMe_3$ radical (−20 kcal mol^{-1}) to tolane are more exergonic. One can trace these differences back to the relative weakness of the C_{sp2}–Sn bond (with bond dissociation energy, BDE < 80 kcal mol^{-1}) in comparison to the C–C (BDE ~90 kcal mol^{-1}) and C–Si (BDE ~89 kcal mol^{-1}) bonds. We note also that the C–Sn BDE is comparable to the strength of the alkyne π-bond (76 kcal mol^{-1}).

The more stabilization the radical gains, the more exergonic the radical addition is. In a simple case, formation of a strong C–X σ-bond will result in an irreversible radical addition, whereas formation of a weak σ-bond will make the addition reversible. However, this simple picture does not take into account the σ_{C-X}/radical hyperconjugation, which can provide substantial stabilization to the vinyl radical (for example, the radical Si and Sn-'β-effect')[76]. Such vicinal hyperconjugative interactions between the C–X bond and the half-empty radical orbitals are relatively large as vinyl radicals are strong acceptors. As expected, the magnitude of this stabilization further correlates with the donor ability of σ_{C-X} bonds: C–Sn (24.4 kcal mol^{-1}) > C–Si (15.9 kcal mol^{-1}) > C–C (5.8 kcal mol^{-1}, according to NBO analysis). The combination of the weak C–Sn bond and strong $\sigma_{C\text{-}Sn}$/radical hyperconjugation in β-Sn-substituted radicals result in a highly non-symmetric complex of the Sn-radical and a π-bond. Furthermore, in a β-scission process, the Sn-β-effect should increase because distorted bonds are better donors[77], providing additional stabilization to the transition state for this process and contributing to the favourable kinetic reversibility of Sn radical addition to the alkyne.

Navacchia et al. confirmed that addition of the ArS radical to an alkyne is also reversible[78] (Fig. 3d). The benzyl thiol **54** and alkyne **55** under the reflux condition of fluorobenzene with AIBN gives a complex

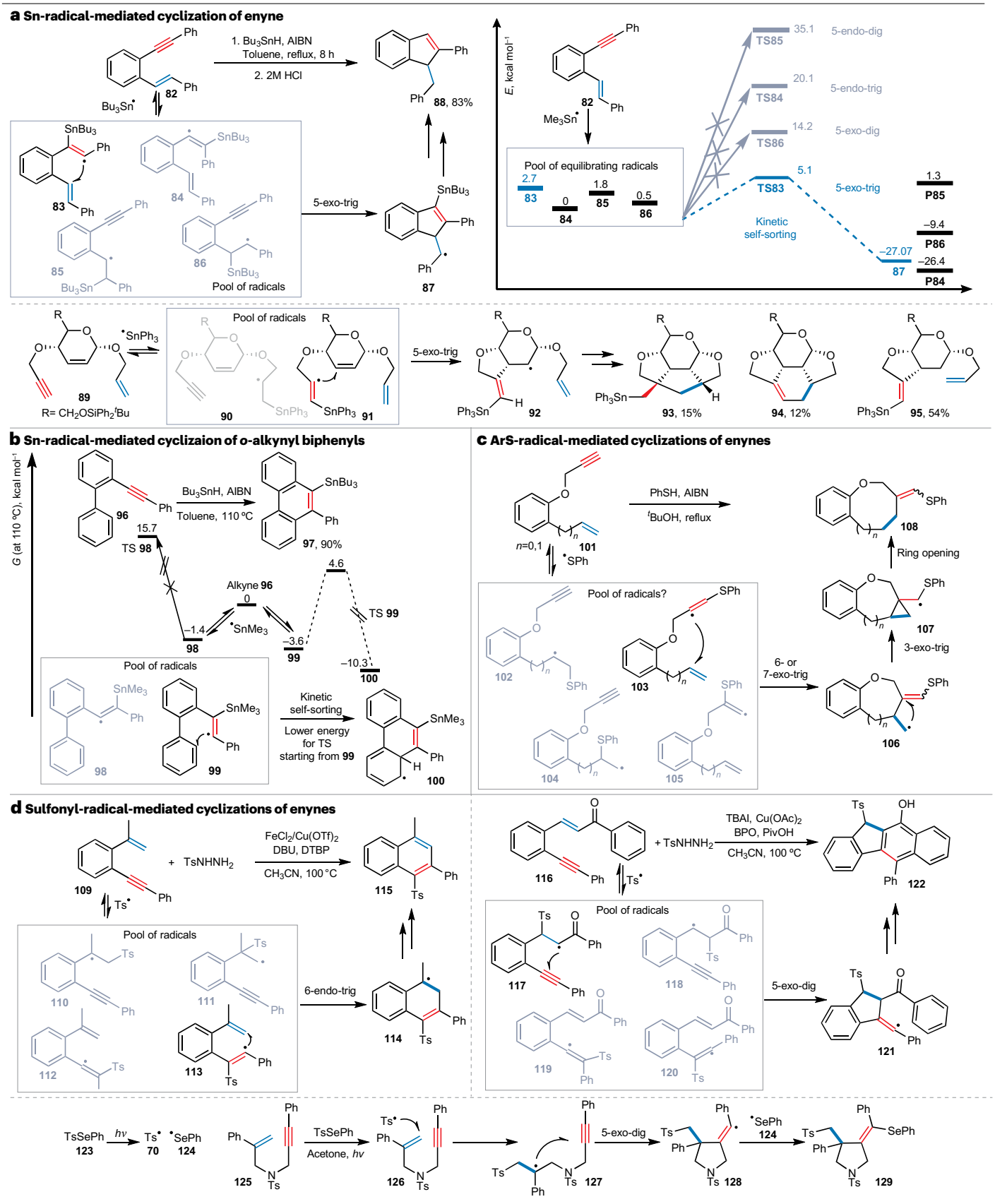

a Sn-radical-mediated cyclization of enyne
1. Bu3SnH, AIBN
Toluene, reflux, 8 h
2. 2M HCl
88, 83%
5-exo-trig
Pool of radicals
87
E, kcal mol−1
Pool of equilibrating radicals
TS85
TS84
TS86
TS83
Kinetic self-sorting
5-endo-dig
5-endo-trig
5-exo-dig
5-exo-trig
P85
P86
P84
89
R= CH2OSiPh2tBu
90
91
92
93, 15%
94, 12%
95, 54%
b Sn-radical-mediated cyclizaion of o-alkynyl biphenyls
G (at 110 °C), kcal mol−1
Bu3SnH, AIBN
Toluene, 110 °C
97, 90%
TS 98
Alkyne 96
TS 99
Pool of radicals
Kinetic self-sorting
Lower energy for TS starting from 99
c ArS-radical-mediated cyclizations of enynes
PhSH, AIBN
tBuOH, reflux
n=0,1
101
108
Ring opening
107
3-exo-trig
6- or 7-exo-trig
106
Pool of radicals?
102
103
104
105
d Sulfonyl-radical-mediated cyclizations of enynes
FeCl2/Cu(OTf)2
DBU, DTBP
CH3CN, 100 °C
109
115
Pool of radicals
6-endo-trig
114
110
111
112
113
TBAI, Cu(OAc)2
BPO, PivOH
CH3CN, 100 °C
116
122
117
118
119
120
5-exo-dig
121
TsSePh
123
hν
70
124
125
Acetone, hν
126
127
128
129

Fig. 4 | Dynamic covalent chemistry in alkyne radical cascades. a, Sn-radical-mediated cyclization of enyne. **b**, Sn-radical-mediated cyclization of *o*-alkynyl biphenyls. **c**, ArS-radical-mediated cyclizations of enyne. **d**, Sulfonyl-radical-mediated cyclizations of enynes. Ac, acetyl; AIBN, azobisisobutyronitrile; BPO, benzoyl peroxide; DBU, 1,8-diazabicyclo(5,4,0)undec-7-ene; DTBP, di-*tert*-butyl peroxide; Piv, pivalyl; TBAI, tetrabutylammoniumiodide; TfO, trifluoromethanesulfonate; TS, transition state; Ts, toluenesulfonyl.

mixture of products instead of the simple addition. Initially, the benzyl thiol radical attacked the alkyne, giving the vinyl radical **57**, which can undergo β-scission, forming the phenylthiyl (PhS) radical. The PhS radical then added both to the alkyne **59** formed in situ and to the original alkyne **55**, as confirmed by the formation of alkenes **62**, **65** and **68**, and benzothiophenes **61**, **64** and **67**. The formation of these products indicates that vinyl radicals can undergo β-scission efficiently, giving the PhS radical. These experiments indicate ArS radical addition to an alkyne is reversible.

The reversibility of the sulfonyl radical (RSO_2) addition to an alkyne has been demonstrated by computational data. The tosyl radical additions to alkyne units are close to thermoneutral and are reversible[41] (Fig. 3e). In the case of sulfonylation and trifluoromethylation of alkynes, the sulfonyl radical addition of **80** to an alkyne **79** is uphill by only 0.8 kcal mol^{-1} (ref. 79).

An important consequence of the reversibility of radical additions to alkynes is that they can be coupled with fragmentations that restore the alkyne moiety. If the same alkyne is re-formed, such transient vinyl radical formation can be used to introduce dynamic covalent chemical control. The fragmentation can either restore the initial alkyne or form a different alkyne. In the latter case, the alkyne moiety is restored with a different substituent. In the first of these scenarios, reversibility of radical additions to alkynes is used for chemoselective and regioselective cascade initiation. In the second, it is used for selective termination of radical cascades. We will discuss these scenarios in the following sections.

Dynamic covalent chemistry in alkyne radical cascades. The reversibility of certain radical additions to alkynes allows them to be considered under the umbrella of dynamic covalent chemistry (DCC)[80]. In essence, DCC is the introduction of elements of thermodynamic control to induce selective transformations mediated by reversible covalent bond formation. DCC can also introduce kinetic traps via 'self-sorting' of the pool of interconverting intermediates through the lowest 'escape' transition state.

The combination of the radical pool with kinetic self-sorting can provide a high level of selectivity in alkyne radical transformations. The reversibility of radical addition to an alkyne and the fast equilibration between the different radicals acts as an 'error-checking' process, in which only one product is formed[81]. The pool of radicals will eventually be depleted by reaction of the radical with the lowest activation barrier for the subsequent reaction. From that point of view, the rich radical interconversion chemistry may be invisible, and the final product seems to be formed from a single component of such mixtures.

In a radical cascade involving enynes, the pool of radicals will contain alkyl and vinyl radicals. If fast equilibration is possible, the products usually come from vinyl radicals even though formation of alkyl radicals from addition to alkene may be thermodynamically favoured. An interesting example of such a system is provided by selective Bu_3Sn-mediated enyne cyclizations where a single indene product (**88**) is formed instead of a mixture of eight possible products derived from two cyclizations (exo and endo) of each of the four possible benzylic radical intermediates (**83**, **84**, **85** and **86**) formed by radical addition to the enyne[81] (Fig. 4a). This dynamic process uses tin radicals, which can reversibly add to π-bonds, allowing for the formation of a single cyclization product from the pool of radicals. The computational analysis of this reaction revealed that the four possible radicals have similar stabilities, but the alkyl radicals formed by radical addition to an alkene are more stable than similar vinyl radicals formed by radical addition to an alkyne. Interestingly, the observed product stems from the least stable radical (**83**). This paradox can be explained by the kinetic self-sorting process. In the pool of four radicals, the product of the cascade is determined by the lowest-energy transition state of the subsequent cyclization steps. Precursors for the non-observed products are either simply recycled back to the reagents or, in the case of unproductive vinyl radicals, can be converted into productive vinyl radicals directly through a low (5.6 kcal mol^{-1}) barrier 1,2-Sn shift[75]. This process illustrates how DCC can allow covalent bonds to reversibly form, break and re-form to ultimately afford one out of several possible products.

When other factors are closely balanced, the lower steric hindrance of the terminal alkyne can shift the balance in favour of radical attack on at the triple bond. For instance, chemo- and regioselective addition of Sn radical to terminal alkyne moiety of enynes is common in the cascades that start with substituted enynes[82–88]. However, when radical additions to both alkenes and alkynes are reversible, DCC could provide a better explanation for the high selectivity of the cyclizations. In the Ph_3Sn-radical-mediated tandem triple addition of dienyne **89**, all products (**93**, **94** and **95**) stem from the addition of the Sn radical to the terminal alkyne, even though a sterically accessible terminal alkene is also present in the molecule[89]. We note that the radical cascade gives product **93** where four new σ-bonds are formed at the alkyne unit.

DCC also assists in synthesis of functionalized phenanthrenes from *o*-alkynyl biphenyls[90] (Fig. 4b). Two vinyl radicals, **98** and **99**, are formed by intermolecular Sn-radical addition to the alkyne. Based on the computational data, the formation of these two radicals is reversible, so that they can interconvert under the reaction conditions. The lower activation barrier for subsequent cyclization of radical **99** makes it the productive species in this pool of radicals that leads to the phenanthrene (**100**) formation.

The selectivity of the thiol radical cascade in cyclizations of enynes also takes advantage of the reversibility of ArS radical addition (Fig. 4c). In the synthesis of oxepin and oxocine (**108**) by Majumdar and coworkers[91,92], an ArS radical can attack either the alkene or alkyne. In the pool of radicals, the vinyl radical (**103**), formed from radical addition to the alkyne, can undergo either a 6- or 7-exo-trig cyclization. The cascade is continued by 3-exo-trig ring closure and ring opening. The alkyl radical, on the other hand, remains unproductive, because of the higher barrier of the cyclization steps.

DCC can also explain the selectivity of sulfonyl radical-mediated cyclizations of enynes. In this radical cascade, the product comes from a path initiated by intermolecular radical addition to the internal alkyne instead of the terminal alkene unit[93] (Fig. 4d). This surprising chemoselectivity can be rationalized by considering the pool of radicals formed by reversible sulfonyl radical addition to both the alkene and alkyne. The productive vinyl radical (**113**), which has a lower barrier for subsequent cyclization, leads to the final product **115**. Interestingly, in other

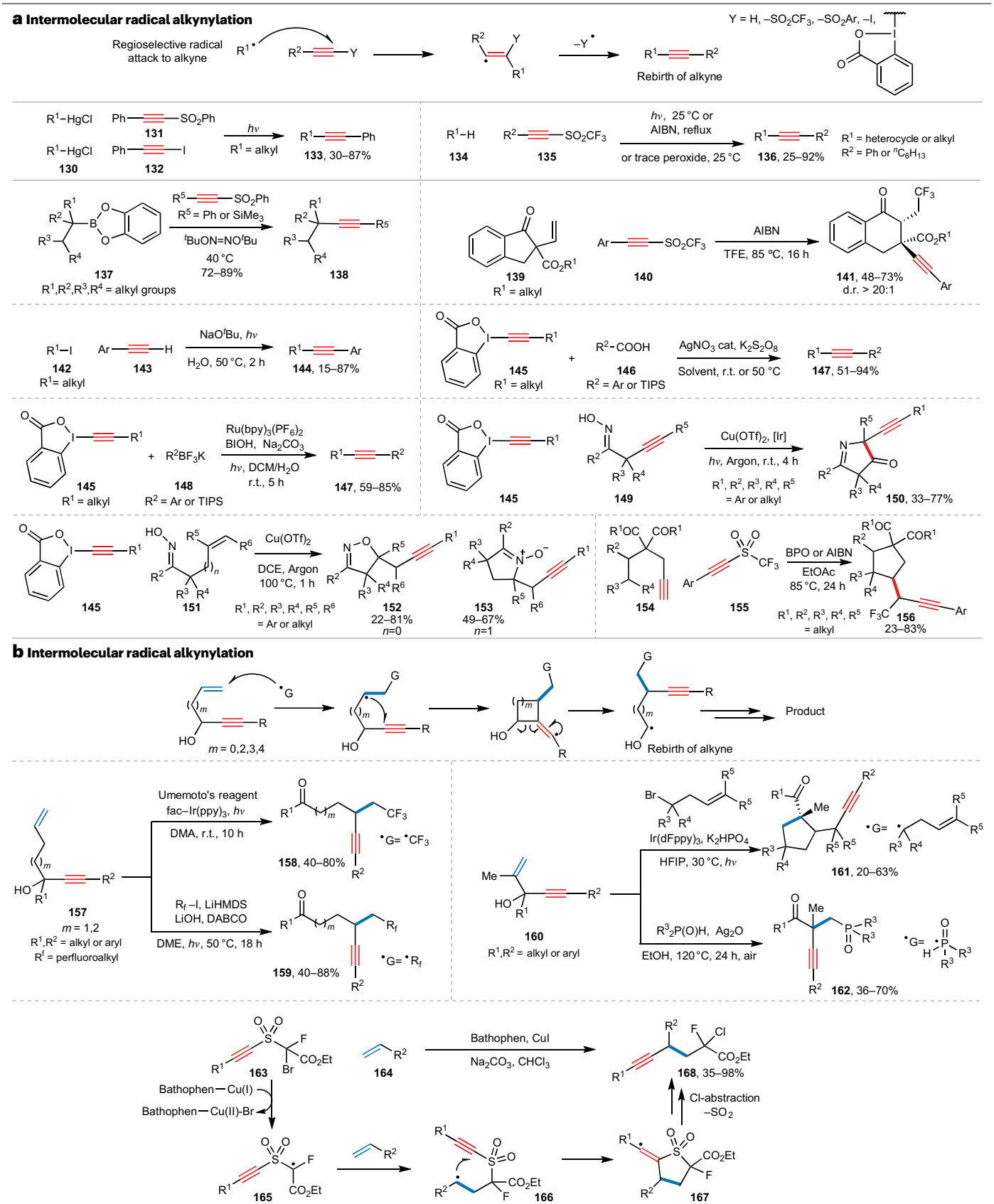

a Intermolecular radical alkynylation
Regioselective radical attack to alkyne
Rebirth of alkyne
Y = H, –SO2CF3, –SO2Ar, –I,
hν
R1 = alkyl
133, 30–87%
hν, 25 °C or AIBN, reflux
or trace peroxide, 25 °C
136, 25–92%
R1 = heterocycle or alkyl
R2 = Ph or nC6H13
137
R1,R2,R3,R4 = alkyl groups
R5 = Ph or SiMe3
tBuON=NOtBu
40 °C
72–89%
138
139
R1 = alkyl
AIBN
TFE, 85 °C, 16 h
141, 48–73%
d.r. > 20:1
NaOtBu, hν
H2O, 50 °C, 2 h
144, 15–87%
145
R1 = alkyl
146
R2 = Ar or TIPS
AgNO3 cat, K2S2O8
Solvent, r.t. or 50 °C
147, 51–94%
Ru(bpy)3(PF6)2
BIOH, Na2CO3
hν, DCM/H2O
r.t., 5 h
147, 59–85%
149
Cu(OTf)2, [Ir]
hν, Argon, r.t., 4 h
150, 33–77%
Cu(OTf)2
DCE, Argon
100 °C, 1 h
152
22–81%
n=0
153
49–67%
n=1
154
155
BPO or AIBN
EtOAc
85 °C, 24 h
156
23–83%
b Intermolecular radical alkynylation
m = 0,2,3,4
Product
Rebirth of alkyne
157
m = 1,2
Umemoto's reagent
fac–Ir(ppy)3, hν
DMA, r.t., 10 h
158, 40–80%
Rf –I, LiHMDS
LiOH, DABCO
DME, hν, 50 °C, 18 h
159, 40–88%
160
R1,R2 = alkyl or aryl
Ir(dFppy)3, K2HPO4
HFIP, 30 °C, hν
161, 20–63%
R3P(O)H, Ag2O
EtOH, 120 °C, 24 h, air
162, 36–70%
163
Bathophen–Cu(I)
Bathophen–Cu(II)-Br
164
Bathophen, CuI
Na2CO3, CHCl3
168, 35–98%
Cl-abstraction
–SO2
165
166
167

Fig. 5 | Alkyne resilience in intermolecular and intramolecular reactions. **a**, Intermolecular radical alkynylation. **b**, Intramolecular radical alkynylation. AIBN, azobisisobutyronitrile; Bathophen, bathophenanthroline; BI, benziodoxole; BPO, benzoyl peroxide; bpy, 2,2′-bipyridine; cat, catalyst; DABCO, 1,4-diazabicyclo[2.2.2]octane; DCE, 1,2-dichloroethane; DCM, dichloromethane; d.r., diastereomeric ratio; dFppy = 2-(2′,4′-difluorophenyl)pyridyl; DMA, dimethylacetamide; DME, dimethoxyethane; DTBP, di-*tert*-butyl peroxide; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol; LiHMDS, lithium bis(trimethylsilyl) amide; ppy, tris(2-phenylpyridine); R^f, perfluoroalkyl; r.t., room temperature; TFE, 2,2,2-trifluoroethanol; TfO, trifluoromethanesulfonate; TIPS, triisopropylsilyl.

cases, the selectivity can be reversed. The cyclization of 1,5-enynes (**116**) initiated by a sulfonyl radical starts from the addition to the alkene (**117**), followed by 5-exo-dig cyclization (**121**)[94]. It is possible that DCC also plays an important part in this transformation and that the alkyl radical has the lowest energy barrier for the subsequent cyclization step from the pool of radicals. An interesting comparison to this work, provided by Wang et al.[95], found that chalcogen radical species (such as sulfonyl, thiyl and selenyl) exclusively targeted the terminal carbon of the 2-Ph-substituted alkene moiety in 1,6-enynes (**125**). Only the 5-exo-dig cyclization product **128** was observed in this cascade, highlighting the absolute regio- and chemoselectivity of these radical species towards the alkene attack. Although DCC could possibly explain this result, the selectivity may simply reflect the preference of RSO_2, an electrophilic radical, for a more electron-rich target, that is, the alkene.

Transient sacrifice of an alkyne moiety. Alkynyl radicals are conceptually interesting but harder to generate and control, compared to vinyl radicals, owing to their high reactivity. As the alkynyl C_{sp}–H bonds are very strong (130 kcal mol^{-1}, about 20 kcal mol^{-1} stronger than the C_{sp2}–H bonds of alkenes), direct generation of alkynyl radicals from alkynes is difficult and these high-energy species are expected to react fast with a variety of targets[96,97]. Use of weaker σ-bonds, such as the C_{sp}–I bond, allows generation of these unstable reactive species[98–100]. Although interesting, these reactions are outside of the scope of this Review as we focus on reactions that involve the alkyne π-bonds.

Several recent reports describe the indirect introduction of alkyne moieties via radical cascades that correspond to radical sp–sp^3/sp–sp^2 couplings. These examples illustrate that radical cascades of alkynes can be used to make new alkynes[101] but through an addition/elimination approach based on the temporary sacrifice and subsequent regeneration of the alkyne moiety. These processes provide useful alternatives to the functionalization of alkynes based on direct nucleophilic addition to an electrophile (such as ketone)[102,103], on palladium-catalysed alkynylation of aryl and vinyl halides (such as Sonogashira and related reactions), or on the Corey–Fuchs reaction and the Seyferth–Gilbert homologation.

Electron-deficient *sp*-hybridized alkynes such as acetylenic triflones readily accept nucleophilic radicals. Such electrophilic alkynylation is an umpolung of the usual synthetic approaches where acetylene (or acetylide) is used as a nucleophilic synthon in reactions with electrophiles[104] (Fig. 5a). The regioselectivity of radical attack stems from a combination of steric factors and electronic effects on the stability of the vinyl radical intermediates. With the recent progress in generating carbon- or heteroatom-centred radicals, this newly emerging radical alkynylation finds broad application (see below).

In 1986, Russel and Ngoviwatchai reported the first radical alkynylation with alkynylsulfones (**131**) or iodoalkynes (**132**)[105–107]. A decade later, the scope of radical alkynylation was extended with acetylenic triflones (**135**) acting as excellent alkyne transfer reagents for radical-mediated reactions involving C–H activation[108]. More progress has been made in radical alkynylation for challenging synthetic goals, such as in the functionalization of quaternary carbons. A one-pot radical-mediated alkynylation of alkylcatecholboranes **137** starting from alkenes has been developed, which can be used to functionalize quaternary carbons[109]. Alkynyl triflone **140** has been used to achieve the alkynylation of a quaternary carbon centre in a ring-expansion process[110] and was further expanded to terminal alkynes as a starting point[111]. Transition-metal-free protocols for alkynylation using terminal alkyne **143** and alkyl iodide **142** under ultraviolet light in an aqueous base has proved useful for the coupling of non-activated alkyl iodides with terminal alkynes[111]. In addition, the use of carboxylic acids, trifluoroborates and boronic acids as a radical source also greatly expanded the boundaries of the application of radical alkynylation. The decarboxylative radical alkynylation of carboxylic acids **146** using EBX (ethynylbenziodoxolone) reagents **145** and silver nitrate as a catalyst in aqueous conditions has also been described[112]. The Chen group reported a deboronative alkynylation reaction in which trifluoroborates (**148**) or boronic acids were used as radical sources[113]. The Han group described the synthesis of alkyne-containing heterocycles from ketoximes (**149** and **151**) and EBX reagents[114,115]. The alkyne unit in ketoxime **149** was used as a building block for the construction 3*H*-pyrrol-3-ones core in **150** where four new bonds were formed from the two π-bonds of alkyne while the alkyne unit of the EBX reagent was used for alkynylation. This approach was used to achieve challenging 1,1,2-trifunctionalization of terminal alkynes (**154**)[116] by intercepting the vinyl radical via intramolecular 1,5-HAT (hydrogen atom transfer) followed by a radical 5-exo-dig cyclization. Two π-bonds of a terminal alkyne reactant were converted into four new σ-bonds of highly functionalized cyclopentane product.

An intramolecular application of this concept leads to alkyne migrations. This strategy also takes advantage of the resilient nature of alkynes (Fig. 5b). In general, after the initial selective radical attack at the terminal alkene, the alkyl radical attacks the alkyne intramolecularly, forming a vinyl radical and closing a ring. The ring opening gives a new alkyne unit and a new alkyl radical. The reactions proceed well when the new radical is stabilized, for example by an adjacent O atom through 2c-3e (2-centre, 3-electron) bond, or when a stable byproduct is formed, for example through the release of SO_2. In 2017, Zhu and Studer independently applied this strategy for the photochemical trifluoromethylation[117] and perfluoroalkyl-alkynylation of alkenes (**157**)[118]. The trifluoromethyl or perfluoroalkyl radical attacks the terminal alkene, setting up the following exo-dig alkyl radical cyclizations. Furthermore, these alkyne migration cascades can be initiated by carbon or heteroatom-centred radicals in the 1,4-enyne **160** (refs. 49,50,119,120). The starting point of the alkyne migration strategy is not limited to enynes. Zhu's group reported an intermolecular monofluoroalkylative alkynylation of alkenes[121]. In contrast to the previous examples, where the alkynes and alkene are in the same molecule, here alkyne **163** is connected to the radical precursor while alkene **164** serves as an intermolecular partner in this cascade. The authors suggest that the activation of the C–Br bond is followed by intermolecular radical addition to the alkene, which apparently proceeds faster than an alternative intramolecular 3-exo-dig closure. The intermolecular addition sets up a 5-exo-dig cyclization. The alkyne moiety is reformed as alkyne

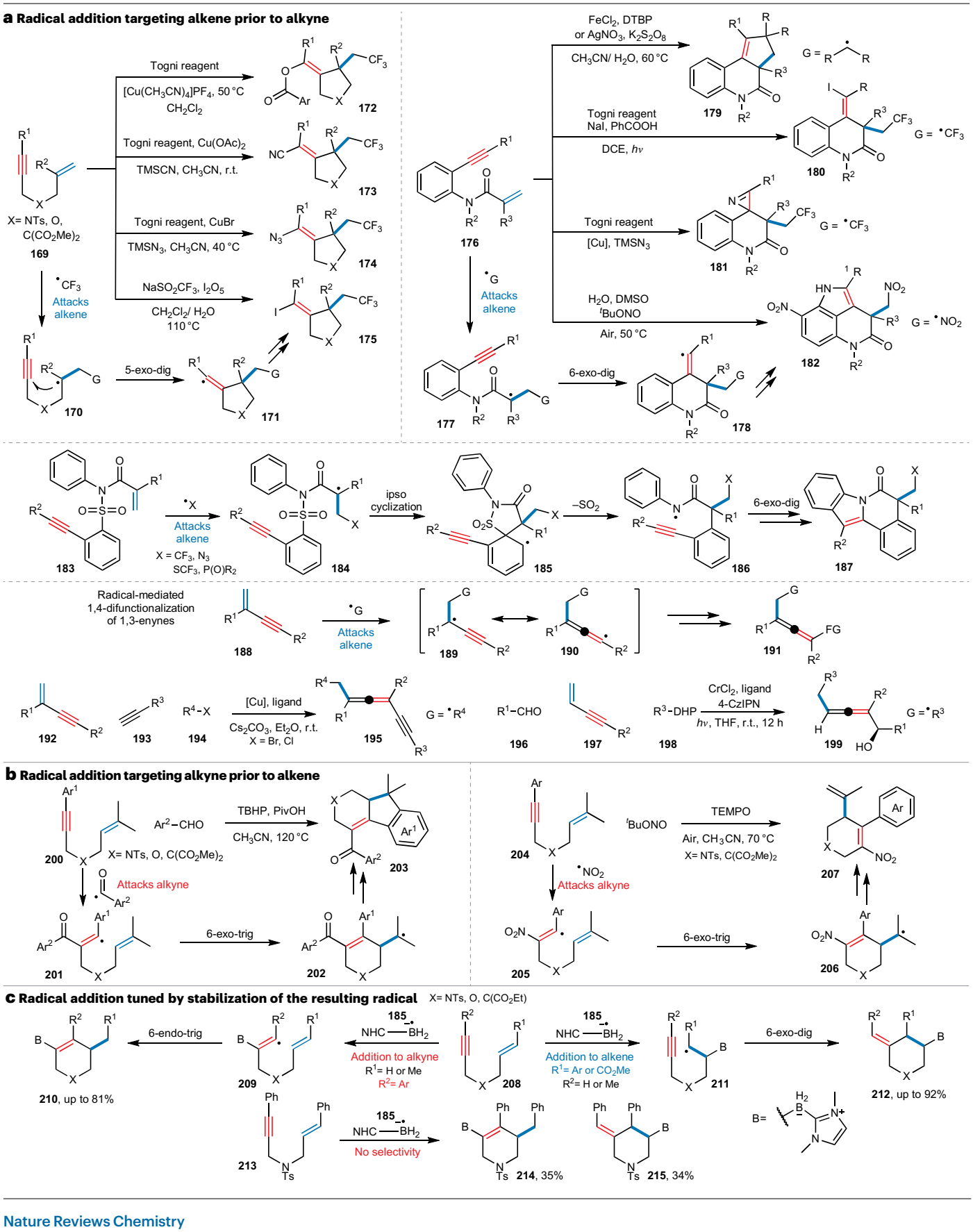

a Radical addition targeting alkene prior to alkyne
Togni reagent
[Cu(CH3CN)4]PF4, 50 °C
CH2Cl2
Togni reagent, Cu(OAc)2
TMSCN, CH3CN, r.t.
Togni reagent, CuBr
TMSN3, CH3CN, 40 °C
NaSO2CF3, I2O5
CH2Cl2/ H2O
110 °C
X= NTs, O, C(CO2Me)2
169
•CF3
Attacks alkene
5-exo-dig
170
171
172
173
174
175
FeCl2, DTBP
or AgNO3, K2S2O8
CH3CN/ H2O, 60 °C
Togni reagent
NaI, PhCOOH
DCE, hν
Togni reagent
[Cu], TMSN3
H2O, DMSO
tBuONO
Air, 50 °C
176
•G
Attacks alkene
6-exo-dig
177
178
179
180
181
182
G = •CF3
G = •NO2
183
•X
Attacks alkene
X = CF3, N3
SCF3, P(O)R2
184
ipso cyclization
185
–SO2
186
6-exo-dig
187
Radical-mediated
1,4-difunctionalization
of 1,3-enynes
188
•G
Attacks alkene
189
190
191
192
193
R4–X
194
[Cu], ligand
Cs2CO3, Et2O, r.t.
X = Br, Cl
195
G = •R4
R1–CHO
196
197
R3–DHP
198
CrCl2, ligand
4-CzIPN
hν, THF, r.t., 12 h
199
G = •R3
b Radical addition targeting alkyne prior to alkene
200
X= NTs, O, C(CO2Me)2
Ar2–CHO
TBHP, PivOH
CH3CN, 120 °C
Attacks alkyne
6-exo-trig
201
202
203
204
tBuONO
TEMPO
Air, CH3CN, 70 °C
X= NTs, C(CO2Me)2
•NO2
Attacks alkyne
205
6-exo-trig
206
207
c Radical addition tuned by stabilization of the resulting radical
X= NTs, O, C(CO2Et)
6-endo-trig
210, up to 81%
209
185
NHC—BH2
Addition to alkyne
R1= H or Me
R2= Ar
208
Addition to alkene
R1= Ar or CO2Me
R2= H or Me
211
6-exo-dig
212, up to 92%
B=
213
No selectivity
214, 35%
215, 34%

Fig. 6 | Selectivity in cyclizations with irreversible intermolecular radical addition. a, Radical addition targeting alkene prior to alkyne. **b**, Radical addition targeting alkyne prior to alkene. **c**, Radical addition targeting alkyne prior to alkene. 4-CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; DHP, dihydropyridine; DMSO, dimethyl sulfoxide; DTBP, di-*tert*-butyl peroxide; FG, functional group; NHC, N-heterocyclic carbene; Piv, pivalyl; TBHB, *tert*-butyl hydroperoxide; TEMPO, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl; Ts, toluenesulfonyl.

migration has completed and the cyclized product **167** is reopened with the subsequent loss of SO_2, rendering the overall process irreversible.

Irreversible intermolecular addition

When radical addition is irreversible, there is no radical pool with kinetic self-sorting. Therefore, the selectivity of the first radical addition becomes essential. In this section, we summarize several selectivity trends for radical cascades in multifunctional molecules, containing both an alkene and an alkyne.

General reactivity of alkenes versus alkynes. Additions to alkenes generally have lower barriers than additions to alkynes, despite having comparable or lower exergonicity. Therefore, radical addition to an alkene is generally faster than the addition to an equivalent alkyne because the alkene π-bonds are weaker. Experimental data indicates that, when all possible radical addition reactions are irreversible, the radical cascade usually starts with addition to the alkene rather than the alkyne, especially for terminal alkenes where steric hindrance is minimal (Fig. 6a).

This reactivity pattern dominates for the formation of strong bonds, such as C–C bonds in an irreversible C-radical addition. For example, when using CF_3 radicals to initiate the radical cyclization of 1,6-enyne **169** (refs. 122–124), the initial intermolecular radical addition occurred at the terminal alkene. In the next step, the intermediate alkyl radical **170** underwent 5-exo-dig cyclization. Analogous selectivity is observed for the radical cyclizations of 1,7-enyne **176**. Although one could argue that electronic factors also contribute to the selectivity in the above examples, such effects cannot be dominant as both nucleophilic and electrophilic radicals were reported to react faster with alkenes (Fig. 3b). Interestingly, despite the polarity mismatch, CF_3 radicals attack the electron-deficient alkene moiety of enyne **176** first, setting up the subsequent 6-exo-dig cyclization[125–127]. We note that the same two functional groups (alkene and alkyne) are involved in the radical cascade in the opposite order to the enyne cyclizations that proceed under the DCC or 'radical pool' conditions.

As N-radical addition to an alkyne is generally irreversible[128], the radical nitration of 1,7-enyne **176** starts with NO_2 radical addition to the alkene[129]. In remarkable cyclization-fragmentation-cyclization 1,8-enyne (**183**) cascades, a variety of radicals ($\cdot CF_3$, $\cdot SCF_3$, $\cdot P(O)Ph_2$, $\cdot N_3$) can initiate the sequence of reactions by selectively attacking the alkene[130]. The alkyne moiety is involved in the second part of the cascade by engaging in a 6-exo-dig cyclization with the electrophilic *N*-amidyl radical to form a vinyl radical that completes the cascade by attacking a pendant aromatic ring.

Radical-mediated 1,4-difunctionalization of 1,3-enynes (**188**) is a useful strategy for building functionalized allenes (**191**)[131–139]. This process starts with the radical addition to alkene, resulting in propargyl radical (**189**) and its resonance structure the allenyl radical (**190**). The following capture of the allenyl radical gives the functionalized allene products. The enantioselective syntheses of chiral allenes were independently described by the Bao and Zhang groups[140], and the Liu group[141]. The Bao and Zhang groups achieved the enantioselective 1,4-oxycyanation of 1,3-enynes. In Liu's work, the radical R^4 attacks the alkene unit in 1,3-enyne **192**, followed by the reaction between the allenyl radical and copper (II) acetylide to afford chiral allenes. In another example, chiral allene derivatives have been synthesized from the, 1,3-enynes **197** by a radical approach with photoredox and chromium catalysis[142].

Reversing the intrinsic preferences by sterics. The preference for radical addition to an alkene can be reversed when the alkene is sterically hindered. Because alkyne carbons are relatively unencumbered, alkynes are more sterically forgiving than alkenes. When a hindered (for example, trisubstituted) alkene is present, the steric effect can override the intrinsic preference for radical addition to the alkene and attack the alkyne instead (Fig. 6b). In the synthesis of tricyclic fluorene **203** from 1,6-enyne **200**, reported by the Liang's group[143], the acyl radical generated from TBHB (*t*-butyl hydroperoxide) targets the alkyne instead of the trisubstituted alkene. In this example, the two methyl groups provide sufficient steric hindrance to the alkene to reverse the intrinsic preference of radical addition, making the alkyne a more favourable target. Similarly, Liang group reports the NO_2 radical initiates a radical cascade by adding to the alkyne instead of the hindered alkene moiety in a 1,6-enyne **204** (ref. 144).

Shifting selectivity by stabilizing the products. Thermodynamic effects can also play a part in controlling selectivity in enyne radical cyclizations. Radical addition that forms a more stabilized radical is generally more favourable. The chemo- and regioselectivity of radical borylation-cyclization cascade of 1,6-enynes (**208**) was controlled by varying the substituents[145] (Fig. 6c). In this case, the high selectivity probably derives from stabilization of the transition state, leading to the intermediate radical by benzylic conjugation. Although N-heterocyclic carbene (NHC)-boryl radical[146] additions to substituted alkenes and alkynes are exergonic, there is not enough information to judge whether the DCC can explain the selectivity. However, useful empirical observations are available. When R^1 (with alkene) is an H or Me group and R^2 (with alkyne) is an aryl group, the boryl radical attacks the alkyne first (**209**). On the other hand, when the alkene has aryl substituents and alkyne has H or Me group, the boryl radical attacks the alkene first (**211**). In the control experiment where both the Ph-substituted alkene and alkyne are present (**213**), the radical cascade is unselective. These observations indicate that the selectivity present in enyne radical cyclization reactions can be controlled by stabilizing the preferred product.

Other selectivity control strategies

In addition to the above methods addressing selectivity in enyne radical cascades, there are other selectivity control strategies for substrates with multiple alkynes and/or alkynes.

Directing groups. Substrates that have more than one alkyne moiety present a challenge for selectivity control. One approach to solving challenging selectivity problems in multifunctional substrates is the use of directing groups[147–151]. However, designing an intermolecular directing group for a short-lived neutral intermediate, such as a radical,

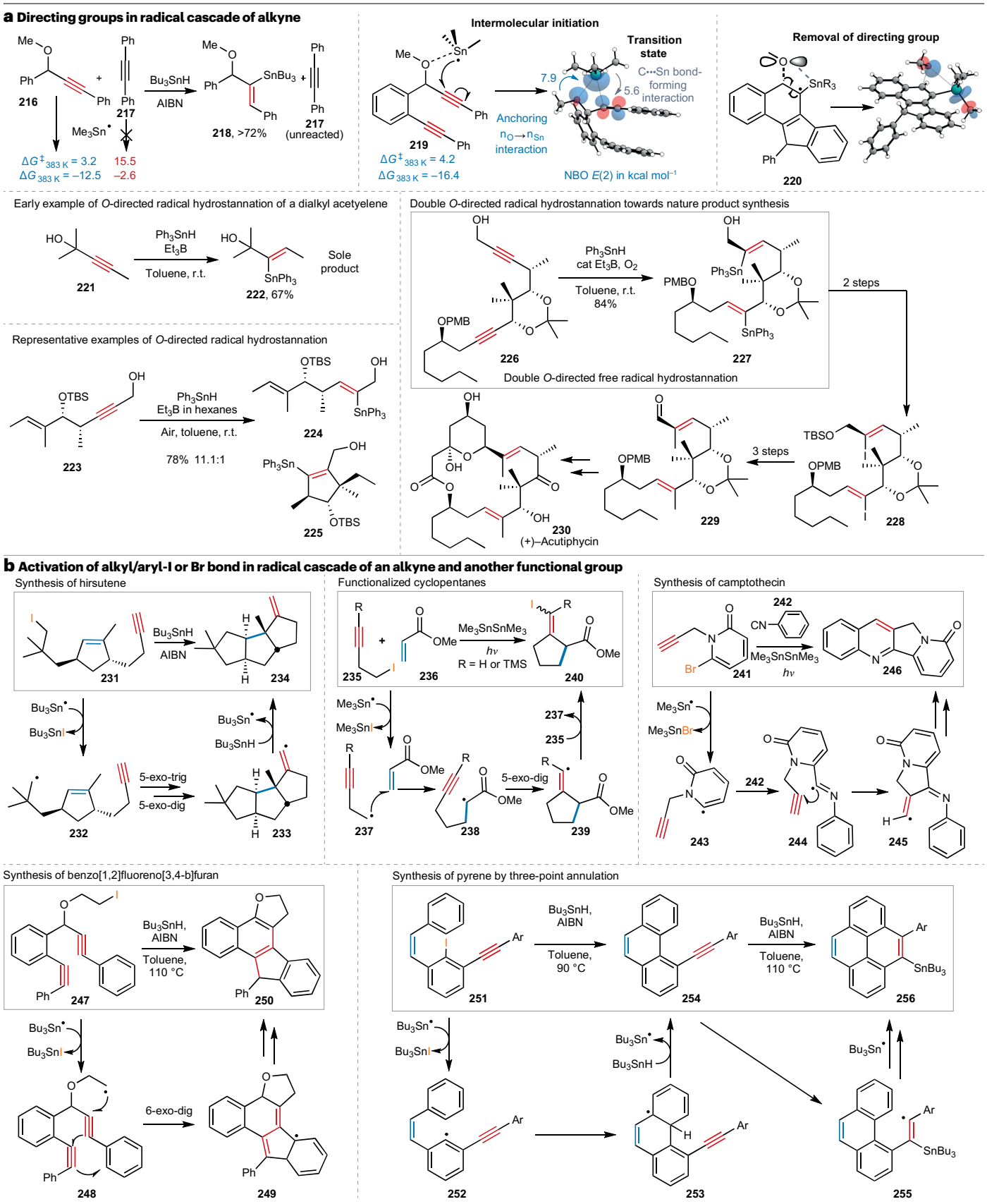

a Directing groups in radical cascade of alkyne
Intermolecular initiation
Transition state
Removal of directing group
Bu3SnH
AIBN
Me3Sn•
216
217
218, >72%
217 (unreacted)
ΔG‡383 K = 3.2
15.5
ΔG383 K = –12.5
–2.6
219
ΔG‡383 K = 4.2
ΔG383 K = –16.4
Anchoring nO→nSn interaction
7.9
5.6
C•••Sn bond-forming interaction
NBO E(2) in kcal mol–1
220
Early example of O-directed radical hydrostannation of a dialkyl acetyelene
Ph3SnH
Et3B
Toluene, r.t.
Sole product
221
222, 67%
Representative examples of O-directed radical hydrostannation
Ph3SnH
Et3B in hexanes
Air, toluene, r.t.
78% 11.1:1
223
224
225
Double O-directed radical hydrostannation towards nature product synthesis
Ph3SnH
cat Et3B, O2
Toluene, r.t.
84%
226
227
Double O-directed free radical hydrostannation
2 steps
3 steps
228
229
230
(+)–Acutiphycin
b Activation of alkyl/aryl-I or Br bond in radical cascade of an alkyne and another functional group
Synthesis of hirsutene
231
234
Bu3Sn•
Bu3SnI
Bu3SnH
5-exo-trig
5-exo-dig
232
233
Functionalized cyclopentanes
Me3SnSnMe3
hν
R = H or TMS
235
236
240
Me3Sn•
Me3SnI
237
238
239
Synthesis of camptothecin
241
242
246
Me3SnBr
243
244
245
Synthesis of benzo[1,2]fluoreno[3,4-b]furan
Bu3SnH, AIBN
Toluene, 110 °C
247
250
6-exo-dig
248
249
Synthesis of pyrene by three-point annulation
Bu3SnH, AIBN
Toluene, 90 °C
Toluene, 110 °C
251
254
256
252
253
255

Fig. 7 | Other selectivity control strategies in radical cascades of alkynes. **a**, Directing groups in radical cascade of alkyne. Energies are given in kcal mol^{-1} at the UM06-2X/Lanl2dZ level. Anchoring $n_O \rightarrow n_{Sn}$ interaction denotes donation from the lone pair of O to the radical orbital at Sn. **b**, Activation of the C–I or C–Br bond in radical cascade of an alkyne and another functional group. AIBN, azobisisobutyronitrile; NBO *E*(2), energy of the stabilizing interaction evaluated by the second-order perturbation theory and natural bond orbital analysis.

is a daunting task. Fortunately, alkynes lend themselves perfectly to supramolecular directing effects based on through-space 2c,3e-interactions of radicals with a propargylic heteroatom lone pair[43]. Such interactions between Me_3Sn radicals and a lone pair at the α-OR substituent (Fig. 7a) can explain the fast and selective addition of Sn radicals to propargylic ethers **216**. This design was extended to highly selective radical cascades of ortho-phenylene oligoalkynes **219**[14,152]. For example, Sn radical addition to the propargylic position is favoured kinetically over addition to diaryl substituted alkyne moieties and other related functionalities. Another interesting feature of these reactions is that the directing group is 'traceless' as it is removed via homolytic C–O scission in the final aromatization step, assisted by the through-space hyperconjugative interaction between the departing OR radical and the SnR_3' group[153].

Such selective reactions assisted by a directing group have been documented in the literature and continue to be creatively used in synthesis[154–161]. A number of examples using this method for the preparation of natural products have been provided by Hale and co-workers[162–167] who used oxygen-directed hydrostannation for the preparation of complex and pharmaceutically relevant compounds such as (+)-acutiphycin. The key step in this sequence is a double O-directed free radical hydrostannation, which provided the key precursor **227** in 84% yield.

Selective activation of alkyl or aryl halides. An additional approach to chemoselective radical initiation in the presence of alkynes is the activation of C–I or C–Br bonds (Fig. 7b). Generally, this is accomplished via a radical atom-transfer process but new photo- and electrochemical methods to generate radicals from C–I or C–Br bonds hold substantial potential[168]. Traditionally, many radical alkyne cascades start from activation of a C–I or a C–Br bond where the relative stability of alkynes allows them to survive the initiation stage of the cascade process, with the reversible addition reactions remaining undetected. From this, an understanding of the relative kinetics of halogen-atom abstraction and alkene/alkyne addition reactions, in addition to subsequent trapping of the initially formed radical by an irreversible cyclization step, is essential for the rational design of such cascades.

The synthetic potential of this approach was elegantly illustrated in the early work of Curran et al., who used chemoselective activation of a C–I bond in the synthesis of hirsutene (**234**)[169]. The alkyl radical (**232**) initiates a sequence of 5-exo-trig/5-exo-dig cyclizations terminated by H-atom abstraction to form the product hirsutene (**234**). One of the notable features of this synthesis is that the Sn-centred radical selectively (and irreversibly) abstracts the I-atom from the starting material in the presence of an alkene and an alkyne. They extended this approach, combining inter- and intramolecular radical additions to make functionalized (methylene)cyclopentanes[170]. This radical cascade is initiated by C–I bond activation of 1-iodo-3-butynes (**235**) with the in situ formed stannyl radicals. Intramolecular 3-exo-dig cyclization of this radical is reversible, so, even though it is likely to proceed, it remains invisible. Instead, the productive reaction path involves an intermolecular alkyl radical attack at an α,β-unsaturated ester. The resulting alkyl radical (**238**) has a sufficiently long tether connecting it to the alkyne unit, allowing the intramolecular radical attack to proceed without the formation of a strained product and instead forming the 5-exo-dig intermediate **239**. Furthermore, the utility of alkynes extends beyond being a target for the cyclization step. The high-energy vinyl radical that results from radical addition to alkynes can be exploited to restart the chain propagation via fast iodine atom transfer from the iodoalkyne reactant, as seen here to provide product **240**.

In some cases, where isonitrile acts as a radical acceptor, the alkyne moiety can survive until the end of the cascade. This selectivity, at least partially, comes from the intrinsic isonitrile radical addition barriers being lower, probably because isonitriles are 'stereoelectronic chameleons'[171] that have additional transition state stabilizing orbital interactions that are not present in alkynes. Alkynes and isonitriles can be combined strategically in the synthesis of camptothecin[172]. After initiation by Br-abstraction, the intermediate radical (**243**) does not engage in an intramolecular (4-exo-dig) closure but rather reacts with the isonitrile intermolecularly. Unlike addition to an alkene, the addition to isonitrile can better explain the tether between the alkyl radical and the alkyne by only one carbon, as isonitriles undergo 1,1-addition while alkenes undergo 1,2-addition. The tether is nevertheless long enough to enable a 5-exo-dig cyclization of the radical and the alkyne (**244**). After that, the high reactivity of the vinyl radical allows it to penetrate through the aromatic armour of a pendant benzene ring and form the last cycle, which completes the tetracyclic core of the product. The subsequent rearomatization produces the final product **246**.

Chemoselective activation of the C–I bond has also been used to selectively initiate the exo-dig radical cascade of skipped enediynes (**247**)[173]. After C–I bond activation, the resulting alkyl radical **248** initiates the cascade by attacking the internal alkyne via the 6-exo-dig pathway. This approach provides an alternative strategy for the preparation of polycyclic frameworks in addition to strategies included in Fig. 2.

A new synthetic application of selective C–I bond activation in the presence of an alkyne is provided by the one-pot conversion of benzenes to pyrenes via '3-point annulations'[174]. In this approach, the Sn radical activates the C–I bond at a relatively low temperature (90 °C). In these circumstances, the alkyne is preserved as a result of the reversible Sn radical addition and the lack of a productive cyclization route. Conversely, the C–I activation results in the generation of an aryl radical that can cyclize irreversibly to form the first cycle (**253**). This step creates a 'bay region', which, after rearomatization (**254**), serves as a target for the second cyclization step that uses the alkyne. Conveniently, the second cyclization proceeds at a higher temperature (110 °C), allowing the cascade to be interrupted at the first cyclization stage or continue until it anneals three rings to an aromatic core. Use of extended aromatic cores in the starting materials provided expedient access to previously unknown polyaromatic systems.

Conclusion and outlook

The two sterically unencumbered energy-rich carbon atoms offer a beautifully primed canvas for the design of cascades where two, four or even six[175–178] new bonds can be added to the alkyne. This property makes alkynes an ideal 'carbon glue'[179], a foundation for connecting smaller molecular pieces into a larger product. Furthermore, diverging

from the common alkyne departure point, a carefully planned reaction route can open access to richly functionalized and structurally complex products through the choice of reaction partners. This versatility makes alkynes valuable participants in synthetic designs.

This Review illustrates that free-radical reactions of alkynes are particularly useful because their thermodynamics is favourable for propagating the intermediate steps in the cascades. We highlight a collection of approaches that help to achieve precise control of selectivity for the reactions of alkynes, even in the presence of other potentially reactive functionalities.

Despite the great progress documented in this Review, not all challenges have yet been met. For instance, so far, radical cascades generally only involve the π-system of alkynes with the formation of either two or four new bonds. Radical reactions that efficiently make six new bonds at the two alkyne carbons are unknown. Another limitation is the relative inefficiency and scarcity of radical endo-dig cyclizations in comparison to their exo-dig counterparts. Not only do endo-dig cyclizations suffer from the unfavourable radical attack trajectory at the alkyne[42] but, unlike the well documented ring expansion of exo-trig products of similar alkene cyclizations (such as the rearrangement of initially formed 5-exo-trig products into their 6-endo-trig isomer[58,59,180,181]), the analogous ring expansion of exo-dig cyclization products is impossible owing to stereoelectronic constraints[6,182]. The new cascades that can overcome such limitations use alkenes as alkyne equivalents by combining exo-trig cyclizations with subsequent fragmentations[75]. Along with the alkyne resilience examples given in Fig. 5, these transformations illustrate that the use of fragmentation termination steps offers additional avenues for creative design of radical cascades that retain π-bonds in the products.

Like a loaded mouse trap, alkynes combine high energy with kinetic stability. The transformative power of the high energy content is illustrated by the crucial role of alkynes in the development of biorthogonal chemistry[3]. A deeper understanding of alkyne stereoelectronics is needed for controlling kinetics of alkyne reactions and for unlocking the reactivity features needed to design cascade reactions that can rapidly build complex chemical structures, both natural and unnatural.

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Author contributions

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Competing interests

The authors declare no competing interests.

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