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Intermolecular Crossed [2 + 2] Cycloaddition Promoted by Visible-Light Triplet Photosensitization: Expedient Access to Polysubstituted 2-Oxaspiro[3.3]heptanes

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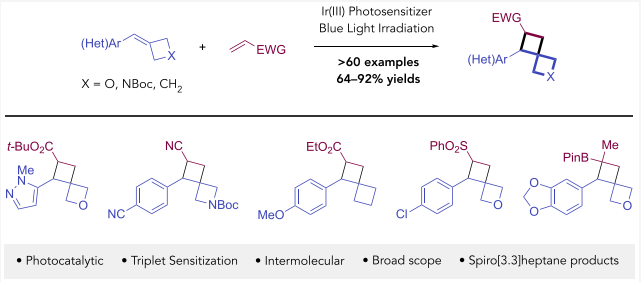
ABSTRACT: This paper describes an intermolecular cross-selective [2 + 2] photocycloaddition reaction of exocyclic arylidene oxetanes, azetidines, and cyclobutanes with simple electron-deficient alkenes. The reaction takes place under mild conditions using a commercially available Ir(III) photosensitizer upon blue light irradiation. This transformation provides access to a range of polysubstituted 2-oxaspiro[3.3]heptane, 2-azaspiro[3.3]heptane, and spiro[3.3]heptane motifs, which are of prime interest in medicinal chemistry as *gem*-dimethyl and carbonyl bioisosteres. A variety of further transformations of the initial cycloadducts are demonstrated to highlight the versatility of the products and enable selective access to either of a *syn*- or an *anti*-diastereoisomer through kinetic or thermodynamic epimerization, respectively. Mechanistic experiments and DFT calculations suggest that this reaction proceeds through a sensitized energy transfer pathway.



INTRODUCTION

Oxetanes are proven isosteres for a variety of functional groups in drug discovery, including *gem*-dimethyl groups and carbonyl compounds (Figure 1A).[1−3] *Gem*-dimethyl groups are widely used in medicinal chemistry for their ability to increase potency, improve metabolic stability, and introduce conformational restriction through the Thorpe-Ingold effect.[4] However, due to the lipophilicity of alkyl groups, their incorporation can often be accompanied by a reduction in aqueous solubility. The replacement of *gem*-dimethyl groups with oxetanes maintains these desirable characteristics while improving the solubility of the drug molecule (Figure 1A).[4] In a similar fashion, oxetanes have found use as replacements for the carbonyl groups of amides, esters, and ketones in drug development. Oxetanes can mimic potential hydrogen-bonding interactions of carbonyl compounds while not being as susceptible to the enzymatic activity of hydrolases and reductases, thus improving the metabolic stability of drug leads.[1]

Oxaspiro[3.3]heptanes, where an oxetane is incorporated into a spirocyclic scaffold, are unique heterocycles which can impart potential therapeutic agents with a variety of desirable properties.[5] Several groups have successfully leveraged the potential of these heterocycles for their pharmaceutical candidates (Figure 1B).[6−8] Expansive efforts to incorporate these spirocycles into candidate molecules however are limited by the current rarity of synthetic methods.[9] The synthesis of compounds containing oxaspiro[3.3]heptanes generally stems from stoichiometric reactions utilizing two building blocks: 3,3-bis(bromomethyl)oxetane or 2-oxaspiro[3.3]heptan-6-one.[10] Indeed, all three of the biologically active compounds in Figure 1B are synthesized using the latter ketone starting material. This typically limits substitution on oxaspiro[3.3]-heptanes to the 5- and 6-position, and the substituent is generally a heteroatom. Thus, rapidly generating oxaspiro[3.3]-heptanes with carbon substituents at multiple positions remains a challenge. For example, accessing the TDO2 inhibitor (Figure 1B) requires a four-step synthetic sequence.[8,11] To date, there have been no catalytic methods described which can synthesize 2-oxaspiro[3.3]heptanes from simple components.[12] Therefore, a general method that could afford functionalized oxaspiro[3.3]heptanes from readily available substrates and in a modular fashion is of interest to the synthetic and pharmaceutical communities.

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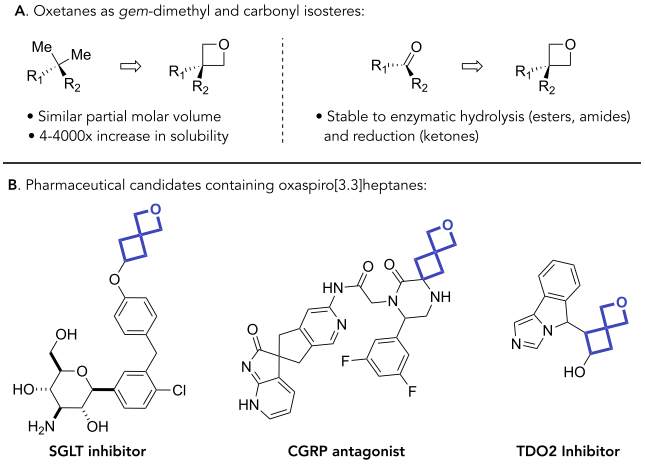
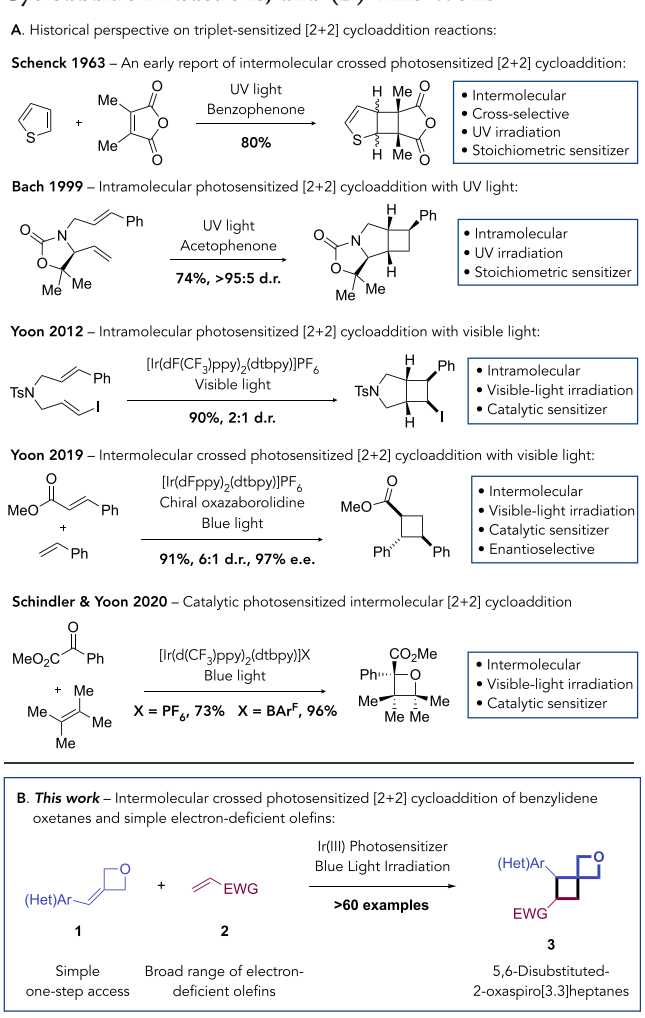


Figure 1. Oxetane and 2-oxaspiro[3.3]heptane motifs in drug-discovery.

A novel and step-economical disconnection to the oxaspiro[3.3]heptane skeleton could involve one of several possible photochemical [2 + 2] cycloaddition reactions, constructing either the oxetane or cyclobutane ring.[13] The earliest examples of these photochemical processes described sunlight-mediated [2 + 2] photodimerization reactions, with the first report published by Liebermann in 1877, concerning the dimerization of thymoquinone in the solid state.[14,15] These early examples proceed through direct irradiation of the organic substrate to form the lowest-energy triplet state (T_1) via excitation to the first singlet excited state (S_1) and subsequent intersystem crossing (ISC). Indirect population of the triplet state of the organic substrate is also possible through an energy transfer process from another photoexcited molecule.[16] This process of sensitization expands the range of organic substrates amenable to [2 + 2] photocycloaddition, and the range of wavelengths of light able to drive the process (Scheme 1A). An early example of a sensitized reaction was reported by Schenck and co-workers in 1963, demonstrating that in the presence of benzophenone under UV irradiation, an intermolecular, crossed [2 + 2] cycloaddition occurs between thiophene and 3,4-dimethylfuran-2,5-dione.[17]

The development of cross-selective intermolecular [2 + 2] cycloaddition reactions remains a challenge, with recent work largely focused on intramolecular variants. For example, in 1999, the Bach group reported a diastereoselective [2 + 2] cycloaddition of a chiral vinylglycine-derived *N*-cinnamyl-*N*-allyl carbamate using acetophenone as a sensitizer under UV irradiation.[18,19] The Yoon group made significant improvements to a similar photosensitized cycloaddition in 2012 by utilizing an Ir(III) dye as a triplet photosensitizer.[20] This enabled the reaction to proceed under visible-light irradiation rather than the highly ionizing UV radiation utilized in previous methods. Since then, the Yoon group has developed a suite of catalytic and enantioselective intermolecular crossed [2 + 2] cycloadditions of cinnamic acid derivatives with 1,3-dienes and styrenes.[21−23] Oderinde, Dhar, and co-workers have recently demonstrated sensitized intra- and intermolecular dearomative [2 + 2] cycloaddition reactions of *N*-acyl (aza)indoles to yield bicyclo-fused (aza)indoline products.[24,25] Very recently, the Schindler and Yoon groups both reported visible light photosensitized [2 + 2] cycloaddition reactions of α-keto esters and alkenes for the synthesis of oxetanes in a notable extension to traditional UV-light mediated Paternò-Büchi reactions.[26,27] Schindler has also described intra- and intermolecular visible light photosensitized aza-Paternò-Büchi reactions between oxime ethers and alkenes for the synthesis of azetidines.[28−30]

Scheme 1. (A) Historical Survey of Photosensitized [2 + 2] Cycloaddition Reactions, and (B) This Work



State-of-the-art intermolecular crossed [2 + 2] cycloadditions are currently limited to these classes of substrates. In this paper, we detail the discovery and development of an intermolecular, cross-selective [2 + 2] cycloaddition reaction between arylidene oxetanes (**1**) and simple electron deficient olefins (**2**) catalyzed by an Ir(III) complex upon blue light irradiation (Scheme 1B). Notably, the reaction generates valuable 5,6-disubstituted 2-oxaspiro[3.3]heptanes (**3**) from these readily available starting materials. In addition, we demonstrate the facile derivatization of these cycloadducts to accomplish broad structural diversification. We note here that these and related exocyclic benzylidene substrates have recently been investigated in the context of copper-catalyzed olefin hydroboration by Engle, Liu, and McAlpine,[31,32] and electrochemical olefin hydrocarboxylation by Malkov and Buckley.[33]

RESULTS AND DISCUSSION

Our studies in this area began through investigation of benzylidene oxetane **1a** toward visible-light mediated olefin hydroamination with secondary alkyl amines, under our

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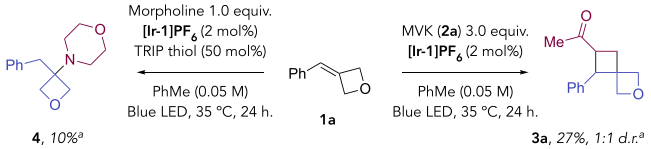
previously described conditions (Scheme 2).[34] In the presence of [Ir(dF(Me)ppy)$_2$(dtbpy)]PF$_6$ ([**Ir-1**]PF$_6$, where dF(Me)-ppy = 2-(2,4-difluorophenyl)-5-methylpyridine and dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) photocatalyst and 2,4,6-triisopropylbenzenethiol (TRIP thiol) HAT cocatalyst, these substrates gave very low yields of the desired tertiary amine products (e.g., **4**, 10% NMR yield). We reasoned that this poor efficiency may be due to competing triplet sensitization of the styrene substrate through energy transfer, as opposed to the intended redox pathway to generate an aminium radical cation intermediate.[35] To probe this hypothesis, we substituted the amine partner for methyl vinyl ketone (MVK, **2a**) and fortuitously observed formation of the corresponding [2 + 2] cycloadducts **3a** as an equal mixture of diastereoisomers in 27% yield by ^{1}H NMR (Scheme 2). Encouraged by this surprising result, we began to further explore this visible-light mediated [2 + 2] photocycloaddition reaction.

We examined the [2 + 2] photocycloaddition of 4-chlorobenzylidene oxetane (**1b**, $E_{p/2}^{ox}$ = +1.33 V vs Fc$^+$/Fc in MeCN, $E_{T\,(calc.)}$ = 56.9 kcal/mol, UB3LYP/6-311++G(d,p) CPCM = MeCN) with methyl vinyl ketone (**2a**) as a model system (Table 1). With 3.0 equiv of acceptor olefin **2a** relative to styrene coupling partner **1b** in PhMe solution under blue light irradiation, [Ir(dF(Me)ppy)$_2$(dtbpy)]PF$_6$ ([**Ir-1**]PF$_6$, E_T = 60.2 kcal/mol)[29] catalyzed the formation of the desired 2-oxaspiro[3.3]heptane **3b** in 25% NMR yield and 1:1 d.r. (entry 1). MeCN proved to be a more suitable solvent for this process, and the same photocatalyst under otherwise identical conditions gave **3b** in 70% NMR yield in 1.6:1 d.r. (entry 2).

Attempting to improve the reaction efficiency, we studied photocatalyst selection. We anticipated that a key determinant in the success of this transformation would be the triplet energy (E_T) of the photocatalyst relative to that of substrate **1b**. Other heteroleptic Ir(III) dyes also proved highly efficient. One of the most commonly employed Ir(III) dyes, [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ ([**Ir-2**]PF$_6$, E_T = 60.1 kcal/mol,[36] where dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine), gave product **3b** in an improved 80% NMR yield and 1.5:1 d.r. (entry 3). [Ir(dF(CF$_3$)-ppy)$_2$(bpy)]PF$_6$ ([**Ir-3**]PF$_6$, E_T = 60.4 kcal/mol)[36] was also highly efficient at promoting the [2 + 2] photocycloaddition, giving 85% NMR yield and 1.4:1 d.r. (entry 4). A related photocatalyst bearing electron-withdrawing −CF$_3$ substituents on the bipyridine ligand, [Ir(dF(CF$_3$)ppy)$_2$(4,4′-d(CF$_3$)bpy)]-PF$_6$ ([**Ir-4**]PF$_6$, E_T = 56.2 kcal/mol),[37] was less efficient (13% NMR yield, 1.7:1 d.r., entry 5), which is consistent with its lower triplet energy. A homoleptic Ir(III) complex, Ir(dFppy)$_3$ ([**Ir-5**], E_T = 60.1 kcal/mol,[36] where dFppy = 2-(2,4-difluorophenyl)pyridine), despite having sufficiently high triplet energy to sensitize styrene **1b**, catalyzed the formation of the desired 2-oxaspiro[3.3]heptane **3b** in only 21% NMR yield and 1.5:1 d.r. (entry 6). On the other hand, the neutral Ir(III) complex [Ir(dF(CF$_3$)ppy)$_2$(pic)] ([**Ir-6**], E_T = 61.1 kcal/mol,[38] where pic = 2-picolinate) displayed high reaction efficiency (82% NMR yield, 1.5:1 d.r., entry 7). Experiments using a cationic Ru photocatalyst with lower triplet energy, [Ru(bpy)$_3$](PF$_6$)$_2$ ([**Ru-1**](PF$_6$)$_2$, E_T = 48.9 kcal/mol,[39] where bpy = 2,2′-bipyridine), led to only trace observable product **3b** (entry 8).

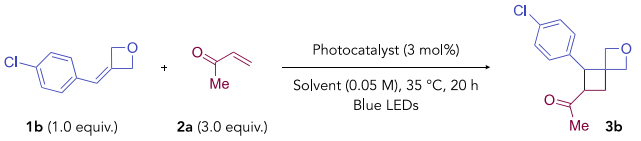
Further improvements were made from an examination of the reaction solvent (Table 1). For example, when performing the [2 + 2] cycloaddition with photocatalyst [**Ir-2**]PF$_6$ in DMF, a more polar solvent than MeCN, a slight increase from 80% to 87% NMR yield was observed (compare entries 3 and 9). An inversion of the major diastereomer and reduction in reaction efficiency is seen when moving to the less polar solvent DCE (entry 11). Best results were obtained when photocatalyst [**Ir-3**]PF$_6$ or [**Ir-6**] were used in *t*-BuCN solvent (94% and 92% NMR yields, entries 13 and 14). Furthermore,

Scheme 2. Reaction Discovery

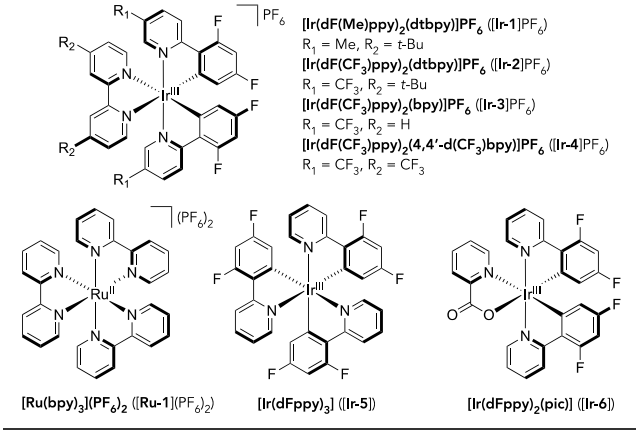


[a]Determined by ^{1}H NMR analysis of crude reaction mixture using dimethyl terephthalate as internal standard.

Table 1. Reaction Optimization



Entry	Photocatalyst	E_T (kcal/mol)	Solvent	d.r.	Yield (%)[a]
1	[**Ir-1**]PF$_6$	60.2	PhMe	1:1	25
2	[**Ir-1**]PF$_6$	60.2	MeCN	1.6:1	70
3	[**Ir-2**]PF$_6$	60.1	MeCN	1.5:1	80
4	[**Ir-3**]PF$_6$	60.4	MeCN	1.4:1	85
5	[**Ir-4**]PF$_6$	56.2	MeCN	1.7:1	13
6	[**Ir-5**]	60.1	MeCN	1.5:1	21
7	[**Ir-6**]	61.1	MeCN	1.5:1	82
8	[**Ru-1**](PF$_6$)$_2$	48.9	MeCN	n.d.	<5
9	[**Ir-2**]PF$_6$	60.1	DMF	1.5:1	87
10	[**Ir-3**]PF$_6$	60.4	DMF	1.6:1	80
11	[**Ir-3**]PF$_6$	60.4	1,2-DCE	1:1.2[b]	46
12	[**Ir-3**]PF$_6$	60.4	*t*-BuCN	1.4:1	95
13[c]	[**Ir-3**]PF$_6$	60.4	*t*-BuCN	1.4:1	94
14[c]	[**Ir-6**]	61.1	*t*-BuCN	1.5:1	92
Changes to entry 14:					
15	No Photocatalyst			n.d.	<5
16	No Light			n.d.	<5



[a]Determined by ^{1}H NMR analysis of crude reaction mixtures using 1,2-dibromoethane as internal standard. [b]Inverse diastereoisomer ratio observed. [c]Carried out at 0.1 M and 2.5 mol % catalyst loading.

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the reaction works equally well when carried out at a higher concentration (0.1 M) and with reduced catalyst loading (2.5 mol %). Control experiments revealed the requirement for both photocatalyst and visible light irradiation (entries 15 and 16). Data from additional optimization experiments are presented in the Supporting Information (Tables S1, S2).[40] Importantly, in its photoexcited state, [**Ir-6**] dye is less oxidizing ($E_{1/2}$ Ir(III)*/Ir(II) = +0.89 V vs Fc^+/Fc in MeCN)[41] than cationic [**Ir-3**]PF_6 ($E_{1/2}$ Ir(III)*/Ir(II) = +0.94 V vs Fc^+/Fc);[42] thus, [**Ir-6**] is expected to be more chemoselective in general for an energy transfer process and was chosen for further investigation of substrate scope.

Having established the optimal reaction conditions, we next examined the scope of this visible-light promoted [2 + 2] cycloaddition. We were pleased to find that a wide array of substituted benzylidene oxetanes **1** participated in the reaction to give 2-oxaspiro[3.3]heptane products **3** in high yields (65−89%, Scheme 3A). Substituents at the *para* (**3b**-**3i**), *meta* (**3j** and **3k**), and *ortho* (**3l**) positions on the phenyl ring are well tolerated. In addition, these substituents can be either electron-withdrawing, such as −Cl, −F, $-CF_3$, and −CN (**3b**, **3c**, **3f**, and **3h**), or electron-donating, such as −Me, −OMe, and $-SiMe_3$ (**3d**, **3e**, and **3i**).

As shown in Scheme 3B,C, this [2 + 2] protocol is highly tolerant of a wide range of heteroaromatic substrates. 2-Oxaspiro[3.3]heptanes appended to thiophene (**3n**), furan (**3o**), imidazole (**3p**), pyrazole (**3q**), indole (**3r**), indazole (**3s**), benzoxazole (**3t**), and isoquinoline (**3u**) rings can all be efficiently synthesized (82−88% isolated yields). Given the prevalence of heteroaromatic rings in pharmaceuticals,[43−45] we are hopeful that this cycloaddition methodology will find utility in drug discovery efforts.

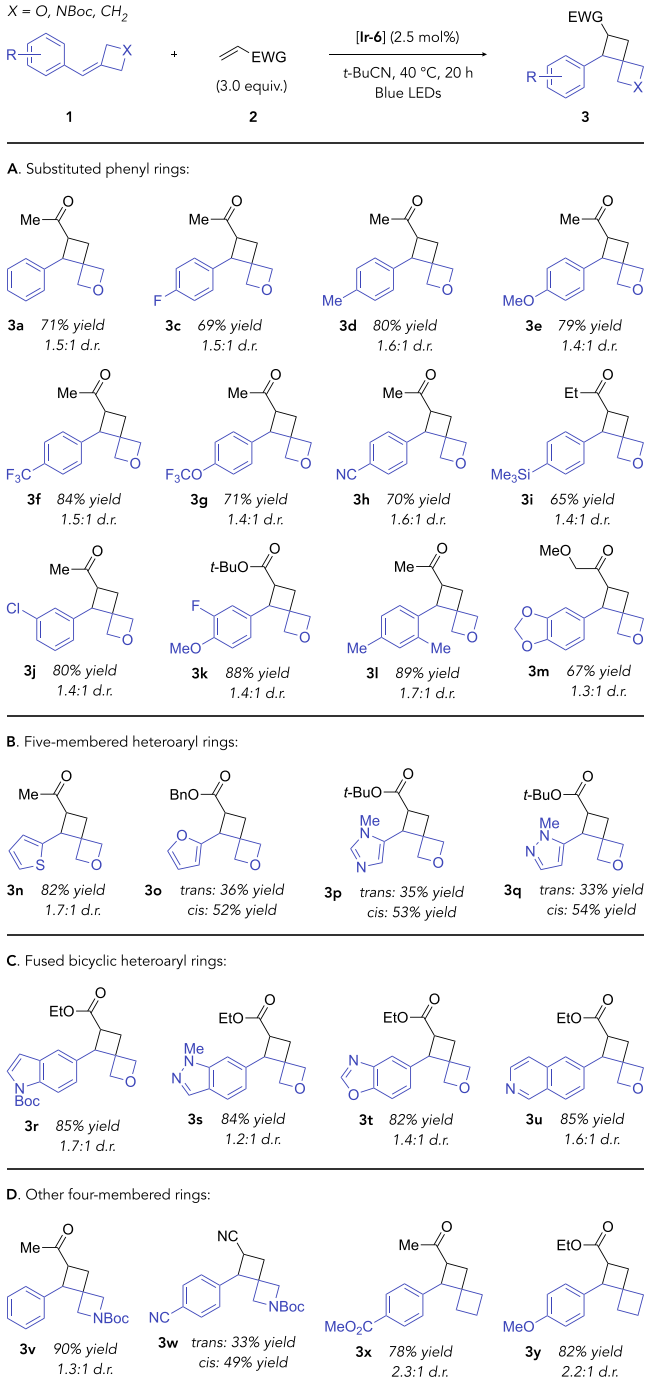
Furthermore, as shown in Scheme 3D, the [2 + 2] reaction is not limited to oxetane substrates but also works well with other exocyclic benzylidene 4-membered ring substrates, such as *N*-Boc azetidines (**3v** and **3w**, 90% and 82% yield) and cyclobutanes (**3x** and **y**, 78% and 82% yield). Indeed, the obtained substituted 2-azaspiro[3.3]heptane and spiro[3.3]-heptane ring systems are important building blocks for pharmaceutical development and are otherwise difficult to synthesize by conventional methods.[9,46]

With respect to the alkene coupling partner **2**, various acrylic acid derivatives behave well, affording the anticipated 2-oxaspiro[3.3]heptane cycloadducts in good yields (64−90%, Scheme 4). Notably, electron-withdrawing groups such as ester (**3zf** and **3aa**), amide (**3ab** and **3ac**), Weinreb amide (**3ad**), nitrile (**3ae**), unprotected carboxylic acid (**3af**), sulfone (**3ag**), and Bpin (pin = pinacolato) (**3ej**) are all are tolerated in the [2 + 2] photocycloaddition process.

Importantly, this protocol also works well with more densely substituted alkenes (Scheme 4). For example, α-methyl substituted acrylate and vinyl-Bpin substrates are converted to 2-oxaspiro[3.3]heptane products with a tetrasubstituted carbon atom in high yields (90% **3ah**, and 88% **3ak**). Additionally, *N*-methyl maleimide is highly reactive toward [2 + 2] cycloaddition and affords the intriguing tricyclic product **3ai** in 86% combined yield of both diastereomers. A more exhaustive list of obtainable 2-oxaspiro[3.3]heptane products (>60 examples) is compiled in the Supporting Information (Figure S3).[40]

Across all substrates, diastereoselectivity remains moderate (up to 2.0:1 d.r.) but, in favorable cases, the two diastereomeric products can be readily separable by silica gel

Scheme 3. Arylidene Scope[a]



[a]Conditions: **1** (1.0 equiv), **2** (3.0 equiv), [**Ir-6**] (2.5 mol %) in *t*-BuCN (0.1 M).

column chromatography and isolated in high yields. Furthermore, diastereomeric ratios can be greatly improved by subjecting crude cycloadducts to base-catalyzed epimerization (Scheme 5A,B). The major diastereomer was assigned as *syn* by comparison of ^{1}H NMR spectra of product **3x** to those of a reported compound with known stereochemistry,[46] and this assignment was extended by analogy across the scope of the transformation.

Of particular significance is the synthetic versatility of the substituted 2-oxaspiro[3.3]heptane cycloadducts. Therefore, we investigated a range of derivatization reactions that convert

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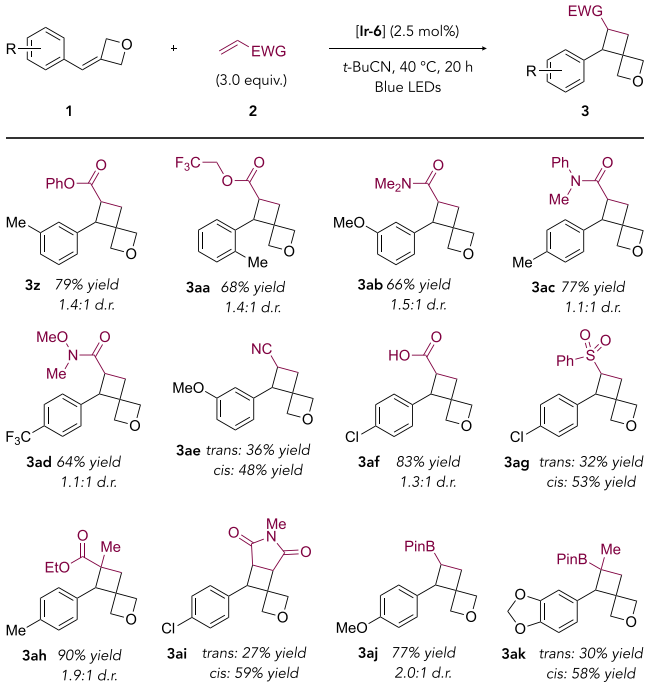
Scheme 4. Electron Deficient Alkene Scope[a]



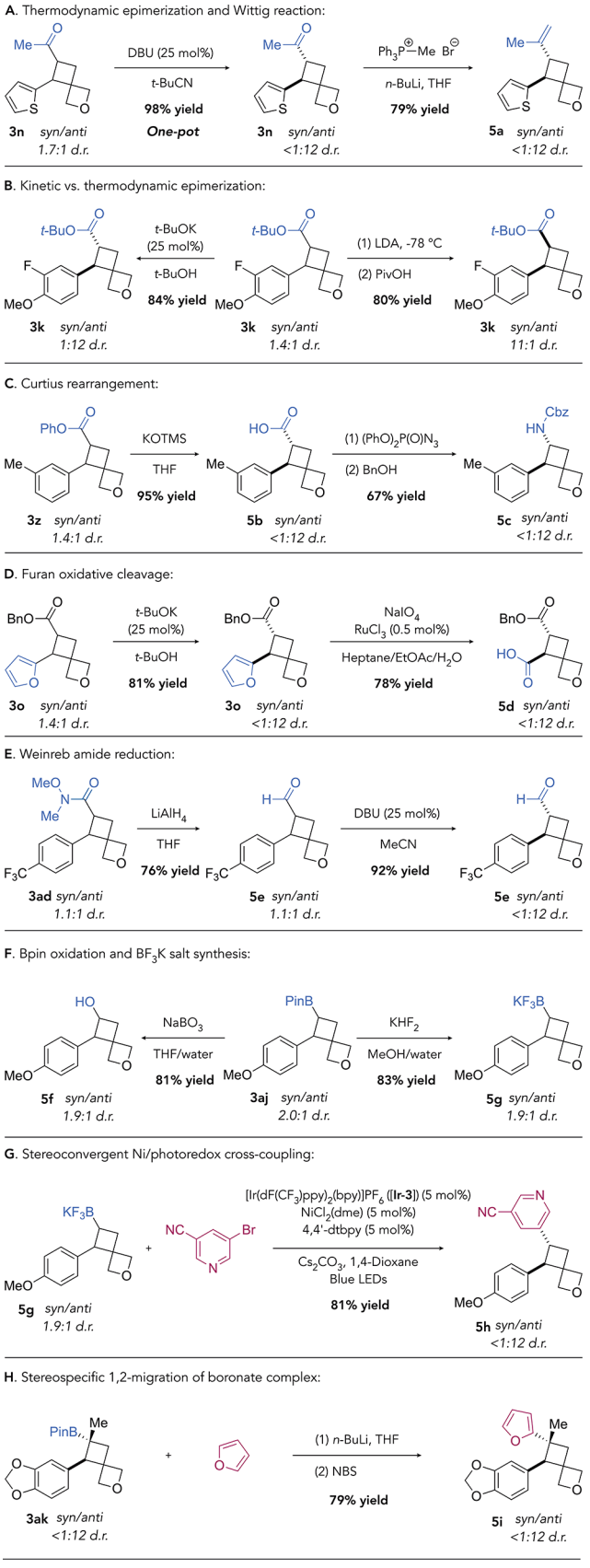
[a]Conditions: **1** (1.0 equiv), **2** (3.0 equiv), [**Ir-6**] (2.5 mol %) in *t*-BuCN (0.1 M).

these primary products into value-added fragments (Scheme 5). Given that a limitation of the above photocycloaddition is the low to moderate diastereoselectivity observed, we sought to investigate the epimerization of the carbonyl substituent. Products such as **3n** that contain a methyl ketone functional group are readily epimerized postreaction by simply stirring the crude mixture with catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 5A). This one-pot procedure gives highly diastereomerically enriched *anti*-stereoisomers (>12:1 d.r.) and is applicable to a broad range of methyl ketone-bearing products (see the Supporting Information for more examples).[40] Epimerized product *anti*-**3n** can be subjected to subsequent reactions such as the Wittig olefination to yield **5a** without erosion of the *anti*-stereochemistry (Scheme 5A).

The stronger base *t*-BuOK is required to epimerize ester-containing products such as **3k** (Scheme 5B). In addition to "thermodynamic" epimerization that affords the *anti*-stereoisomer, these products are readily converted to the opposite *syn*-stereoisomer *via* "kinetic" epimerization with lithium diisopropylamide (LDA) at low temperature, followed by protonation with pivalic acid (PivOH). This ability to selectively access both diastereomers of product **3k** compensates for the low diastereoselectivity in the [2 + 2] cycloaddition step and showcases the synthetic value of the method.

In addition, pharmaceutically relevant cyclobutylamines are easily accessed from [2 + 2] cycloaddition products by Curtius rearrangement (Scheme 5C). For example, the ester moiety of 2-oxaspiro[3.3]heptane **3z** is first hydrolyzed with potassium trimethylsilanoate (KOTMS) (**5b**), followed by conversion to the acyl azide and Curtius rearrangement to the desired *N*-Cbz cyclobutylamine **5c** in 64% yield over the two steps. Importantly, the initial ester hydrolysis takes place with concomitant *anti*-epimerization, while the subsequent Curtius rearrangement is stereospecific. The net result is thus a

Scheme 5. Synthetic Derivatization of Products[a]



[a]A diastereomeric ratio >12:1 d.r. refers to the limit of detection of the NMR instrument.

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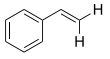
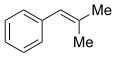
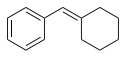
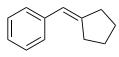
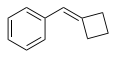
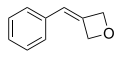
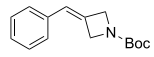
Table 2. Collected Voltammetric, Computational, and Spectroscopic Results

	 6	 7	 8	 9	 10	 1a	 1v
Yield of [2+2] with MVK (**2a**) /NMR%[a]	<5%	28%, 1:1 d.r.	17%, 2.4:1 d.r.	13%, 2:1 d.r.	88%, 2.7:1 d.r.	83%, 1.5:1 d.r.	95%, 1.1:1 d.r.
Oxidation Potential $E_{p/2}^{ox}$ /V vs Fc^+/Fc in MeCN	+1.52	+1.20	+1.16	+1.12	+1.16	+1.35	+1.35
E_T (calc.) /kcalmol^{-1} [b]	57.8	58.0	58.4	56.7	56.8	57.4	57.7
K_{SV} /M^{-1} in MeCN (with **Ir-6**)	1619	664	284	3423[c]	3295	3130	2650

[a]Conditions: Styrene (1.0 equiv), **2a** (3.0 equiv), [**Ir-6**] (2.5 mol %) in *t*-BuCN (0.1 M), blue LED irradiation, 40 °C, 20 h. [b]UB3LYP/6-311++G(d,p), CPCM MeCN. [c]Nonlinear quenching observed at high sample concentration. Linear fit made at low sample concentration to determine K_{SV}. See Supporting Information and ref 53.

stereoconvergent process where the starting *syn*/*anti*-**3z** 1.4:1 mixture is converted to highly enriched *anti*-cyclobutylamine product **5c**.

The furan ring of cycloadduct **3o** is oxidatively cleaved in 78% yield under mild conditions using a recent Ru-catalyzed protocol from Bull and co-workers (Scheme 5D).[47] This affords a versatile diacylated 2-oxaspiro[3.3]heptane building block (**5d**) with two orthogonal functional handles—a free carboxylic acid and a benzyl ester—for subsequent incorporation into drug candidates.

Being unstable and prone to polymerization, acrolein is not a competent substrate for this [2 + 2] photocycloaddition. However, the readily accessible product **3ad** is converted to its corresponding aldehyde in 76% yield by reduction of the Weinreb amide moiety (Scheme 5E). Moreover, the product aldehyde is readily epimerized to its pure *anti*-stereoisomer with catalytic DBU to afford **5e**.

2-Oxaspiro[3.3]heptane products obtained by [2 + 2] cycloaddition of vinyl-Bpin are versatile synthetic intermediates. For example, the Bpin group of **3aj** is oxidized in 81% yield to give a valuable cyclobutanol derivative (**5f**, Scheme 5F). Alternatively, cycloadduct **3aj** is smoothly converted to its corresponding BF_3K salt (**5g**) by treatment with potassium hydrogen difluoride. This BF_3K salt can then be cross-coupled to a pyridyl bromide under Molander's Ni/photoredox conditions[48,49] to give a drug-like 2-oxaspiro[3.3]heptane derivative in 81% yield (**5h**, Scheme 5G). Importantly, this process is stereoconvergent,[50] affording highly enriched *anti*-product (<1:12 d.r.) starting from a 1.9:1 *syn*/*anti* BF_3K salt mixture.

A more complex product containing an all-carbon quaternary center is derived from cycloadduct **3ak** by 1,2-migration of a boronate complex (Scheme 5H).[51] Starting from the purified diastereomer *anti*-**3ak**, the Bpin "ate" complex is first formed *in situ* by addition of lithiated furan. Stereospecific 1,2-migration is then induced by electrophilic bromination with *N*-bromosuccinimide (NBS) to give desired product **5i** in 79% yield. Additional synthetic product derivatizations are compiled in the Supporting Information.[40]

Excited by the synthetic utility of this methodology, we sought to study its mechanism through electrochemical and spectroscopic techniques and density-functional theory (DFT) calculations. These studies were carried out across a series of seven styrenes (**6**−**10**, **1a**, **1v**), where the nature of the *β*,*β*-substituents and ring size at the styrene terminus were systematically varied (Table 2). We were particularly interested to probe the origin of the superior reactivity of this class of benzylidene-substituted 4-membered ring substrates toward intermolecular [2 + 2] photocycloaddition in comparison to other styrenes in this series and in general (Table 2, line 1). For example, only trace reactivity was observed between parent styrene (**6**) and methyl vinyl ketone (**2a**) under the optimized reaction conditions for this photochemical [2 + 2] reaction. With *β*,*β*-dimethylstyrene (**7**), benzylidene cyclohexane (**8**), and benzylidene cyclopentane (**9**), only low levels of reactivity were observed (≤28% NMR yields). Only with four-membered ring benzylidene cyclobutane (**10**), oxetane (**1a**), and azetidine (**1v**) substrates were highly efficient cycloaddition reactions realized (≥83% NMR yields). In all cases, remaining mass balance was recovered starting material.

Cyclic voltammetry was performed on each of these substrates to study the feasibility of a redox mechanism for this transformation (Table 2, line 2). The oxidation potentials $E_{p/2}^{ox}$ of all seven styrene derivatives in this series are significantly greater than ($\Delta E_{p/2}^{ox} \geq 240$ mV) that of the photoexcited state of the [**Ir-6**] catalyst ($E_{1/2}$ Ir(III)*/Ir(II) = +0.88 V vs Fc^+/Fc in MeCN).[41] Triplet energies of the seven substrates at the planar 1,2-triplet geometry were computed (Table 2, line 3, UB3LYP/6-311++G(d,p) CPCM = MeCN). These show little difference across the series and all fall within the range 56.7−58.4 kcal/mol, slightly below that of the triplet energy of the optimal [**Ir-6**] photocatalyst (E_T = 61.1 kcal/mol).[38] These combined data, in addition to the observed trends in reaction efficiency as a function of the photocatalyst triplet energy (Table 1), strongly suggest that this [2 + 2] process proceeds via an energy transfer mechanism as opposed to an electron transfer pathway.[52] We can also rule out a change in mechanism between sensitization and electron transfer accounting for the differential reactivity observed across the series.

Steady-state Stern−Volmer luminescence quenching studies were performed to study the possibility of a selective quenching mechanism (Table 2, line 4). All styrene substrates across this series show efficient quenching of the photoexcited state of [**Ir-6**].[53] Methyl vinyl ketone (**2a**) showed very minimal luminescence quenching (K_{SV} = 0.02 M^{-1}) with [**Ir-6**]. This observation is consistent with the triplet energy of acyclic enones being higher than that of this Ir(III) dye (typically ≥63 kcal/mol).[54,55] These data indicate that the styrene component of the reaction is selectively sensitized before reaction with the closed-shell electron-deficient olefin. Compared to the parent styrene (**6**, K_{SV} = 1619 M^{-1}), *β*,*β*-

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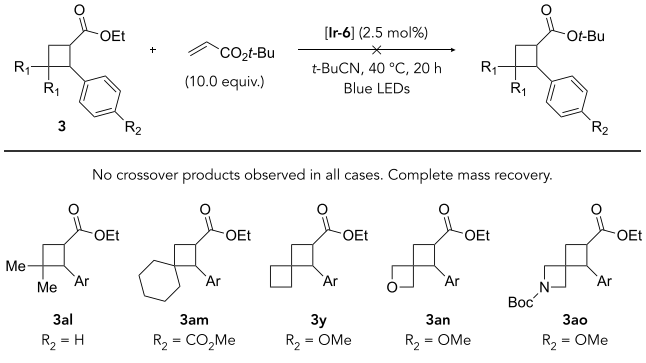
dimethylstyrene (**7**) and benzylidene cyclohexane (**8**) quench the photocatalyst less efficiently (K_{SV} = 664 M^{-1}, and 284 M^{-1} respectively). This can be understood when considering the torsional strain across the olefin-arene C−C bond ($\theta_{calc.}$ = 38° and 43°, respectively) twisting the olefin out of conjugation due to a destabilizing steric interaction between the β-substituent and the arene. This unfavorable interaction is alleviated through contraction of the ring size on moving to 5- and 4-membered rings, and thus more efficient quenching is seen (K_{SV} = 3423 M^{-1}, 3295 M^{-1}, 3130 M^{-1}, and 2650 M^{-1} for **9**, **10**, **1a**, and **1v**, respectively). Though our studies indicate that the reactive 4-membered ring substrates are indeed more efficient quenchers than some poorly reactive examples, the magnitude of this increase is not sufficient to account for their privileged reactivity. In addition, benzylidene cyclopentane (**9**) quenches this photocatalyst most efficiently across this series, yet still displays poor reactivity in this protocol (13% NMR yield with **2a**). Thus, a selective quenching mechanism does not account for the superior efficiency of these 4-membered ring substrates.

To study whether the [2 + 2] cycloaddition is reversible under the reaction conditions and if isolated yields are in fact a reflection of varying photostationary states, we carried out a set of crossover experiments (Scheme 6). A number of reaction products of the efficient 4-membered ring substrates and inefficient benzylidene cyclohexane and dimethylstyrene substrates were subjected to otherwise standard reaction conditions in the presence of 10.0 equiv of *t*-Bu acrylate. In all cases, no *t*-Bu ester-containing crossover products were observed, confirming that the reaction is irreversible from the closed-shell spiro[3.3]heptanes. Mass recovery was essentially complete in all cases and diastereoisomeric ratios were unchanged.

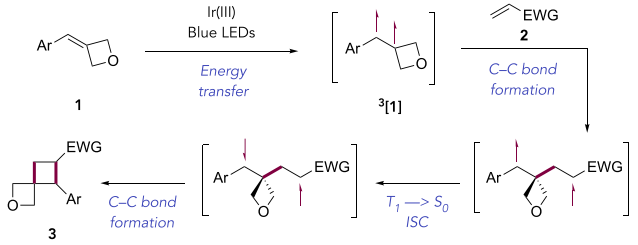
Taken together, our studies are supportive of the following mechanistic picture (Scheme 7). Visible light excitation of the Ir(III) photocatalyst yields an excited state complex which sensitizes the benzylidene oxetane substrate (**1**) through energy transfer. The resultant 1,2-triplet styrene (^{3}[**1**]) engages in intermolecular C−C bond formation with a closed-shell electron deficient olefin partner (**2**), yielding a 1,4-triplet diradical. Intersystem crossing (ISC) then forms a 1,4-singlet diradical, through which subsequent C−C bond formation yields the [2 + 2] product **3**. Success or failure to yield [2 + 2] product across a series of seven studied styrenes is a function

Scheme 6. Crossover Experiments to Rule Out Reaction Reversibility[a]



[a]Conditions: **3** (1.0 equiv), *t*-Bu acrylate (10.0 equiv), [**Ir-6**] (2.5 mol %) in *t*-BuCN (0.1 M).

Scheme 7. Proposed Mechanism for the Formation of 2-Oxaspiro[3.3]heptanes



of the ring size at the styrene terminus, with 4-membered rings exclusively displaying high reactivity. The collected spectroscopic, voltammetric and computational observations to date (Table 2) do not yet explain the superior reactivity toward intermolecular [2 + 2] cycloaddition of this substrate class compared to other styrenes. Neither a selective quenching of the photoexcited state Ir(III) complex across the series, nor a change in mechanism between energy and electron transfer, for example, is operative. The reaction is irreversible from the closed-shell cyclobutane products, so isolated yields are not a reflection of any photostationary state. This unusual observation will be the subject of follow-up theoretical studies which are beyond the scope of this initial synthetic report.

In summary, we have developed an intermolecular cross-selective [2 + 2] cycloaddition of exocyclic arylidene oxetanes, azetidines, and cyclobutanes with electron-deficient alkenes promoted by visible-light triplet photosensitization. The described methodology is remarkably general in terms of scope, and its high synthetic value is showcased by the synthetic versatility of the obtained cycloadducts. The reaction reported herein provides expedient access to polysubstituted 2-oxaspiro[3.3]heptane, 2-azaspiro[3.3]heptane, and spiro[3.3]-heptane ring systems which are frequently incorporated into drug candidates as *gem*-dimethyl and carbonyl bioisosteres.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01173.

Coordinate files (ZIP)

Reaction Procedures, product characterizations, mechanistic and computational details, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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