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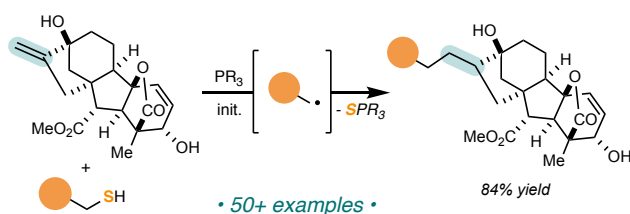
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Intermolecular Phosphite-Mediated Radical Desulfurative Alkene Alkylation Using Thiols.

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Supporting Information Placeholder



ABSTRACT: We report herein the development of an S-atom transfer process using triethyl phosphite as the S-atom acceptor that allows thiols to serve as precursors of C-centered radicals. A range of functionalized and electronically unbiased alkenes including those containing common heteroatom-based functional groups readily participate in this reductive coupling. This process is driven by the exchange of relatively weak S-H and C-S bonds of aliphatic thiols for C-H, C-C, and S-P bonds of the products formed.

Renewed enthusiasm surrounding the ability of open-shell intermediates to forge carbon frameworks has spurred the development of new methods of accessing C-centered radicals.¹ Sulfur-based reagents have been developed for C-C bond construction via polar processes² and radical substitutions.³ Xanthate-based reductive alkylation⁴ presents the most general method for radical-based C-C bond construction though this does require xanthate removal with a discrete synthetic step and an excess of H-atom donor such as *n*-tributyl tin hydride, tris(trimethylsilyl)silane, hydrophosphorous acid, or isopropanol is generally needed.⁵ Thiyl radicals, themselves valuable H-atom transfer reagents (Scheme 1A),⁶ are commonly generated via disulfide bond cleavage or H-atom abstraction and undergo reversible addition to π -systems. As a result, thiols have become a mainstay of many radical-mediated processes. Despite this ubiquity, thiols have been relegated to essentially one role: a source of S-centered radicals.⁷

Walling and Hoffman were among the first to report that alkyl thiols were cleanly reduced to the corresponding alkanes using UV light or thermal initiators and triethyl phosphite via the intermediacy of a C-centered radical from cleavage of the C-S bond (Scheme 1B).^{8,9} Subsequently, radical thiol desulfurization via S-atom transfer to phosphorous-based reagents was reported using thermal¹⁰ and photochemical conditions.¹¹ Minozzi and Nanni reported that alkene alkylations could be achieved through a *tert*-butyl isocyanide induced thiol desulfurization and interception of the C-centered radical intermediate with an alkene.¹² This work outlined 3 thiols that were successful alkylating agents for 4 electron-rich vinyl ethers and vinyl silanes.¹³ Hashmi and co-workers recently reported a photochemical, Au-catalyzed reductive C-C coupling using thiols and

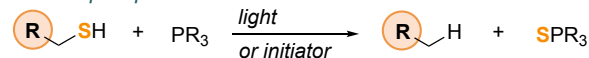
vinyl arenes.¹⁴ Despite these developments, radical-mediated methods for C-C bond formation using thiols remain limited.¹⁵

Scheme 1. Atom-transfer reactivity of thiols

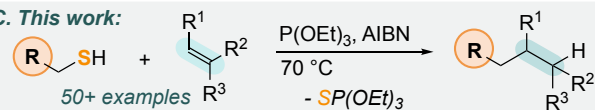
A. Thiols as H-atom transfer reagents^a



B. Radical phosphorous reductions of thiols^b



C. This work:

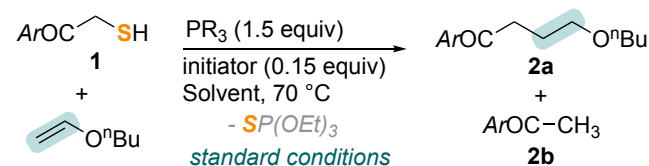


^aSee ref. 6. ^bSee refs. 8-11.

We recently reported a regioselective O-atom transfer enabled, alkene hydroamination using *N*-hydroxyphthalimide as both the H-atom and phthalimide sources.^{16,17} Considering the thermodynamics that propel that process – relatively weak N-O and O-H bonds exchanged for stronger C-N, C-H, and O-P bonds – we hypothesized that thiols could analogously serve as alkyl and H-atom sources when paired with an S-atom accepting phosphite under mild reaction conditions.¹⁸ Application of this strategy would provide an orthogonal role for thiols in synthetic radical chemistry as alkylating agents and provide a transition metal free alternative to radical-mediated reductive alkene alkylations.^{19,20}

We began our investigations by subjecting 2-mercaptoacetanisole (**1**)²¹ and *n*-butyl vinyl ether (NBVE, 1.5 equiv) to a small excess of triethyl phosphite (1.5 equiv) and 2,2'-azobis(2-methylpropionitrile) (AIBN, 0.15 equiv) in benzene for 12 h at 70 °C. The desired desulfurized alkylation product, **2a**, was isolated in 42% yield alongside 50% yield of the unwanted thiol reduction product, **2b** (Table 1, entry 1). Assessment of a range of other phosphites and phosphines produced similar or less efficient results.²² Similarly, replacing AIBN with other thermal radical initiators diminished the yield of **2a**. In the absence of either triethyl phosphite or AIBN, **2a** was not detected (entries 2 and 3, respectively) confirming their necessity in the observed radical desulfurative alkylation. Notably, thiol-ene reaction products resulting from thiyl radical addition to alkenes throughout these studies were not observed.²³

Table 1. Desulfurative alkylation reaction conditions^a



Entry	Deviation from standard conditions	Yield of 2a ^b
1	None	42% (50% 2b)
2	No P(OEt) ₃	<i>n.d.</i>
3	No AIBN	<i>n.d.</i>
4	1 added over 2 h	80% (8% 2b)
5	1 added over 7.5 h ^c	93% (7% 2b)

^aReactions carried out with **1** (1 equiv), P(OEt)₃ (1.5 equiv), *n*-butyl vinyl ether (1.5 equiv), and AIBN (0.15 equiv) in 0.1M degassed benzene at 70 °C for 14 h; *Ar* = 4-OMe(C₆H₄); *n.d.* = not detected. ^bYields are of isolated material following purification via silica gel chromatography. ^cA 0.16M solution of **1** in benzene was added at a rate of 2.3 μL/min.

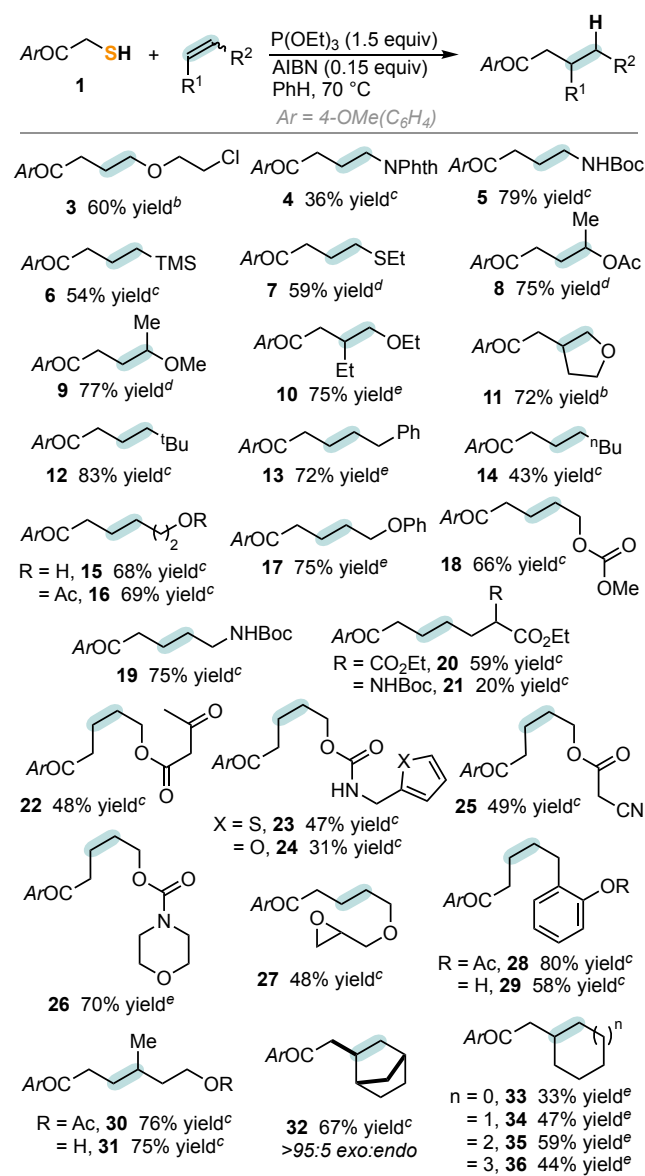
Observing a suboptimal ratio of **2a**:**2b** regardless of the phosphorous reagent, solvent, or initiator used, we hypothesized that **2b** was formed via competitive H-atom transfer from the thiol starting material to the intermediately formed C-centered radical prior to olefin addition.

To promote olefin addition without increasing the equivalents used, we opted to keep the concentration of thiol low with respect to alkene by adding the thiol to the reaction mixture over time. Adding a benzene solution of **1** and AIBN via syringe pump to the remaining reaction components over 2 h improved the selectivity for **2a** production (80% yield, entry 4). Decreasing the rate of addition so that **1**/AIBN was added over 7.5 h resulted in the isolation of **2a** in 93% yield (entry 5) while decreasing the rate of addition further failed to provide additional benefits.

We then investigated the scope of alkenes that participated in this radical desulfurative alkylation using **1** as a model thiol (Scheme 2). An array of functionalized alkenes containing an alkyl chloride (**3**), protected N-based groups (**4** and **5**), silyl (**6**), thioether (**7**), and vinyl ethers (**8-11**) underwent desulfurative alkylation with moderate to excellent efficiencies.

Electronically unbiased alkenes such as *tert*-butyl ethylene (**12**), allyl benzene (**13**), and 1-hexene (**14**), were also easily alkylated to exclusively give the linear products. Attempts at analogously alkylating styrene was unsuccessful, resulting in mixtures of unidentified oligomers.

Scheme 2. Alkene scope^a



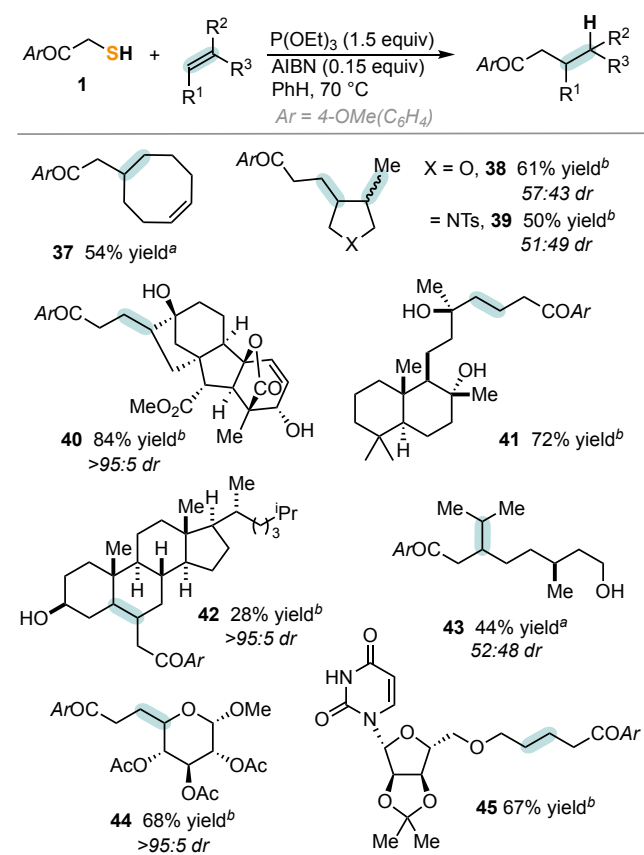
^aAll reactions carried out using **1** (1 equiv), P(OEt)₃ (1.5 equiv), AIBN (0.15 equiv), and alkene in benzene at 70 °C by adding **1** via syringe pump over 7.5 h followed by continued heating for an additional 6 h; yields are of isolated material following chromatography on silica gel. Diastereomeric ratios determined by analysis of crude reaction mixtures by ¹H NMR with the structure of the major diastereomer shown. Phth = phthalimidyl, Boc = *tert*-butyl carbamoyl, TMS = trimethyl silyl, Ac = acetyl, Ts = *para*-tolylsulfonyl. ^bUsing 1.5 equiv alkene. ^cUsing 5 equiv alkene. ^dUsing 3 equiv alkene. ^eUsing 10 equiv alkene.

Alkenes with pendant functionality were also evaluated. 3-Buten-1-ol was reductively alkylated with **1** in nearly identical efficiency whether the primary alcohol was protected as an

acetate (**16**, 69% yield) or not (**15**, 68% yield). Phenyl ether (**17**), alkyl carbonate (**18**), carbamate protected 1° amine (**19** and **21**), and ester (**20**) groups were also well tolerated. Olefins in the presence of base sensitive β-keto ester (**22**) and nitrile (**25**) groups, as well as heterocycles such as thiophene (**23**), furan (**24**), and morpholine (**26**) were successfully alkylated using **1** and triethyl phosphite.

Notably, an epoxide-containing allyl ether resulted in the formation of the desired reductive alkylation product **27** in 48% yield with no observed epoxide degradation despite the reducing ability of phosphites.²⁴ We observed diminished reaction efficiency in the presence of a phenol (**29** in 58%) as compared to its acetyl protected analog (**28** in 80% yield).²⁵ Similar to the case of 3-butene-1-ol, geminal disubstituted alkene, 3-methylbut-2-en-1-ol (**31**) and its acetylated congener (**30**) were alkylated with essentially the same efficiencies (76% and 75% yields, respectively). Cyclic alkenes were alkylated with good reaction efficiencies (**32** – **36**) with norbornene being the most efficient likely due to the release of ring strain upon addition.

Scheme 3. Alkenes in complex molecules undergo reductive alkylation^a



^aAll reaction carried out using conditions outlined in Scheme 2; yields are of isolated material following chromatography on silica gel; diastereomeric ratios determined by analysis of crude reaction mixtures by ¹H NMR with the major diastereomer shown; Ac = acetyl, Ts = *para*-tolylsulfonyl. ^bUsing 10 equiv alkene. ^cUsing 5 equiv alkene.

Cyclic diene, 1,5-*cis,cis*-cyclooctadiene, underwent reductive alkylation to produce **37** in 54% yield without observation

of the bicyclic product arising from intramolecular cyclization (Scheme 3). Subjecting diallyl ether and *N,N*-diallyl tosylamine to our standard reaction conditions resulted in the formation of each of the alkylated, cyclized products **38** (61% yield), **39** (50% yield), respectively. We did not observe alkylation products for either of these 1,6-heptadienes without cyclization. This agrees with the rate of cyclization in 1,5-*cis,cis*-cyclooctadiene ($\sim 1 \times 10^5 \text{ s}^{-1}$)²⁶ being slower than H-atom transfer from alkyl thiols to C-centered radicals ($4 \times 10^6 - 2 \times 10^7 \text{ s}^{-1}$)²⁷ but 5-*exo*-trig cyclization being faster ($\sim 9 \times 10^8 \text{ s}^{-1}$)²⁶ in 1,6-heptadienes.

Table 2. Scope of thiols that serve as alkylating agents^a

Entry	R	R ¹	
		= O ⁿ Bu	= ^t Bu
1		2a 93% yield	12 83% yield
2		46a 94% yield	46b 45% yield
3		47a 96% yield	47b 43% yield
4		48a 98% yield	48b 75% yield
5		49a 68% yield	49b 52% yield
6		50a 60% yield	50b 55% yield
7		51a 47% yield	51b 40% yield
8		52a 32% yield ^b	52b 30% yield

^aAll reactions were carried out using conditions outlined in Scheme 2; yields are for isolated material following chromatography on silica gel; 1-Ada = 1-adamantyl. ^bCarried out using 5 equiv alkene.

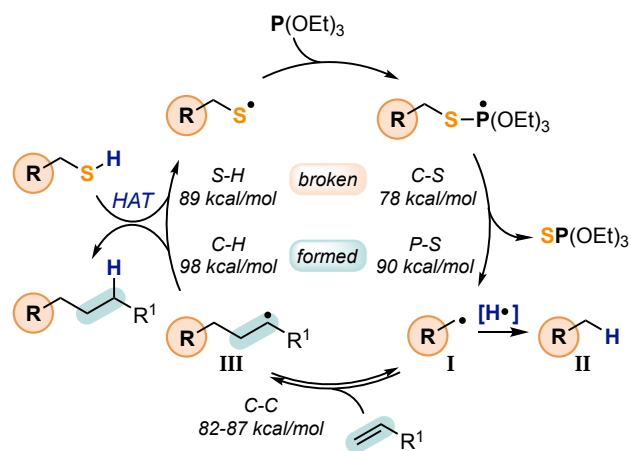
We next turned our attention to more complex, alkene containing compounds (Scheme 3). The methyl ester of gibberellic

acid underwent chemoselective reductive alkylation with **1** at the geminal alkene with high reaction efficiency (**40** in 84% yield) without indication of alkene alkylation of the allylic alcohol.²⁸ Naturally occurring bicyclic diterpene, sclareol, was converted to **41** in 72% yield. Alkylated cholesterol (**42**) and (-)-citronellol (**43**) provide two examples of trisubstituted alkenes contained within functionalized frameworks that successfully participated in this process. A vinyl enol ether derivative of D-(+)-glucose was successfully alkylated using **1**, producing **44** in 68% yield with no evidence of unwanted epimerization as was a 5'-O-allyl uridine nucleoside derivative (**45** in 67% yield).

We then focused on assessing the variety of thiols that could serve as alkylating agents in this desulfurative process (Table 2). We elected to conduct this thiol survey using NBVE and *tert*-butyl ethylene as model alkene because of their favorable spectroscopic and physical properties. While our model thiol, **1**, featuring a 4-methoxy aryl ketone motif efficiently afforded the reductive alkylation of both model alkenes (entry 1, compounds **2a** and **12**), reaction efficiencies were only moderately influenced when the methoxy group was replaced with either a H- or F-atom (entries 2 and 3, compounds **46a-b** and **47a-b**). The primary thiol derived from 1-adamantyl methyl ketone also resulted in excellent reaction efficiencies with NBVE and *tert*-butyl ethylene (entry 4, compounds **48a-b**).

Thiols derived from a benzyl ester, trifluoroethyl phosphonate ester, and amide also proved capable alkylating agents in this S-atom transfer alkylation process (entries 5 – 7, compounds **49a-b**, **50a-b**, and **51a-b**) allowing installation of synthetically valuable functional handles in the product. The secondary thiol derived from γ -butyrolactone also successfully produced the desired alkylation products from both model alkenes used albeit with decreased efficiency (entry 8, compounds **52a-b**).

Scheme 4. Mechanistic proposal



A mechanistic proposal in line with our experimental results is provided in Scheme 4. Thermal radical initiation followed by H-atom abstraction from thiol produces the corresponding thiyl radical which undergoes addition to triethyl phosphite.⁸ This thiyl-phosphite adduct then undergoes rapid and preferential β -cleavage of the C-S bond, forming triethyl phosphorothioate and C-centered radical **I**. We observed that with high relative concentrations of thiol, this C-radical abstracts an H-atom from the thiol, resulting in alkane **II**; maintaining low relative concentrations of thiol through slow addition, **I** undergoes

regioselective alkene addition resulting in 2° or 3° C-centered radical, **III**. Radical **III** can now serve as the H-atom abstraction agent to deliver the desired alkylation product and regenerate the thiyl radical. This process is driven by the cleavage of relatively weak S-H and C-S bonds of the starting materials (~89 and 78 kcal/mol, respectively) to form stronger P-S, C-C, and C-H bonds of the products (90, ~85, 98 kcal/mol).²⁹

In conclusion, we describe an S-atom transfer, phosphite-mediated reductively alkylation of a wide range of alkenes, including examples of those present in naturally occurring, biologically active compounds, using thiols as C-centered radical precursors. We demonstrate that a variety of 1° and 2° thiols adjacent to anion stabilizing groups serve as precursors to achieve C-C bond formation with olefins. This expands the ability of thiols in radical-mediated processes and opens orthogonal pathways in strategic synthetic planning.³⁰

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details, characterization data including NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interests.

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REFERENCES

- (1) For leading references, see: (a) Hart, D. J. Free-Radical Carbon-Carbon Bond Formation in Organic Synthesis. *Science* **1984**, *223*, 883 – 887. DOI: 10.1126/science.223.4639.883. (b) Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds; Pergamon Press: Oxford, UK, 1986. (c) Crich, D.; Quintero, L. Radical chemistry associated with the thiocarbonyl group. *Chem. Rev.* **1989**, *89*, 1413 – 1432. DOI: 10.1021/cr00097a001. (d) Ollivier, C.; Renaud, P. Organoboranes as a Source of Radicals. *Chem. Rev.* **2001**, *101*, 3415 – 3434. DOI: 10.1021/cr010001p. (e) Zard, S. Z. Xanthates and Related Derivatives as Radical Precursors. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001; Vol. 1, pp 90 – 106. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322 – 5363. DOI: 10.1021/cr300503r. (g) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075 – 10166. DOI: 10.1021/acs.chemrev.6b00057. (h) Wang, C.-S.; Dixneuf, P. H.; Soulé, J.-F. Photoredox Catalysis for Building C-C Bonds from C(sp²)-H Bonds. *Chem. Rev.* **2018**, *118*, 7532 – 7585. DOI: 10.1021/acs.chemrev.8b00077. (i) Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M.

- A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019**, *141*, 6726 – 6739. DOI: 10.1021/jacs.9b02238.
- (j) Chen, T.-G.; Zhang, H.; Mykhailiuk, P. K.; Merchant, R. R. Smith, C. A.; Qin, T.; Baran, P. S. Quaternary Centers by Nickel-Catalyzed Cross-Coupling of Tertiary Carboxylic Acids and (Hetero)Aryl Zinc Reagents. *Angew. Chem. Int. Ed.* **2019**, *58*, 2454 – 2458. DOI: 10.1002/anie.201814524.
- (k) Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. Alkyl Sulfonates: Radical Precursors Enabling Drug Discovery. *J. Med. Chem.* **2019**, *62*, 2256 – 2264. DOI: 10.1021/acs.jmedchem.8b01303.
- (l) Pitre, S. P.; Muuronen, M.; Fishman, D. A.; Overman, L. E. Tertiary Alcohols as Radical Precursors for the Introduction of Tertiary Substituents into Heteroarenes. *ACS Catal.* **2019**, *9*, 3413 – 3418. DOI: 10.1021/acscatal.9b00405.
- (2) (a) Yamada, Y.; Miljkovic, D.; Wehrli, P.; Golding, B.; Löfliger, P.; Keese, R.; Müller, K.; Eschenmoser, A. A New Type of Corrin Synthesis. *Angew. Chem. Int. Ed.* **1969**, *8*, 343 – 348. DOI: 10.1002/anie.196903431. (b) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. Sulfidkontraktion via Kupplung: Eine methode zur darstellung von β -dicarbonylderivaten. Über synthetische methoden, I. Mitteilung. *Helv. Chim. Acta.* **1971**, *54*, 710 – 734. DOI: 10.1002/hlca.19710540229.
- (3) (a) Lewis, S. N.; Miller, J. J.; Winstein, S. 1,2-Migrations in alkyl radicals. *J. Org. Chem.* **1972**, *37*, 1478 – 1485. DOI: 10.1021/jo00975a003. (b) Keck, G. E.; Byers, J. H. A new one-electron carbon-carbon bond-forming reaction: separation of the chain-propagation steps in free-radical allylation. *J. Org. Chem.* **1985**, *50*, 5442 – 5444. DOI: 10.1021/jo00225a107. (c) Barton, D. H. R.; Crich, D. Carboethoxyallylation using radical chemistry. *Tetrahedron Lett.* **1984**, *25*, 2787 – 2790. DOI: 10.1016/S0040-4039(01)81290-9. (d) Dang, H.-S.; Kim, K.-M.; Roberts, B. P. Radical-Chain Desulfurization of α -(Alkylthiomethyl)acrylates with Triphenylphosphine: a New Route to α -Alkylacrylates. *Tetrahedron Lett.* **1998**, *39*, 501 – 504. DOI: 10.1016/S0040-4039(97)10587-1. (e) Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. Tin-Free Generation of Alkyl Radicals from Alkyl 4-Pentynyl Sulfides via Homolytic Substitution at the Sulfur Atom. *Org. Lett.* **2008**, *10*, 1127 – 1130. DOI: 10.1021/ol800046k.
- (4) For an overview of xanthate radical alkylation chemistry, see: (a) Zard, S. Z.; Quiclet-Sire, B. Powerful carbon-carbon bond forming reactions based on a novel radical exchange process. *Chem. Eur. J.* **2006**, *12*, 6002–6016. DOI: 10.1002/chem.200600510. (b) Quiclet-Sire, B.; Zard, S. Z. The degenerative radical transfer of xanthates and related derivatives: An unusually powerful tool for the creation of carbon-carbon bonds. *Top. Curr. Chem.* **2006**, *264*, 201–236. DOI: 10.1007/128_029. (c) S. Z. Zard, in *Radicals in Organic Synthesis*, Vol 1, (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, New York, 2001, pp 90–106.
- (5) (a) Barton, D. H. R.; Crich, D.; Löffberding, A.; Zard, S. Z. On the mechanism of reduction of dithiocarbonates (xanthates) with tributylstannane. *J. Chem. Soc. Chem. Commun.* **1985**, 646–647. DOI: 10.1039/C39850000646. (b) Chatgililoglu, C. Organosilanes as radical-based reducing agents in synthesis. *Acc. Chem. Res.* **1992**, *25*, 188–194. DOI: 10.1021/ar00016a003. (c) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. On the Reduction of *S*-Alkyl-thionocarbonates (Xanthates) with Phosphorous Compounds. *Org. Lett.* **2003**, *10*, 1645–1648. DOI: 10.1021/ol0342610. (d) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. A practical method for the reductive cleavage of the sulfide bond in xanthates. *Tetrahedron. Lett.* **1996**, *37*, 5877–5880. DOI: 10.1016/0040-4039(96)0125301.
- (6) (a) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 2587 – 2693. DOI: 10.1021/cr400441lm. (b) Glass, R. S. Top Curr Chem (Z) (2018) 376:22. DOI: 10.1007/s41061-018-0197-0. (c) Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. Catalytic Olefin Hydroamination Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 13492–13495. DOI: 10.1021/jacs.5b09671. (d) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **2017**, *355*, 727–730. DOI: 10.1126/science.aal3010. (e) Protti, S.; Fagnoni, M.; Ravelli, D. Photocatalytic C-H Activation by Hydrogen-Atom Transfer in Synthesis. *Chem. Cat. Chem.* **2015**, *7*, 1516–1523. DOI: 10.1002/cctc.201500125. (f) Kawamoto, T.; Oritani, K.; Curran, D. P.; Kamimura, A. Thiol-Catalyzed Radical Decyanation of Aliphatic Nitriles with Sodium Borohydride. *Org. Lett.* **2018**, *20*, 2084–2087. DOI: 10.1021/acs.orglett.8b00626.
- (7) For a selection of recent, leading examples of thiols used as H-atom transfer reagents, see: (a) Margrey, K. A.; Nicewicz, D. A. A General Approach to Catalytic Alkene Anti-Markovnikov Hydrofunctionalization Reactions via Acridinium Photoredox Catalysis. *Acc. Chem. Res.* **2016**, *49*, 1997 – 2006. DOI: 10.1021/acs.accounts.6b00304. (b) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. Radical Transfer Hydroamination with Aminated Cyclohexadienes Using Polarity Reversal Catalysis: Scope and Limitations. *J. Am. Chem. Soc.* **2007**, *129*, 4498 – 4503. DOI: 10.1021/ja0692581. (c) Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. Catalytic Olefin Hydroamination Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 13492 – 13495. DOI: 10.1021/jacs.5b09671. (d) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic intermolecular hydroaminations of activated olefins with secondary alkyl amines. *Science* **2017**, *355*, 727 – 730. DOI: 10.1126/science.aal3010. (e) Protti, S.; Fagnoni, M.; Ravelli, D. Photocatalytic C-H Activation by Hydrogen-Atom Transfer in Synthesis. *Chem. Cat. Chem.* **2015**, *7*, 1516 – 1523. DOI: 10.1002/cctc.201500125. (f) Kawamoto, T.; Oritani, K.; Curran, D. P.; Kamimura, A. Thiol-Catalyzed Radical Decyanation of Aliphatic Nitriles with Sodium Borohydride. *Org. Lett.* **2018**, *20*, 2084 – 2087. DOI: 10.1021/acs.orglett.8b00626.
- (8) (a) Hoffman, F. W.; Ess, R. J.; Simmons, T. C.; Hanzel, R. S. The Desulfurization of Mercaptans with Trialkyl Phosphites. *J. Am. Chem. Soc.* **1956**, *78*, 6414 – 6414. DOI: 10.1021/ja01605a034. (b) Walling, C.; Rabinowitz, R. The Reaction of Thiyl Radicals with Trialkyl Phosphites. *J. Am. Chem. Soc.* **1957**, *79*, 5326 – 5326. DOI: 10.1021/ja01576a077. (c) Walling, C.; Rabinowitz, R. The Reaction of Trialkyl Phosphites with Thiyl and Alkoxy Radicals. *J. Am. Chem. Soc.* **1959**, *81*, 1243 – 1249. DOI: 10.1021/ja01514a057. (d) Walling, C.; Basedow, O. H.; Savas, E. S. Some Extensions of the Reactions of Trivalent Phosphorus Derivatives with Alkoxy and Thiyl Radicals; a New Synthesis of Thioesters. *J. Am. Chem. Soc.* **1960**, *82*, 2181 – 2184. DOI: 10.1021/ja01494a023. (e) Dang, H.-S.; Kim, K.-M.; Roberts, B. P. Radical-Chain Desulfurization of α -(Alkylthiomethyl)acrylates with Triphenylphosphine: a New Route to α -Alkylacrylates. *Tetrahedron Lett.* **1998**, *39*, 501 – 504. DOI: 10.1016/S0040-4039(97)10587-1.
- (9) Attempts of trapping the proposed C-radical intermediate formed from S-atom transfer with alkenes resulted in only trace amounts of alkylated products with styrene and methyl acrylate, see: Walling, C.; Pearson, M. S. Some Radical Reactions of Trivalent Phosphorus Derivatives with Mercaptans, Peroxides, and Olefins. A New Radical Cyclization. *J. Am. Chem. Soc.* **1964**, *86*, 2262 – 2266. DOI: 10.1021/ja01065a032.
- (10) (a) Wan, Q.; Danishefsky, S. J. Free-Radical-Based, Specific Desulfurization of Cysteine: A Powerful Advance in the Synthesis of Polypeptides and Glycopolypeptides. *Angew. Chem. Int. Ed.* **2007**, *46*, 9248 – 9252. DOI: 10.1002/anie.200704195. (b) Jin, K.; Li, T.; Chow, H. Y.; Liu, H.; Li, X. P-B Desulfurization: An Enabling Method for Protein Chemical Synthesis and Site-Specific Deuteration. *Angew. Chem. Int. Ed.* **2017**, *56*, 14607 – 14611. DOI: 10.1002/anie.201709097.
- (11) (a) González, A.; Valencia, G. Photochemical desulfurization of L-cysteine derivatives. *Tetrahedron Asymm.* **1998**, *9*, 2761 – 2764. DOI: 10.1016/S0957-4166(98)00295-X. (b) Cuesta, J.; Arsequell, G.; Valencia, G.; González, A. Photochemical desulfurization of thiols and disulfides. *Tetrahedron: Asymm.* **1999**, *10*, 2643 – 2646. DOI: 10.1016/S0957-4166(99)00265-7. (c) Arsequell, G.; González, A.; Valencia, G. Visible light promoted organic reaction on a solid support. *Tetrahedron Lett.* **2001**, *42*, 2685 – 2687. DOI: 10.1016/S0040-4039(01)00281-7. (d) Gao, X.-F.; Du, J.-J.; Liu, Z.; Guo, J. Visible-Light-Induced Specific Desulfurization of Cysteinyll Peptide and Glycopeptide in Aqueous Solution. *Org. Lett.* **2016**, *18*, 1166 – 1169. DOI: 10.1021/acs.orglett.6b00292. (e) Ge, J.-T.; Li, Y.-Y.; Tian, J.; Liao, R.-Z.; Dong, H. Synthesis of Deoxyglycosides by Desulfurization under

- UV Light. *J. Org. Chem.* **2017**, *82*, 7008 – 7014. DOI: 10.1021/acs.joc.7b00896. (f) Discekici, E. H.; Shankel, S. L.; Anastasaki, A.; Oschmann, B.; Lee, I.-H.; Niu, J.; McGrath, A. J.; Clark, P. G.; Laiter, D. S.; Read de Alaniz, J.; Hawker, C. J.; Lunn, D. J. Dual-pathway chain-end modification of RAFT polymers using visible light and metal-free conditions. *Chem. Comm.* **2017**, *53*, 1888 – 1891. DOI: 10.1039/C6CC08370F.
- (12) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spangnolo, P.; Strazzari, S.; Zanardi, G. A Novel Tin-Free Procedure for Alkyl Radical Reactions. *Angew. Chem. Int. Ed.* **2004**, *43*, 3598 – 3601. DOI: 10.1002/anie.200454245.
- (13) We similarly applied the *tert*-butyl isocyanide conditions reported by Minozzi and Nanni (see ref. 12) towards the reductive alkylation of *tert*-butyl ethylene using thiol **1** and obtained a 13% yield of the alkylation product. See Scheme S1 of the SI for additional details.
- (14) Zhang, L.; Si, X.; Yang, Y.; Witzel, S.; Sekine, K.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Reductive C-C Coupling by Desulfurizing Gold-Catalyzed Photoreactions. *ACS Catal.* **2019**, *9*, 6118–6123. DOI:10.1021/acscatal.9b01368.
- (15) For examples of thiols used to generate C-C bonds via addition of thiy radical to vinyl cyclopropanes, see: (a) Hashimoto, T.; Kawamata, Y.; Maruoka, K. An organic thiy radical catalyst for enantioselective cyclization. *Nature Chem.* **2014**, *6*, 702 – 705. DOI: 10.1038/nchem.1998. (b) Hashimoto, T.; Takino, K.; Hato, K.; Maruoka, K. A Bulky Thiy-Radical Catalyst for the [3+2] Cyclization of *N*-Tosyl Vinylaziridines and Alkenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 8081 – 8085. DOI: 10.1002/anie.201602723. (c) Ryss, J. M.; Turek, A. K.; Miller, S. J. Disulfide-Bridged Peptides That Mediate Enantioselective Cycloadditions through Thiy Radical Catalysis. *Org. Lett.* **2018**, *20*, 1621 – 1625. DOI: 10.1021/acs.orglett.8b000364.
- (16) Lardy, S. W.; Schmidt, V. A. Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination using *N*-Hydroxyphthalimide. *J. Am. Chem. Soc.* **2018**, *140*, 12318 – 12322. DOI: 10.1021/jacs.8b06881.
- (17) For recent examples of photoredox approaches to phosphorous oxidation to achieve deoxygenation, see: (a) Zhang, M.; Xie, J.; Zhu, C. A general deoxygenation approach for synthesis of ketones from aromatic carboxylic acids and alkenes. *Nature Commun.* **2018**, *9*, 3517. DOI: 10.1038/s41467-018-06019-1. (b) Stache, E. E.; Ertel, A. B.; Rovis, T.; Doyle, A. G. Generation of Phosphoranyl Radicals via Photoredox Catalysis Enables Voltage-Independent Activation of Strong C-O Bonds. *ACS Catal.* **2018**, *8*, 11134 – 11139. DOI: 10.1021/acscatal.8b03592. (c) Xia, P.-J.; Ye, Z.-P.; Hu, Y.-Z.; Song, D.; Xiang, H.-Y.; Chen, X.-Q.; Yang, H. Photocatalytic, Phosphoranyl Radical-Mediated N-O Cleavage of Strained Cycloketone Oximes. *Org. Lett.* **2019**, *21*, 2658 – 2662. DOI: 10.1021/acs.orglett.9b00651.
- (18) During the preparation of this manuscript a similar communication became available online: Qin, Q.; Wang, W.; Zhang, C.; Song, S.; Jiao, N. A metal-free desulfurizing radical reductive C-C coupling of thiols and alkenes. *Chem. Commun.* **2019**, Advance article. DOI: 10.1039/C9CC05378F.
- (19) For examples of metal-free, radical reductive alkene alkylations, see: (a) Povie, G.; Suravarapu, S. R.; Bircher, M. P.; Mojzes, M. M.; Rieder, S.; Renaud, P. Radical chain repair: The hydroalkylation of polysubstituted unactivated alkenes. *Sci. Adv.* **2018**, *4*, eaat6031. DOI: 10.1126/sciadv.aat6031. (b) Sumino, S.; Fusano, A.; Ryu, I. Reductive Bromine Atom-Transfer Reaction. *Org. Lett.* **2013**, *15*, 2826 – 2829. DOI: 10.1021/ol4011536. (c) Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P. Radical-chain reductive alkylation of electron-rich alkenes mediated by silanes in the presence of thiols as polarity-reversal catalysts. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061 – 2068. DOI: 10.1039/A9039611.
- (20) (a) Lu, X.; Xiao, B.; Zhang, Z.; Gong, T.; Su, W.; Yi, J.; Fu, Y.; Liu, L. Practical carbon-carbon bond formation from olefins through nickel-catalyzed reductive olefin hydrocarbonation. *Nature Comm.* **2016**, *7*, 11129. DOI: 10.1038/ncomms11129. (b) Wang, Z.; Yin, H.; Fu, G. C. Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins. *Nature* **2018**, *563*, 379 – 383. DOI: 10.1038/s41586-018-0669-y. (c) Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. Cobalt-Catalyzed Reductive Coupling of Saturated Alkyl Halides with Activated Alkenes. *J. Org. Chem.* **2006**, *71*, 655 – 658. DOI: 10.1021/jo052065w. (d) Schnermann, M. J.; Overman, L. E. A Concise Synthesis of (-)-Aplyviolenone Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem. Int. Ed.* **2012**, *51*, 9576 – 9580. DOI: 10.1002/anie.201204977. (e) Nakajima, M.; Lefebvre, Q.; Rueping, M. Visible light photoredox-catalysed intermolecular radical addition of α -halo amides to olefins. *Chem. Commun.* **2014**, *50*, 3619 – 3622. DOI: 10.1039/C4CC00753K. (f) Liu, X.; Xiao, B.; Liu, L.; Fu, Y. Formation of C(sp³)-C(sp³) Bonds through Nickel-Catalyzed Decarboxylative Olefin Hydroalkylation Reactions. *Chem. Eur. J.* **2016**, *22*, 11161 – 11164. DOI: 10.1002/chem.201602486. (g) Sumino, S.; Uno, M.; Fukuyama, T.; Ryu, I.; Matsuura, M.; Yamamoto, A.; Kishikawa, Y. *J. Org. Chem.* **2017**, *82*, 5469 – 5474. DOI: 10.1021/acs.joc.7b00609. (h) Ramirez, N. P.; Gonzalez-Gomez, J. C. Decarboxylative Giese-Type Reaction of Carboxylic Acids Promoted by Visible Light: A Sustainable and Photoredox-Neutral Protocol. *Eur. J. Org. Chem.* **2017**, *2017*, 2154 – 2163. DOI: 10.1002/ejoc.201601478. (i) Sun, S.-Z.; Börjesson, M.; Martin-Montero, R.; Martin, R. Site-Selective Ni-Catalyzed Reductive Coupling of α -Haloboranes with Unactivated Olefins. *J. Am. Chem. Soc.* **2018**, *140*, 12765 – 12769. DOI: 10.1021/jacs.8b09425. (j) Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. Hydroalkylation of Olefins to Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709 – 7714. DOI: 10.1021/jacs.9b02844.
- (21) Selected as a model thiol substrate due to its ease of preparation and handling because it is a solid at room temperature.
- (22) See the SI for an extended optimization table.
- (23) (a) Posner, T. Beiträge zur Kenntniss der ungesättigten Verbindungen. II. Ueber die Addition von Mercaptanen an ungesättigte Kohlenwasserstoffe. *Ber.* **1905**, *38*, 646 – 657. DOI: 10.1002/cber.190503801106. (b) Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. Thiol-click chemistry: a multifaceted toolbox for small molecule and polymer synthesis. *Chem. Soc. Rev.* **2010**, *39*, 1355 – 1387. DOI: 10.1039/B901979K.
- (24) Scott, C. Notes – Oxidation of Trialkyl Phosphites by Epoxides. *J. Org. Chem.* **1957**, *22*, 1118 – 1119. DOI: 10.1021/jo01260a613.
- (25) This effect is in-line with the usage of aryl phenols as radical inhibitors, see: Lloyd, W. G.; Lange, C. E. Antioxidant Inhibition by Phenol. *J. Am. Chem. Soc.* **1964**, *86*, 1491 – 1494. DOI: 10.1021/ja01062a007.
- (26) Newcomb, M. Radicals in Organic Synthesis; Wiley-VCH Verlag GmbH: Weinheim, Germany, **2001**; pp 327 – 329.
- (27) (a) Tronche, C.; Martinez, F. N.; Horner, John, H.; Newcomb, M.; Senn, M.; Giese, B. Polar substituent and solvent effects on the kinetics of radical reactions with thiols. *Tetrahedron Lett.* **1996**, *37*, 5845 – 5848. DOI: 10.1016/0040-4039(96)01241-5. (b) Huston, P.; Espenson, J. H.; Bakac, A. Kinetics of formation and reactions of thiy radicals in aqueous solution. *Inorg. Chem.* **1992**, *31*, 720 – 722. DOI: 10.1021/ic00031a003.
- (28) The methyl ester of gibberellic acid was used due to the insolubility of gibberellic acid in benzene solvent.
- (29) Y.-R. Luo, Handbook of Bond Dissociation Energies in Organic Compounds, CRC Press: Boca Raton, **2003**.
- (30) This manuscript appears as a pre-print in *ChemRxiv* DOI: 10.26434/chemrxiv.9682685.v1.