JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/jacsau
Article

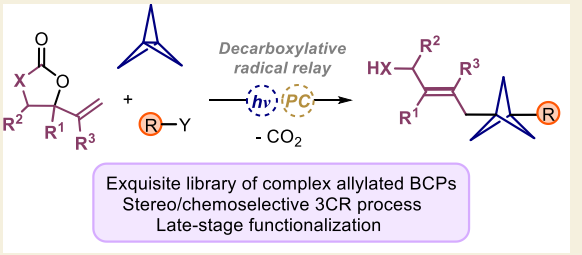
Highly Functional Allyl-Bicyclo[1.1.1]pentane Synthesis by Radical-Initiated Three-Component Stereoselective Allylation

Qian Zeng,[#] Wangyu Shi,[#] and Arjan W. Kleij*

Cite This: *JACS Au* 2025, 5, 913–921
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Rapid access to highly functional allylated BCP synthons can be achieved with good selectivity and yield through a radical, three-component reaction (3CR) regime using various combinations of radical precursors and vinyl-appended heterocycles acting as versatile and modular precursors. This practical process combines mild operating conditions, a wide scope of reaction partners, and the ability to diversify the functionalized allylic scaffolds further using the allyl and other functional groups as synthetic branching points. The developed protocol allows structural alteration and increases the molecular complexity through late-stage drug modifications and drug conjugation approaches. Mechanistic probes demonstrate that the 3CR process is initiated by a selective, light-promoted radical addition to [1.1.1]-propellane, followed by coupling with the vinyl-substituted heterocycle, which represents a formal decarboxylative radical addition/double bond relay/protonation sequence.



KEYWORDS: *allylation, bicyclo[1.1.1]pentanes, 3CR, photocatalysis, radical chemistry*

INTRODUCTION

In drug discovery, target drug candidates should feature favorable pharmaceutical performance in terms of metabolic stability, lipid solubility, and membrane permeability.[1] In this regard, sp^3-rich scaffolds such as bicyclo[1.1.1]pentanes (BCPs) have been shown to be bioisosteric replacements for *para*-substituted aromatic rings in promising pharma lead compounds.[2] The presence of such BCP units has been vital, as demonstrated by several examples of compounds with improved medicinal activities (Scheme 1a).[3] Eugenol, containing a *para*-substituted, allylated arene fragment, has been shown to be a topical antiseptic and local anesthetic. Its derivatives display pharmacological properties and were only recently discovered as compounds with very high binding to breast cancer receptors.[4] Strategies for exploring allylated-bioisosteres of *para*-substituted arenes remain so far underdeveloped despite their apparent huge potential in increasing relevant medicinal properties and expanding the general importance of allylarene structures in drug development.[4a]

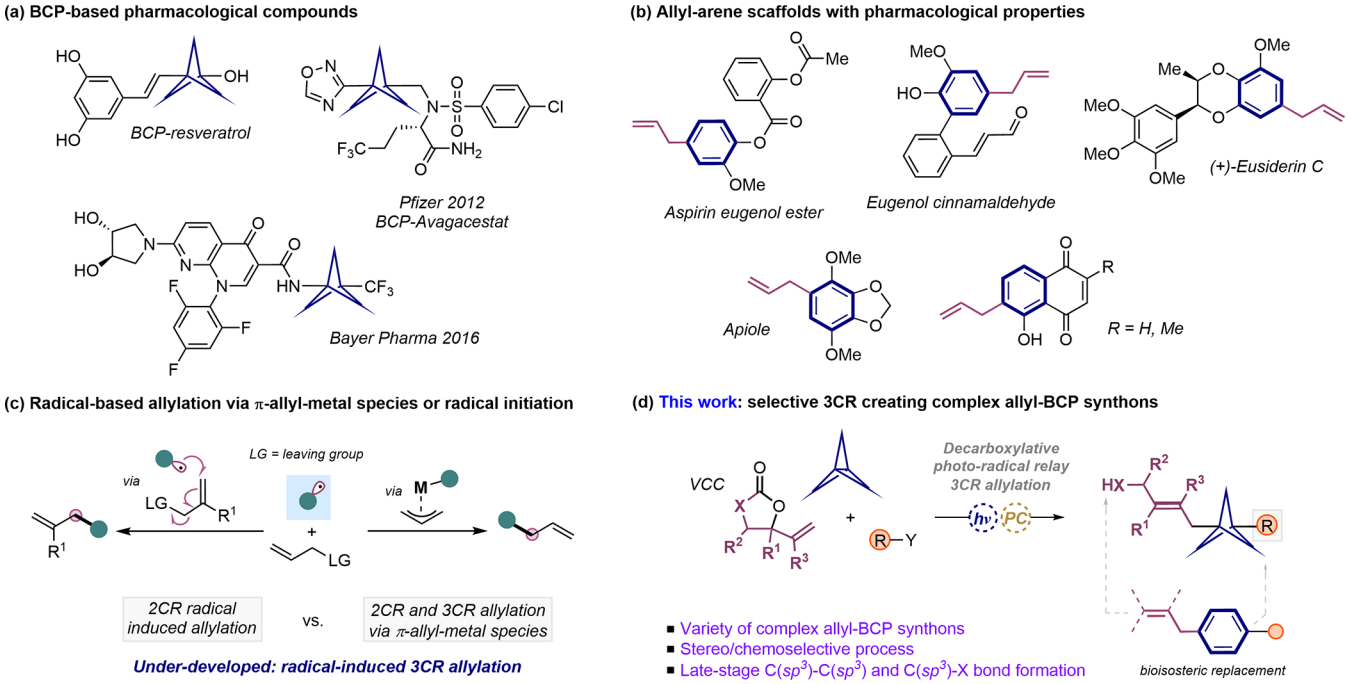
Classic allylation protocols (Scheme 1b) have been well-established, allowing the development of synthetic transformations that give access to a variety of structural and functionalized allyl-mediated molecules.[5] Historically, transition-metal catalysis, including Tsuji−Trost reactions, involves a π−allyl-metal intermediate that either reacts with external nucleophiles or electrophiles via proper umpolung conditions. In addition, C−H activation/allylation has also significantly matured as a valuable reactivity mode, contributing to an even wider development and impact of allylation procedures in synthetic chemistry.[6] More recently, photoredox-assisted metal-based transformations (Scheme 1c) have evolved as highly competitive and complementary strategies. These approximations facilitate the formation of key metal-allyl or radical species from suitable precursors, providing mild and reliable strategies for the generation of envisioned allylated products.[7] In this realm, successful dual metal/photoredox catalysis methods, mostly based on Ni, Pd, Co, Cr, and Ti, have significantly enhanced the synthesis of allylated products with excellent functional group tolerance. This has allowed the rapid synthesis of libraries of structurally complex synthons based on two- and even three-component reaction processes.[7−9] As an example, our group recently disclosed a photoredox/Ni-cocatalyzed 3CR allylic allylation between vinyl cyclic carbonates, olefins, and various radical precursors to provide multisubstituted allylic alcohols.[10]

Thus, many of these transformations rely on metal-stabilized allylic species,[7] while radical addition-induced allylation is a much less explored, though simpler, approach to forge allylic skeletons.[11,12] Such processes can productively occur via homolytic fragmentation of carbon-heteroatom bonds[13] or via sequential photocatalytic radical addition/ring opening pro-

Received: November 22, 2024
Revised: January 9, 2025
Accepted: January 17, 2025
Published: February 11, 2025

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913–921

Scheme 1. (a) Examples of Bioactive BCP Derivatives, (b) Pharmacological Molecules Containing a *Para*-Substituted Allyl-Arene Motif, (c) Photocatalytic Radical Allylation Approaches, and (d) This Work



cesses.[14] With BCPs being recognized as effective bioisosteres, the functionalization of [1.1.1]-propellane as a precursor has been the subject of intense studies promoting photomediated radical regimes, allowing the preparation of functional building blocks.[15] In this realm, the allylation of [1.1.1]-propellane has thus far been possible through stepwise approaches[16a,b] or using Grignard reagents.[16c,e] Both Aggarwal and Fañanás-Mastral independently reported the asymmetric allylation of *in situ* prepared Grignard-BCP intermediates that, through Ir- and *N*-heterocyclic carbene (NHC) catalysis, were converted into relatively simple allylated BCPs.[16d,e]

Despite these significant advancements in constructing allylated BCPs, a more generic approach capitalizing on radical-initiated multicomponent reactions that enables the stereoselective and simultaneous introduction of structurally advanced allyl groups and pharmacologically relevant functionality could create new incentives for *para*-substituted allyl-arene mimics[4] in new drug discovery/development programs. Given the current lack of photocatalytic and stereoselective three-component reaction (3CR) allylation approaches leading toward such synthons, we considered the radical-triggered functionalization of vinyl cyclic carbonates (VCCs)[17] in the presence of [1.1.1]-propellane. Such a strategy would be practical and versatile, obviating the use of moisture-sensitive organometallic reagents, the application of harsh conditions, and the presence of transition metals to stabilize π-allyl species.[6,7] We thus set out to harness the excellent radical scavenging nature of [1.1.1]-propellane providing a transient BCP-based radical that would then initiate a sequence of steps culminating in advanced allyl-BCP building blocks (Scheme 1d and mechanistic details in Scheme 8e). Here, we detail our recent findings while realizing a selective radical-relay, 3CR process amenable to a wide scope of reaction partners and various postsynthetic branching-out options, thereby creating new opportunities for functionalized allyl-BCPs.

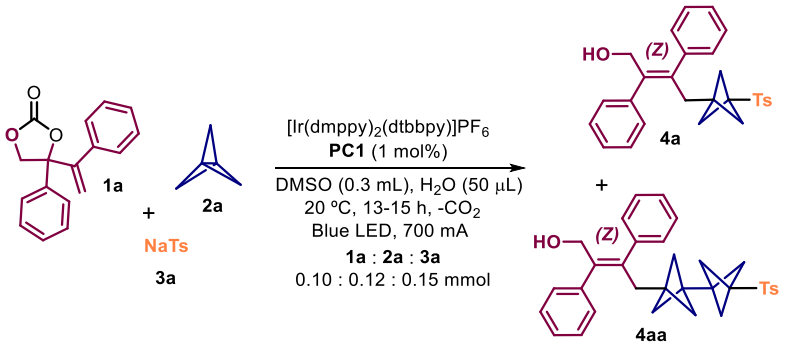
RESULTS AND DISCUSSION

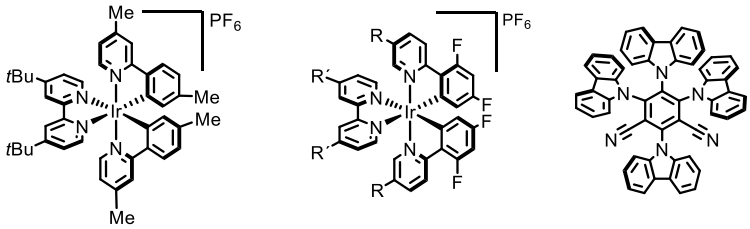
At the onset of the screening stage (see Table 1), we selected VCC **1a**, [1.1.1]-propellane **2a**, and sodium 4-methylbenzenesulfinate (NaTs, **3a**) and various reaction conditions (solvent, photocatalyst).[17] Various photocatalysts (**PC1-4**, entries 1−4) were scrutinized in CH_3CN as a medium under ambient conditions, affording two major products, *viz.* the target mono-BCP derivative **4a** and bis-BCP **4aa**. Interestingly, under these conditions, we were not able to detect significant amounts of undesired coupling between **1a** and **3a** when **PC1** (entry 1; combined yield of **4a** and **4aa** is 87%) was used, demonstrating high chemoselectivity for the 3CR coupling process. Compared with the utilization of the other PCs (entries 2−4), the yield for **4a** (77% by NMR, 76% isolated) in the presence of **PC1** was the highest. Switching to other solvent systems (entries 5 and 6; CH_3CN and dioxane) resulted in lower chemoselectivity toward **4a** (42−47%), and in the absence of a light source or the [Ir] photocatalyst **PC1**, no substrate conversion was observed (entries 7 and 8). The dual effect of water is shown in entry 9 and Table S3, where a lower yield of **4a** is noted when performing the reaction either in an anhydrous way or by further increasing the amount of water as an additive. We speculate that a certain amount of water can promote the anticipated protonation of the intermediate prior to product formation, leading thus to an improved yield. Alternatively, the presence of water may improve the solubility/miscibility of the sulfinate salts.

With the conditions reported in entry 1 of Table 1 as a focal point, we first examined the scope of VCCs **1** (see Scheme 2). The great modularity of VCCs allows for varying the R^1-R^3 substituents, giving access to BCP incorporating substituted aryl and heteroaryl groups in good yields (**4a−4g**; up to 87%) and as single stereoisomers (Z/E > 99:1). Other combinations, such as aryl/alkyl groups, as illustrated by the isolation of compounds **4h** (53%) and **4i** (70%) are also feasible, while the use of a VCC featuring a 1,2,3-triazole group in its structure allowed access to

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Table 1. Screening of a 3CR Involving VCC 1a, [1.1.1]-Propellane 2a, and NaTs 3a Under Various Conditions[a]





PC1: $[Ir(dmppy)_2(dtbbpy)]PF_6$ **PC2**: R = CF_3, R′ = H **PC3**: R = CF_3, R′ = *t*Bu **PC4**: 4CzIPN

entry	change to std conditions	conv. of **1a** (%)[b]	yield of **4a**:**4aa** (%)[b]	*Z*/*E*-**4a**[b]
1	–	>99	77:10[c]	>99:1
2[d]	**PC2**	74	39:12	>99:1
3[d]	**PC3**	86	41:13	>99:1
4[d]	**PC4**	88	44:15	>99:1
5[e]	CH_3CN	>99	47:14	>99:1
6[e]	dioxane	>99	42:15	>99:1
7	no light	<1	–	–
8	no [Ir]PC	<1	–	–
9	no H_2O	>99	64:23	>99:1

[a]Optimized procedure entry 1: **1a** (0.1 mmol), **2a** (0.12 mmol, 0.12 M [1.1.1]-propellane in pentane), **3a** (0.15 mmol), $[Ir(dmppy)_2(dtbbpy)]PF_6$, **PC1** (1.0 mol %), DMSO (0.30 mL), H_2O (50 μL), 700 mA blue LED, 20 °C for 13−15 h. [b]Yields and *E*/*Z* values were determined by ^{1}H NMR, 1,3,5-trimethyloxybenzene was used as internal standard. [c]The yield of isolated **4a** was 76%. [d]0.15 equiv of **2a** and 0.2 equiv of **3a** were used in 1.0 mL CH_3CN without adding H_2O. [e]0.15 equiv of **2a** and 0.20 equiv of **3a** were used, and 1.0 mL solvent without adding H_2O. Std stands for standard.

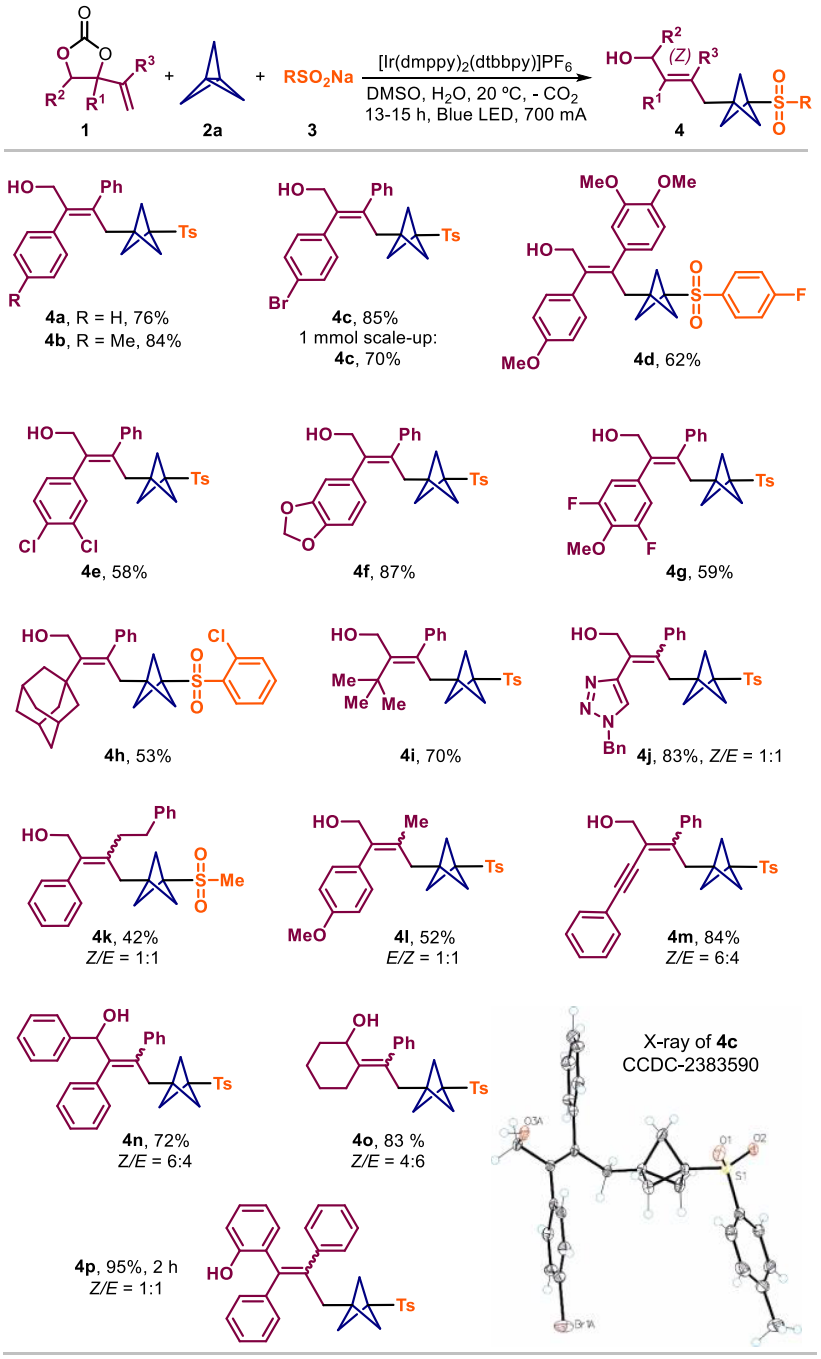
1,3-disubstituted BCP **4j** in 83% as a nearly equimolar mixture of *Z* and *E* stereoisomers. The loss of stereocontrol in this latter case is most likely because of undesired photoisomerization or a result of energy-transfer events involving the product, which may be the result of a different degree of conjugation compared to the other BCP derivatives (**4a**−**i**).[18,19] Along these lines, products **4k**-**4p** were also isolated as mixtures of *E*+*Z* isomers in moderate to good yields (42−95%), showing that more complex organic fragments originating from VCCs can be introduced. The presence of relatively small alkyl groups (R^1 and R^3 in the VCCs in Scheme 2) was previously also shown to deliver mixtures of *E*+*Z* alkenes, and thus the stereo-outcomes for products **4k**−**m** and **4o** may be anticipated.[18] The assignment of the stereochemistry in **4c** was corroborated by X-ray analysis (see the inset at the bottom of Scheme 2).[20]

Next, we varied the nature of the radical precursor **3** (Scheme 3) to diversify the scope of BCPs. We selected a few VCCs to extend the scope, with BCPs now mostly diversified in the sulfone group. A wide range of sulfone-based BCPs could be prepared using readily accessible sodium sulfinate reagents, allowing the introduction of aryl-, heteroaryl-, and various alkyl-derived sulfone groups in the BCP product. Sulfinate salts containing simple linear alkyl (**5a**, **5b**, **5d**, and **5g**; 66−81%), cycloalkyl analogues (**5c**, **5e**, and **5f**; 63−82%) and functionalized versions thereof, such as those containing a CF_3, ester, or terminal alkyne group (**5h**−**j**; 60−86%) were compatible in the 3CR with high levels of stereocontrol (*Z*/*E* > 99:1). Apart from the aliphatic reagents, various heteroaryl-based sulfinates were also productive, providing access to BCP products **5k**−**5o** in yields of up to 86%, and as a single stereoisomer. The results in Scheme 3 underline the facile and valuable nature of rapidly accessing BCP sulfones of pharmaceutical importance.[21]

To challenge the developed 3CR further, we prepared several drug-based sulfones via reduction/neutralization from their sulfonyl chloride precursors or by using sulfonyl amide derivatives through diazotization-enabled deamination. These reagents were then engaged as precursors (of type 3) in the standard protocol (see the SI for preparative details and Scheme 4). Fortunately, several sulfone-based drug-like molecules, including sildenafil-, glibenclamide-, D-(+)-camphor-, and celecoxib-based precursors, participated productively toward the formation of structurally complex compounds **5p**−**5s** in yields of up to 89%. This simple access to drug-derived BCPs is a clear advantage in terms of extending the chemical space within new drug discovery.

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Scheme 2. Scope of VCCs 1 in the 3CR leading to BCP Derivatives 4a−4p[a]



[a]Standard reaction conditions were used as reported in entry 1 of Table 1.

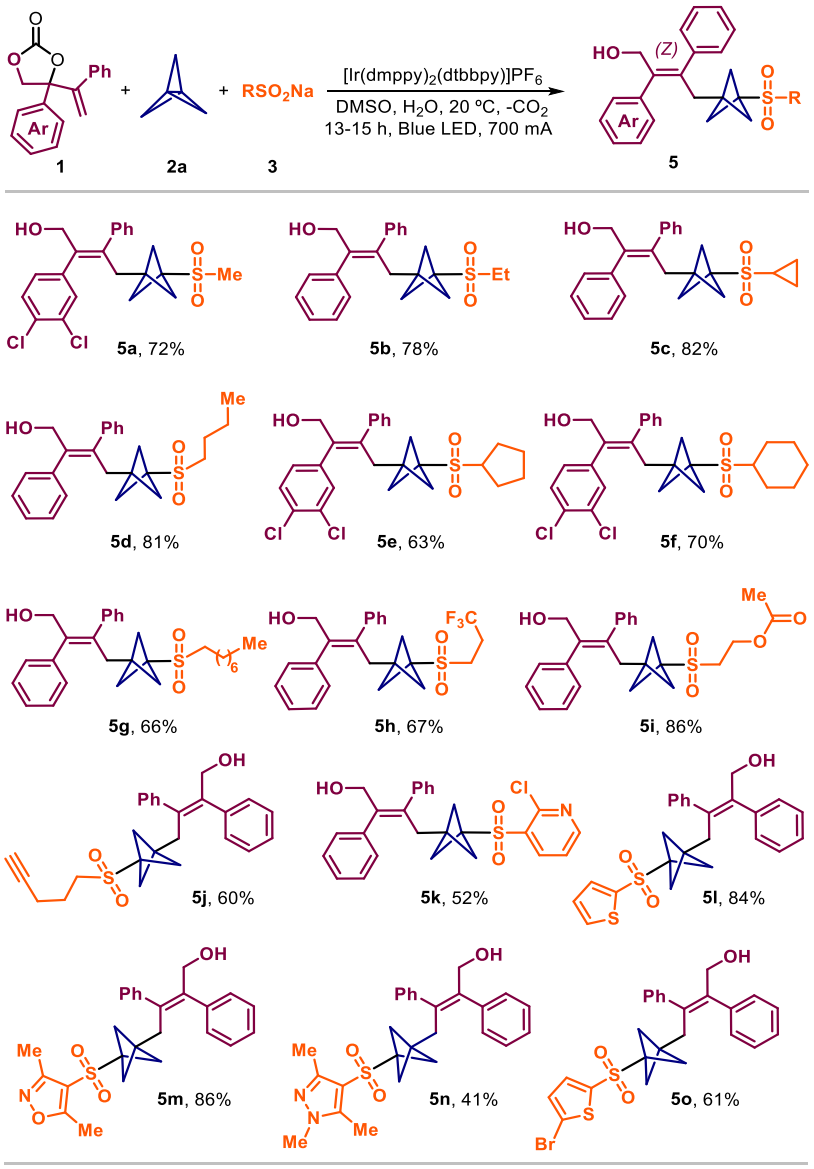
In order to demonstrate that other potential BCP-type libraries can also be designed, we used related vinyl-substituted heterocycles **6** akin to VCCs (Scheme 5), i.e., cyclic carbamates and oxazolidine-2,4-diones. The utilization of both types of alternative, vinyl-derived heterocycles created another useful embodiment of sulfone-based BCPs, allowing the introduction of allylic amide (**7a**, 52%), allylic sulfonamide (**7b**, 56%), allylic carbamate (**7c**: 51% and **7d**: 58%) and allylic amine groups (**7e**, 65%). These latter results clearly demonstrate the highly adaptive nature of the developed 3CR protocol in the creation of functionalized BCP building blocks.

Apart from pharma-relevant BCPs, other types of radical precursors can also be used to cover an additional chemical space (Scheme 6). For instance, we first used nBu$_4$NN$_3$ as a radical source, providing access to azide-appended BCP synthons **8a-8d**, with the azide-based BCP **8a** undergoing a facile Cu-mediated "click" reaction with phenyl acetylene, producing 1,2,3-triazole derivative **8A** in 81% yield. When sodium trifluoromethanesulfinate (CF_3SO_2Na) is the radical source, CF_3-substituted BCPs **8e** (43%) can be forged, being of relevance toward new drug design as illustrated in Scheme 1 (Bayer Pharma 2016). In these preparations, 4CzIPN (**PC4**, 2 mol%) instead of **PC1** was used as photocatalyst.

Subsequently, we set out to demonstrate the synthetic value and stability of the stereodefined allylic alcohol groups in the 1,3-difunctionalized BCPs (Scheme 7). Treatment of **4a** with PBr_3

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Scheme 3. Scope of Sulfinyl Radical Precursors 3 in the 3CR leading to BCP Derivatives 5a−5o[a]



[a]Standard reaction conditions were used as reported in entry 1 of Table 1. All *Z*/*E* ratios here are >99:1.

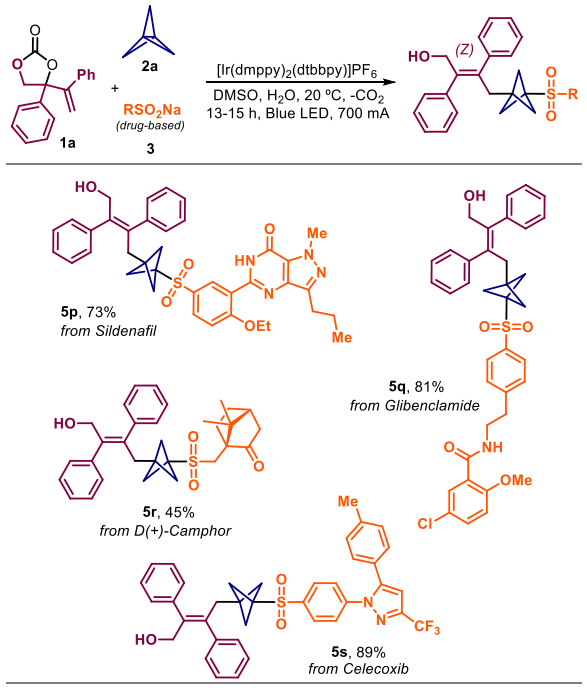
followed by the addition of sodium sulfinate afforded bis-sulfone functionalized **9a** in 70% yield. The latter scenario shows that BCPs can be easily equipped with either one (on either side of the BCP) or two sulfones, depending on the starting materials. Compound **4a** was further oxidized by DMP, providing access to α,β-unsaturated aldehyde **9b** (76%), while converting the allylic alcohol in the presence of a carbon-based pronucleophile allowed the preparation of ester derivative **9c** in 61% yield.

Terminal alkyne-based BCP **5j** undergoes smooth coupling with benzyl azide under suitable Cu-catalysis to give the 1,2,3-triazole product **9d** in nearly quantitative yield (97%). One further type of transformation was probed, and productive Steglich-type esterification of **5s** in the presence of telmisartan (a drug used to treat high blood pressure, heart failure, and diabetic kidney disease) delivers the hybrid drug-based molecule **9e** in high yield (91%). A similar procedure that involves **4c** furnishes Probenecid-derived **9f** in 98% yield, with Probenecid being a medication that increases uric acid excretion in the urine. The latter processes describe a potentially useful entry toward drug "conjugation" based on allylic alcohol-functionalized BCPs.

We finally performed some control experiments and Stern−Volmer quenching studies (Scheme 8). As mentioned before, in the absence of [1.1.1]-propellane **2a**, a 2CR occurs between **1a** and **3a** under the optimized conditions (entry 1, Table; see Scheme 8a) giving the anticipated product **10** in 79% yield. This result shows the facile nature of direct radical addition to the C═C bond of the VCC substrate. If we replace [1.1.1]-propellane **2a** with another radical acceptor (i.e., styrene: Scheme 8b), predominant formation of 2CR product **10** in 75% yield occurs with only <5% of a 3CR product. This highlights the essential nature of the [1.1.1]-propellane to create a chemoselective 3CR coupling between a VCC, **2a**, and a radical precursor. Finally, when the VCC is devoid of a substituent on the C═C bond (Scheme 8c, **1A**), very low amounts of the desired BCP-derived product **4A** (<5%) can be observed, and 32% of the starting VCC remained in the reaction mixture. These combined experiments (Scheme 8a−c) help to establish

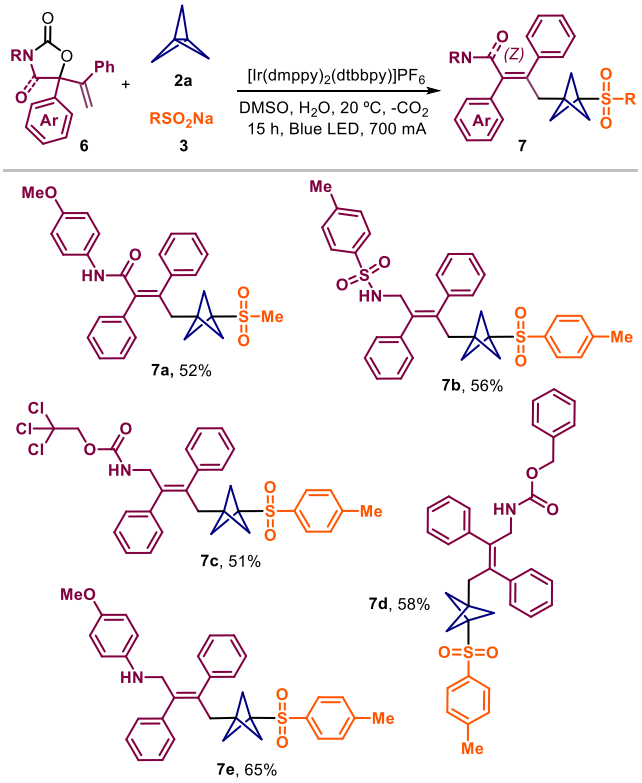
https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Scheme 4. 3CR Examples using Sulfone-Based Drug Molecules[a]



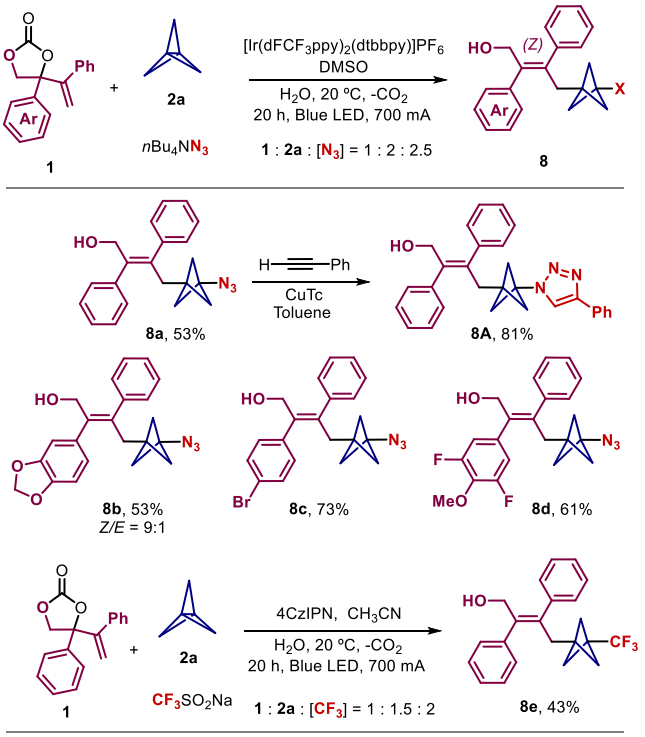
[a]Standard reaction conditions were used as reported in entry 1 of Table 1. All *Z*/*E* ratios are >99:1 using 0.5 mL of solvent.

Scheme 5. 3CRs using other Types of Heterocyclic Precursors[a]



[a]Standard reaction conditions were used as reported in entry 1 of Table 1. All *Z*/*E* ratios are >99:1.

Scheme 6. 3CR Based Protocol Using Different Radical Precursors Leading to BCP Products 8a−8e



that the nature of the VCC (and related heterocyclic substrates, Scheme 5) and the presence of [1.1.1]-propellane **2a** benefit a high chemoselectivity toward the target 3CR product. Various Stern−Volmer quenching experiments were then performed (Scheme 8d, and the SI) showing that sodium sulfinate **3a** is an efficient photoquencher, whereas both VCC **1a** and [1.1.1]-propellane **2a** are not under the experimental conditions. Thus, it is reasonable to assume that the excited photocatalyst (**PC1***) is quenched by **3a** and then adds to **2a** following a second radical addition to VCC **1a**, thereby inducing a decarboxylative double bond relay and protonation sequence (Scheme 8e).

CONCLUSIONS

In summary, we here report a highly versatile 3CR approach toward the formation of functionalized BCPs that incorporate a stereodefined allylic alcohol fragment as a synthetically useful branching point for follow-up chemistry. Apart from the presence of a tetrasubstituted C═C bond, the simultaneous introduction of pharma-interesting (hetero)aryl and alkyl sulfone, azide, or CF_3 groups can be realized using appropriate radical sources. The scope of this new 3CR transformation is easily extended to other types of heterocycles, potentially accessing a plethora of new libraries of various allylic derivatives, drug-derived synthons, and drug conjugates. We believe that our methodology unfolds new chemical space for structurally diverse and versatile synthons with value within pharmaceutical discovery and development.

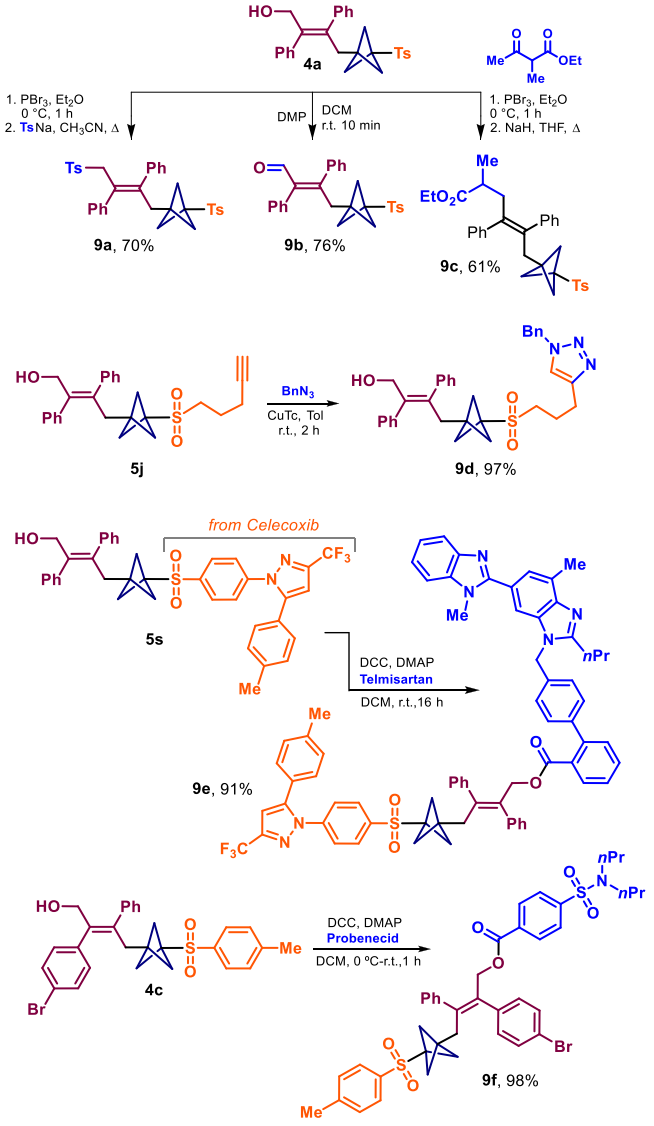
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01129.

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Scheme 7. Post-Synthetic Transformations of Allyl Alcohol-Functionalized BCPs



Additional experimental details, materials, and methods, copies of all relevant NMR, IR spectra (PDF), and crystallographic data in CIF format (PDF)

Crystallographic data of the prepared compounds(CIF)

AUTHOR INFORMATION

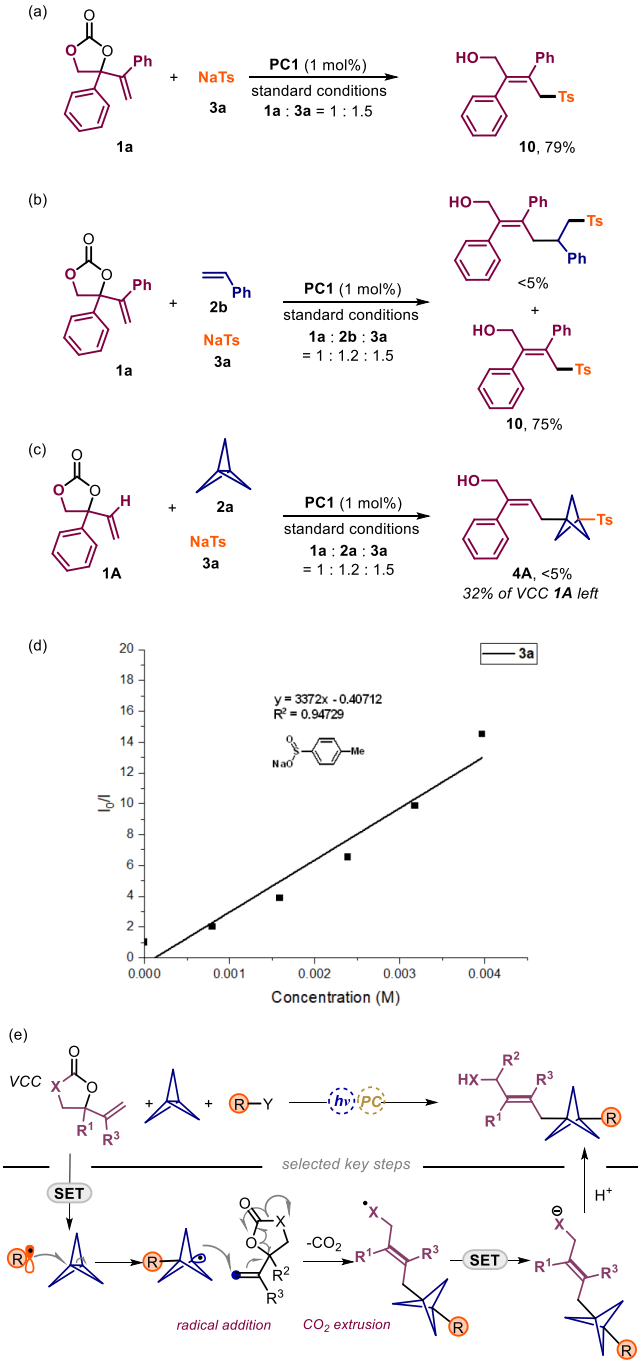
Corresponding Author

Arjan W. Kleij − *Institute of Chemical Research of Catalonia (ICIQ-Cerca), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Catalan Institute of Research and Advanced Studies (ICREA), 08010 Barcelona, Spain;* orcid.org/0000-0002-7402-4764; Email: akleij@iciq.es

Authors

Qian Zeng − *Institute of Chemical Research of Catalonia (ICIQ-Cerca), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, 43007 Tarragona, Spain*

Scheme 8. Control Experiments, Stern−Volmer Quenching Studies and Possible Mechanism



Wangyu Shi − *Institute of Chemical Research of Catalonia (ICIQ-Cerca), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, 43007 Tarragona, Spain*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.4c01129

Author Contributions

#Q.Z. and W.S. contributed equally to this work. The manuscript was written through contributions from all authors. All authors have given approval to the final version of the manuscript.

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

CRediT: **Qian Zeng** formal analysis, investigation, methodology, validation, writing - original draft; **Wangyu Shi** investigation, methodology, validation, writing - review & editing; **Arjan W. Kleij** conceptualization, funding acquisition, project administration, supervision, validation, writing - review & editing.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the ICIQ-CERCA Program/Generalitat de Catalunya, ICREA, MICINN (PID2020-112684GB-100, PID2023-149295NB-I00, and CEX2019-000925-S), and AGAUR (2021-SGR-00853) for support. Q.Z. and W.S. thank the Chinese Research Council for providing PhD fellowships (2020-06920024 and 2021-06350046). We thank Dr. Jordi Benet-Buchholz for the X-ray crystallographic measurement involving compound **4c**.

■ REFERENCES

(1) (a) Honorio, K. M.; Moda, T. L.; Andricopulo, A. D. Pharmacokinetic Properties and In Silico ADME Modeling in Drug Discovery. *Med. Chem.* **2013**, *9*, 163−176. (b) Jia, C.-Y.; Li, J.-Y.; Hao, G.-F.; Yang, G.-F. A drug-likeness toolbox facilitates ADMET study in drug discovery. *Drug Discov.* **2020**, *25*, 248−258. (c) Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a ring on it: application of small aliphatic rings in medicinal chemistry. *RSC Med. Chem.* **2021**, *12*, 448−471.

(2) (a) 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. (b) 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 $LpPLA_2$ Inhibitor. *ACS Med. Chem. Lett.* **2017**, *8*, 43−48. (c) Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; Vecchia, L. L.; Briard, E. Improving Nonspecific Binding and Solubility: Bicycloalkyl Groups and Cubanes as para-Phenyl Bioisosteres. *ChemMedChem* **2017**, *12*, 590−598.

(3) (a) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1−11. (b) Meanwell, N. A. *Burger's Medicinal Chemistry and Drug Discovery*; Wiley: Hoboken, 2003; pp. 1−81. (c) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529−2591.

(4) (a) Astrain-Redin, N.; Sanmartin, C.; Sharma, A. K.; Plano, D. From Natural Sources to Synthetic Derivatives: The Allyl Motif as a Powerful Tool for Fragment-Based Design in Cancer Treatment. *J. Med. Chem.* **2023**, *66*, 3703−3731. (b) Ulanowska, M.; Olas, B. Biological Properties and Prospects for the Application of Eugenol—A Review. *Int. J. Mol. Sci.* **2021**, *22*, 3671. (c) Zari, A. T.; Zari, T. A.; Hakeem, K. R. Anticancer Properties of Eugenol: A Review. *Molecules* **2021**, *26*, 7407. (d) Pilkington, L. I.; Barker, D. Asymmetric Synthesis and CD Investigation of the 1,4-Benzodioxane Lignans Eusiderins A, B, C, G, L, and M. *J. Org. Chem.* **2012**, *77*, 8156−8166.

(5) (a) Trost, B. M. Designing a Receptor for Molecular Recognition in a Catalytic Synthetic Reaction: Allylic Alkylation. *Acc. Chem. Res.* **1996**, *29*, 355−364. (b) Süsse, L.; Stoltz, B. M. Enantioselective Formation of Quaternary Centers by Allylic Alkylation with First-Row Transition-Metal Catalysts. *Chem. Rev.* **2021**, *121*, 4084−4099. (c) Dutta, S.; Bhattacharya, T.; Werz, D. B.; Maiti, D. Transition-metal-catalyzed C−H allylation reactions. *Chem* **2021**, *7*, 555−605. (d) Zhou, J. L.; Xiao, Y.; He, L.; Gao, X.-Y.; Yang, X.-C.; Wu, W.-B.; Wang, G.-Q.; Zhang, J.-L.; Feng, J.-J. Palladium-Catalyzed Ligand-Controlled Switchable Hetero-(5 + 3)/Enantioselective [2σ+2σ] Cycloadditions of Bicyclobutanes with Vinyl Oxiranes. *J. Am. Chem. Soc.* **2024**, *146*, 19621−19628. (e) Gao, X.-Y.; Tang, L.; Zhang, X.; Feng, J.-J. Palladium-catalyzed decarboxylative (4 + 3) cycloadditions of bicyclobutanes with 2-alkylidenetrimethylene carbonates for the synthesis of 2-oxabicyclo[4.1.1]octanes. *Chem. Sci.* **2024**, *15*, 13942−13948.

(6) Spielmann, K.; Niel, G.; de Figueiredo, R. M.; Campagne, J.-M. Catalytic nucleophilic 'umpoled' π-allyl reagents. *Chem. Soc. Rev.* **2018**, *47*, 1159−1173.

(7) (a) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74−108. (b) Huang, H.-M.; Bellotti, P.; Glorius, F. Transition metal-catalysed allylic functionalization reactions involving radicals. *Chem. Soc. Rev.* **2020**, *49*, 6186−6197. (c) Xue, S.; Cristofol, À.; Limburg, B.; Zeng, Q.; Kleij, A. W. Dual Cobalt/Organophotoredox Catalysis for Diastereo- and Regioselective 1,2-Difunctionalization of 1,3-Diene Surrogates Creating Quaternary Carbon Centers. *ACS Catal.* **2022**, *12*, 3651−3659.

(8) (a) Lu, F.-D.; He, G.-F.; Lu, L.-Q.; Xiao, W.-J. Metallaphotoredox catalysis for multicomponent coupling reactions. *Green Chem.* **2021**, *23*, 5379−5393. (b) Matsui, J. K.; Gutiérrez-Bonet, L.; Rotella, M.; Alam, R.; Gutierrez, O.; Molander, G. A. Photoredox/Nickel-Catalyzed Single-Electron Tsuji−Trost Reaction: Development and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2018**, *57*, 15847−15851. (c) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. Redox-Neutral α-Allylation of Amines by Combining Palladium Catalysis and Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625−1628. (d) Zhang, H.-H.; Zhao, J.-J.; Yu, S. Enantioselective Allylic Alkylation with 4-Alkyl-1,4-dihydropyridines Enabled by Photoredox/Palladium Cocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16914−16919. (e) Jin, Y.; Ng, E. W. H.; Fan, T.; Hirao, H.; Gong, L.-Z. Photochemical Allylation of Alkanes Enabled by Nickel Catalysis. *ACS Catal.* **2022**, *12*, 10039−10046.

(9) (a) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 12705−12709. (b) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cp_2TiCl_2-Catalyzed Photoredox Allylation of Aldehydes with Visible Light. *ACS Catal.* **2020**, *10*, 3857−3863. (c) Wang, P.-Z.; Wu, X.; Cheng, Y.; Jiang, M.; Xiao, W.-J.; Chen, J.-R. Photoinduced Copper-Catalyzed Asymmetric Three-Component Coupling of 1,3-Dienes: An Alternative to Kharasch−Sosnovsky Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 22956−22962.

(10) Zeng, Q.; Gao, F.; Benet-Buchholz, J.; Kleij, A. W. Stereoselective Three-Component Allylic Alkylation enabled by Dual Photoredox/Ni Catalysis. *ACS Catal.* **2023**, *13*, 7514−7522.

(11) Chu, X.-Q.; Ge, D.; Cui, Y.-Y.; Shen, Z.-L.; Li, C.-J. Desulfonylation via Radical Process: Recent Developments in Organic Synthesis. *Chem. Rev.* **2021**, *121*, 12548−12680.

(12) (a) Qi, L.; Chen, Y. Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enabled by Hantzsch Ester in Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 13312−13315. (b) Gualandi, A.; Calogero, F.; Pinosa, E.; Corbisiero, D.; Cozzi, P. G. Developing Organometallic Nucleophilic Reagents Via Photoredox Catalysis. *Synthesis* **2023**, *55*, 3737−3758. (c) Gualandi, A.; Calogero, F.; Corbisiero, D.; Pinosa, E.; Cozzi, P. G. Reactivities of Photoredox Generated Nickel-Nucleophilic Reactive Organometallic Species. *Asian J. Org. Chem.* **2024**, *13*, No. e202300574.

(13) (a) Russell, G. A. Free radical chain reactions involving alkyl- and alkenylmercurials. *Acc. Chem. Res.* **1989**, *22*, 1−8. (b) Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D. P. Synthesis of 2-functionalized allyl tris(trimethylsilyl)silanes. *Tetrahedron Lett.* **1996**, *37*, 6383−6386. (c) Cardinal-David, B.; Guerin, B.; Guindon, Y. Synthesis of Tertiary and Quaternary Stereogenic Centers: A Diastereoselective Tandem Reaction Sequence Combining Mukaiyama and Free Radical-Based

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921

Allylation. *J. Org. Chem.* **2005**, *70*, 776−784. (d) Charrier, N.; Quiclet-Sire, B.; Zard, S. Z. Allylic Alcohols as Radical Allylating Agents. An Overall Olefination of Aldehydes and Ketones. *J. Am. Chem. Soc.* **2008**, *130*, 8898−8899. (e) Salomon, P.; Zard, S. Z. A Practical Source of Chlorodifluoromethyl Radicals. Convergent Routes to gem-Difluoroalkenes and -dienes and (2,2-Difluoroethyl)-indoles, -azaindoles, and -naphthols. *Org. Lett.* **2014**, *16*, 2926−2929.

(14) (a) Qu, W.-Y.; Zhou, X.-S.; Xiao, W.-J.; Chen, J.-R. Asymmetric radical allylation of β-keto esters with vinyl cyclopropanes by dual photoredox/nickel catalysis. *Sci. China: Chem.* **2024**, *67*, 3807−3816. (b) Zhang, Y.; Zhao, C.; Ma, C.; Cai, Z.; Trienes, S.; Ackermann, L. Photocatalytic C−C Cleavage of Methylenecyclobutanes for γ,δ-Unsaturated Aldehydes by Strain Release. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202300166.

(15) (a) Levin, M. D.; Kaszynski, P.; Michl, J. Bicyclo[1.1.1]pentanes, [*n*]Staffanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.$0^{2,5}$]pentanes. *Chem. Rev.* **2000**, *100*, 169−234. (b) Cuadros, S.; Paut, J.; Anselmi, E.; Dagousset, G.; Magnier, E.; Dell'amico, L. Light-Driven Synthesis and Functionalization of Bicycloalkanes, Cubanes and Related Bioisosteres. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202317333.

(16) Difunctionalized BCPs with terminally mono- or disubstituted double bonds: (a) Pickford, H. D.; Nugent, J.; Owen, B.; Mousseau, J. J.; Smith, R. C.; Anderson, E. A. Twofold Radical-Based Synthesis of N,C-Difunctionalized Bicyclo[1.1.1]pentanes. *J. Am. Chem. Soc.* **2021**, *143*, 9729−9736. (b) Zhang, M.-D.; Zhao, H.-Y.; Zhang, X. Difluorocarbene Enables Modular Synthesis of Difluoroalkylated Bicyclopentanes. *Eur. J. Org. Chem.* **2024**, *27*, No. e202400572. (c) Wu, Z.; Xu, Y.; Zhang, H.; Wu, X.; Zhu, C. Radical-mediated sulfonyl alkynylation, allylation, and cyanation of propellane. *Chem. Commun.* **2021**, *57*, 6066−6069. (d) Schwärzer, K.; Zipse, H.; Karaghiosoff, K.; Knochel, P. Highly Regioselective Addition of Allylic Zinc Halides and Various Zinc Enolates to [1.1.1]Propellane. *Angew. Chem., Int. Ed.* **2020**, *59*, 20235−20241. (e) Yu, S.; Jing, C.; Noble, A.; Aggarwal, V. K. Iridium-Catalyzed Enantioselective Synthesis of α-Chiral Bicyclo[1.1.1]pentanes by 1,3-Difunctionalization of [1.1.1]-Propellane. *Org. Lett.* **2020**, *22*, 5650−5655. (f) Barbeira-Arán, S.; Sánchez-Sordo, I.; Fañanás-Mastral, M. Enantioselective Synthesis of α-Chiral Bicyclo[1.1.1]pentanes via Multicomponent Asymmetric Allylic Alkylation. *Org. Lett.* **2024**, *26*, 3784−3789.

(17) Zeng, Q.; Nirwan, Y.; Benet-Buchholz, J.; Kleij, A. W. An Expedient Radical Approach for the Decarboxylative Synthesis of Stereodefined All-Carbon Tetrasubstituted Olefins. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202403651.

(18) (a) Siemeister, G.; Lucking, U.; Wengner, A. M.; Lienau, P.; Steinke, W.; Schatz, C.; Mumberg, D.; Ziegelbauer, K. BAY 1000394, a Novel Cyclin-Dependent Kinase Inhibitor, with Potent Antitumor Activity in Mono- and in Combination Treatment upon Oral Application. *Mol. Cancer Ther.* **2012**, *11*, 2265−2273. (b) Meanwell, N. A. Improving Drug Design: An Update on Recent Applications of Efficiency Metrics, Strategies for Replacing Problematic Elements, and Compounds in Nontraditional Drug Space. *Chem. Res. Toxicol.* **2016**, *29*, 564−616. (c) Pickford, H. D.; Ripenko, V.; McNamee, R. E.; Holovchuk, S.; Thompson, A. L.; Smith, R. C.; Mykhailiuk, P. K.; Anderson, E. A. Rapid and Scalable Halosulfonylation of Strain-Release Reagents. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202213508.

(19) (a) Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem* **2020**, *6*, 1888−1903. (b) Nevesely, T.; Wienhold, M.; Molloy, J. J.; Gilmour, R. Advances in the $E \rightarrow Z$ Isomerization of Alkenes Using Small Molecule Photocatalysts. *Chem. Rev.* **2022**, *122*, 2650−2694. (c) Zhou, Y.; Maisonneuve, S.; Maurel, F.; Xie, J.; Métivier, R. Competitive Photoisomerization and Energy Transfer Processes in Fluorescent Multichromophoric Systems. *Chem.Eur. J.* **2022**, *28*, No. e202202071.

(20) *Deposition number 2383590 contains the supplementary crystallographic data for compound 4c. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service, see:* https://www.ccdc.cam.ac.uk/structures/.

(21) Anderson reported on a convenient method for a range of pharma-relevant (hetero)arylsulfone-based BCPs using in situ prepared or preisolated sulfonyl halide reagents, see: Pickford Pickford, H. D.; Ripenko, V.; McNamee, R. E.; Holovchuk, S.; Thompson, A. L.; Smith, R. C.; Mykhailiuk, P. K.; Anderson, E. A. Rapid and Scalable Halosulfonylation of Strain-Release Reagents. *Angew. Chem., Int. Ed* **2023**, *62*, No. e202213508.

https://doi.org/10.1021/jacsau.4c01129
JACS Au 2025, 5, 913−921