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Transition-metal-free radical cleavage of a hydrazonyl N–S bond: tosyl radical-initiated cascade C(sp³)–OAr cleavage, sulfonyl rearrangement and atropisomeric cyclopropanation†

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For the first time, the combination of catalytic 1,10-phenanthroline and potassium carbonate enables a radical cleavage of a hydrazonyl N–S bond to deliver a tosyl radical and a diazo compound, along with releasing molecular hydrogen spontaneously. The tosyl radical and hydrogen evolution are witnessed by radical trapping, EPR experiment and gas chromatography. An innovative application of this strategy into metal-free coupling of *N*-tosylhydrazone and phosphinyl allene provides a one-step synthesis of novel atropisomeric 3-tosyl-1-enyl-cyclopropyl-diphenylphosphine oxide derivatives with excellent diastereoselectivity and *E*-selectivity. Moreover, these atropisomeric products, verified by ¹H-NMR, DFT calculations and X-ray crystallography, are controllably formed. Mechanistic studies indicate that the multistep cascade reaction occurs through radical hydrazonyl N–S bond cleavage, radical C(sp³)–OAr bond cleavage, sulfonyl rearrangement and atropisomeric cyclopropanation.

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Introduction

In the past decade, the green and sustainable strategy for free-radical generation from a diamine/alkali metal salt system has contributed greatly to cross-coupling reactions, which received significant attention from scientific and industrial communities.¹ Contributions by Hayashi, Shi, Lei, Murphy and others have witnessed the blooming of this chemistry,² lately classified as base-promoted homolytic aromatic substitution (BHAS),³ in various inter/intramolecular C–C couplings between aryl halides and arenes or olefins (Scheme 1a). Although potassium *t*-butoxide alone was reported to enable the couplings,⁴ a wide range of organic additives including 1,10-phenanthroline derivatives, aliphatic 1,2-diamines, imines, amino acids, hydrazine derivatives, *N*-heterocyclic carbenes, and diphosphines have been used in initiating the radical chain process more efficiently.^{2a–g,3b,5} From both experimental facts and theoretical calculation considerations,²ⁱ

a single electron transfer process has been verified, for example, 1,10-phenanthroline/*t*-BuOK initiated radical cleavage of the aryl–I bond will deliver an aryl radical and an iodide anion. We believe that this strategy should be ideally suitable for developing novel radical chain reactions other

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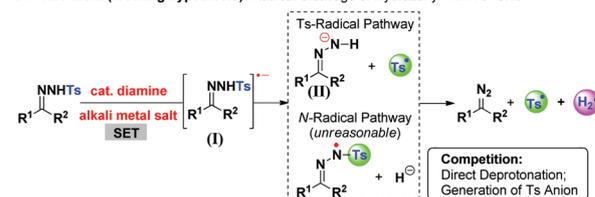
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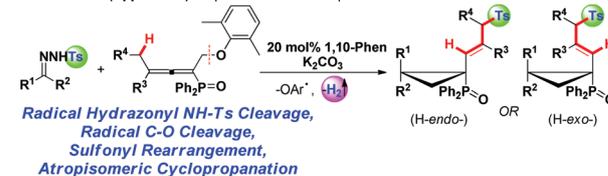
a. Cross-Coupling Reactions Enabled by Diamine/Alkali Metal Salt System:



b-1. This Work (Working hypothesis): Radical Cleavage of Hydrazonyl "NH-Ts" Unit



b-2. This Work (Application): Unprecedented Multistep Cascade Reaction



Scheme 1 Previous work with diamine/alkali metal salt combination (a) and this work (b-1, b-2).

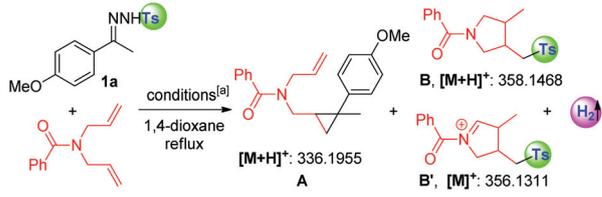
than C–C couplings; however, to the best of our knowledge, this field remains untouched so far.

The pursuit of *N*-tosylhydrazone chemistry dates back to the mid-20th century, as well-known as the Bamford–Stevens reaction and Shapiro reaction.⁶ Since the first report of palladium-catalyzed coupling of *N*-tosylhydrazones with aryl bromides in 2007, this chemistry has been attracting extensive interest in providing diazo precursors in building versatile functionalities for synthetic compounds, led by the groups of Barluenga and Valdés,⁷ Wang⁸ and others.⁹ Despite these great achievements, only a handful of methods have been established regarding free-radical generation from *N*-tosylhydrazone, albeit confined to a transition metal-catalysis system.¹⁰ For example, Xiao's group has established a photocatalytic hydroamination of *N*-tosylhydrazones with intramolecular alkenes, in which *N*-radical formation from single-electron oxidation of deprotonated *N*-tosylhydrazones was involved.^{10a,b} Very recently, cobalt^{III}–carbene radicals, generated through metalloradical activation of *N*-tosylhydrazones by cobalt^{II} complexes, were developed in the reactions of *N*-tosylhydrazones and olefins, alkynes or alkanes.^{10d–f,10h–i} Inspired by the aforementioned studies and our previous studies,¹¹ we hypothesized that, a diamine/alkali metal salt excited hydrazone radical anion might undergo a probable Ts-radical pathway (N–S bond cleavage)¹² to furnish a diazo compound, tosyl radical and molecular hydrogen (Scheme 1b-1), and this unprecedented strategy should offer a powerful and important platform for discovering new radical chemistry of *N*-tosylhydrazones with allenes toward complex molecules.

Results and discussion

With an aim to rationalize our hypothesis, an EPR experiment for the reaction of 1-(1-(4-methoxyphenyl)ethylidene)-2-tosylhydrazine (**1a**), 20 mol% of 1,10-phen and 1.5 equivalents of *t*-BuOK was conducted to monitor the formation of radical species, which indicated the formation of the tosyl radical (see more details in the ESI†).¹³ The tosyl radical could also be captured by TEMPO as monitored by HR-MS (in ESI†). As shown in Table 1, *N,N*-diallylbenzamide was subsequently applied to trap the fragments cleaved from *N*-tosylhydrazone (**1a**). In preliminary results, 20 mol% of 1,10-phen and 1.5 equivalents of *t*-BuOK or K₂CO₃ successfully enabled radical cleavage of the “NHTs” unit (entries 1 and 2), which was strongly supported by the detection of adducts **A**, **B** and **B'**, deriving from the diazo precursor and the tosyl radical, respectively. Interestingly, a catalytic amount of potassium carbonate afforded the same result of fragment abundance in the HRMS spectrum, even for the case with high purity reagents (entries 3 and 4). A parallel experiment without 1,10-phen gave only the cyclopropanation product (**A**, entry 5). The observations in entries 3 and 4 deserve to be highlighted since the tosyl anion could be generated in the presence of excess base, and a single-electron oxidation of the tosyl anion by metal catalysts has been reported to afford the tosyl radical;¹⁴ however, the

Table 1 Studies on cleavage of *N*-tosylhydrazones: evidence of tosyl radical and molecular hydrogen evolution^a

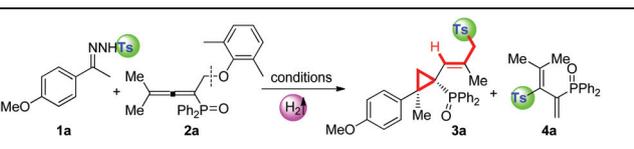


Entry	Radical initiator	HR-MS result	H ₂ evolution
1	20 mol% 1,10-phen/1.5 equiv. <i>t</i> -BuOK	A + B + B'	Yes
2	20 mol% 1,10-phen/1.5 equiv. K ₂ CO ₃	A + B + B'	Yes
3	20 mol% 1,10-phen/15 mol% K ₂ CO ₃	A + B + B'	Yes
4 ^b	20 mol% 1,10-phen/15 mol% K ₂ CO ₃	A + B + B'	Yes
5	1.5 equiv. K ₂ CO ₃	Only A	No
6 ^c	20 mol% 1,10-phen/15 mol% K ₂ CO ₃	—	No
7	0.2 equiv. TBAI/2 equiv. TBHP	B + B'	No
8	5 mol% Pd(OAc) ₂ /20 mol% 1,10-phen/15 mol% K ₂ CO ₃	A + B + B'	Yes
9	5 mol% Pd(PPh ₃) ₂ Cl ₂ /15 mol% K ₂ CO ₃	Only A	No

^a *N*-Tosylhydrazone (**1a**, 0.1 mmol), *N,N*-diallylbenzamide (0.12 mmol), catalyst or oxidant in 3 mL refluxing 1,4-dioxane for 2 hours. ^b High purity reagents: 1,10-phen (anhydrous, purity > 99 + %), K₂CO₃ (purity: 99.997%). ^c TsNa was used instead of **1a**.

negative result of sodium 4-methylbenzene-sulfinate and *N,N*-diallylbenzamide entirely ruled out the possibility of forming the tosyl radical from the tosyl anion under the current conditions (entry 6). Although TBAI/TBHP evidenced a positive result in producing the trapping products (**B** and **B'**) from the tosyl radical as monitored by HR-MS, it was found that the diazo precursor decomposed rapidly (entry 7). The results in entries 8 and 9 showed that a palladium catalyst would not inhibit the radical process but did not deliver the tosyl radical without the participation of 1,10-phen. Intriguingly, molecular hydrogen evolution was detected by gas chromatography in entries 1–4 and 8, indicating that the hydrogen radical or hydrogen anion might be produced in the system (in ESI†).

Subsequently, we applied this strategy in the coupling of *N*-tosylhydrazones and phosphinyl allenes (Scheme 1b-2). This choice was based on our previous report of a transition-metal-catalyzed coupling of *N*-tosylhydrazones with phosphinyl allenes to form phosphinyl [3]dendralenes,^{11a} which we believe would be a model reaction suitable for providing an expeditious platform for investigating the reactivity of the tosyl radical and diazo compound *in situ* generated from *N*-tosylhydrazones and differentiating the 1,10-phen/K₂CO₃ system from metal contamination.^{14,15} The study was initiated by examining the coupling of **1a** with phosphinyl allene (**2a**). As shown in Table 2, for a preliminary experiment with a catalytic amount of 1,10-phen and *t*-BuOK, 6% yield of (*E*)-(2-(4-methoxy phenyl)-2-methyl-1-(2-methyl-3-tosylprop-1-en-1-yl) cyclopropyl)diphenyl-phosphine oxide (**3a**) was obtained with high diastereoselectivity, along with 50% yield of tosylated 1,3-diene (**4a**) (entry 2). The ratios of **3a**/**4a** changed in proportion to the amount of base used (entries 3–5), in which 2.5 equiva-

Table 2 Metal-free coupling of *N*-tosylhydrazone (**1a**) with phosphinyl allenes (**2a**): screening of conditions^a


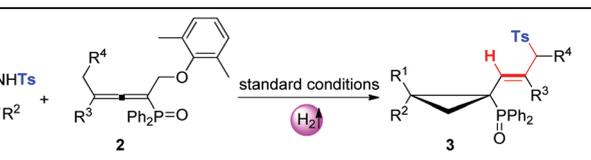
Entry	Catalyst (20 mol%)	Base	Yield (%) (3a/4a) ^b
1	1,10-Phen	<i>t</i> -BuOK (15 mol%)	0/14
2	1,10-Phen	<i>t</i> -BuOK (40 mol%)	6/50
3	1,10-Phen	K ₂ CO ₃ (15 mol%)	<5/85
4	1,10-Phen	K ₂ CO ₃ (1.5 equiv.)	35/30
5	1,10-Phen	K₂CO₃ (2.5 equiv.)	74/0
6	1,10-Phen	NaHCO ₃ (2.5 equiv.)	56/0
7	1,10-Phen	CsF (2.5 equiv.)	53/0
8	1,10-Phen	Cs ₂ CO ₃ (2.5 equiv.)	17/0
9	1,10-Phen	DBU (2.5 equiv.)	0/0
10	2,2'-Bipyridine	K ₂ CO ₃ (2.5 equiv.)	38/13
11	2,9-Dimethyl-1,10-phenanthroline	K ₂ CO ₃ (2.5 equiv.)	36/11
12	2,2':6',2''-Terpyridine	K ₂ CO ₃ (2.5 equiv.)	42/9
13	4,7-Dimethoxy-1,10-phenanthroline	K ₂ CO ₃ (2.5 equiv.)	50/0
14 ^{c,d}	Pd(PPh ₃) ₂ Cl ₂	K ₂ CO ₃ (2.5 equiv.)	0/0
15 ^c	Pd(OAc) ₂ /1,10-phen	K ₂ CO ₃ (2.5 equiv.)	40/0
16 ^c	Cu(OAc) ₂ /1,10-phen	K ₂ CO ₃ (2.5 equiv.)	0/0
17 ^c	CoCl ₂ /1,10-phen	K ₂ CO ₃ (2.5 equiv.)	21/0
18 ^e	1,10-Phen	K ₂ CO ₃ (2.5 equiv.)	75/0

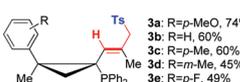
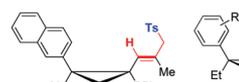
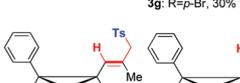
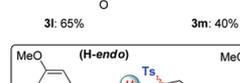
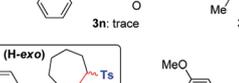
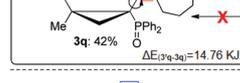
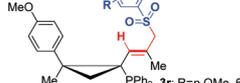
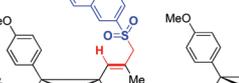
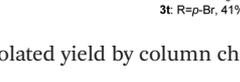
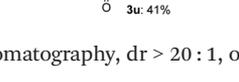
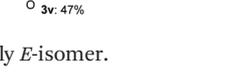
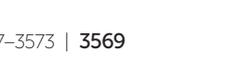
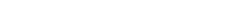
^a Reaction conditions: *N*-Tosylhydrazone (**1a**, 0.9 mmol), phosphinyl allene (**2a**, 0.3 mmol), catalyst (20 mol%) and base in 3 mL refluxing 1,4-dioxane for 8 hours. ^b Isolated yield by column chromatography (dr > 20 : 1, only *E*-isomer for all cases). ^c 5 mol% palladium catalyst. ^d The major product was phosphinyl[3]dendralenes, see our previous work in ref. 11a. ^e High purity reagents: 1,10-phen (anhydrous, purity > 99 + %), K₂CO₃ (purity: 99.997%).

lents of K₂CO₃ improved the isolated yield of **3a** up to 74% (Note: this observation does not conclude that stoichiometric base is necessary to generate the tosyl radical, instead, excess base plays a vital role in converting **4a** into **3a** in a sulfonyl rearrangement step). A series of bases, including inorganic and organic bases, were then screened. Weaker inorganic bases, such as Na₂CO₃, NaHCO₃ and CsF, enabled the cascade reactions with yields ranging from 26 to 56%, whereas organic bases entirely inhibited the reaction (see the ESI[†]). Other catalysts of pyridine or phenanthroline derivatives were tested, which exhibited considerable activities as well (entries 10–13). The cascade reaction was also susceptible to solvents and catalyst loadings (in ESI[†]). Control experiments under transition-metal catalysis were conducted as a comparison. Transition metals, including palladium, cobalt, nickel, rhodium, copper, zinc, manganese, iron and iridium, were investigated; however, all of the results were not comparable (entries 14–17, also in the ESI[†]). Most importantly, a high-impurity of 1,10-phenanthroline and potassium carbonate delivered the final product **3a** in a slightly better yield of 75% (entry 18), excluding the possibility of a metal-catalytic pathway and keeping in line with the HR-MS evaluations given in Table 1. The above

observations indicated that the tosyl radical produced by 1,10-phenanthroline and an alkali metal cation plays a key role in cleavage of the C(sp³)-OAr bond, probably *via* a radical pathway, achieving a multistep cascade reaction with high efficiency.

With the optimal conditions in hand, we then evaluated the substrate scopes of various *N*-tosylhydrazones (**1**) with phosphinyl allenes (**2**). As summarized in Table 3, the cascade reactions gave adducts (**3**) in yields ranging from acceptable to medium with excellent diastereoselectivities and *E*-selectivities, relying on the structure and electronic properties of substituents. For instance, electron-neutral *N*-tosylhydrazones and *para*-electron-rich ones afforded the products **3a–3c** with medium yields. Otherwise, electron-deficient substituents, including *p*-F, *p*-Cl, and *p*-Br, impaired the efficiency to some extent, with yields dropping to below 50%. *N*-Tosylhydrazones bearing strong electron-deficient substituents of *p*-CF₃ and *p*-NO₂ performed very sluggishly without formation of the corresponding products. 56% yield of **3h** was obtained for β-naphthyl substituted substrates. Notably, the X-ray crystal structure of **3h** unambiguously displayed the location of the tosyl group and the dimensional orientations of anchored moieties,¹⁶ with methyl and diphenylphosphine oxide groups at *syn*-positions. Ethyl, *n*-butyl, and benzyl derived *N*-tosylhydrazones were also applicable to the system with acceptable to medium yields (**3i–3m**). Nevertheless, diphenyl derived *N*-tosyl-hydrazone performed

Table 3 1,10-Phen/K₂CO₃ catalyzed coupling of *N*-tosyl-hydrazones (**1**) with phosphinyl allenes (**2**): formation of H-*endo*-isomers^a


 3a: R= <i>p</i> -MeO, 74%	 3b: R=H, 60%	 3c: R= <i>p</i> -Me, 60%
 3d: R= <i>m</i> -Me, 45%	 3e: R= <i>p</i> -F, 49%	 3f: R= <i>p</i> -Cl, 36%
 3g: R= <i>p</i> -Br, 30%	 3h: 56%, X-ray	 3i: R=H, 40%
 3j: R= <i>p</i> -MeO, 40%	 3k: R= <i>p</i> -Cl, 43%	 3l: <i>n</i> -Bu, 65%
 3m: Bn, 40%	 3n: Ph, 40%	 3o: <i>n</i> -Hex, 40%
 3q: (H- <i>endo</i>), 42%	 3q': (H- <i>exo</i>), 9%	 3p: <i>n</i> -Hex, 31%
 3r: R= <i>p</i> -OMe, 61%	 3s: R= <i>m</i> -CH ₃ , 32%	 3u: 41%
 3t: R= <i>p</i> -Br, 41%	 3v: 47%	 3w: 47%

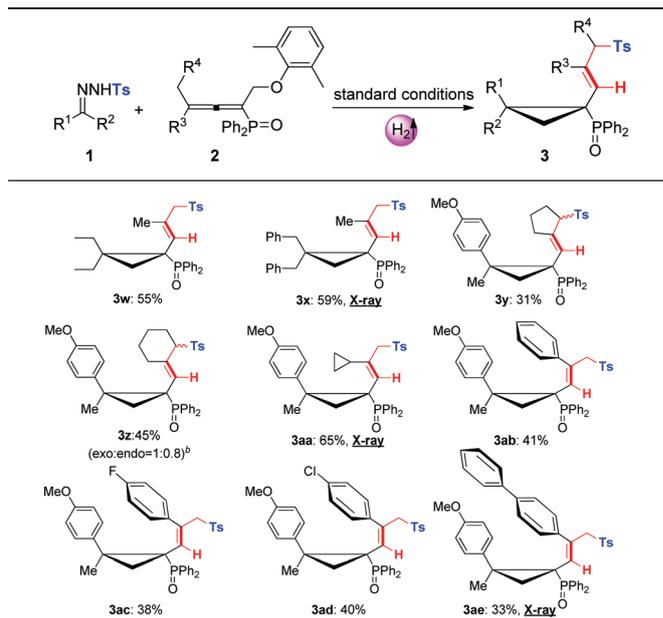
ΔE(3q-3q') = 14.76 KJ/mol

^a Isolated yield by column chromatography, dr > 20 : 1, only *E*-isomer.

sluggishly under current conditions. The phosphinyl allenes could be expanded to other aliphatic substitutions. For instance, the allenes with distal *n*-propyl, *n*-hexyl substituents furnished the target products (**3o**, **3p**) in yields of 40% and 31%, respectively. Other *N*-sulfonylhydrazone derivatives, including *p*-methoxyphenyl, *m*-methylphenyl, *p*-bromophenyl, polyaromatic and aliphatic ones, maintained certain reactivities in the radical cleavage and sulfonyl rearrangement step, giving exclusively *E*-isomers (**3r–3v**) with slightly lower yields. Moreover, it is worth mentioning that most of the proton chemical shifts of products (**3a–3p**, **3r–3v**) locate in a range of 5.20–5.46 ppm, with alkenyl-H pointing to the top side of the three-membered ring (denoted as the H-*endo*-isomer). An exceptional case was found in the reaction of allenes bearing cycloheptyl substitution with **1a**. Interestingly, 42% yield of H-*endo*-isomer **3q** and 9% yield of H-*exo*-isomer **3'q** were both isolated, and ¹H-NMR spectra of **3'q** showed a significant downfield shift to 6.04 ppm. No reciprocal transformation was detected for these two isomers under thermal conditions, indicating that the cyclopropanation step should be decisive to obtain either atropisomer. Besides, this spatial configuration could be attributed to the congestion of moieties on a three-membered ring, in which aryl and diphenylphosphine oxide substituents strongly restricted the single bond rotation of the alkenyl moiety. DFT calculations showed that **3'q** possesses higher energy than **3q** with an energy gap of 20 kJ mol⁻¹, and the torsion energy associated with the dihedral angle between **3q** and **3'q** is as high as 59 kJ mol⁻¹ (see details in the ESI†).

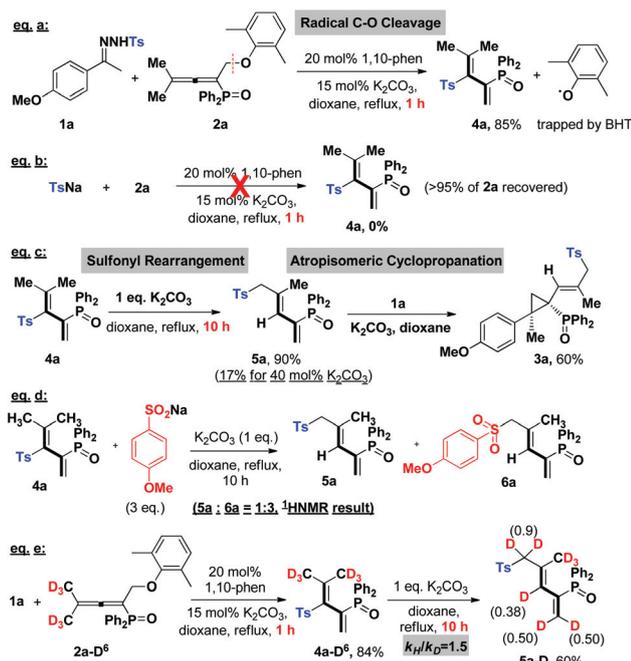
To our delight, dominant H-*exo*-isomers appeared while altering the substitutions on *N*-tosylhydrazones and phosphinyl allenes (Table 4). In the case of diethyl and dibenzyl derived *N*-tosylhydrazones, products **3w** and **3x** were characterized as H-*exo*-configurations, evidenced by distinct alkene-H chemical shifts (5.62, 5.86 ppm) and an X-ray crystal structure of **3x**.¹⁶ The ORTEP drawing of **3x** unambiguously manifested the spatial proximity of the alkene-H atom to the P=O moiety, thus the deshielding effect resulted in an apparent downfield chemical shift. The scope of phosphinyl allenes was subsequently investigated. In general, the allenes bearing distal cyclopropyl, cyclopentyl and various aryl substituents furnished the corresponding H-*exo*-isomers exclusively in yields of 31–65% (**3y–3ae**), except for the cyclohexyl one (**3z**, *exo:endo* = 1:0.8). Meanwhile, the DFT calculation results were also well consistent with the ratio of product configurations (in the ESI†). X-ray crystal structures of **3aa** and **3ae** supported the formation of single atropisomers as well. Distinct from the substituents on hydrazones, electron effects were not apparent for allenes with terminal aromatics. Electron-deficient groups of *para*-fluoro and *para*-chloro gave indistinctive results compared to that of the electron-neutral substrate. Note that the development of atropisomers is currently a central task and hot research topic in organic chemistry.¹⁷ However, as far as we know, atropisomeric cyclopropanation has never been reported and this cascade reaction provides highly efficient construction of multi-substituted atropisomers in one pot.

Table 4 1,10-Phen/ K_2CO_3 catalyzed coupling of *N*-tosyl-hydrazones (**1**) with phosphinyl allenes (**2**): formation of H-*exo*-isomers^{a,b}



^a Isolated yield by column chromatography, dr > 20 : 1, H-*exo* : H-*endo* > 20 : 1 with an exception of **3z**. ^b The ratio of H-*exo*- and H-*endo*-isomers was determined by ¹H NMR, which cannot be separated even by preparative HPLC.

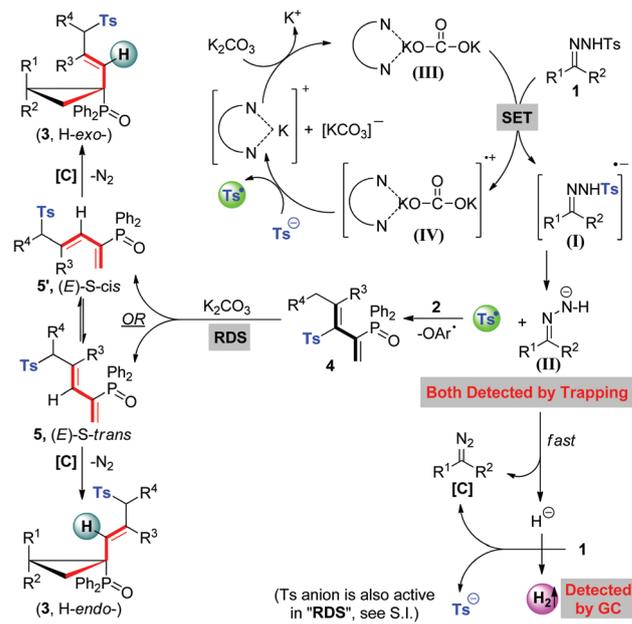
Next, in order to understand the reaction mechanism, control experiments were performed. Delightfully, while shortening the reaction time to 1 hour, we isolated the key intermediate, tosylated 1,3-dienes (**4a**), in a good yield of 85% (eqn (a), Scheme 2). Kinetic studies on this step verified that it proceeds through a radical pathway, and the aromatic ether moiety left in the radical form is trapped by BHT (in ESI†). The parallel reaction of tosyl sodium and allene **2a** left all substrates intact (eqn (b)), implying that the tosyl anion cannot cleave the C–O bond to initiate the cascade reaction. Eqn (c) presented that the intermediate **4a** could be converted into a sulfonyl rearrangement product **5a**,¹⁸ but stoichiometric K_2CO_3 turned out to be necessary, otherwise, this step severely retarded the cascade process. A crossover experiment with sodium 4-methoxybenzenesulfonate in eqn (d) indicated that the sulfonyl rearrangement step occurs inter-molecularly. After that, **5a** underwent atropisomeric cyclopropanation rapidly to afford final product **3a** in 60% yield. Besides, deuterium labeling experiments were conducted to investigate the kinetic isotope effects (KIE) (eqn (e)). The reaction of **1a** and **2a-D⁶** afforded deuterated product **4a-D⁶** in 84% yield, which transformed into **5a-D** in 60% yield with deuterium atoms distributed over all of the alkenyl positions. The KIE value from two parallel reactions between **4a** and **4a-D⁶** was found to be $k_H/k_D = 1.5$, suggesting that the rate-determining step probably involves in the sulfonyl rearrangement step, but does not contain a C(sp³)-H bond cleavage. Therefore, the mechanism studies and results in Table 1 collectively pointed out that the



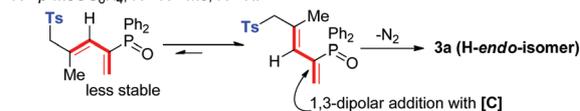
Scheme 2 Mechanism studies.

cascade reaction consists of four steps: 1,10-phen/ K_2CO_3 catalysed cleavage of the NH-Ts bond to generate the tosyl radical, radical cleavage of the $C(sp^3)$ -OAr bond, base-promoted sulfonyl rearrangement, and atropisomeric cyclopropanation.

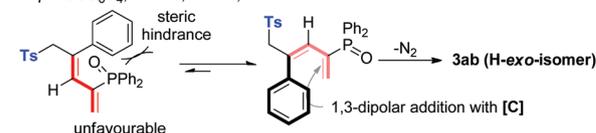
Based on our experimental facts and previous reports,^{2a,10g,19} a proposed mechanism is outlined in Scheme 3. Initially, single electron transfer (SET) from the 1,10-phen/ K_2CO_3 complex to *N*-tosylhydrazone (**1**) gives a radical anion (**I**), which undergoes N-S bond cleavage to result in a tosyl radical and an *N*-anion intermediate (**II**) (**II** could be trapped by the CF_3 cation source and detected by HR-MS, see details in the ESI†). The *N*-anion intermediate (**II**) will leave the hydrogen anion rapidly to give a diazo compound [C]. Molecular hydrogen evolution comes from the deprotonation of **1** by the *in situ* generated hydrogen anion. Meanwhile, the accompanying tosyl anion helps to quench the associated radical cation (**IV**) to end the catalytic cycle and releases another portion of the tosyl radical. This proposed catalytic cycle keeps in line with the result of catalytic amounts of 1,10-phen and K_2CO_3 in eqn (a), Scheme 2. Afterwards, the tosyl radical attacks allene **2** to yield tosylated 1,3-butadienes (**4**). Base-promoted sulfonyl rearrangement of **4** leads to the formation of thermally reversible (*E*)-*S*-*trans* or (*E*)-*S*-*cis* isomers (**5/5'**), depending on the nature of substituents on the olefin double bond. Eventually, these two isomers undertake 1,3-dipolar cycloaddition with diazo intermediate [C] to give atropisomers **3** in the H-*exo* or H-*endo* configuration, along with the extrusion of nitrogen. Above all, the equilibrium ratios of **5** and **5'** are associated directly with the dominant stereo-configuration of atropisomers. For instance, when the R^3



$R^1=p\text{-MeOC}_6\text{H}_4$, $R^2=R^3=\text{Me}$, $R^4=\text{H}$:



$R^1=p\text{-MeOC}_6\text{H}_4$, $R^2=\text{Me}$, $R^3=\text{Ph}$, $R^4=\text{H}$:



Scheme 3 Proposed mechanism and rationalization of atropisomer formation.

group is a bulky phenyl group, an (*E*)-*S*-*cis* isomer is favourably formed and rapidly transforms into an H-*exo*-isomer (**3ab**).

Experimental

General procedure

To a 15 mL sealed reaction tube were added *N*-tosylhydrazones (**1a**, 286 mg, 0.9 mmol), phosphinyl allenes (**2a**, 120 mg, 0.3 mmol), 1,10-phen (12 mg, 20 mol%), K_2CO_3 (103.5 mg, 0.75 mmol), and 3 mL degassed 1,4-dioxane. The reaction mixture was then heated to reflux for 8 hours until the complete consumption of **2a** monitored by TLC. After all of the volatiles were removed under vacuum, the crude product was purified by flash chromatography (eluent: 1 : 2 : 1 (v/v) of ethyl acetate/petroleum ether) to afford product **3a** as a white solid.

Conclusions

In conclusion, we disclosed, for the first time, a transition-metal-free radical cleavage of a hydrazonyl "NH-Ts" unit with a catalytic amount of 1,10-phenanthroline and potassium car-

bonate. The cleavage of *N*-tosylhydrazone through a radical anion pathway toward a tosyl radical, diazo compound and molecular hydrogen was rationalized by DFT calculations and verified by radical trapping, EPR experiment and gas chromatography. Further application of this novel strategy into metal-free coupling of *N*-tosylhydrazones and phosphinyl allenes provides expeditious synthesis of unprecedented atropisomeric 3-tosyl-1-enyl-cyclopropyldiphenyl-phosphine oxide derivatives with excellent diastereoselectivity and *E*-selectivity. A variety of atropisomeric products, confirmed by ¹H NMR, DFT calculations, and X-ray crystallography, were controllably formed depending on the substitutions of *N*-tosyl-hydrazone and phosphinyl allenes. Mechanistic studies indicate that the cascade reaction proceeds through a tosyl radical initiated successive C(sp³)-OAr cleavage, sulfonyl rearrangement and atropisomeric cyclopropanation. We expect that this strategy will enrich the blooming radical chemistry and offer new scaffolds for the development of potential chiral molecules.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- For selected reviews: (a) N. E. Leadbeater, *Nat. Chem.*, 2010, **2**, 1007; (b) A. Stude and D. P. Curran, *Nat. Chem.*, 2014, **6**, 765; (c) Y. Qin, L. Zhu and S. Luo, *Chem. Rev.*, 2017, **117**, 9433.
- (a) E. Shirakawa, K. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537; (b) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, **2**, 1044; (c) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737; (d) M. Rueping, M. Leiendecker, A. Das, T. Poisson and L. Bui, *Chem. Commun.*, 2011, **47**, 10629; (e) C.-L. Sun, Y.-F. Gu, W.-P. Huang and Z.-J. Shi, *Chem. Commun.*, 2011, **47**, 9813; (f) H. Zhang, R. Shi, A. Ding, L. Lu, B. Chen and A. Lei, *Angew. Chem., Int. Ed.*, 2012, **51**, 12542; (g) S. Zhou, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2014, **136**, 17818; (h) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (i) L. Zhang, H. Yang and L. Jiao, *J. Am. Chem. Soc.*, 2016, **138**, 7151; (j) J. Ahmed, P. Sreejyothi, G. Vijaykumar, A. Jose, M. Raj and S. K. Mandal, *Chem. Sci.*, 2017, **8**, 7798.
- (a) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2011, **50**, 5018; (b) A. Dewanji, S. Murarka, D. P. Curran and A. Studer, *Org. Lett.*, 2013, **15**, 6102.
- (a) S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673; (b) M. P. Drapeau, I. Fabre, L. Grimaud, I. Ciofini, T. Ollevier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2015, **54**, 10587; (c) Q. Shi, S. Zhang, J. Zhang, V. F. Oswald, A. Amassian, S. R. Marder and S. B. Blakey, *J. Am. Chem. Soc.*, 2016, **138**, 3946; (d) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402; (e) J. Chen and J. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3951.
- (a) W.-C. Chen, Y.-C. Hsu, W.-C. Shih, C.-Y. Lee, W.-H. Chuang, Y.-F. Tsai, P. P.-Y. Chen and T.-G. Ong, *Chem. Commun.*, 2012, **48**, 6702; (b) S. Zhou, G. M. Anderson, B. Mondal, E. Doni, V. Ironmonger, M. Kranz, T. Tuttle and J. A. Murphy, *Chem. Sci.*, 2014, **5**, 476; (c) J. P. Barham, G. Coulthard, R. G. Kane, N. Delgado, M. P. John and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2016, **55**, 4492; (d) M. Li, S. Berritt, L. Matuszewski, G. Deng, A. Pascual-Escudero, G. B. Panetti, M. Poznik, X. Yang, J. J. Chruma and P. J. Walsh, *J. Am. Chem. Soc.*, 2017, **139**, 16327; (e) Z. Guo, M. Li, X.-Q. Mou, G. He, X.-S. Xue and G. Chen, *Org. Lett.*, 2018, **20**, 1684.
- (a) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735; (b) R. H. Shapiro, J. H. Duncan and J. C. Clopton, *J. Am. Chem. Soc.*, 1967, **89**, 471; (c) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, 1967, **89**, 5734; (d) R. H. Shapiro, *Org. React.*, 1976, **23**, 405; (e) R. M. Adlington and A. G. M. Barrett, *Acc. Chem. Res.*, 1983, **16**, 55. For selected recent reviews, see: (f) J. Barluenga and C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **8**, 7486; (g) Y. Zhang and J. Wang, *Top. Curr. Chem.*, 2012, **1**, 1; (h) Z.-H. Shao and H.-B. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (i) Y. Xia, Y. Zhang and J. Wang, *ACS Catal.*, 2013, **3**, 2586; (j) M. Jia and S. Ma, *Angew. Chem., Int. Ed.*, 2016, **55**, 9134; (k) Y. Xia and J. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2306; (l) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810.
- (a) J. Barluenga, P. Moriel, C. Valdés and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 5587; (b) J. Barluenga, M. Tomás-Gamasa, F. Aznar and C. Valdés, *Nat. Chem.*, 2009, **1**, 494; (c) J. Barluenga, M. Tomás-Gamasa, F. Aznar and C. Valdés, *Angew. Chem., Int. Ed.*, 2010, **122**, 5113; (d) J. Barluenga, M. Escribano, F. Aznar and C. Valdés, *Angew. Chem., Int. Ed.*, 2010, **49**, 6856; (e) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar and C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 2350; (f) J. Barluenga, M. Tomás-Gamasa and C. Valdés, *Angew. Chem., Int. Ed.*, 2012, **51**, 5950; (g) M. C. Pérez-Aguilar and C. Valdés, *Angew. Chem., Int. Ed.*, 2013, **52**, 7219; (h) M. C. Pérez-Aguilar and C. Valdés, *Angew. Chem., Int. Ed.*, 2015, **54**, 13729; (i) M. Plaza and

- C. Valdés, *J. Am. Chem. Soc.*, 2016, **138**, 12061; (j) M. Paraja and C. Valdés, *Org. Lett.*, 2017, **19**, 2034.
- 8 (a) Q. Xiao, J. Ma, Y. Yang, Y. Zhang and J. Wang, *Org. Lett.*, 2009, **11**, 4732; (b) Z.-H. Zhang, Y.-Y. Liu, M.-X. Gong, X.-K. Zhao, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1139; (c) Q. Xiao, Y. Xia, H. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 1114; (d) X. Zhao, G.-J. Wu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 3296; (e) F. Ye, X.-S. Ma, Q. Xiao, H. Li, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 5742; (f) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236; (g) Q. Xiao, B. Wang, L. Tian, Y. Yang, J. Ma, Y. Zhang, S. Chen and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 9305; (h) F. Hu, Y. Xia, F. Ye, Z. Liu, C. Ma, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1364; (i) Z.-X. Liu, H.-C. Tan, L. Wang, T.-R. Fu, Y. Xia, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 3056; (j) S. Xu, G.-J. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 4669; (k) Z. Liu, H. Tan, T. Fu, Y. Xia, D. Qiu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 12800; (l) W.-D. Chu, L. Zhang, Z.-K. Zhang, Q. Zhou, F.-Y. Mo, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 14558; (m) Q. Zhou, S. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 16013.
- 9 (a) T. Yao, K. Hirano, T. Satoh and M. Mira, *Angew. Chem., Int. Ed.*, 2012, **51**, 775; (b) van S. S. Berkel, S. Brauch, L. Gabriel, M. Henze, S. Stark, D. Vasilev, L. A. Wessjohann, M. Abbas and B. Westermann, *Angew. Chem., Int. Ed.*, 2012, **51**, 5343; (c) X. Li, X. Liu, H. Chen, W. Wu, C. Qi and H. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 14485; (d) W. Xiong, C. Qi, H. He, L. Ouyang, M. Zhang and H. Jiang, *Angew. Chem., Int. Ed.*, 2015, **54**, 3084; (e) N. Su, J. A. Theorell, D. J. Wink and T. G. Driver, *Angew. Chem., Int. Ed.*, 2015, **54**, 12942; (f) A. R. Reddy, F. Hao, K. Wu, C.-Y. Zhou and C.-M. Che, *Angew. Chem., Int. Ed.*, 2016, **55**, 1810; (g) S. Mai and Q. Song, *Angew. Chem., Int. Ed.*, 2017, **56**, 7952; (h) T. Ishikawa, M. Kimura, T. Kumoi and H. Lida, *ACS Catal.*, 2017, **7**, 4986.
- 10 (a) X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. B. Beauchemin and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 12163; (b) X.-Q. Hu, X. Qi, J.-R. Chen, Q.-Q. Zhao, Q. Wei, Y. Lan and W.-J. Xiao, *Nat. Commun.*, 2016, **7**, 11188; (c) S. Mao, Y.-R. Gao, X.-Q. Zhu, D.-D. Guo and Y.-Q. Wang, *Org. Lett.*, 2015, **17**, 1692; (d) N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang and de B. Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090; (e) B. G. Das, A. Chirila, M. Tromp, J. N. H. Reek and de B. Bruin, *J. Am. Chem. Soc.*, 2016, **138**, 8968; (f) Y. Wang, X. Wen, X. Cui, L. Wojtas and X. P. Zhang, *J. Am. Chem. Soc.*, 2017, **139**, 1049; (g) F. Wang, P. Xu, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2018, **20**, 2204; (h) te C. Grotenhuis, van den N. Heuvel, van der J. I. Vlugt and de B. Bruin, *Angew. Chem., Int. Ed.*, 2018, **57**, 140; (i) Y. Wang, X. Wen, X. Cui and X. P. Zhang, *J. Am. Chem. Soc.*, 2018, **140**, 4792.
- 11 (a) M. Mao, L. Zhang, Y.-Z. Chen, J. Zhu and L. Wu, *ACS Catal.*, 2017, **7**, 181; (b) L. Zhang, J. Zhu, J. Ma, L. Wu and W.-H. Zhang, *Org. Lett.*, 2017, **19**, 6308; (c) J. Zhu, M. Mao, H.-J. Ji, J.-Y. Xu and L. Wu, *Org. Lett.*, 2017, **19**, 1946; (d) T. Liu, X. Sun and L. Wu, *Adv. Synth. Catal.*, 2018, **360**, 2005–2012; (e) X.-D. Wang, J.-J. Wu, X. Sun, W.-C. Yang, J. Zhu and L. Wu, *Adv. Synth. Catal.*, 2018, **360**, 3518.
- 12 Taking into account the single-electron reduction properties of a diamine/alkali metal salt system and thermodynamic stabilities, other pathways either through producing a (Ts)N-radical and hydrogen anion or direct single-electron oxidation of deprotonated N-tosylhydrazone (ref. 10a and b) are unlikely here.
- 13 For the EPR study on a *t*-BuOK/1,10-phen system, see: H. Yi, A. Jutand and A. Lei, *Chem. Commun.*, 2015, **51**, 545.
- 14 For the selected tosyl radical generation from the tosyl anion: (a) X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu and H. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4205; (b) H. Yue, C. Zhu and M. Rueping, *Angew. Chem., Int. Ed.*, 2018, **57**, 1371.
- 15 I. Thomé, A. Nijs and C. Bolm, *Chem. Soc. Rev.*, 2012, **41**, 979.
- 16 CCDC 1573911 (3h), 1573912 (3x), 1573906 (3aa) and 1573907 (3ae) contain the supplementary crystallographic data for this paper.†
- 17 For selected studies on synthesizing atropisomers: (a) E. Kumarasamy, R. Raghunathan, M. P. Sibi and J. Sivaguru, *Chem. Rev.*, 2015, **115**, 11239; (b) E. Kumarasamy, A. J.-L. Aytou, N. Vallavoju, R. Raghunathan, A. Lyer, A. Clay, S. K. Kandappa and J. Sivaguru, *Acc. Chem. Res.*, 2016, **49**, 2713; (c) S.-C. Zheng, S. Wu, Q. Zhou, L. W. Chung, L. Ye and B. Tan, *Nat. Commun.*, 2017, **8**, 15238; (d) Y.-B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534.
- 18 Although the mechanism of this sulfonyl rearrangement needs to be further studied, preliminary results show that a non-radical pathway is involved, and an extramolecular sulfonyl source will render competitive rearrangement products; please see the details and proposed mechanism in the ESI.†
- 19 (a) H. Qiu, H. D. Srinivas, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2016, **138**, 1808; (b) D. F. Taber and P. Guo, *J. Org. Chem.*, 2008, **73**, 9479; (c) C. Zhu, J. Li, P. Chen, W. Wu, Y. Ren and H. Jiang, *Org. Lett.*, 2016, **18**, 1470; (d) W. Zhang, Y. Yue, D. Yu, L. Song, Y.-Y. Xu, Y.-J. Tian and Y.-J. Guo, *Adv. Synth. Catal.*, 2012, **354**, 2283.