

Spiro-C(sp³)-atom transfer: Creating rigid 3D structures with Ph₂SCN₂

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Abstract:

The introduction of a single C-atom into organic substrates typically results in the formation of flat molecules containing unsaturated C(sp)-centers. Adding a single C(sp³)-atom surrounded by four σ-C-C bonds is an unresolved problem in synthetic chemistry which opens up the three-dimensional space. We report the synthesis and application of a Ph₂S=C=N₂ reagent which combines the reactivity of both sulfur ylides and diazo compounds to create carbon spiro-centers in a general fashion by the sequential or single-step installation of a C(sp³)-atom. New C-C and C-X (X = O, N) bonds can be created around the C(sp³)-atom, which can ultimately be extended to four C-C σ-bonds in one step without resorting to transition metal catalysis. Ph₂SCN₂ can also be used to access highly strained frameworks containing (oxa)spiro[2.2]pentanes as well as tricyclic spiro-compounds.

One Sentence Summary:

Four new σ-C-C bonds are generated around a C(sp³)-atom to access (bridged) (oxa)spirocyclopentanes by utilizing a C-atom transfer reagent containing both sulfur-ylide and diazo entities.

Main Text:

The formation of three-dimensional (3D) structures is of fundamental importance in organic chemistry and fragment-based drug discovery (1–2). In particular, the quest to create 3D scaffolds such as cubanes (3), propellanes (4–5), bicyclobutanes (6), or spiro[2.2]pentanes (7–9) has pushed the development of synthetic methods and triggered strong interest to deviate from the widely explored two-dimensional landscape. Carbon insertion in the context of skeletal editing (10) in general relates to methods introducing “C–R” fragments into C(sp²)–C(sp²) bonds typically generating flat, aromatic (hetero)cycles (11–15). Pure C-atom transfer reactions, in which a single atom is transferred, include text-book reactions such as the Seyferth–Gilbert homologation (**I**) (16), the Corey–Fuchs reaction (**IV**) (17) (Fig. 1A) or the Doering–LaFlamme allene synthesis (18). Recently, we were able to expand the repertoire for C-atom transfer by introducing Ph₃PCN₂ (**III**) (19). However, all of the previous described methods proceed via an unsaturated carbene/vinylidene intermediate (**VI**) which results in sp-hybridized C-atoms. Hence, three-dimensionality is not generated by these types of C(sp)-atom transfer reactions. In contrast, C-atom transfer reactions which accomplish the transfer of a C(sp³)-atom have rarely been documented and represent a challenging endeavor (Fig. 1B) (20–21). Carbon arc discharge methods (22–24), C-atom precursors such as carbon suboxide or diazotetrazole (25), or chromium carbido complexes (26), were reported to react unselectively and resulted in only very low yields of C-atom transfer products (20–21). In 2010, Kato, Baceiredo and coworkers reported the synthesis of the bis(ylide) **VIII**, which exhibited promising activity (27); however, no further studies regarding applications have been carried out. A different approach was described by Tobisu and coworkers in 2023, who succeeded in using *N*-heterocyclic carbenes (**X**) as a C(sp³)-atom transfer reagent (28–29). By forming one new C–C bond, acrylamides **IX** could be cyclized to γ -lactams **XI**. Nevertheless, a generalizable strategy for precise and high-yielding installation of C(sp³)-atoms to efficiently form four new C–C single bonds remains a major challenge for synthetic chemistry.

Both the Seyferth–Gilbert reagent **I** and bis(ylide) **VIII** can be regarded as C-atom transfer reagents of the general structure X=C=Y, which we aimed to modify in such a way that carbene/vinylidene intermediates during the C-atom transfer process are avoided. Both sulfur ylides (30–31) and diazo compounds (32–33) are known to exhibit carbene-free cyclopropanation reactivity (Fig. 1C). Combining both functionalities in one molecule should give access to an ideal reagent for the creation of spiro-C-centers, particularly for the direct formation of spiro[2.2]pentanes in which four new C–C bonds are created. Here, we describe the synthesis and isolation of the crystalline diazosulfur ylide Ph₂S=C=N₂ (**3**) and its successful application as a single-step C(sp³)-atom transfer reagent for the construction of sp³-rich, three-dimensional and rigid spirocyclic scaffolds from readily available two-dimensional feedstock molecules.

Preparation, structure, and computational investigation of diazosulfur ylide **3**

Recently, we described the reaction of hexaphenylcarbodiphosphorane (Ph₃P=C=PPh₃) with nitrous oxide (N₂O) to generate Ph₃P=C=N₂ along with triphenylphosphine oxide (Ph₃P=O) via a Ph₃P/N₂ exchange (19). Considering the formal exchange of phosphorus and sulfur ylides (R₃P=[C] vs. R₂S=[C]), we aimed at using N₂O to access the desired diazosulfur ylide Ph₂S=C=N₂ (**3**); hence Ph₂S=C=PPh₃ (**2a**) was considered to be a suitable precursor. Inspired by the work of Kato and Baceiredo (27), we deprotonated the phosphonium salt **1a** (see Supplementary Materials for experimental details) with potassium bis(trimethylsilyl)amide (KHMDS) to obtain the new mixed P/S-ylide **2a** (57%). Subsequent reaction of **2a** with N₂O (-78 °C to rt) showed full conversion after 1 h. Additionally, ³¹P NMR indicated the formation of Ph₃P=O (**4a**) (Fig. S32), while in-situ IR spectroscopy showed a characteristic diazo N=N stretching band at 1960 cm⁻¹ (Fig. S33) (34). Note that the concomitant formation of diphenyl sulfoxide (Ph₂S=O) was not observed. Isolation and separation of the desired diazosulfur ylide **3** from Ph₃P=O proved challenging, which however was solved by switching to Kato–Baceiredo ylide **2b**, in which the phosphine oxide **4b** could be simply separated by washing. This procedure resulted in the isolation of the target **3** as a crystalline light-yellow solid with a yield of 84%.

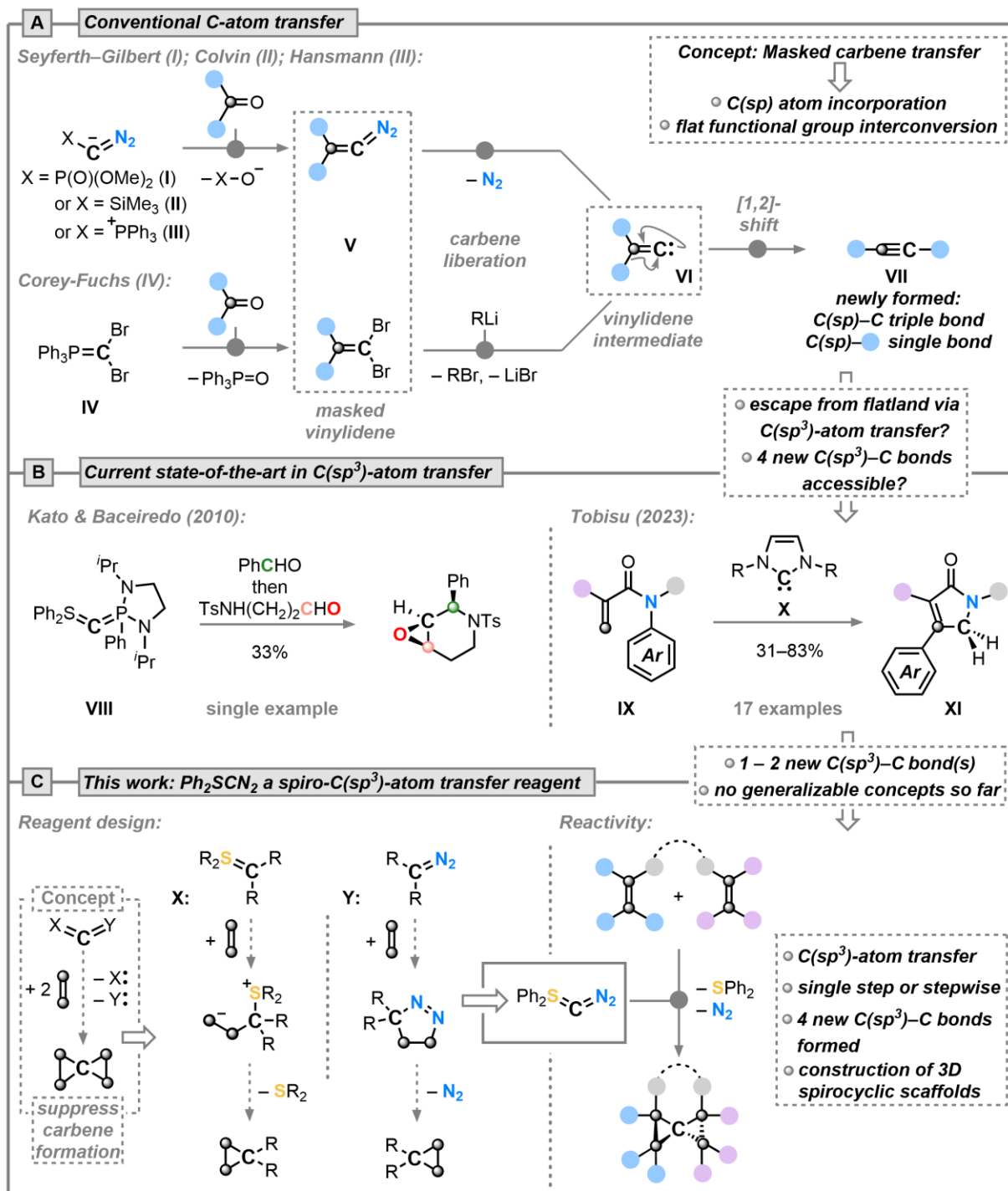


Figure 1. Progress towards a general C(sp³)-atom transfer reagent. (A) Alkyne syntheses via one-carbon homologation. (B) Limited literature precedents for C(sp³)-atom transfer reagents (20–21). (C) Diazosulfur ylide Ph₂SCN₂ as a C(sp³)-atom transfer reagent for the single step construction of 3D scaffolds.

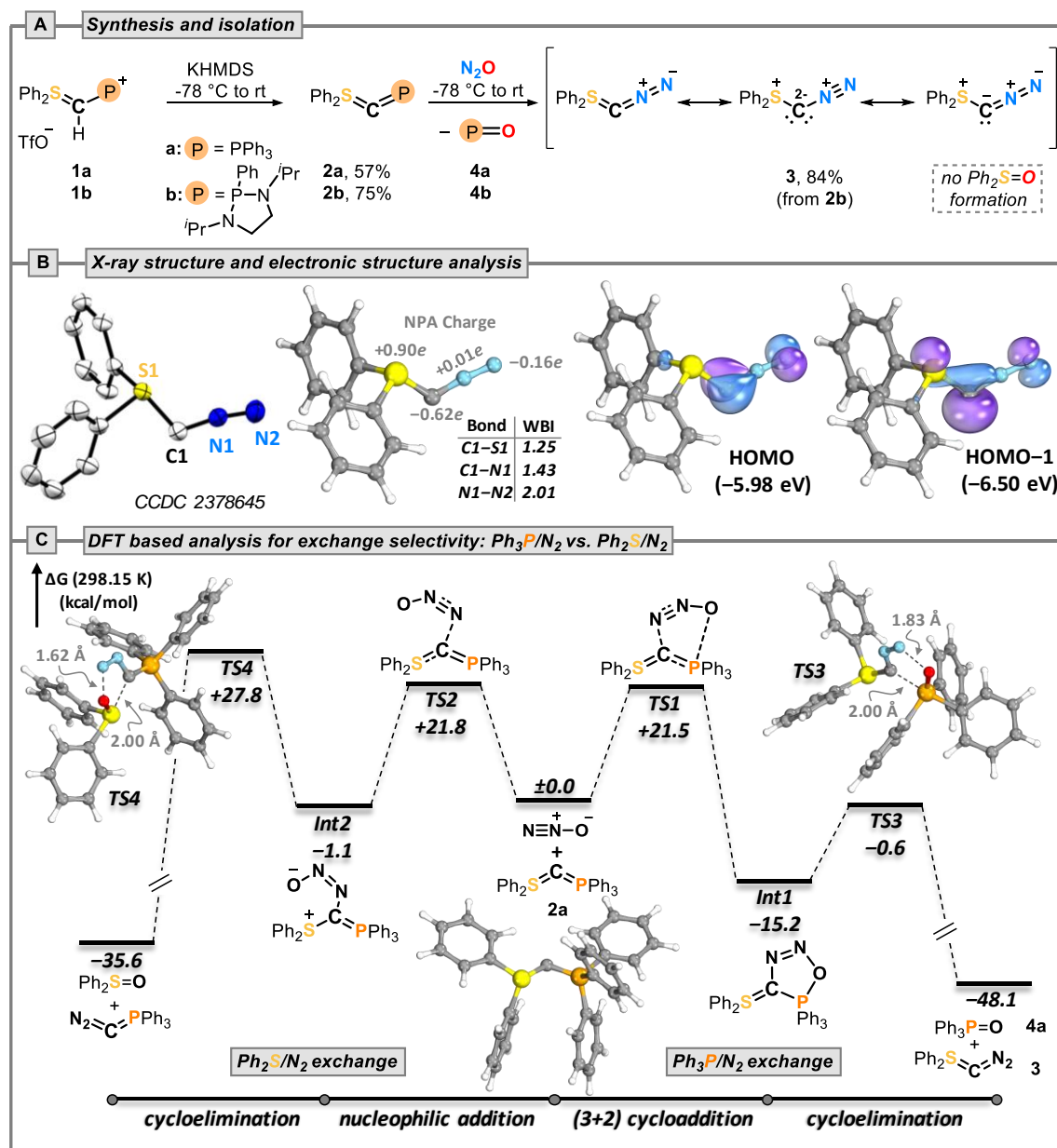


Figure 2. Preparation, structure, and computational investigation of diazosulfur ylide 3. (A) PR_3/N_2 exchange to access diazosulfur ylide **3**. Conditions: N_2O (1.0 bar), $-78\text{ }^\circ\text{C}$ to rt, 1 h in THF. (B) Frontier molecular orbitals (isovalue = 0.6), charges and Wiberg bond indices. (C) Energy profile at the PBE0-D3(BJ)/def2-TZVP/SMD(THF) level of theory.

The crystalline structure of **3** from x-ray diffraction analysis (Fig. 2B) shows a S1–C1 bond length [1.727(2) Å] longer than that of its precursor (**2b**) [1.684(3) Å], but still in the range of the S=C bond lengths of sulfur ylides (Fig. S288). The C1–N1 bond [1.286(3) Å] is longer, and the N1–N2 bond [1.151(3) Å] shorter than in Ph_3PCN_2 [1.268(5) Å and 1.169(5) Å] (*19*) which hints at the increased lability towards dinitrogen release. The angle at the central carbon S1–C–N1 [112.6(2) $^\circ$] is slightly increased compared to its precursor (**2b**) [109.8(2) $^\circ$], however, more acute compared to Ph_3PCN_2 [121.6(3) $^\circ$], as well as all diazoalkene structures deposited in the Cambridge Crystallographic Database (CCD) [118.5(2) $^\circ$ – 125.9(3) $^\circ$] (*35*). The ^{13}C NMR shift of the central carbon resonance appears at 21.3 ppm (THF- d_8), which

was confirmed by ^{13}C -labeling experiments ($\text{Ph}_2\text{S}^{13}\text{CN}_2$; Fig. S36) and *gauge*-invariant atomic orbital (GIAO) calculations (Fig. S312).

Natural population analysis (NPA) indicates the central C-atom of **3** bears a negative charge ($-0.62 e$), while the sulfur atom possesses an almost entirely positive charge ($+0.90 e$). The internal N-atom is neutral ($+0.01 e$), and the terminal N-atom has a slightly negative charge ($-0.16 e$). Wiberg bond indices (WBI) indicate a pronounced C–S single bond character (WBI = 1.25) and a N–N double bond (WBI = 2.01), while the C–N bond lies in between a single and a double bond (WBI = 1.43). These values are positioned in the range of other unsaturated S-ylides [WBI(S–C) in **2b** = 1.21 (27); WBI(S–C) in $\text{Ph}_2\text{S}=\text{C}=\text{SPh}_2$ = 1.22 (36)] and unsaturated diazo compounds (37). Molecular orbital analysis and natural bond orbital (NBO) analysis (Fig. S313–314) indicate that the central C atom bears two orthogonal lone pairs. The HOMO-1 possesses σ -symmetry, while the HOMO has π -symmetry (Fig. 2B). In addition to the heterocumulene representation, the resonance structures $[\text{R}_2\text{S}^+-\text{C}^{2-}-\text{N}^+\equiv\text{N}]$ and $[\text{R}_2\text{S}^+-\text{C}^--\text{N}^+=\text{N}^-]$ (see Fig. 2A) are required to adequately describe the binding situation in **3**. Hence, **3** can also be attributed to a divalent carbon(0) substance class (38). Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) experiments of **3** show a sharp exergonic decomposition at 80°C ($\Delta H \sim 1100 \text{ J/g}$; Figs. S27–29), highlighting the lower stability of S- vs. P-ylides. **3** decomposes slowly over hours in solution at room temperature to diphenyl sulfide and a solid precipitate which we assume to be carbon. Nevertheless, **3** can be easily generated cleanly and stored for more than six months as a solid at -40°C under inert conditions.

To get an understanding of the exclusive $\text{Ph}_3\text{P}/\text{N}_2$ over $\text{Ph}_2\text{S}/\text{N}_2$ exchange selectivity, DFT calculations were performed (Fig. 2C). High HOMO-1 and HOMO energy levels (Fig. S313) make **2a** a pronounced carbon nucleophile, triggering a nucleophilic attack on the terminal N-atom of N_2O (39). Two competing transition states **TS1** ($\Delta G^\ddagger = 21.5 \text{ kcal/mol}$) and **TS2** ($\Delta G^\ddagger = 21.8 \text{ kcal/mol}$), can be accessed which finally lead to $\text{Ph}_3\text{P}/\text{N}_2$ or $\text{Ph}_2\text{S}/\text{N}_2$ exchange. While **TS1** leads irreversibly to the P–O adduct **Int1** via a highly asynchronous concerted (3+2) cycloaddition, **TS2** leads to the almost energy-neutral formation of the zwitterion **Int2**. Furthermore, a low rotation barrier along the newly formed C–N bond enables a rapid interconversion of **Int2** to **Int1** (Fig. S315). While both cycloelimination processes possess high thermodynamic driving force ($\Delta G_{\text{P}\rightarrow\text{N}_2} = -47.0 \text{ kcal/mol}$; $\Delta G_{\text{S}\rightarrow\text{N}_2} = -35.6 \text{ kcal/mol}$), the barrier for the elimination of the sulfoxide is drastically higher (**TS4**: $\Delta G^\ddagger = +27.8 \text{ kcal/mol}$ vs. **TS3**: $\Delta G^\ddagger = -0.6 \text{ kcal/mol}$), most likely due to the intrinsic property of sulfur to avoid the tetravalent species (sulfuranes; for a more in depth analysis, see the SM) (40).

Reactivity studies: (3+2) cycloaddition and consecutive C(sp³)-atom transfer

Reactivity studies of **3** towards consecutive C(sp³)-atom transfer were subsequently carried out (Fig. 3). Upon treatment of **3** with π -acceptor-substituted olefins, complete consumption of the starting materials was observed in a few minutes at room temperature (Fig. 3, *step A*). For instance in the case of *N*-methyl maleimide, the desired pyrazoline sulfur ylide **5a** can be isolated after 15 min with an excellent yield (91%). 1,1-disubstituted olefins with one or two ester groups (**5b–5d**), and *tri*- and *tetra*-substituted olefins all yielded the desired cycloadducts (**5e** and **5f**) cleanly. Olefinic reactants that are not π -acceptor-substituted were also reactive. Norbornene led to **5g** isolated as a single *exo* diastereomer (91%), even cyclopentene afforded very slowly (4 days) the desired cycloadduct **5h** (31%), while cyclohexene or 1-octene were unreactive. The reactivity of angle-tensioned double bonds follows the same trend as observed for the kinetics of the reaction of azides with dipolarophiles (41). Non-activated styrene derivatives required longer reaction times (48 h for **5i** and **5j**, 15 min for **5k**) but afforded the desired cycloadducts (**5i–5k**) in moderate to good yields (59–71%). Heteroaromatic olefins such as a 2-pyridine derived olefin, alkyl/aryl olefins as well as fluorinated (CF_3) olefins afforded the (3+2) cycloaddition products **5l–5n** respectively. If longer reaction times were chosen for the reaction of **3** with mono-substituted olefins or 1,2-disubstituted olefins, instead of the expected cycloaddition products **5**, the functionalized pyrazoles **6a–6f** could also be obtained in high yields (49%–99%) (42). In this case the fast (3+2) cycloaddition is followed by a slower 1,3-proton shift and Ph_2S elimination which leads to the aromatic pyrazoles (Fig. 3, *step B*). **5g** and **5h** do not aromatize

to the pyrazoles most likely due to the lack of C–H acidity. Low temperature NMR studies with dimethyl fumarate and dimethyl malonate confirmed a step-wise (3+2) cycloaddition mechanism in which both afforded the same *trans*-stereochemical outcome (**5o**) (Figures S76-77).

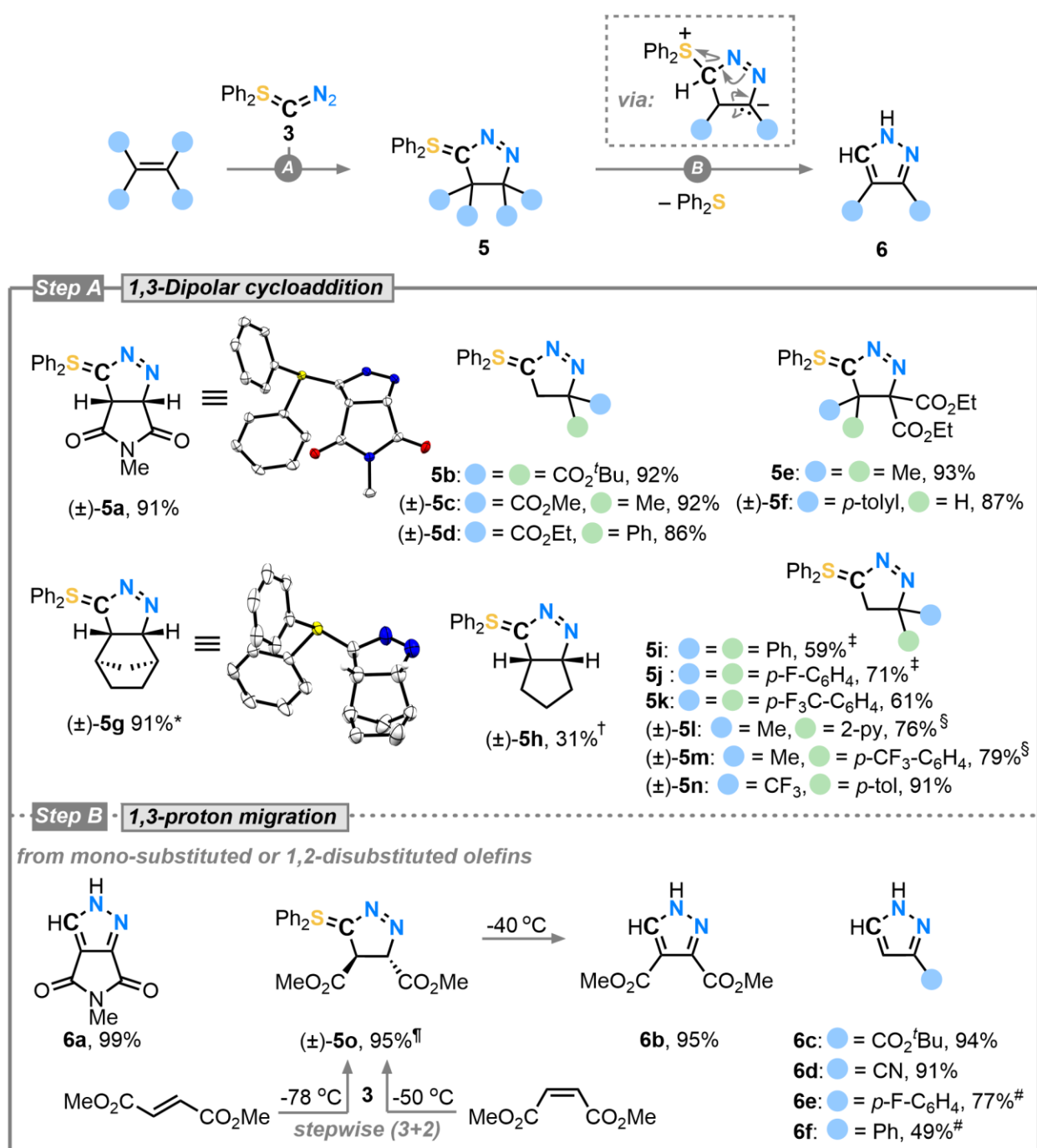


Figure 3.

Figure 3. (3+2) Cycloaddition to sulfur ylides **5 (step A) and pyrazoles **6** (step B).** Step A: The reaction with olefins (1 equiv.) were conducted in THF at rt for 15 min; * 5.0 equiv. of norbornene for 12 h, † 20.0 equiv. of cyclopentene for 96 h, ‡ 48 h reaction time, § 24 h reaction time. Step B: The reaction with mono-substituted or 1,2-disubstituted olefins were conducted in THF at rt in 1 h; ¶ NMR yield, # 12 h reaction time.

Next, we investigated whether the remaining S-ylide moiety of the pyrazolines **5** shows the desired cyclopropanation reactivity (Fig. 4, step *BI*). The maleimide-based sulfur ylide **5a** was treated with one equiv. of *N*-methyl maleimide to afford cyclopropane **7a** in good yield (67%), which could also be obtained directly from **3** with 3.0 equiv. of *N*-methyl maleimide in a one-pot process with the same yield (67%). This result showcases a C(sp³)-atom transfer, forming three new C–C bonds in a single step. The use of the sulfur ylides **5b** and **5c** together with *N*-methyl maleimide led to the corresponding cyclopropanes **7b** and **7c** in excellent yields. The reaction of the S-ylides **5** with fumaric and maleic acid esters afforded the spiro compounds **7d** with the same relative configuration in agreement with a stepwise Corey–Chaykovsky–type mechanism (43). Diester S-ylide **5b**, ester/alkyl S-ylides **5c**, diaryl S-ylides **5i–5k**, heteroaromatic/alkyl S-ylides **5l** and fluorinated S-ylides **5m–5n** could all be trapped with dimethyl fumarate to afford the cyclopropanation products **7e–7l**. Only S-ylides substituted in α -position (**5e–5f**) were unreactive, however, the α -substituted cyclopentane containing S-ylide **5h** also gave the desired product **7m**. The trapping was not limited to maleimide and dimethyl fumarate but could also be applied to other electron deficient olefins including acrylonitrile or 1,1-diester olefins to give **7n** and **7o** in high yields (94–95%).

The next step was to complete the consecutive C(sp³)-atom transfer (Fig. 4, step *CI*). Spirocyclopropane-containing 1-pyrazolines are known substrates for ring contraction processes, which can be used to synthesize spiro[2.2]pentanes via liberation of N₂ (44–45). This strategy was exemplified for all fifteen 1-pyrazolines **7a–7o**, which were typically heated to 130 °C. Regardless of the substitution pattern (except **7b**, **7d** featuring 1,1-diester moieties and **7m** containing the cyclopentane fragment) N₂ was released smoothly and highly substituted spiro[2.2]pentanes **8a**, **8c**, **8e–8o** were obtained in typical excellent yields.

As a proof-of-concept, a one-pot sequence was developed for the intermolecular C-atom transfer starting from the bench-stable S/P salt **1a** with *in situ* generated **3**. Without isolation of neither **2a** nor **3**, sequential addition of two different olefins afforded the cyclopropanation product **7e** in 97% yield (561 mg). N₂-liberation under heating gives the C-atom transfer product **8e** in 85% yield (413 mg) (see SM for details).

S-ylides are also established in the synthesis of epoxides (30–31). Aiming to broaden the applicability of reagent **3** the synthesis of spirocyclic epoxides was targeted. As a proof-of-concept, sulfur ylides **5i** and **5k** reacted with formaldehyde or (hetero)aromatic aldehydes to give the spiro-heterocycles **9a–9e** in good to excellent yields (69%–95%; Fig. 4, step *B2*). In the case of the unsubstituted epoxides **9a** and **9b** the desired thermally induced release of N₂ proved to be unproblematic (80 °C for 24 h in C₆D₆) to afford the oxaspiro[2.2]pentanes **10a** and **10b** in high yields (91%; Fig. 4, step *C2*). Aromatic epoxides **9c–9e** gave the substituted cyclobutanones **11a–11c** in excellent yields (90–94%), which could also be accessed in one-step without isolation of the spiro-cycle (45% for **11d**). In the latter case the generation of the desired spirocyclic epoxide is most likely followed by a Meinwald-type rearrangement, whereby the higher substituted carbon atom migrates (46–47). The three step sequence presented demonstrates the capacity of **3** to incorporate two flat olefins or olefin/aldehyde moieties into a 3D (oxa)spiro[2.2]pentane scaffold via C(sp³)-atom transfer in excellent overall yields.

Reactivity studies: Single-step spiro-C(sp³)-atom transfer

Encouraged by the reaction sequence leading to (oxa)spiro[2.2]pentanes, we aimed at a single-step spiro-C(sp³)-atom transfer and selected acceptor-substituted 1,5-hexadienes **12a–d** as starting materials in which cycloaddition and cyclopropanation can occur in the same molecule. Intriguingly, after only 30 minutes at room temperature the reaction of **3** with dimethyl or diethyl 2,5-dimethylenehexanedioate afforded in one step the complex tricyclic spiro-pentanes **13a–b** (69–72%) in which N₂ loss occurred (Fig. 5). The underlying highly strained (strain energy ca. 80 kcal/mol) (48, 49) tricyclic scaffold (tricyclo[4.1.0.0^{1,3}]heptane) was first reported by Skattebøl in 1966 (50). However, synthetic access proved to be problematic and low-yielding and for functionalized representatives synthetic approaches are completely lacking. As a proof-of-concept, the reaction could also be performed with ¹³C-labeled **3**-¹³C cleanly resulting in **13a**-¹³C in which a single ¹³C-atom is directly incorporated.

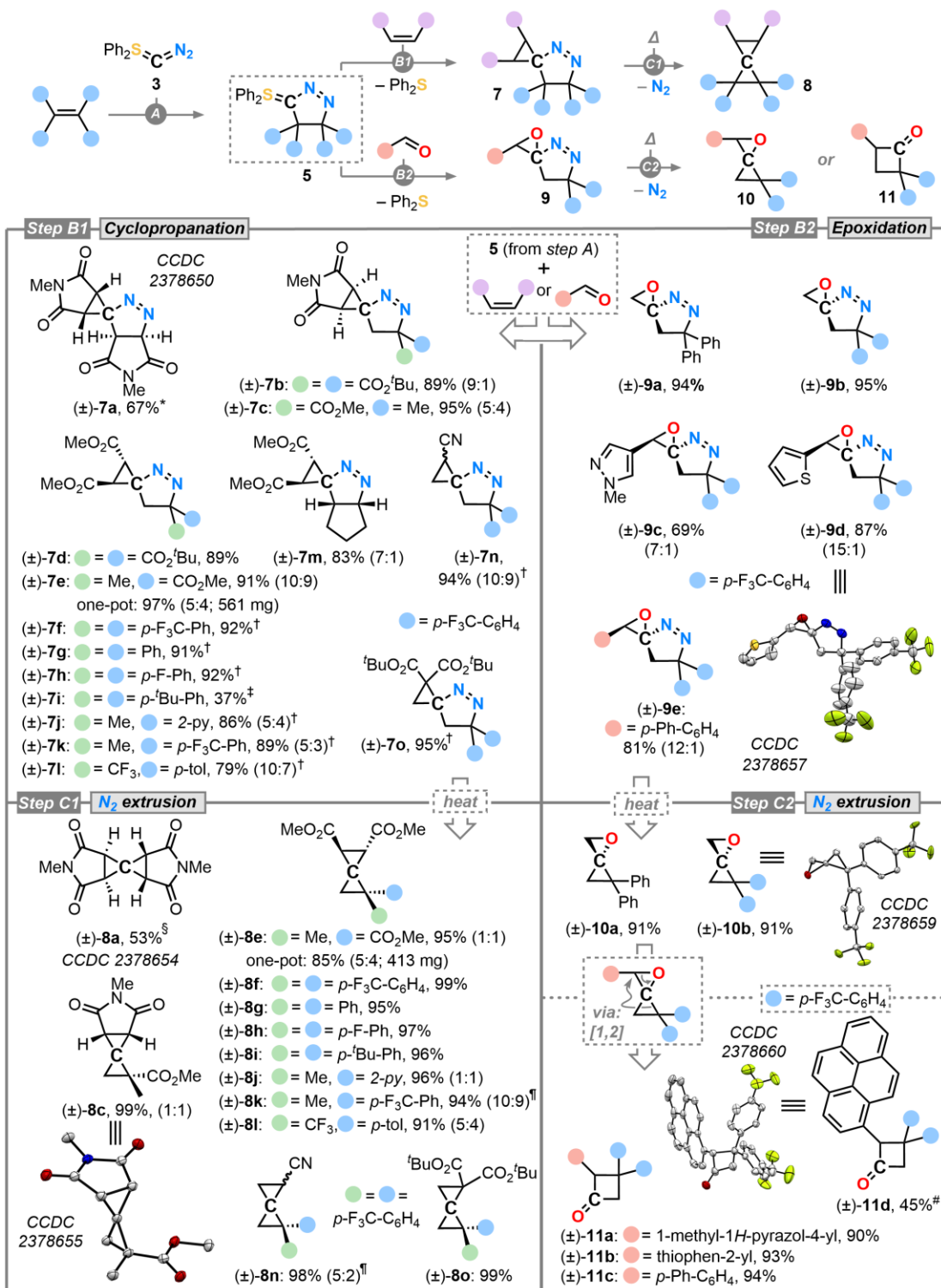


Figure 4. Stepwise C(sp³)-atom transfer to access spiro[2.2]pentanes (steps B1 and C1) and oxaspiro[2.2]pentanes (steps B2 and C2). Step B1: One-pot reaction with olefins in two steps were conducted in THF at 50 °C for 2 h. * conducted from -40 °C and warmed up to rt with 3.0 equiv. of *N*-methyl maleimide, † conducted with isolated S-ylides, ‡ One-pot reaction in which the first step took 96 h. Step C1: N₂ extrusion reaction at 130 °C in C₆D₅Br for 3 h. § at 165 °C for 48 h, || at 150 °C for 5 h. Step B2: the reactions of pyrazoline 5 with aldehydes were conducted in THF. Step C2: N₂ extrusion at 80 °C in C₆D₆. # conducted in one-step from 5k and pyrene-1-carbaldehyde.

Such labeling could be interesting for future advanced labeling strategies (^{11}C or ^{14}C). Also a one-pot strategy was developed for the intramolecular C(sp³)-atom transfer with *in situ* generated **3** (Figure 5; top right). Without isolation of any air-sensitive intermediate the one-pot transformation afforded tricyclic **13a** in 81% yield (862 mg; see SM for details). Additionally post-functionalization of the tricyclo[4.1.0.0^{1,3}]heptane building block was demonstrated by reduction to give the diol **13a^I** (91%) which proved to be robust towards degradation at 80 °C over several hours (Figure S283). Selective mono saponification afforded the stable ester/acid building block **13a^{II}** (98%) which could be coupled to give the amide **13a^{III}** (81%) paving the way towards embedding the 3D structures into pharmaceutical relevant drug targets.

The *ortho*-phenyl bridged diene gave the tetracyclic system (**13c**) with a yield of 85%. This is remarkable considering the complexity of the underlying mechanism, the number of elementary steps involved in this one-pot transformation, as well as the remarkably high strain of the system. The newly introduced spiro-C-atom contains four new C–C bonds and is highly distorted into a seesaw/disphenoidal geometry, in which the annulated C–C bond [1.412(2) Å] is elongated to decrease the strain (51). Due to the high strain, **13c** undergoes slow decomposition in solution (Fig. S225) (51), while all the other saturated tricycles are stable at room temperature. The C₂ symmetric tricycle class features two ester moieties which, based on x-ray analysis, are oriented *para* in 3D-space, but with a sideways shifted offset (Fig. S311). The C-atom transfer is also applicable to a unsymmetrical C2-linker starting material affording the ester/nitrile functionalized tricyclo[4.1.0.0^{1,3}]heptane **13d**.

Ring size variation and heteroatom incorporation were then investigated. Switching to a longer three-atom tether (CH₂, O and S moieties) enables isolation of the hetero-substituted tricyclo[5.1.0.0^{1,3}]octanes **15e–g** in high yields in which three new stereocenters are introduced. Presumably due to the decreased ring strain of the tricyclic intermediate no spontaneous dinitrogen liberation occurred. A non-symmetrical diene afforded the tricycle **15i**, in which the (3+2) cycloaddition occurred on the ester substituted olefin, while the cyclopropanation occurred on the nitrile substituted olefin.

Using a 1,6-heptadiene also containing heteroatoms (O, S) in the linker chain gave upon heating the desired bridged spirotricycles **13e–g** in moderate (**13e**, 55%, **13f**, 28% and **13g**, 53%) yield, without the isolation of the intermediate **15** being required. Besides the desired products (**13e–g**) azabicyclo[3.2.0]heptanes **14e–f** were formed as by-products. Thermal isomerization of spiro[2.2]pentanes to methylenecyclobutanes is well-known but usually requires harsh reaction conditions, e.g. 355 °C, 27 h (52), and does not proceed with isolated **13e–g** under the reaction conditions. A *N*-tosyl (*N*-Ts) bridge leads to tricycle **15h**, which could be scaled up in a one-pot sequence (67%, 516 mg) analogous to the conditions for **13a**. Heating at 70 °C affords the expected tricycle **13h** in low yield (15%), while the main product is the bicycle **14h**. However, irradiation of **15h** with a LED (370 nm) leads in 81% yield to the unknown *cis*-tricyclo[5.1.0.0^{1,3}]octane **13h** (*cis:trans* = 9:1). Addition of a triplet photosensitizer such as benzophenone (53) leads to a decrease in the *cis:trans* selectivity (3:1; Figure S261). The *cis*-tricyclo[5.1.0.0^{1,3}]octane core was calculated to have a high strain energy (97 kcal/mol vs. 66 kcal/mol for *trans*) (54), which shows the largest structural deformation (twisting) of any reported spiro-cyclopentane based on a CCD search (see Figure S310). At room temperature the *cis*-compound slowly rearranges to the olefin **14h**. We assume that the thermal N₂ liberation generates both *cis* and *trans* tricycles, while under these conditions the *cis* product rearranges to **14** (for a mechanistic proposal, see Figure S273).

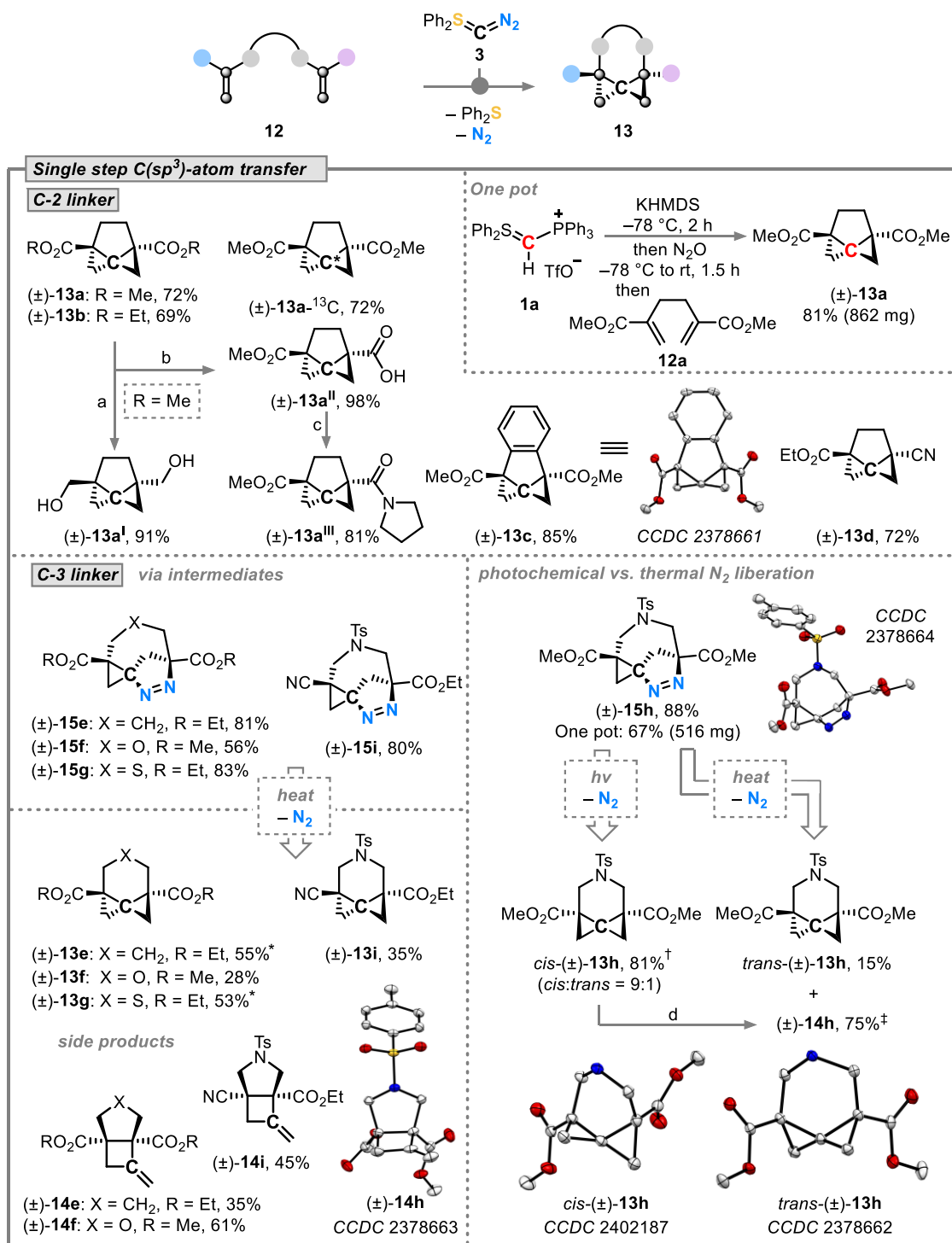


Figure 5. Single step spiro-C(sp³)-atom transfer to afford bridged spiropentanes. The reactions were performed in THF. The C-2 linker reactions (**13a-d**) were conducted at rt. The C-3 linker reactions were conducted from -78 °C gradually increasing the temperature to 70 °C. The generation of tricycles **15** was conducted at -78 °C and warmed up to room temperature. * conducted at -78 °C and heated to 120 °C, † The irradiation reaction was conducted with 370 nm light at rt for 12 h, ‡ 70 °C for the thermolysis reaction of *cis*-**13h**. In the x-ray structures of *cis/trans*-**13h** the *N*-tosyl group was omitted for clarity. a: LiAlH₄ (2.0 equiv.) in THF, 0 °C, 40 min; b: NaOH (1.05 equiv.), THF-MeOH (40:1), rt, 17 h; c: pyrrolidine (1.4 equiv.), EDC (1.6 equiv.), DMAP (0.2 equiv.), CH₂Cl₂, rt, 16 h; d: slow reaction at rt or quantitative upon heating, see SM.

These fascinating, rigid 3D scaffolds have so far received no attention in drug design as bioisosteres (55). Considering the ease of accessing the functionalized tricyclo[4.1.0.0^{1,3}]heptane and *cis* or *trans*-heteroatom-substituted tricyclo[5.1.0.0^{1,3}]octane cores we are convinced that besides applications of these scaffolds, other distinct chiral 3D building blocks could easily be assembled using the new C(sp³)-atom transfer reagent.

In summary, we have demonstrated that diazosulfur ylide Ph₂S=C=N₂ (**3**) is a broadly applicable C(sp³)-atom transfer reagent for the step-wise or single-step construction of up to four new C–C bonds around a highly-strained spiro-C-atom. (Oxa)spiropentanes can be rapidly generated and even embedded into rigid tricyclic scaffolds. We are convinced that these findings will stimulate the exploration of additional C(sp³)-atom transfer reactions, enable access to advanced 3D scaffolds and extend C-atom transfer into other fields such as main group and transition metal chemistry.

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General Method

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Author Contributions

Q. S. initial devised and synthesized this reagent, Q. S., J.-N. B., J. H., P. W. A. and D. T. performed the synthetic experiments, P. W. A. and R. G. performed the x-ray analysis and D. T. the computational studies. Q. S., D. T. & M.M.H. discussed and wrote the manuscript. M.M.H. managed the project.

Competing Interests

A patent application with the inventors: Qiu Sun (Chinese) and Max M. Hansmann (German), both TU Dortmund, is pending.

Data and materials availability

The details of the experimental methods, NMR spectra, x-ray analysis, IR spectra, and computational studies are available in the supplementary materials. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers

5 CCDC 2378645/2378646 (**3**), 2378647 (**5a**), 2378648 (**5g**), 2378649 (**6a**), 2378650 (**7a**), 2378651 (**7b-A**), 2378652 (**7c-A**), 2378653 (**7d**), 2378654 (**8a**), 2378655 (**8c-A**), 2378656 (**8d**), 2378657 (**9d**), 2378658 (**9e**), 2378659 (**10b**), 2378660 (**11d**), 2378661 (**13c**), 2378662 (*trans*-**13h**), 2402187 (*cis*-**13h**), 2378663 (**14h**), and 2378664 (**15h**). These data are provided free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this project are available within the article or Supplementary Materials. Correspondence and requests for materials should be addressed to M.M.H (max.hansmann@tu-dortmund.de).

Materials & Correspondence

Supplementary Materials

10 Materials and Methods
Experimental Details
Figures S1 to S334
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