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Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2023 December 28.

Published in final edited form as:

J Am Chem Soc. 2022 December 28; 144(51): 23685–23690. doi:10.1021/jacs.2c11501.

Photochemical Intermolecular [3σ+2σ]-Cycloaddition for the Construction of Aminobicyclo[3.1.1]heptanes

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Abstract

The development of synthetic strategies for the preparation of bioisosteric compounds is a demanding undertaking in medicinal chemistry. Numerous strategies have been developed for the synthesis of bicyclo[1.1.1]pentanes (BCPs), bridge-substituted BCPs and, bicyclo[2.1.1]hexanes. However, progress on the synthesis of bicyclo[3.1.1]heptanes, which serve as *meta*-substituted arene bioisosteres, has not been previously explored. Herein, we disclose the first photoinduced [3σ+2σ] cycloaddition for the synthesis of trisubstituted bicyclo[3.1.1]heptanes using bicyclo[1.1.0]butanes and cyclopropylamines (CPAs). This transformation not only uses mild and operationally simple conditions, but also provides unique *meta*-substituted arene bioisosteres. The applicability of this method is showcased by some derivatization reactions.

Graphical Abstract

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Supporting Information.
A general procedure for the preparation of starting materials as well as the protocol for the [3+2] cycloaddition is described. Derivatization reactions details, quantum yield experiment, TEMPO experiment, X-ray details and full characterization (including NMR spectra) of all materials prepared is also included.

Keywords

Bicyclo[3.1.1]heptanes; Photoredox; Cyclopropylamines; Bicyclo[1.1.0]butane; [3σ+2σ]-Cycloaddition

Bicyclic hydrocarbons have demonstrated the ability to replace aromatic rings in therapeutic molecules, providing greater solubility and metabolic stability, along with enhanced pharmacokinetic properties. Because of these enhanced properties, these bioisosteric scaffolds have received considerable attention in drug molecular design.[1] One of the most studied among small-ring cage hydrocarbons are bicyclo[1.1.1]pentanes (BCPs),[2] which serve as a bioisosteric replacement of *ortho*- and *para*-substituted phenyl rings as well as the *tert*-butyl group.[3] Synthetic organic chemists have also made great progress in the development of new synthetic methods that provide geometrically complementary *meta*-substituted arene bioisosteres. However, these architectures have been explored using mainly bridge-substituted BCPs[4] and bicyclo[2.1.1]hexanes,[4,5] although these motifs do not exactly mimic the bond vectors displayed in *meta*-substituted arenes. The preparation of bioisosteres that precisely reproduce the geometrics of *meta*-substituted arenes is a challenge from a synthetic point of view. Recently, the preparation of difunctionalized bicyclo[3.1.1]heptanes using [3.1.1]propellane as a feedstock demonstrates that these substructures can serve as *meta*-substituted arene analogues (Figure 1).[6]

Cyclopropylamines (CPAs) have shown their versatility as building blocks to access highly valuable nitrogenated organic motifs.[7] They are extremely useful in [3+2] annulation reactions with alkenes for the construction of more complex cyclic amines.[7c] Their use as synthetic scaffolds arises from an irreversible ring-opening upon an initial oxidation to the nitrogen radical cation.[7f] In 1998 Cha[8] and Iwata[9] disclosed the use of *N,N*-dialkyl aminocyclopropanes bearing an alkene group for the construction of amino octahydropentalenes. In the development of photochemical [3+2] cycloadditions for the synthesis of bicycloaminoalkanes, bicyclic cyclopropylamines were used in an intermolecular approach using a ruthenium photocatalyst.[7a] Later, intra-[10] and intermolecular[11] cycloaddition reactions utilizing amino/iminocyclopropanes and alkenes (Figure 2) were reported.

Bicyclo[1.1.0]butanes (BCBs) have received increasing attention[12] by the chemistry community for the synthesis of small ring systems because of their ability to engage in ring-opening reactions with different partners,[13] including radical species. We envisioned that a photoredox [3σ+2σ] cyclization reaction could be applied using cyclopropylamines

and bicyclo[1.1.0]butanes. This reaction design would provide unique functionalized bicyclo[3.1.1]heptanes, which expands chemical space because of the several diversifiable positions on the bicyclo[3.1.1]heptane ring. Additionally, this bicyclic motif can potentially act as a precise *meta*-substituted arene bioisostere.[6] To the best of our knowledge, the photoinduced construction of bicyclo[3.1.1]heptanes has never been previously explored. This photocatalytic approach would overcome the challenge for the construction of multifunctionalized bicyclo[3.1.1]heptanes in a sustainable and straightforward manner.

BCB **1a** and CPA **2a** were chosen as representative substrates for optimization of reaction conditions. First, considering that the choice of photocatalyst significantly impacts the product formation, and that the oxidation potential of cyclopropylanilines is around 0.80 V vs SCE,[7a,f] we initiated the studies utilizing $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ ($E_{1/2}$ $*Ir^{III}/Ir^{II}$ = 1.21 V vs SCE)[14] in DMSO as solvent. Under these conditions the bicyclic compound **3** was obtained in 70% yield (Table 1 entry 1). The exploration of other photocatalysts (Table 1 entries 2–5) did not provide better efficiency toward the formation of the desired product. Next, other solvents were examined using the optimal photocatalyst, but no improvement was achieved (Table 1 entries 6–9). The photochemical nature of this transformation was confirmed when the reaction was performed either in the absence of photocatalyst (Table 1, entry 10) or light (Table 1, entry 11). Finally, the presence of the radical scavenger TEMPO in the reaction completely inhibited the formation of compound **3** (Table 1, entry 12) and unreacted **1a** was observed by GCMS analysis (see Supporting Information). Of note, this transformation provides unprecedented access to functionalized, fully assembled bicyclo[3.1.1]heptane **3** in a single step from readily available BCB[15] **1a** and CPA **2a**.

Once the optimization reaction conditions were suitable for the development of this [3σ+2σ] cyclization reaction, the scope of the process using different CPAs was explored. This transformation works especially well with electron-withdrawing groups in the aryl ring of the *N*-cyclopropylaniline. The *p*-chlorophenyl-substituted CPA gave the desired compound **4** in 36% yield, but the presence of a fluorine atom in the *meta* position (**5**) as well as in the *ortho*- and *para* positions (**6**) provided the desired products in much higher yield. The presence of strongly deactivating groups such as trifluoromethyl (**7**) and difluoromethyl (**8**) gave the corresponding aminobicyclo[3.1.1]heptanes in 63 and 65%, respectively. Incorporation of the medicinally relevant trifluoromethoxy group afforded access to compound **9** in 62% yield. Of note, detailed NMR studies as well as the single crystal X-ray analysis of compound **9** (see Supporting Information) confirm the 3-dimensional structures of the 4-aminobicyclo[3.1.1]heptanes. Phenyl- and 1,3-dioxolanyl-substituted CPAs provided **10** and **11**, respectively, in moderate yields. An electron-rich methoxy-substituted derivative group showed reactivity, although the desired product (**12**) was accessed in low yield. This result is not surprising given that the more electronically rich cyclopropylanilines are known to promote easier SET, while at the same time undergoing CPA ring-opening at a slower rate.[16] Alkyl groups in the *para*- or *ortho* position showed good reactivity (**13** and **14**). Finally, some heteroarene-based amines were tested because of their outsized use in medicinal chemistry. Of note, benzothiophene (**15**) and benzofuran (**16**) motifs were well tolerated, providing the desired products in 51 and 47% yield, respectively. To explore further the use of heterocycles in this transformation, quinoline (**17**) and pyridine

(**18**) derivatives were incorporated, although the desired products were isolated in lower yields.

Subsequently, the scope was further extended to the modification of the BCB ring. In general, we observed good reactivity toward the formation of the desired 4-aminobicyclo[3.1.1]heptanes when the BCB was tethered to an electron-poor arene. Thus, the presence of fluorine (**20** and **21**) and chlorine (**22**) substituents, as well as the *p*-trifluoromethylphenyl derivative (**23**), gave the corresponding products in good yields. Finally, *m*-CF_3 (**24**) and more electronically rich substituents (**25**-**28**) furnished the final compounds in moderate yields.

Given previous literature precedents,[10,11,17] a mechanism for the presented photoinduced aminobicyclo[3.1.1]heptane synthesis is postulated in Scheme 1. After photoexcitation of the Ir^{III} photocatalyst by blue light irradiation, the photoexcited state (Ir^{III}*) ($E_{1/2}$ *Ir^{III}/Ir^{II} = 1.21 V vs SCE) is accessed.[14] Single-electron transfer to the cyclopropylaniline (**2**) ($E_{1/2}$ = 0.80 V vs SCE)[7a,f] induces the formation of the radical cation species (***I***) followed by ring opening *via* β-scission to the distonic radical cation (***II***). Subsequent addition of this reactive intermediate to BCB **1** furnishes another relatively stabilized distonic radical cation where the radical is localized in a secondary benzylic position (***III***). Subsequently, this species (***III***) undergoes cyclization, providing access to the radical cation (***IV***). At this stage, (***IV***) could be reduced by the Ir^{II} species generated in the reductive quenching photoredox cycle or it can be reduced by the presence of the cyclopropylaniline **2a**. Given these two mechanistic scenarios, we explored the photochemical quantum yield of this transformation. We observed a quantum yield (ϕ) value of 0.47. Although the quantum yield is lower than 1, it does not guarantee a closed catalytic cycle.[18] Given that single-electron transfer processes with amines are highly influenced by post-oxidation reactivity, a propagative mechanistic pathway is a more likely process because the reduction of ***IV*** by **2a** is an enthalpically-driven step.[19] This artificially low quantum yield value was also observed in other photochemical [3+2] cycloadditions reactions based on the use of CPA.[10a]

To showcase the applicability of the preparation of bicyclo[3.1.1]heptanes toward further functionalization, we prepared four different 4-anilinyl bicyclo[3.1.1]heptane derivatives (Scheme 2, **29**-**32**), forming new C-C, C-O and C-N bonds. First, compound **25** was functionalized to the corresponding 3-oxobutanenitrile **29** in 73% yield using a combination of acetonitrile and LDA. This functional unit, containing α-methylene active protons, offers further opportunities for postfunctionalization. Subsequently, **25** was hydrolyzed to the corresponding carboxylic acid (**30**) in excellent yield, which was further coupled with estrone to provide **31** in 80% yield. Additionally, **30** was transformed to amide **32** in 85% yield. This Weinreb-type[20] amide **32** serves as a carbonyl precursor for the formation of ketones, aldehydes, or alcohols.

In summary, a general and highly practical method for the construction of 4-aminobicyclo[3.1.1]heptanes under mild conditions has been developed. The well-orchestrated and serialized mechanism steps furnished new bicyclo[3.1.1]heptanes containing a wide range of functional groups. Derivatization to other functional groups has also been achieved. Overall, the photochemical [3σ+2σ] annulation reaction presented

herein enables access to unprecedented 4-aminobicyclo[3.1.1]heptanes assembled from BCBs and CPAs. These structures appear likely to serve as useful *meta*-disubstituted arene bioisosteres in the drug discovery field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The authors thank Dr. Jun Gu for assistance in carrying out 2D NMR studies, Dr. Charles W. Ross, III (University of Pennsylvania) for obtaining HRMS data, and Kessil Lighting for lights used in this study.

Funding Sources

The authors are grateful for financial support provided by NIGMS (R35 GM 131680 to G.M.) and NIH NCI (R21 EB 032027 to M.M.). Financial support for this research was also provided in part by AbbVie. The NSF Major Research Instrumentation Program (Award NSF CHE-1827457), the NIH Supplement Awards 3R01GM118510-03S1 and 3R01GM087605-06S1, and the Vagelos Institute for Energy Science and Technology supported the purchase of the NMRs used in this study.

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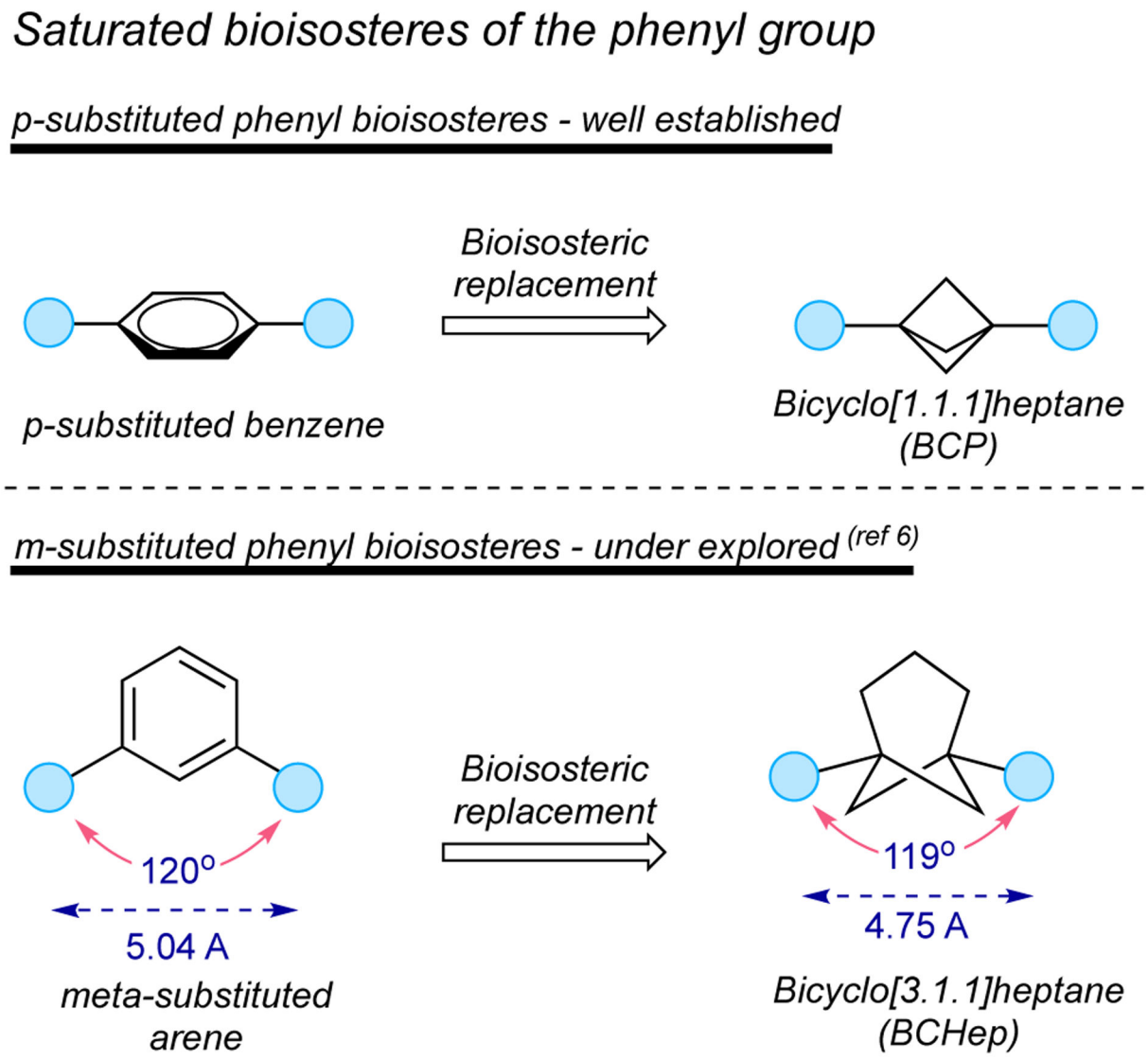


Figure 1.
Comparison of *para*- and *meta*-substituted arene ioisosteres

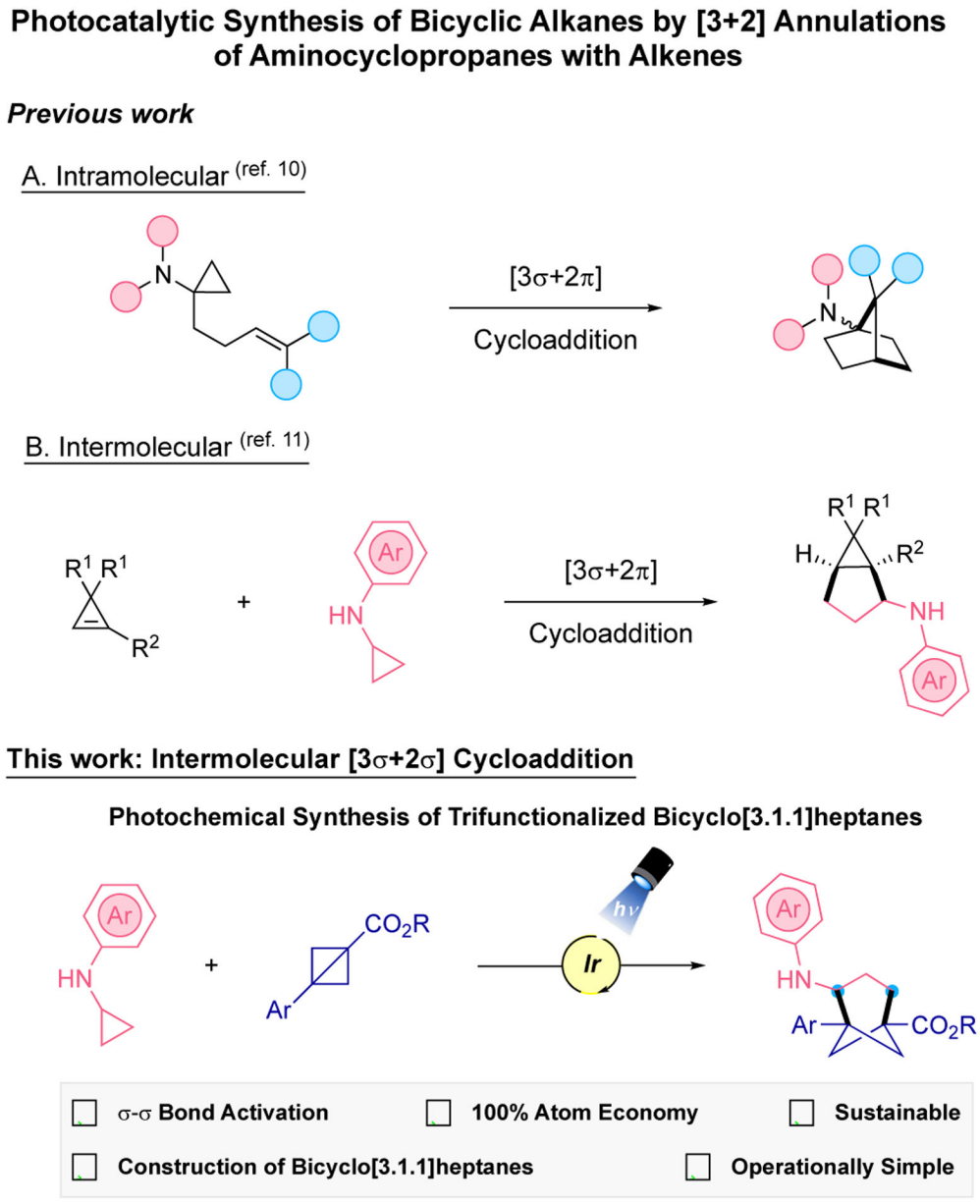
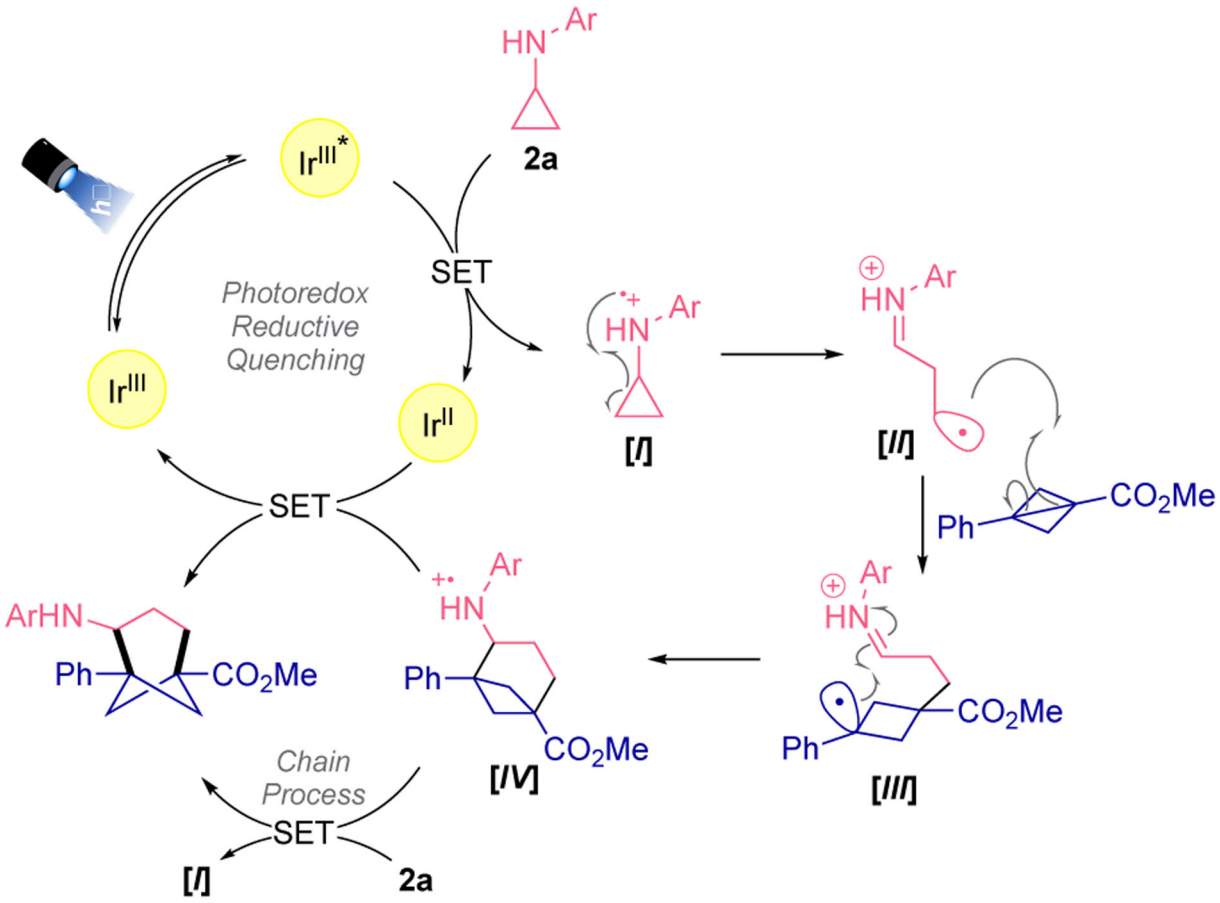


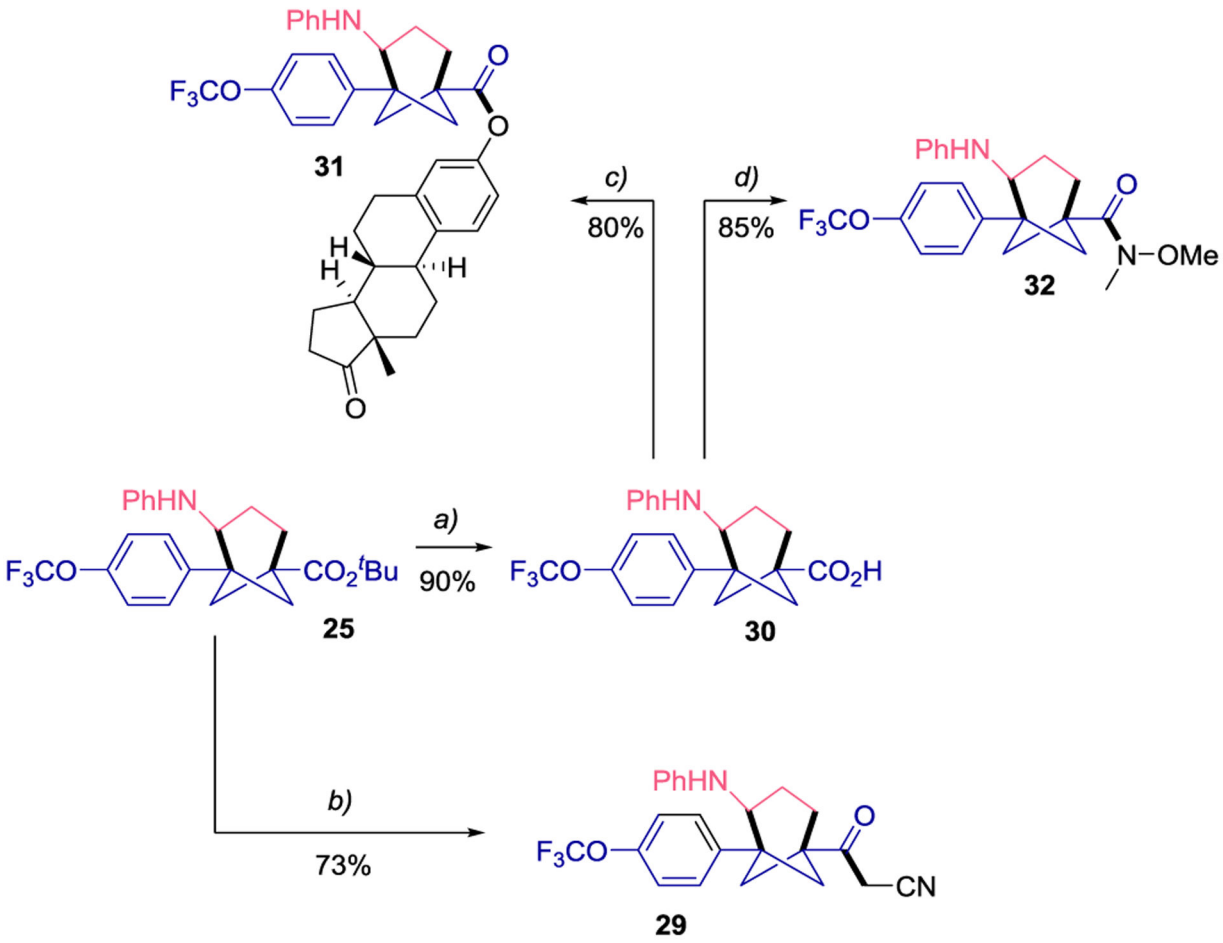
Figure 2.

Photocatalytic [3+2] annulations of alkenes using aminocyclopropanes for the construction of bicyclic systems.



Scheme 1.

Proposed reaction mechanism for the photoinduced synthesis of 4-aminobicyclo[3.1.1]heptanes.

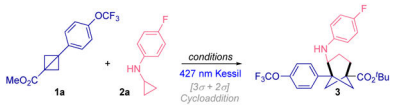


Scheme 2.

Derivatization reactions of **25**. Reaction conditions: a) LiOH in MeOH, then HCl 1 M. b) LDA (2.2 equiv) and MeCN (2 equiv). c) Estrone (1 equiv), DMAP (0.05 equiv), DIC (1.2 equiv) in CH_2Cl_2. d) *N,O*-dimethylhydroxylamine (1 equiv), DMAP (0.05 equiv), DIC (1.2 equiv) in CH_2Cl_2. See Supporting Information for more details.

Table 1.

Exploration of the reaction conditions[a] for the photochemical synthesis of functionalized bicyclo[3.1.1]heptanes.



Entry	Solvent	PC	Yield of 3 (%)[b]
1	DMSO	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	72 (70)[e]
2	DMSO	$Ir(ppy)_3$	<10
3	DMSO	$Ru(bpy)_3(PF6)_2$	30
4	DMSO	MesAcr	traces
5	DMSO	4CzIPN	27
6	DMA	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	46
7	MeCN	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	40
8	1,4-dioxane	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	0
9	$MeNO_2$	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	traces
10	DMSO	none	0
11[c]	DMSO	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	0
12[d]	DMSO	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	0

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv), **2a** (0.2 mmol, 2 equiv), photocatalyst (2 mol % metal-based PC or 5 mol % organic based PC), in dry and degassed solvent (0.2 M) under blue Kessil irradiation (λ_{max} = 427 nm) at rt.

[b] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

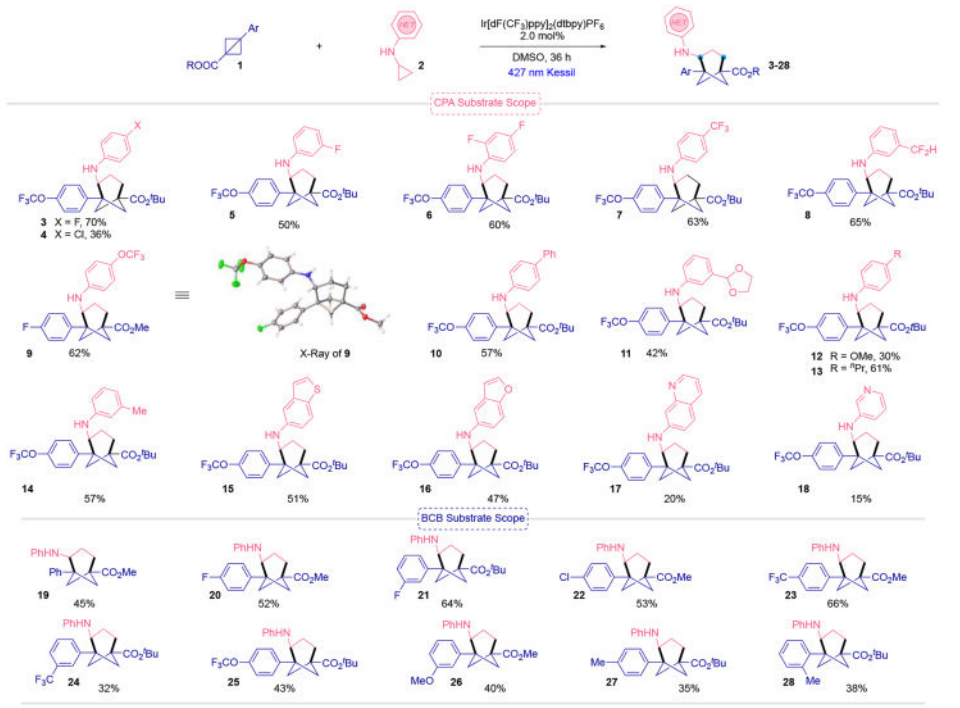
[c] Reaction in the absence of light irradiation.

[d] Reaction as in entry 5 but in the presence of 5 equiv of TEMPO.

[e] Isolated yield from 0.2 mmol scale.

Table 2.

Substrate Scope Exploration for the Synthesis of Bicyclo[3.1.1]heptanes[a]



[a]Reaction conditions: BCB **1** (0.2 mmol, 1 equiv), CPA **2a** (0.4 mmol, 2 equiv), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2 mol %), in dry and degassed DMSO (0.2 M) under blue Kessil irradiation (λ_{max} = 427 nm) at room temperature.