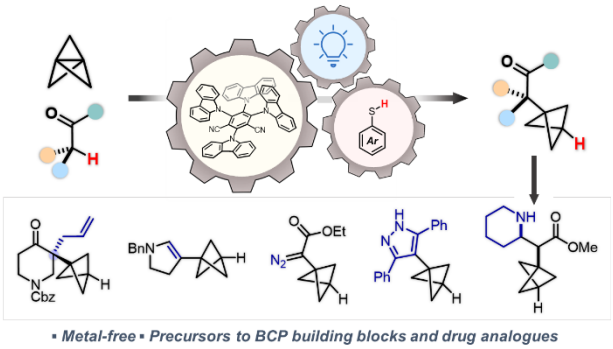
Synthesis of α-quaternary bicyclo[1.1.1]pentanes through synergistic organophotoredox and hydrogen atom transfer catalysis

Jeremy Nugent,[†] Alistair J. Sterling,[†] Nils Frank,[†] James J. Mousseau[‡¶] and Edward A. Anderson*[†]

[†]Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom

[‡]Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States

Supporting Information Placeholder



ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs) are of importance in drug design as sp^3-rich bioisosteres of arenes and *tert*-butyl groups, however the preparation of BCPs with adjacent quaternary carbons is barely known. We report a facile synthesis of α-quaternary BCPs using organophotoredox and hydrogen atom transfer catalysis in which α-keto radicals, generated through oxidation of β-ketocarbonyls, undergo efficient addition to [1.1.1]propellane. The BCP products can be transformed into a variety of useful derivatives including enantioenriched BCPs featuring α-quaternary stereocenters.

Sp^3-rich 'cage' hydrocarbons such as bicyclo[1.1.1]pentanes (BCPs) and cubanes are increasingly deployed in agrochemical and pharmaceutical drug design due to their distinctive and beneficial physicochemical properties.[1] The conformational rigidity of these carbocycles confers a well-defined three-dimensional structure that can be exploited in the specific positioning of substituents along well-defined vectors. For example, 1,3-disubstituted BCPs can be used as bioisosteres for *p*-substituted arenes[2] and alkynes,[3] retaining the geometrical properties of the parent motif while also enhancing pharmacokinetic profiles.[4] Similarly, monosubstituted BCPs have been employed as analogues of *t*-butyl and phenyl groups (Figure 1a).[2, 5]

BCPs are predominantly synthesized via ring opening reactions of [1.1.1]propellane (**1**, Figure 1b), a highly strained yet easily accessible caged hydrocarbon, using one- and two-electron chemistry.[6] Monosubstituted BCPs are most typically prepared through the addition of anions to **1**: The use of aryl Grignard reagents,[3] turbo amides,[7] enolates,[8] dithiane[9] and azaallyl[10] anions is well-established, but these methodologies are air/moisture sensitive, and intolerant of functional groups such as carbonyls, limiting applications. Single-electron strategies also enable the synthesis of a variety of *C*- or *N*-monosubstituted BCPs; indirect routes involving the reduction of BCP halide intermediates are also known.[11] However, these methods are less explored and limitations nonetheless remain, in particular for the synthesis of BCPs featuring adjacent quaternary centers, where significant steric hindrance must be overcome in the C–C bond forming step.

We previously described a range of methods for the preparation of BCPs through photoredox-catalyzed additions of alkyl / (hetero)aryl radicals[12] and α-iminyl radical cations[11d] to **1**. However, these methodologies are unable to access highly functionalized α-quaternary BCPs. To address this, we questioned whether we could use photoredox catalysis to directly access tertiary α,α'-dicarbonyl radicals via the single electron oxidation of substituted β-ketoesters.[13] The addition of these intermediates to **1** would result in the direct formation of two contiguous quaternary centers;[14] the resulting BCP radical could then engage in hydrogen atom transfer (HAT) with a suitable H-atom source to afford densely-functionalized BCP products **3**. Here we report the realization of this three-component photocatalytic strategy, and the diversification of the resulting *C*-substituted BCP products into a variety of pharmaceutical building blocks, including enantioenriched BCPs containing α-chiral quaternary stereocenters (Figure 1c).

α-Acetylbutyrolactone **2a** was selected for reaction optimization (Table 1). A variety of moderately oxidizing photocatalysts were screened in the reaction of **2a** (5 equiv.) with **1** in acetonitrile (entries 1–3). Pleasingly, under blue LED irradiation for 20 h, ($Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (**Ir 1**), $Ru(bpy)_3(PF_6)_2$ and the

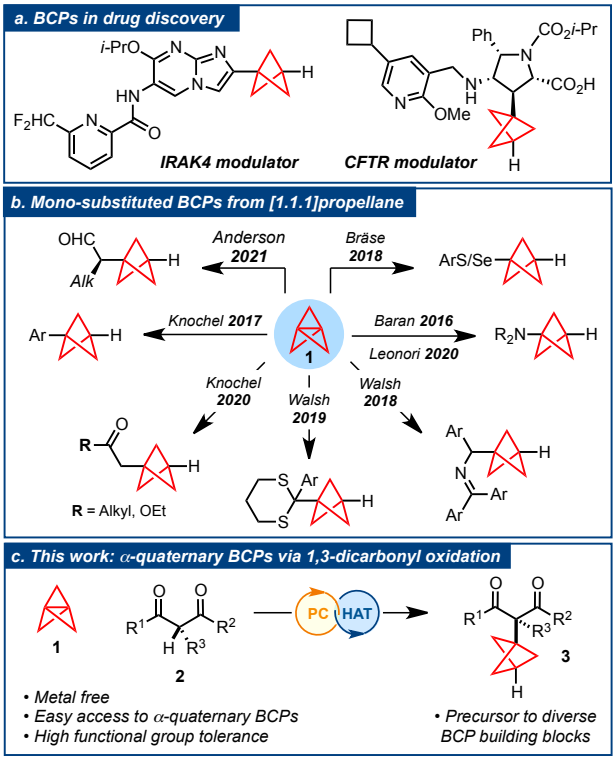
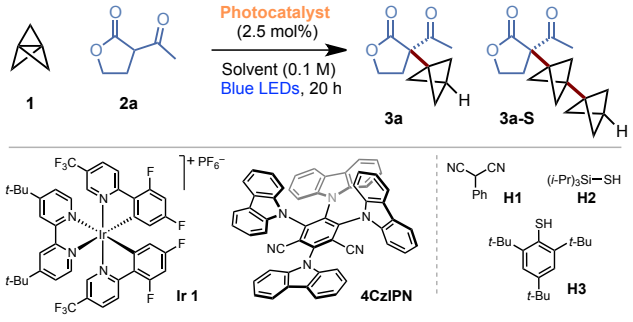


Figure 1. a Bicyclo[1.1.1]pentanes in drug discovery; **b** Routes to 1-substituted BCPs; **c** This work: Synthesis of bicyclo[1.1.1]pentanes using synergistic photoredox/HAT catalysis.

organophotocatalyst 4CzIPN generated **3a** in moderate to good yields (48–67%). Consistent with our previous work,[11a, 12a] we found that staffane byproduct **3a-S**, formed through addition of the BCP radical intermediate to another molecule of **1**, was produced in moderate amounts (6:1, **3a**:**3a-S**). Using 4CzIPN, variation of the solvent led to diminished yields (entries 4–5), while the addition of H_2O offered no benefit (entry 6). We next explored the use of various HAT catalysts, which could minimize the formation of byproduct **3a-S**. While catalysts such as 2-phenylmalononitrile (**H1**)[15] and triisopropylsilanethiol (**H2**)[16] led to no improvement (entries 7–8), we found that the use of 10 mol% of the sterically-demanding thiophenol **H3** resulted in an excellent yield of **3a**, and suppressed the formation of **3a-S** (entry 9, 90%, **3a**:**3a-S** >20:1). Notably, the thiol-BCP adduct which would arise from the direct reaction of **H3** with **1** was not observed.[11b] Under this combination of photocatalyst and HAT catalyst, the amount of ketoester **2a** could be reduced to 1.5 equiv. with no change in yield (entry 10, 93% isolated yield, >20:1 **3a**:**3a-S**). Control experiments demonstrated that both the photocatalyst and light were necessary for reaction (entries 11–12).

Under the optimized conditions, this methodology proved a highly versatile strategy for the synthesis of α-quaternary BCPs (Scheme 1). β-Ketoesters featuring 5-membered ring cores including cyclopentane, pyrrolidine, pyrrolidinone, lactone and indanone rings all smoothly afforded the corresponding BCP products in good to excellent yields (**3a**–**d**, 50–93%). Notably, in the reaction of **2c**, BCP **3c** was the sole reaction product despite the presence of a readily oxidizable aniline nitrogen atom. Piperidine and tetrahydronaphthalene derived BCPs were also formed in high yields (**3h**–**i**, 77–95%), as were tertiary (**3j**, 50%) and secondary (**3k**, 76%) acyclic β-ketoesters. We were pleased to find that the methodology could be applied to allyl β-ketoesters, as these products offer the potential for

Table 1. Reaction optimization.[a]



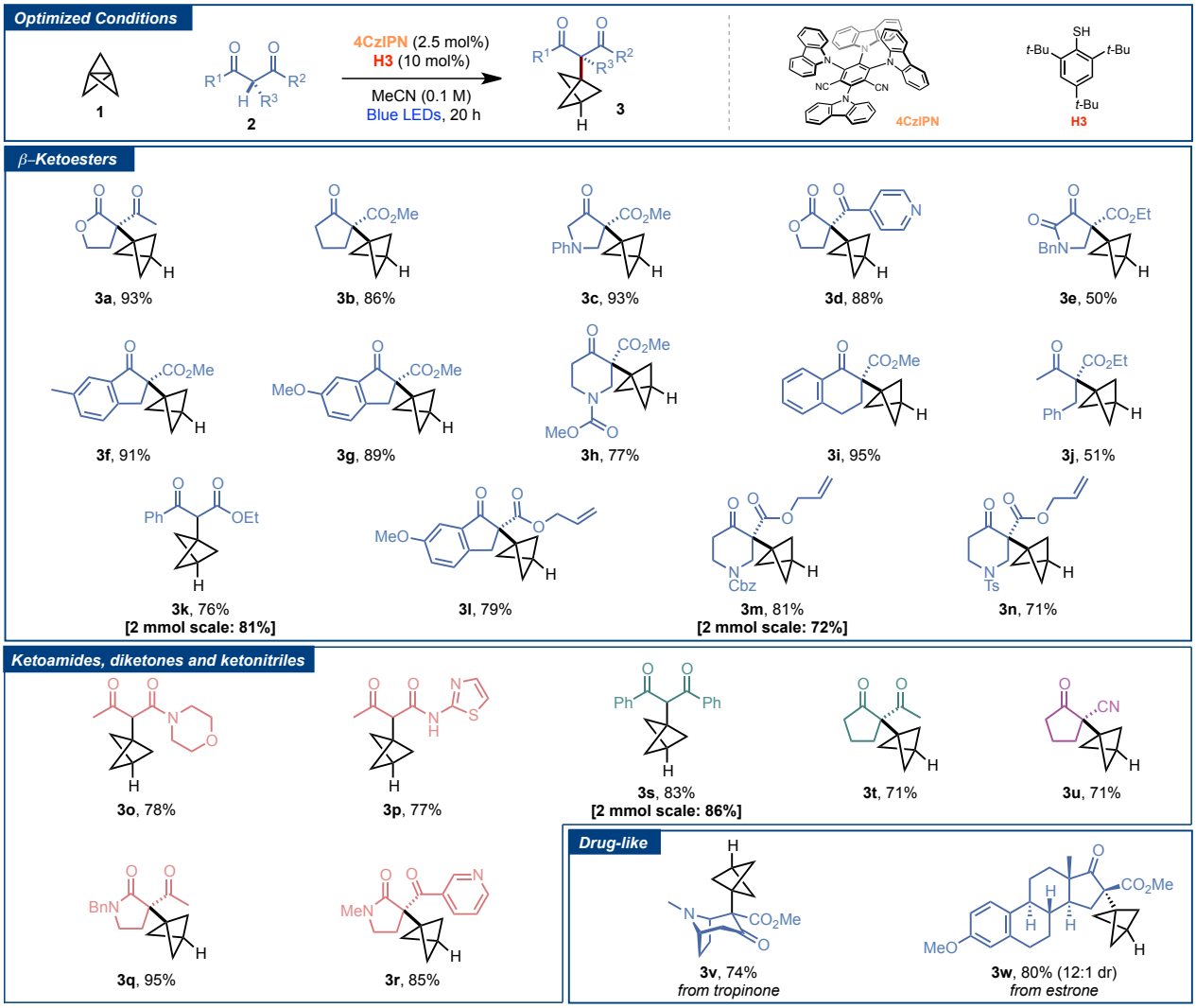
Entry	Photocatalyst	Solvent	**2a** (equiv.)	Additive	Yield[b]	**3**:**3-S**
1	Ir 1	MeCN	5	-	54%	6:1
2	$Ru(bpy)_3(PF_6)_2$	MeCN	5	-	48%	6:1
3	4CzIPN	MeCN	5	-	67%	6:1
4	4CzIPN	DMA	5	-	54%	6:1
5	4CzIPN	MeOH	5	-	58%	6:1
6	4CzIPN	MeCN	5	H_2O[c]	67%	6:1
7	4CzIPN	MeCN	5	H1[d]	50%	6:1
8	4CzIPN	MeCN	5	H2[d]	61%	6:1
9	4CzIPN	MeCN	5	H3[d]	88%	>20:1
10	4CzIPN	MeCN	1.5	H3[d]	90% (93%)[e]	>20:1
11	-	MeCN	1.5	H3[d]	-	-
12[f]	4CzIPN	MeCN	1.5	H3[d]	-	-

[a]Reactions were conducted using 0.2 mmol **1**. [b]Determined through ^1H NMR spectroscopic analysis of the crude reaction mixture with mesitylene as internal standard. [c]0.2 mL. [d]10 mol%. [e]Isolated yield. [f]Reaction conducted in the dark.

subsequent asymmetric installation of an α-stereocenter through decarboxylative allylation (*vide infra*).[17] Both 5- and 6-membered ring substrates were well-tolerated, affording the desired BCP products in excellent yields (**3l**–**n**, 71–81%). To the best of our knowledge, there have been no reports on the photocatalytic single electron oxidation of β-ketoamides. Pleasingly, we found both acyclic (**3o**–**p**, 77–78%) and cyclic (**3q**–**r**, 85–95%) ketoamides to be excellent substrates, affording the corresponding BCP products in excellent yields. The chemistry could be further extended to both acyclic and cyclic 1,3-diketones (**3s**–**t**, 71–83%), and β-ketonitriles (**3u**, 71%) with no decrease in efficiency. We also demonstrated the ability of this process to operate in more complex settings through the bicyclopentylation of a tropinone analogue (**3v**, 71%) and an estrone analogue (**3w**, 80%, 12:1 dr).

The 1,3-dicarbonyl-functionalized BCPs formed in this methodology are attractive precursors to a range of BCP building blocks of potential utility in drug design. For example, α-BCP ketones can be generated through a one-pot hydrolysis/decarboxylation sequence (**4**, 95%), with the pendent ester group serving as a traceless mediator for ketone bicyclopentylation. Acyclic ketoesters such as **3k** can be used for deacylative generation of potentially useful α-diazo BCPs (**5**, 84%).[18] $LiAlH_4$ reduction of ketoamide **3q** enables the preparation of BCP-substituted enamines through a retro-aldol-type fragmentation (**6**, 89%). Acyclic 1,3-diketones are precursors to valuable 5-membered heterocycle-substituted BCPs including pyrazoles (**7**, 94%) and oxazoles (**8**, 70%). β-keto allyl esters **3l** and **3m** can be

Scheme 1. Substrate scope.[a]

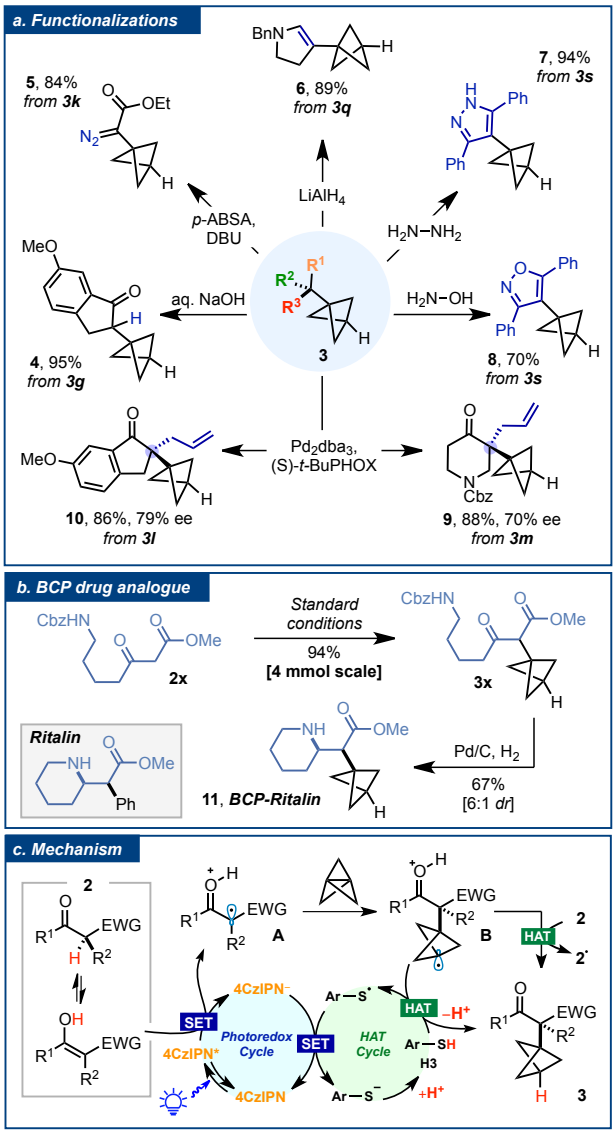


[a]Reactions conducted on 0.2 mmol scale unless otherwise stated, isolated yields shown.

used for the enantioselective synthesis of BCPs featuring α-quaternary centers via asymmetric Pd[0]/(*S*)-*t*BuPHOX catalyzed Carroll rearrangements.[19] The resulting chiral α-BCP-α'-allyl ketones are formed in excellent yields and high enantiomeric excess (**9**–**10**, 86–88%, 70–79% ee); these represent the first examples of the asymmetric synthesis of quaternary α-chiral BCPs.

To underline the utility of this chemistry in a medicinal chemistry setting, we targeted the synthesis of a BCP analogue of Ritalin, a first-line treatment for attention-deficit/hyperactivity disorder. Bioisosteric replacement of the α-phenyl ester motif of Ritalin was achieved using β-ketoester **2x**, which was accessed in a single step from commercially-available materials. Reaction under the standard conditions afforded BCP **3x** in excellent yield on gram scale (94%, 1.4 g of **3x**). Hydrogenation of this product gave BCP-Ritalin in good yield and diastereoselectivity (**11**, 67%, 6:1 dr, 47% over 3 steps).

While this β-ketocarbonyl bicyclopentylation proceeds with moderate efficiency in the absence of any additives, the significant increase in yields in the presence of an H-atom transfer catalyst (93% vs 45%) suggest a mechanistic cycle involving both photoredox and hydrogen atom transfer catalysis (Figure 2b). We propose that initial photoexcitation of 4CzIPN gives a short-lived highly oxidizing species (+1.43 V vs SCE, τ_θ = 12.7 ns)[20] which is capable of removing an electron from the β-ketocarbonyl compound (**2**, +1.15–1.43 vs SCE)[13b, 21] to form radical cation **A**. This proposal is supported by Stern-Volmer quenching studies, in which β-ketoester **2k** quenches the luminescence of the photocatalyst ($k_q = 6\times10^7$ $M^{-1}s^{-1}$, see the Supporting Information for further discussion). The resultant radical cation adds to the inter-bridgehead bond of [1.1.1]propellane to form BCP radical **B**, which abstracts an H atom from HAT catalyst **H3**. This process outcompetes addition to another molecule of **1**, which would form staffane by-product **3-S**. Reduction of the thiyl radical by 4CzIPN$^-$ regenerates the photocatalyst, with proton exchange affording BCP product **3** and regenerating thiophenol **H3**. To explain the (less efficient) formation of **3** in the absence of HAT catalyst, we propose a secondary propagation mechanism may be possible, where radical intermediate **B** abstracts a hydrogen atom from another molecule of ketoester **2**.



Scheme 2. a Further functionalizations; b Three step synthesis of BCP-Ritalin; c Proposed reaction mechanism.

In summary, the visible-light promoted single electron oxidation of β-ketocarbonyl compounds offers a versatile and convenient route to prepare highly congested α- quaternary bicyclo[1.1.1]pentanes. This chemistry displays high functional group tolerance and is applicable to a wide range of substrates including β-ketoesters, β-ketoamides, β-ketonitriles and 1,3-diketones. These products can be further functionalized to afford structurally diverse and medicinally-relevant BCP building blocks, including first-of-kind BCP drug analogues and enantioenriched α-quaternary BCPs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org, including experimental details and copies of ^{1}H and ^{13}C NMR spectra.

AUTHOR INFORMATION

Corresponding Author

* Email: edward.anderson@chem.ox.ac.uk

Present Addresses

¶ Current address: Halda Therapeutics, Branford, CT

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