JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Twofold Radical-Based Synthesis of *N,C*-Difunctionalized Bicyclo[1.1.1]pentanes

Helena D. Pickford, Jeremy Nugent, Benjamin Owen, James. J. Mousseau, Russell C. Smith, and Edward A. Anderson*

Cite This: *J. Am. Chem. Soc.* 2021, 143, 9729–9736
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Bicyclo[1.1.1]pentylamines (BCPAs) are of growing importance to the pharmaceutical industry as sp^3-rich bioisosteres of anilines and *N*-*tert*-butyl groups. Here we report a facile synthesis of 1,3-disubstituted BCPAs using a twofold radical functionalization strategy. Sulfonamidyl radicals, generated through fragmentation of α-iodoaziridines, undergo initial addition to [1.1.1]propellane to afford iodo-BCPAs; the newly formed C−I bond in these products is then functionalized via a silyl-mediated Giese reaction. This chemistry also translates smoothly to 1,3-disubstituted iodo-BCPs. A wide variety of radical acceptors and iodo-BCPAs are accommodated, providing straightforward access to an array of valuable aniline-like isosteres.

Bicyclo[1.1.1]pentanes (BCPs) are of significant interest to the pharmaceutical, agrochemical, and materials industries as sp^3-rich surrogates for 1,4-disubstituted arenes, *tert*-butyl groups, and alkynes.[1−9] Bicyclo[1.1.1]pentylamines (BCPAs) are similarly attractive due to their potential use as nontoxic bioisosteres for aniline and *N*-*tert*-butyl motifs in drug candidates. BCPAs have been shown to improve properties such as metabolic tolerance and bioactivity (Figure 1a),[10,11] and they are featured as desirable derivatives in numerous patents.[12−16]

Early approaches to BCPAs involved multistep routes using preformed BCP building blocks (derived from [1.1.1]-propellane **1**, Figure 1b), such as acyl nitrene rearrangements[17−20] or reduction of BCP azides or hydrazines.[21,22] More recently, methods have been developed that prepare BCPAs directly from **1** by reaction with amide anions,[23−25] which can also provide access to *N*,*C*-disubstituted BCPAs (Figure 1b, path a). However, these processes can require elevated temperatures, restricting functional group tolerance. The amination of BCP radicals formed by addition of *C*-centered radicals to **1** (generated under Fe(II)[26] or metallaphotoredox[27] catalysis) offers alternative solutions (paths b, c). In marked contrast to the addition of *C*-centered radicals to **1**, reactions with *N*-centered radicals are underexplored as an entry to BCPAs. Following the seminal work of Wiberg on the reaction of **1** with nitric oxide,[28] this area lay dormant until the elegant demonstration by Leonori et al. of a three component construction of 1,3-disubstituted BCPAs via photoredox decarboxylative generation of amidyl radicals (path d).[29] However, even this chemistry is restricted to the installation of halogen or sulfur substituents at the 3-position of the BCPA. Very recently, an amidopyridylation of [1.1.1]propellane has been described by Hong and co-workers.[30]

In previous work we described the efficient synthesis of iodo-BCPs by atom transfer radical addition (ATRA) of alkyl and (hetero)aryl iodides to the C1−C3 bond of **1**[31,32] and questioned whether this approach could be applied to the

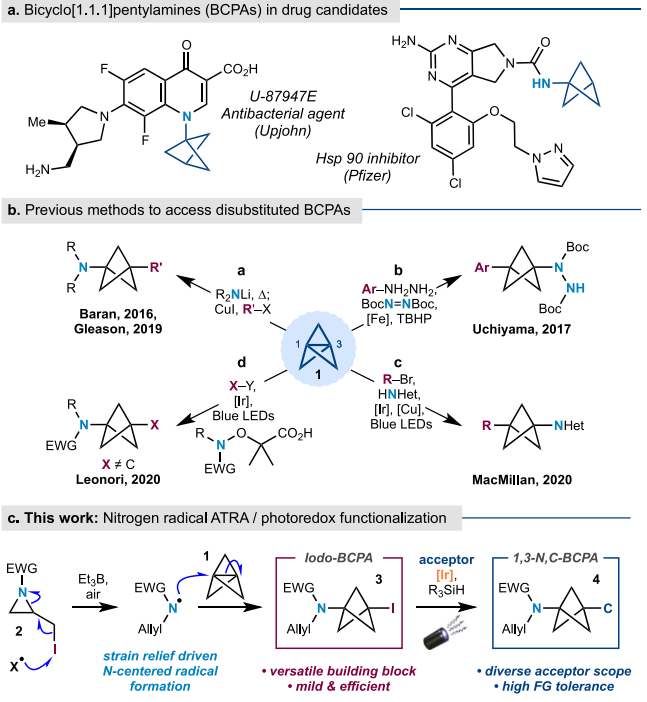


Figure 1. (a) Bicyclopentyl[1.1.1]amines (BCPAs) in pharmaceuticals. (b) Methods to access BCPAs. (c) Fragmentation/*N*-centered radical ATRA and photocatalyzed functionalization of iodo-BCPAs.

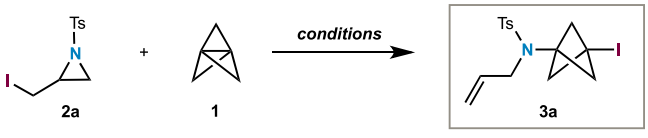
Received: April 21, 2021
Published: June 23, 2021

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729−9736

synthesis of BCPAs. We recognized that *N*-centered radicals can be conveniently accessed by fragmentation of α-iodoaziridines (**2**, Figure 1c)[33,34] and hypothesized that **1** could serve as a suitable radical acceptor, with the resulting BCP radical then abstracting an iodine atom from the α-iodoaziridine starting material. The C−I bond resident in the iodo-BCPA product **3** would then provide a handle for further functionalization, potentially via reformation of a BCP radical. Here we report the realization of this α-iodoaziridine fragmentation/ATRA to form iodo-BCPAs and the application of these products in photoredox-catalyzed Giese-type processes[35,36] to access *C*-substituted BCPAs **4**.[37]

α-Iodoaziridine **2a** was selected for reaction optimization (Table 1). Based on the studies of Taguchi[33,34] and our

Table 1. Optimization of α-Iodoaziridine Fragmentation/*N*-Centered Radical Addition to 1



Entry	Conditions[a]	1[b] (equiv)	Cosolvent[c]	Temp (°C)	Yield (%)[d]	3a:3a-S[e]
1	A	2.0		20	67	6:1
2	A	2.0		0	63	11:1
3	A	1.3		20	71	17:1
4	**A**	**1.3**	**CH_2Cl_2**	**20**	72 (75)[f]	>20:1
5	A	1.3	CH_2Cl_2[g]	20	64	>20:1
6	A	1.0[h]	CH_2Cl_2	20	65	>20:1
7	**A**	**1.1**	**CH_2Cl_2**	**20**	**67**	>20:1
8	B	1.3	*t*-BuCN	30	31	20:1
9	B	2.0	*t*-BuCN	30	57	14:1

[a]Conditions A: Et_3B (10 mol %), air, 5 h. Conditions B: *fac*-Ir(ppy)$_3$ (2.5 mol %), blue LEDs (18 W), N_2, 18 h. [b]**1** was used as a 0.6−0.8 M solution in Et_2O unless indicated otherwise. [c]**2a** was prepared as a 1.0 M solution in the cosolvent, where used. [d]NMR yield, determined using mesitylene as internal standard. [e]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [f]Yield in parentheses is the isolated yield, including <5% **3a-S** and **3a-H** impurities. [g]**1** was prepared as a 1.06 M solution in CH_2Cl_2. [h]1.5 equiv of **2a**.

experience with the addition of *C*-centered radicals to **1**,[31,32] triethylborane was first tested as an initiator. Pleasingly, the desired C−N σ bond fragmentation/ATRA proceeded efficiently using 2.0 equiv of **1**, giving iodo-BCP sulfonamide **3a** in 67% yield (entry 1); small amounts of staffane **3a-S**, H-atom abstraction product **3a-H**, and *N*-allylsulfonamide **5a** were also observed. The proportion of staffane (6:1) could be significantly reduced by lowering the reaction temperature (11:1, entry 2) or the equivalents of **1** (17:1, entry 3). Suspecting that **3a-H** and **5a** might arise from H-atom abstraction from the solvent, use of CH_2Cl_2 as cosolvent was tested and indeed reduced the levels of these byproducts (entry 4), giving a 75% yield of **3a** with <5% of **3a-S** and **3a-H**. A solution of **1** in CH_2Cl_2 was prepared; however, no further benefit in yield was observed (entry 5). Employing **1** as the limiting reagent proved equally effective (entry 6). Pleasingly, the reaction could also be performed on multigram scale with near-equivalent efficiency using just 1.1 equiv of **1** (entry 7, 6.50 mmol (2.19 g) of **2a**, 67%). Comparable yields were achieved under photoredox catalysis,[38] with *fac*-Ir(ppy)$_3$ performing the best;[39] however, a higher loading of **1** was required (entries 8−9).

Under the optimized conditions, iodo-BCPA synthesis was found to be applicable to a wide range of α-iodoaziridines (Figure 2). Aryl sulfonamide aziridines bearing electron-donating (**3a−c**, 61%−75%), electron-neutral (**3d**, 75%), and electron-withdrawing (**3e−i**, 55−73%) substituents all gave high yields of the desired products, although aryl nitro-sulfonamides were less successful (**3j** and **3k**,10−36%). Notably, an aryl ketone (**3f**) was also tolerated, which would likely not be possible under anionic conditions for amide additions to **1**. Aziridines featuring heterocyclic sulfonamides including thiophenes (**3l−m**), oxazole (**3n**), pyrazole (**3o**), benzothiophene (**3p**), and imidazothiazole (**3q**) all reacted smoothly, affording the corresponding BCPA products in good to excellent yields (52−81%).

Alkyl sulfonamide (**3r−t**, 37−66%) and sulfamide substituted aziridines (**3u−3v**, 21−61%) were also accommodated.[40]

We next investigated substitution of the α-iodoaziridine backbone. Pleasingly, aziridines featuring substituents at the 1-, 2-, and 3-positions were tolerated, including fused cyclopentane and cyclohexane aziridines (**3w−aa**, 30−73%), although reaction of a trisubstituted aziridine was low yielding (**3ab**, 4%). Finally, the potential of this chemistry to operate in settings relevant to medicinal chemistry research was demonstrated via iodobicyclopentylation of the nonsteroidal anti-inflammatory drug celecoxib (**3ac**, 70%).

The C−I bond in the iodo-BCPA product is an attractive handle for C−C bond formation. However, attempted lithiation/electrophilic trapping of iodo-BCPA **3a** was unsuccessful due to ejection of the sulfonamide anion, presumably accompanied by reformation of **1**.[39] Precedent for radical-based BCP bridgehead C−C bond formation in *N*,*C*-BCPs is limited: to date only a handful of azide or triazole *N*-substituents have been studied, with reliance on organotin reagents[22] or the radical acceptor as reaction solvent.[41] We questioned whether photoredox catalysis could offer a solution to this challenge, where the bridgehead C−I bond could be functionalized through Giese-type reactions.[35,36] Previous studies have demonstrated the use of silane and silanol mediators[42] to generate radicals from simple alkyl[43−47] and aryl[48] halides under photoredox catalysis; however, use on the BCP scaffold is unprecedented.

Iodo-BCPA **3a** was selected for reaction optimization (Table 2), with allyl sulfone **6a** as an acceptor (Table 2). Initial attempts using Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ with (Me$_3$Si)$_3$SiH(TTMSS) as a radical mediator delivered addition product **4a** in 16% yield, along with a significant amount of the deiodination product **3a-H** (entry 1).[49] This competing H-atom abstraction by the presumed BCPA radical intermediate could be avoided by using (Me$_3$Si)$_3$SiOH, which acts as a silyl radical source via silanolate oxidation/radical-Brook rearrangement.[48,50] This led to a significant improvement in yield (38%, entry 2), which was further enhanced to 60% using CH_2Cl_2 as solvent, likely due to improved solubility of **6a** (entry 3). Variation of the photocatalyst led to decreased yields of **4a**, although the organocatalyst 4-CzIPN was also well-suited to

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729−9736

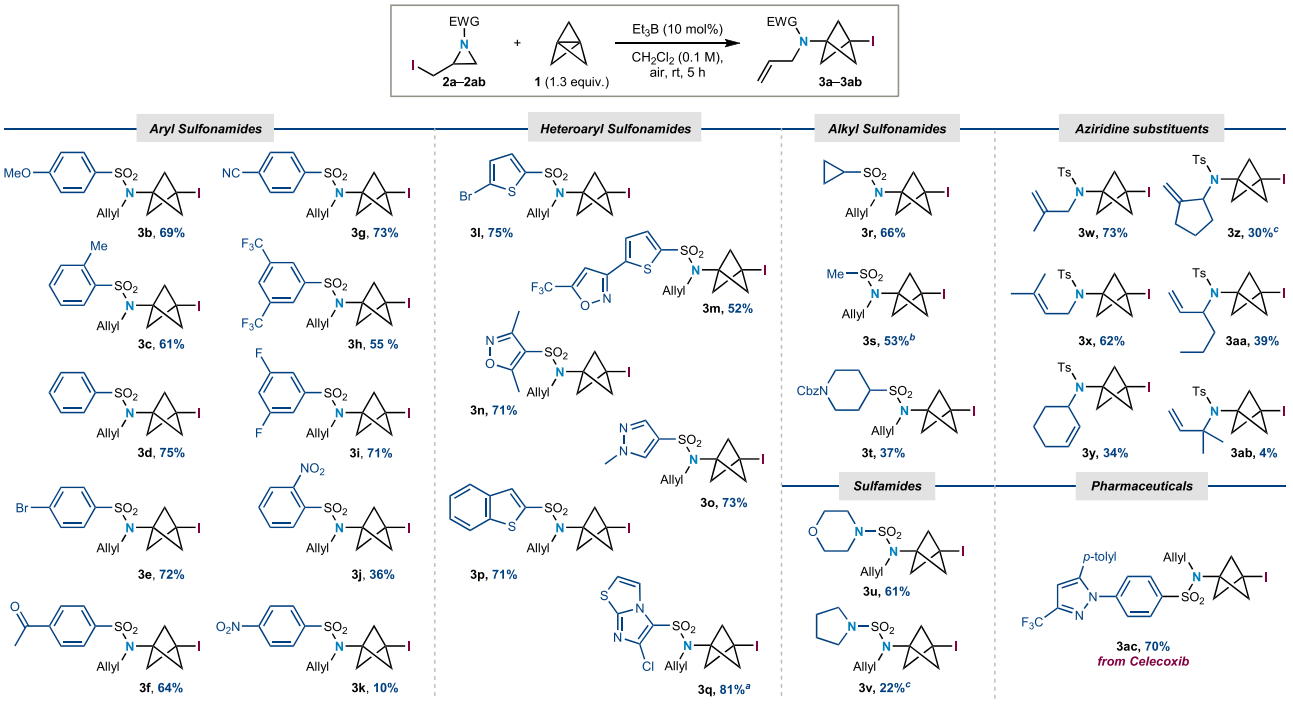
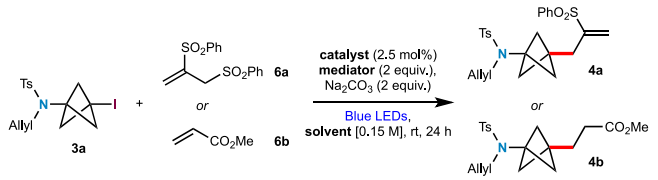


Figure 2. Scope of α-iodoaziridine fragmentation/ATRA with **1**. Reactions conducted on 0.15 mmol scale, yields are isolated yields. [a]Isolated as an inseparable 7:1 mixture with the corresponding staffane **3q–S**; yield of **3q**. [b]1.6 equiv of **1**. [c]0.09 mmol scale.

Table 2. Giese Reaction Optimization



Entry	Catalyst	**6** (equiv)	Mediator	Solvent	Yield (%)[a]
1	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6a** (3)	$(Me_3Si)_3SiH$	MeOH	16
2	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6a** (3)	$(Me_3Si)_3SiOH$	MeOH	38
3	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6a** (3)	$(Me_3Si)_3SiOH$	CH_2Cl_2	60[b]
4	4-CzIPN[c]	**6a** (3)	$(Me_3Si)_3SiOH$	CH_2Cl_2	56
5	$Ru(bpz)_3(PF_6)_2$	**6a** (3)	$(Me_3Si)_3SiOH$	CH_2Cl_2	6
6	$Ir[(dF(F)ppy)_2(dCF_3bpy)]PF_6$	**6a** (3)	$(Me_3Si)_3SiOH$	CH_2Cl_2	41
7	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6b** (3)	$(Me_3Si)_3SiOH$	CH_2Cl_2	3
8	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6b** (6)	$(Me_3Si)_3SiOH$	CH_2Cl_2	9
9	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6b** (6)	$(Me_3Si)_3SiH$	CH_2Cl_2	48
10	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6b** (6)	$(Me_3Si)_3SiH$	$MeOH/H_2O$[d]	60[b]
11	$Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**6b** (3)	$(Me_3Si)_3SiH$	$MeOH/H_2O$[d]	44

[a]NMR yield, determined using mesitylene as internal standard. [b]Isolated yield. [c]5 mol % catalyst. [d]$MeOH/H_2O$ (9:1).

this chemistry (entries 4–6). To our surprise, use of methyl acrylate (**6b**) as a radical acceptor under these conditions resulted in poor yields of product **4b**, even with increased acceptor loading (3–9%, entry 7–8). Use of TTMSS restored productive reactivity (48%, entry 9), and changing the reaction solvent to $MeOH/H_2O$ (9:1) (entry 10) delivered an optimum yield of **6b** of 60%.

With two sets of reaction conditions in hand (Conditions—Table 2, entry 3; Conditions B—Table 2, entry 10), the Giese methodology was applied to a wide range of radical acceptors (Figure 3). Under Conditions A, various 2-substituted allylic sulfones delivered the corresponding allyl-BCPA products **4a**, **4c**, and **4d** (29–60%). Reaction of a benzothiazole sulfone delivered the heteroarylated BCPA **4e** in modest yield, while sulfurization with *N*-(phenylthio)phthalimide also proved possible (**4f**, 32%). Variation of the sulfonamide group was also well tolerated (**4g** and **4h**, 50–53%), the former of which demonstrates functionalization of the anti-inflammatory agent Celecoxib. Encouraged by these results, we further tested the methodology on *C*-substituted iodo-BCPs; to our delight, these readily accessible substrates,[31,32] featuring ester, piperidine, and pyridine functionalities, reacted well with allyl sulfone **6a** to give **4i–k** in 40–59% yield.

Conditions B proved suitable for acrylonitrile, acrylate, and acrylamide type acceptors (**4b**, **4l–4o**, 42–60%); reaction on a 1.0 mmol scale proceeded with similar efficiency, giving a yield

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729–9736

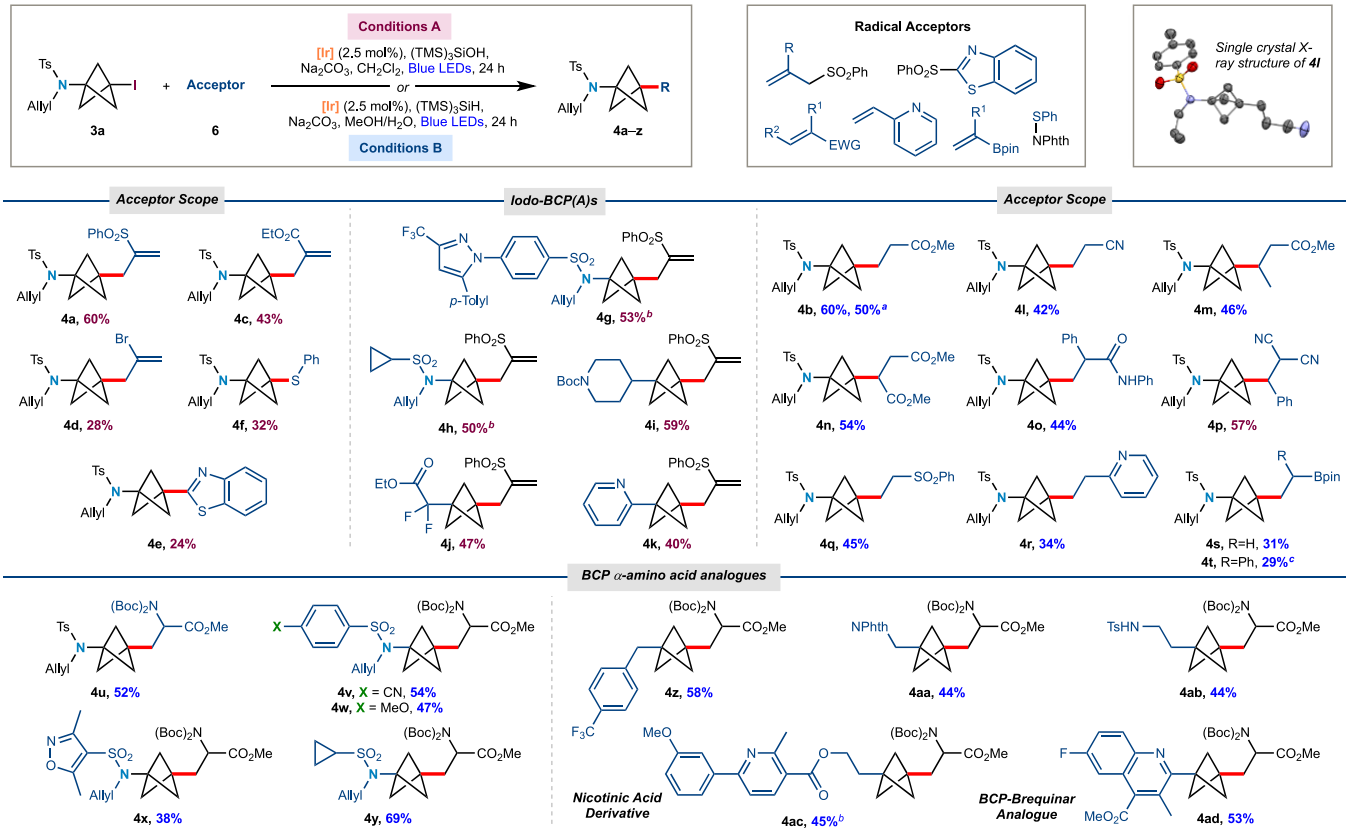


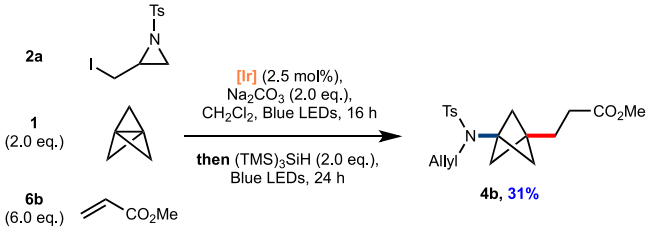
Figure 3. Scope of iodo-BCPA functionalization; reactions conducted on 0.15 mmol scale with Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (2.5 mol %). Red yields indicate Conditions A; blue yields indicate Conditions B. [a]1.00 mmol scale. [b]0.13 mmol scale. **4l** was determined by single crystal X-ray diffraction.[51] [c]The crude boronic ester was directly oxidized with H_2O_2/NaOH (aq); the yield refers to the isolation of the corresponding alcohol.

of 50% of **4b**. Somewhat surprisingly, the use of 2-benzylidene malononitrile proceeded poorly under these conditions but delivered **4p** in 57% yield using Conditions A. Variation of the electron-withdrawing group to a vinyl sulfone (**4q**) and even a vinylpyridine (**4r**) or vinylboronic esters (**4s**–**4t**) was also successful. In the latter cases, the boronic esters proved challenging to purify, and for **4t** an oxidative workup instead directly provided the corresponding alcohol.

The photocatalytic iodo-BCPA functionalization also offers a powerful strategy for the mild generation of previously unobtainable, pharmaceutically relevant BCPA α-amino acid derivatives. This was demonstrated through the reaction of dehydroalanine with a range of iodo-BCPAs (under Conditions B) to give BCPA analogues of 4-amino phenylalanine (**4u**–**4y**, 38–69%). Once again, we were pleased to find that this chemistry translated well to *C*-substituted iodo-BCPs. This two-step approach thus provided access to diverse BCP phenylalanine derivatives **4z**–**4ad** (44–58%), including nicotinic acid derivative **4ac** (45%) and BCP-Brequinar analogue **4ad** (53%). Collectively, these examples illustrate the excellent functional group tolerance of this Giese chemistry, which should render it of significant utility in drug discovery programs.

With both the iodoaziridine fragmentation/ATRA and Giese addition established, we questioned whether the two processes might take place in a single reaction, such that the intermediate BCPA radical is captured directly by the radical acceptor or that the intermediate iodo-BCPA undergoes an *in situ* Giese reaction. Attempts to realize a one-pot cascade resulted only in formation of *N*-allyl sulfonamide **4a**, where direct HAT from the silane to the *N*-centered radical outcompeted addition to [1.1.1]propellane **1** (Scheme 1). However, by delaying

Scheme 1. One-Pot Synthesis of *C,N*-Difunctionalized BCP 4b



addition of the silane until complete consumption of the iodoaziridine **2a** (16 h, [Ir] catalysis), the entire ATRA/Giese process could be performed without isolation of the intermediate iodo-BCPA. The overall yield for this transformation (31%, 55% per step) is consistent with that for the isolated steps (57%, 60%).

The distinct nature of the two silanes used in these Giese functionalizations may suggest that different mechanisms operate in the two cases. Previous studies[42−44,48] have suggested that reaction with either mediator requires initial formation of a silyl radical. In the case of (Me$_3$Si)$_3$SiOH (Figure 4a, Conditions A), this can be achieved by oxidation of the silanolate ion (generated on deprotonation of the silanol under basic conditions) by the redox-active excited triplet state of the iridium catalyst (E^{red} Ir(III)*/Ir(II) = +1.21 V vs SCE in MeCN),[52,53] followed by radical Brook rearrangement.[54] The

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729−9736

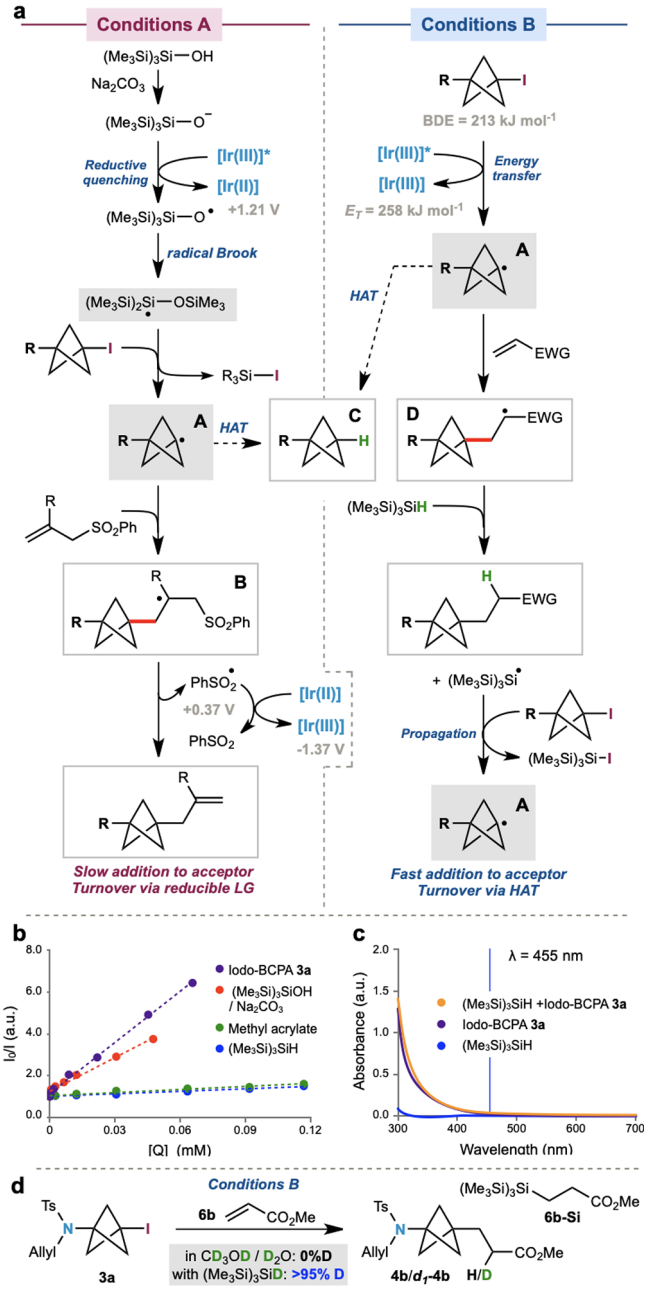


Figure 4. (a) Possible mechanisms of Giese reaction of iodo-BCPAs. (b) Stern–Volmer quenching study using **3a**, $(Me_3Si)_3SiH$, $(Me_3Si)_3SiOH$, and methyl acrylate. (c) UV/visible spectra of **3a**, $(Me_3Si)_3SiH$, and $(Me_3Si)_3SiH$ + **3a**. (d) Deuterium labeling study.

resulting silyl radical then abstracts an iodine atom from the iodo-BCP(A) to give the BCP(A) radical **A**, which then undergoes addition to the radical acceptor. For acceptors such as allyl sulfones (Conditions A, radical **B**), this addition is presumably sufficiently slow that H atom transfer to **A** can compete when using $(Me_3Si)_3SiH$ as mediator (to give **C**), rationalizing the need for $(Me_3Si)_3SiOH$. Catalyst turnover is then achieved via reduction of the sulfinyl radical to the sulfinate ion (E^{red} $PhSO_2^{\bullet}/PhSO_2^{-}$ = +0.37 V vs SCE;[55] E^{ox} Ir(II)/Ir(III) = +1.37 V vs SCE in MeCN).[52]

For Conditions B ($(Me_3Si)_3SiH$ mediator), it has been proposed that $(Me_3Si)_3Si\bullet$ can be generated by direct oxidation of the silane ([E^{ox} $(Me_3Si)_3SiH/(Me_3Si)_3SiH^{\bullet+}$ = +0.73 V vs SCE in MeCN),[56] followed by deprotonation. To explore this possibility, a Stern–Volmer quenching study was carried out (Figure 4b). To our surprise, this revealed that $(Me_3Si)_3SiH$ is a poor quencher of the excited state photocatalyst (blue line), but iodo-BCPA **3a** is an efficient quencher (purple line). In contrast, $(Me_3Si)_3SiOH$ (in the presence of Na_2CO_3 to mimic basic reaction conditions) *is* able to quench the catalyst excited state (red line), which offers support that Conditions A can proceed according to the proposed mechanism.

Voltammetry experiments[39] revealed that the first (irreversible) reduction of **3a** occurs at −2.29 V, which is in excess of the reducing power of most common photocatalysts and renders an oxidative quenching pathway unlikely. We further considered that visible light might effect homolysis of the C–I bond; however, UV/visible spectroscopy (Figure 4c) revealed no absorption at 455 nm (blue LEDs). Control experiments (see the SI) further demonstrated that all reaction components were essential for the success of the reaction and that no addition occurred in the absence of the silane. We therefore suggest that the efficient quenching of the photocatalyst excited state by iodo-BCPA may be due to Dexter energy transfer.[57,58] The energy of the T_1 triplet state of Ir[(dF-(CF_3)ppy$)_2$(dtbbpy)]PF_6 is 258 kJ mol^{-1};[52] given the bond dissociation energy of C–I bonds is in the region of ∼213 kJ mol^{-1}, homolysis of the C–I bond by this mechanism appears feasible. The resulting BCP radical **A** can then undergo addition to the acceptor to give the EWG-stabilized radical **D** (or competing HAT to generate **C**). Radical **D** then undergoes H atom transfer with $(Me_3Si)_3SiH$ to generate the Giese product, along with $(Me_3Si)_3Si\bullet$, which propagates the reaction by I atom abstraction from the iodo-BCPA. Deuteration studies were carried out to gain support for this reaction pathway or whether a possible reduction by Ir(II) operates (E^{red} $^{\bullet}CH(CH_3)CO_2Et/^{-}CH(CH_3)CO_2Et$ = +0.66 V vs SCE in MeCN) as in Conditions A (Figure 4d).[59] In contrast to findings by ElMarrouni et al.,[45] no product deuteration was observed on conducting the reaction in CD_3OD/D_2O, suggesting SET from Ir(II) is not operative. However, use of $(Me_3Si)_3SiD$ led to complete deuteration at the α-position (>95%), which strongly supports the proposed propagation pathway. The observation of the silane adduct of methyl acrylate (**6b-Si**) further supports the intermediacy of the silyl radical.

With methods to access diverse 1,3-disubstituted BCPAs established, we briefly investigated a selection of further transformations (Figure 5). Principal among these was the ability to cleave either the allyl or sulfonyl substituent from the nitrogen atom. The former was achieved on BCPA **3a** under

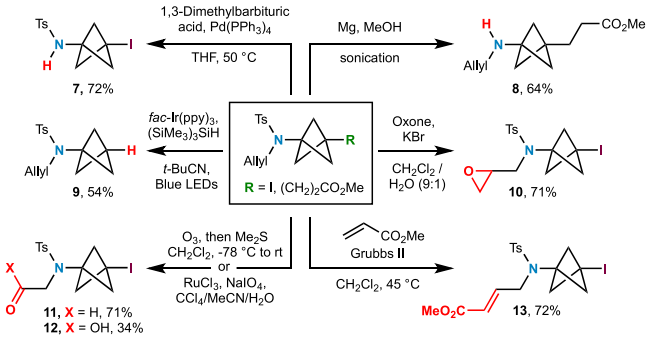


Figure 5. Further transformations.

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729–9736

mild conditions using $Pd(PPh_3)_4$ and 1,3-dimethylbarbituric acid (**7**, 72%),[60] while smooth detosylation was effected on **4b** via sonication with Mg/MeOH, which gave amine **8** in 64% yield. Simple deiodination of **3a** was carried out under photoredox conditions (**9**, 54%), while the *N*-allyl group could be oxidized to epoxide **10** (oxone/KBr, 71%),[61] aldehyde **11** (O_3, 71%), or BCP glycine analogue **12** ($RuCl_3/NaIO_4$, 34%). Finally, cross metathesis with methyl acrylate gave **13** (Grubbs II, 72%).

In summary, this twofold radical functionalization of [1.1.1]propellane offers a versatile and convenient route to prepare 1,3-*N*,*C*-disubstituted BCPs, opening up a new route to valuable aniline isosteres. The chemistry displays high functional group tolerance, affording products that are unobtainable by previous methods. The application of this chemistry to amino acid and drug analogues highlights the potential utility of this methodology for the pharmaceutical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04180.

Experimental details and copies of both ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2078089 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Edward A. Anderson − *Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, United Kingdom;* orcid.org/0000-0002-4149-0494; Email: edward.anderson@chem.ox.ac.uk

Authors

Helena D. Pickford − *Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, United Kingdom*

Jeremy Nugent − *Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, United Kingdom*

Benjamin Owen − *Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, United Kingdom*

James. J. Mousseau − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Russell C. Smith − *Janssen PRD, San Diego, California 92121, United States;* Present Address: (R.C.S.) Abbvie, Drug Discovery Science & Technology (DDST) Dept. R467, AP10-208, 1 North Waukegan Road, North Chicago, IL 60064.

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c04180

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

H.D.P. thanks the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine for a studentship (EP/L015838/1) generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Jannsen, Novartis, Pfizer, Syngenta, Takeda, UCB, and Vertex. J.N. thanks the Marie Skłodowska-Curie actions for an Individual Fellowship (GA No 786683). E.A.A. thanks the EPSRC for support (EP/S013172/1). We thank the reviewers for useful insight concerning the mechanisms of the Giese reactions.

■ REFERENCES

(1) For recent reviews of BCP synthesis and previous references, see: Ma, X.; Nhat Pham, L. Selected Topics in the Syntheses of Bicyclo[1.1.1]Pentane (BCP) Analogues. *Asian J. Org. Chem.* **2020**, *9*, 8−22.

(2) Kanazawa, J.; Uchiyama, M. Recent advances in the synthetic chemistry of bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1−11.

(3) For a review, see: Mykhailiuk, P. K. Saturated Bioisosteres of Benzene: Where to go Next? *Org. Biomol. Chem.* **2019**, *17*, 2839−2849.

(4) Locke, G. M.; Bernhard, S. S. R.; Senge, M. O. Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. *Chem. - Eur. J.* **2019**, *25*, 4590−4647.

(5) Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J. Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **2012**, *55*, 3414−3424.

(6) Measom, N. D.; Down, K. D.; Hirst, D. J.; Jamieson, C.; Manas, E. S.; Patel, V. K.; Somers, D. O. Investigation of a bicyclo[1.1.1]-pentane as a phenyl replacement within an LpPLA2 inhibitor. *ACS Med. Chem. Lett.* **2017**, *8*, 43−48.

(7) Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; La Vecchia, L.; Briard, E. Improving Nonspecific Binding and Solubility: Bicycloalkyl Groups and Cubanes as *para*-Phenyl Bioisosteres. *ChemMedChem* **2017**, *12*, 590−598.

(8) Westphal, M. V.; Wolfstädter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. Evaluation of *tert*-butyl isosteres: Case studies of physicochemical and pharmacokinetic properties, efficacies, and activities. *ChemMedChem* **2015**, *10*, 461−469.

(9) For related cross-coupling of small-ring bridgehead organozincs, see: Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of bicyclo[1.1.1]pentane bioisosteres of internal alkynes and *para*-disubstituted benzenes from [1.1.1]propellane. *Angew. Chem., Int. Ed.* **2017**, *56*, 12774−12777.

(10) Barbachyn, M. R.; Hutchinson, D. K.; Toops, D. S.; Reid, R. J.; Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W. U-87947E, A Potent Quinolone Antibacterial Agent Incorporating a Bicyclo[1.1.1]pent-1-yl (BCP) subunit. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 671−676.

(11) Bennett, M. J.; Zehnder, L. R.; Ninkovic, S.; Kung, P.-P.; Meng, J. J.; Huang, B. 2-Amino-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine Derivatives as HSP-90 Inhibitors and their Preparation, Pharmaceutical Compositions and use in the Treatment of Cancer. WO 2008096218 A1, 2008.

(12) Rogers, M.; Kirby, R.; Shomi, G.; Matsuo, T.; Kobayashi, S.; Kanazawa, J.; Yamaoka, N.; Torizuka, M.; Suzawa, K. Heterocyclic Sulfonamide Derivates and Pharmaceutical Uses Thereof. WO 2020008206 A1, 2020.

(13) Bunker, K. D.; Chuangxing, G.; Grier, M. C.; Hopkins, C. D.; Pinchman, J. R.; Slee, D. H.; Qinhua, H.; Mehmet, K. Bicyclic Compounds. US 20160075654 A1, 2016.
(14) Bartels, B.; Cook, X. A. F.; Ratni, H.; Reutlinger, M.; Vifian, W. Pyrimidine Derivatives. WO 2019101984 A1, 2018.
(15) Bartels, B.; Cook, X. A. F.; Ratni, H.; Reutlinger, M.; Vifian, W. Triazolo-Azepine Derivatives. WO 2019121434 A1, 2018.
(16) Kung, P.; Meng, J. J., 2-Amino Pyrimidine Compounds as Potent HSP-90 Inhibitors. WO 2010018481 A1, 2009.
(17) Applequist, D. E.; Renken, T. L.; Wheeler, J. W. Polar substituent effects in 1,3-disubstituted bicyclo[1.1.1]pentanes. *J. Org. Chem.* **1982**, *47*, 4985−4995.
(18) Della, E. W.; Kasum, B.; Kirkbride, K. P. Properties of bridgehead-substituted polycycloalkanes. Synthesis and NMR analysis of nitrogen-15-labeled 1-aminobicycloalkanes and their hydrochlorides. *J. Am. Chem. Soc.* **1987**, *109*, 2746−2749.
(19) Hossain, M. T.; Timberlake, J. W. Synthesis of Bisbicyclo[1.1.1]pentyldiazene. The Smallest Bridgehead Diazene. *J. Org. Chem.* **2001**, *66*, 6282−6285.
(20) Pätzel, M.; Sanktjohanser, M.; Doss, A.; Henklein, P.; Szeimies, G. 3-Aminobicyclo[1.1.1]pentane-1-carboxylic Acid Derivatives: Synthesis and Incorporation into Peptides. *Eur. J. Org. Chem.* **2004**, *2004*, 493−498.
(21) Bunker, K. D.; Sach, N. W.; Huang, Q.; Richardson, P. F. Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction. *Org. Lett.* **2011**, *13*, 4746−4748.
(22) Goh, Y. L.; Tam, E. K. W.; Bernardo, P. H.; Cheong, C. B.; Johannes, C. W.; William, A. D.; Adsool, V. A. A New Route to Bicyclo[1.1.1]pentan-1-amine from 1-Azido-3-iodobicyclo[1.1.1]-pentane. *Org. Lett.* **2014**, *16*, 1884−1887.
(23) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-release amination. *Science* **2016**, *351*, 241−246.
(24) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C. M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209−3226.
(25) Hughes, J. M. E.; Scarlata, D. A.; Chen, A. C.; Burch, J. D.; Gleason, J. L. Aminoalkylation of [1.1.1]Propellane Enables Direct Access to High-Value 3-Alkylbicyclo[1.1.1]pentan-1-amines. *Org. Lett.* **2019**, *21*, 6800−6804.
(26) Kanazawa, J.; Maeda, K.; Uchiyama, M. Radical Multicomponent Carboamination of [1.1.1]Propellane. *J. Am. Chem. Soc.* **2017**, *139*, 17791−17794.
(27) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C. Copper-mediated synthesis of drug-like bicyclopentanes. *Nature* **2020**, *580*, 220−226.
(28) Wiberg, K. B.; Waddell, S. T. Reactions of [1.1.1]Propellane. *J. Am. Chem. Soc.* **1990**, *112*, 2194−2216.
(29) Kim, J. H.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Sheikh, N. S.; Leonori, D. Divergent Strain-Release Amino-Functionalization of [1.1.1]-Propellane with Electrophilic Nitrogen-Radicals. *Angew. Chem., Int. Ed.* **2020**, *59*, 8225−8231.
(30) Shin, S.; Lee, S.; Choi, W.; Kim, N.; Hong, S. Visible-Light-Induced 1,3-Aminopyridylation of [1.1.1]Propellane with N-Aminopyridinium Salts. *Angew. Chem., Int. Ed.* **2021**, *60*, 7873−7879.
(31) Caputo, D. F. J.; Arroniz, C.; Durr, A. B.; Mousseau, J. J.; Stepan, A. F.; Mansfield, S. J.; Anderson, E. A. Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **2018**, *9*, 5295−5300.
(32) Nugent, J.; Arroniz, C.; Shire, B. R.; Sterling, A. J.; Pickford, H. D.; Wong, M. L. J.; Mansfield, S. J.; Caputo, D. F. J.; Owen, B.; Mousseau, J. J.; Duarte, F.; Anderson, E. A. A General Route to Bicyclo[1.1.1]pentanes through Photoredox Catalysis. *ACS Catal.* **2019**, *9*, 9568−9574.
(33) Kitagawa, O.; Miyaji, S.; Yamada, Y.; Fujiwara, H.; Taguchi, T. Iodine Atom Transfer [3 + 2] Cycloaddition Reaction with Electron-Rich Alkenes Using N-Tosyliodoaziridine Derivatives as Novel Azahomoallyl Radical Precursors. *J. Org. Chem.* **2003**, *68*, 3184−3189.
(34) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. Iodoaziridine Derivatives as Novel Azahomoallyl Radical Precursors for [3 + 2] Cycloaddition Reactions with Alkenes. *Angew. Chem., Int. Ed.* **2001**, *40*, 3865−3867.
(35) Kanegusuku, A. L. G.; Roizen, J. L., Recent Advances in Photoredox-Mediated Radical Conjugate Addition Reactions: An Expanding Toolkit for the Giese Reaction. *Angew. Chem., Int. Ed.* **2021**, DOI: 10.1002/anie.202016666.
(36) Ye, S.; Xiang, T.; Li, X.; Wu, J. Metal-catalyzed radical-type transformation of unactivated alkyl halides with C-C bond formation under photoinduced conditions. *Org. Chem. Front.* **2019**, *6*, 2183−2199.
(37) For a single example of photoinduced Cu-catalyzed cross-coupling of methoxy-iodo-BCP with a terminal alkyne, see: Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G. Photoinduced copper-catalyzed coupling of terminal alkynes and alkyl iodides. *Angew. Chem., Int. Ed.* **2018**, *57*, 5492−5496.
(38) Fodran, P.; Wallentin, C.-J. Harnessing Energy-Transfer in N-Centered Radical-Mediated Synthesis of Pyrrolidines. *Eur. J. Org. Chem.* **2020**, *2020*, 3213−3218.
(39) See the Supporting Information for details.
(40) See the Supporting Information for details of unsuccessful electron-withdrawing groups.
(41) Thirumoorthi, N. T.; Jia Shen, C.; Adsool, V. A. Expedient synthesis of 3-phenylbicyclo[1.1.1]pentan-1-amine via metal-free homolytic aromatic alkylation of benzene. *Chem. Commun.* **2015**, *51*, 3139−3142.
(42) Li, J.-S.; Wu, J. Recent Developments in the Photo-Mediated Generation of Silyl Radicals and Their Application in Organic Synthesis. *ChemPhotoChem.* **2018**, *2*, 839−846.
(43) Kornfilt, D. J. P.; MacMillan, D. W. C. Copper-Catalyzed Trifluoromethylation of Alkyl Bromides. *J. Am. Chem. Soc.* **2019**, *141*, 6853−6858.
(44) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 8084−8087.
(45) ElMarrouni, A.; Ritts, C. B.; Balsells, J. Silyl-mediated photoredox-catalyzed Giese reaction: addition of non-activated alkyl bromides. *Chem. Sci.* **2018**, *9*, 6639−6646.
(46) Zhou, Q.-Q.; Düsel, S. J. S.; Lu, L.-Q.; König, B.; Xiao, W.-J. Alkenylation of unactivated alkyl bromides through visible light photocatalysis. *Chem. Commun.* **2019**, *55*, 107−110.
(47) Dong, J.; Lyu, X.; Wang, Z.; Wang, X.; Song, H.; Liu, Y.; Wang, Q. Visible-light-mediated Minisci C-H alkylation of heteroarenes with unactivated alkyl halides using O_2 as an oxidant. *Chem. Sci.* **2019**, *10*, 976−982.
(48) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **2018**, *360*, 1010−1014.
(49) Other byproducts included direct addition of the silane to the acceptor and the formation of higher oligomers of the acceptor following addition of the BCPA radical. See the Supporting Information for details.
(50) Lucarini, M.; Marchesi, E.; Pedulli, G. F.; Chatgilialoglu, C. Homolytic Reactivity of Group 14 Organometallic Hydrides toward Nitroxides. *J. Org. Chem.* **1998**, *63*, 1687−1693.
(51) Low-temperature single-crystal X-ray diffraction data for **4l** was collected with a (Rigaku) Oxford Diffraction SuperNovaA diffractometer at 150 K. All data were reduced using CrysAlisPro, solved using SuperFlip [Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786−790] and the structures were refined using CRYSTALS [(a) Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent. J.* **2015**, *9*, 30. (b) Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100−1107.]; see the Supporting Information

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729−9736

(CIF) for further details. CCDC 2078089 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
(52) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **2005**, *17*, 5712−5719.
(53) The oxidation potential for $(Me_3Si)_3SiOH/(Me_3Si)_3SiOH^{\bullet+}$ has been measured at + 1.54 V vs SCE in MeCN. The silanolate ion is likely to be signifcantly lower; see: Smith, R. T.; Zhang, X.; Rincon, J. A.; Agejas, J.; Mateos, C.; Barberis, M.; Garcia-Cerrada, S.; de Frutos, O.; MacMillan, D. W. C. Metallaphotoredox-Catalyzed Cross-Electrophile Csp^3-Csp^3 Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018**, *140*, 17433−17438.
(54) Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. Reactions of tris(trimethylsilyl)silyl radicals with nitro alkanes. EPR, kinetic, and product studies. *J. Org. Chem.* **1992**, *57*, 948−952.
(55) Meyer, A. U.; Jäger, S.; Prasad Hari, D.; König, B. Visible Light-Mediated Metal-Free Synthesis of Vinyl Sulfones from Aryl Sulfinates. *Adv. Synth. Catal.* **2015**, *357*, 2050−2054.
(56) Zhu, J.; Cui, W.-C.; Wang, S.; Yao, Z.-J. Radical Hydrosilylation of Alkynes Catalyzed by Eosin Y and Thiol under Visible Light Irradiation. *Org. Lett.* **2018**, *20*, 3174−3178.
(57) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.
(58) Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem.* **2020**, *6*, 1888−1903.
(59) Bortolamei, N.; Isse, A. A.; Gennaro, A. Estimation of standard reduction potentials of alkyl radicals involved in atom transfer radical polymerization. *Electrochim. Acta* **2010**, *55*, 8312−8318.
(60) Moradei, S. M. L. D.; Therrien, E. Acly inhibitors and uses thereof. WO 2020097408 A1, 2019.
(61) Moriyama, K.; Nakamura, Y.; Togo, H. Oxidative debenzylation of *N*-benzyl amides and *O*-benzyl ethers using alkali metal bromide. *Org. Lett.* **2014**, *16*, 3812−3815.

https://doi.org/10.1021/jacs.1c04180
J. Am. Chem. Soc. 2021, 143, 9729−9736