Decarboxylative C-N coupling of 2,2-difluorobicyclo[1.1.1]pentane (BCP-F_2) building blocks

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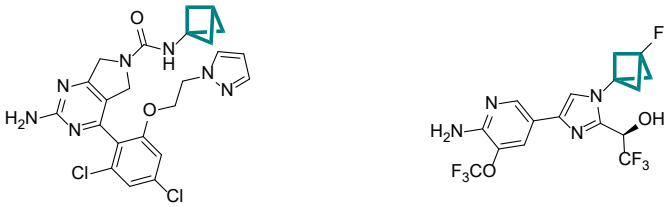
ABSTRACT: Described herein is our effort towards achieving the decarboxylative functionalization of 2,2-difluorobicyclo[1.1.1]pentane (BCP-F_2) building blocks. When compared with the non-fluorinated bicyclo[1.1.1]pentane (BCP) analogues, we discovered divergent reactivities. This is the first successful decarboxylative coupling of BCP-F_2 building blocks reported via photoredox mechanism.

Bicyclo[1.1.1]pentane (BCP) analogues, first synthesized by the Wiberg group in 1964,[1] have been recognized and used recently as unique bioisosteres for phenyl and *tert*-butyl groups, as well as linear linkers within the realm of medicinal chemistry.[2] BCP groups introduce C(sp^3) characters which has been observed to improve aqueous solubility, membrane permeability, oral absorption, and metabolic stability, making BCP one of the ideal scaffolds for drug design.[3] Two examples were shown in Figure 1 as BCP groups incorporated in bioactive compounds. Compound **I** was exemplified by Pfizer as an Hsp90 inhibitor analogue[4] and compound **II** (IACS-52825) was disclosed recently by scientists from the University of Texas MD Anderson Cancer Center as the lead DLK inhibitor advancing into preclinical development.[5]

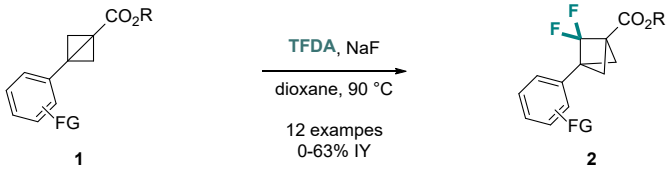


I *Hsp 90 inhibitor*

II (IACS-52825) *DLK inhibitor*

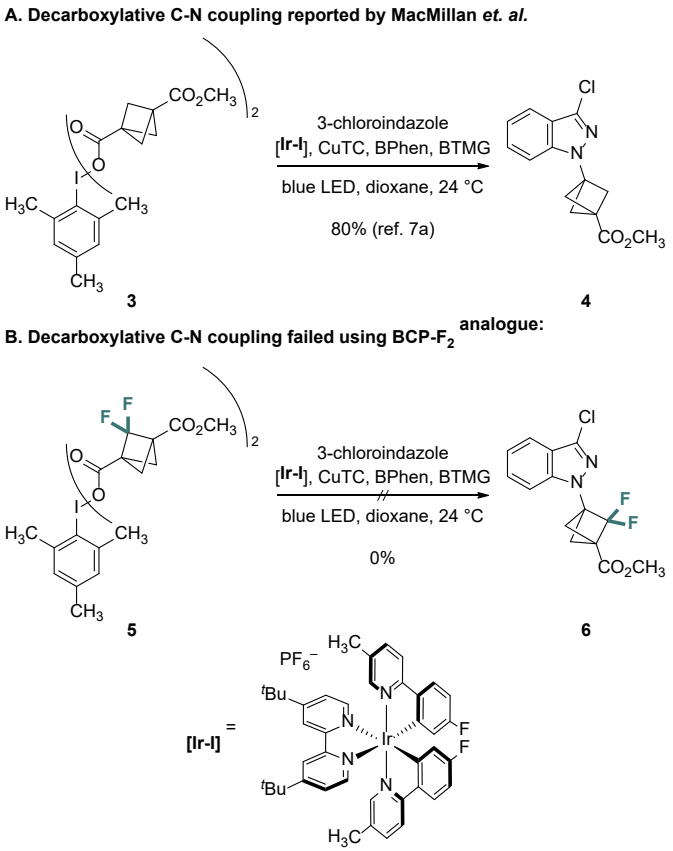
Figure 1. Bioactive compounds containing BCP groups.

In the last decade, the research in synthetic methodologies blossomed to explore ways to access and install BCP groups into structures relevant to medicinal chemists.[2b-e] We have been interested in the pursuit of functionalization at the methylene position to mimic *ortho*- and *meta*-substitutions on arenes. In 2019, we reported a methodology to access 2,2-difluorobicyclo[1.1.1]pentane (BCP-F_2) derivatives **2** via difluorocarbene insertion into bicyclo[1.1.0]butanes (BCB) **1** bearing an aryl group and an ester functionality at the bridge heads (Scheme 1).[6] It is worth noting that a similar strategy to access the same type of motifs was reported by Mykhailiuk and co-workers concomitantly.[7] We later expanded the scope of BCP-F_2 building blocks by known transformations analogous to the non-fluorinated BCP derivatives.[8] However, throughout our exploration of functionalizing BCP-F_2 derivatives, the decarboxylative functionalization efforts have been unsuccessful. [9]



Scheme 1. Synthesis of BCP-F_2 from BCB.

Inspired by the metallaphotoredox transformations developed by the MacMillan lab,[9h] specifically the synthesis of divergently functionalized BCPs utilizing hypervalent iodine species,[9g,i,10] we decided to examine the reactivity differences between BCP and BCP-F_2 in further detail.

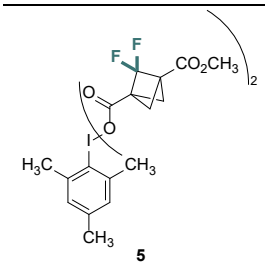


Scheme 2. Decarboxylative C-N coupling results of hypervalent iodine species **3** and **5**.

We started by examining the decarboxylative C-N coupling conditions reported by the MacMillan group (Scheme 2A).[10] Application of these conditions to the parent BCP, the hypervalent iodine species **3** provided the desired indazole analogue in 80% yield.[10] However, when we applied the same conditions to the BCP-F_2 derivative **5**, the C-N coupling product 6 was not observed based on liquid chromatography-mass spectrometry (LC-MS) analyses (Scheme 2B). During reaction set-up using **5**, we observed a drastic color change as soon as the solvent was added into the reaction vessel, which was not observed when we used **3**. As a result, we suspected that the BCP-F_2-derived hypervalent iodine species **5** could present compatibility issues with certain reagents in the reaction conditions. To study the stability of **5** in the reaction mixture, we treated a solution of **5** in acetonitrile-d_3 with individual species in the reaction mixture and monitored the ^{19}F NMR signal (Table 1).

From this study, we concluded that the hypervalent iodine species **5** was compatible with the iridium photoredox catalyst (entry 1), the nucleophile (3-chloroinrazole, entry 3), and the ligand bathophenanthroline (BPhen, entry 4); however, **5** decomposed rapidly in the presence of copper(I) thiophene-2-carboxylate [CuTC, entry 2] and 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG, entry 5). In a follow-up study (not shown), we found that **5** was incompatible with a variety of copper(I) species; however, copper(II) species did not induce such rapid decomposition. Unfortunately, despite extensive condition optimization, we were not able to observe any desired product using 3-chloroindazole as the nucleophile. Consequently, we decided to include other classes of heterocycles as the nucleophile.

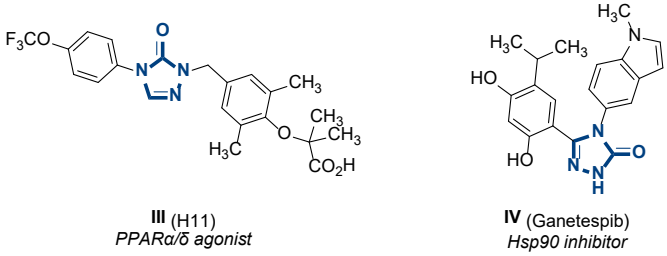
Table 1. Stability studies of hypervalent iodine species **5**.



entry	reagent added	decomposition of **5**? (Y/ N)
1	**[Ir-I]**	Y
2	CuTC	N
3	Nu[a]	Y
4	BPhen	Y
5	BTMG	N

[a]Nu = 3-chloroindazole; [b]Stability of **5** was judged by ^{19}F NMR.

To effectively identify a suitable heterocyclic substrate for this transformation, we selected a library of various nitrogen-containing 5-membered heterocycles casting a wide net of varieties. After several rounds of experimentation, we were delighted to discover that triazolol **7** was a suitable nucleophile for the decarboxylative C-N coupling with hypervalent iodine **5** using **[Ir-I]** as the photoredox catalyst, copper(II) acetylacetonate [Cu(acac)$_2$] as the copper coupling catalyst, and acetonitrile as the solvent (Table 2, entry 1). Under these conditions, the desired C-N coupling product **8** was obtained in 48% isolated yield. Triazoles are an important class of heterocycles utilized as core scaffolds in medicinal chemsitry.[11] Among various triazole analogues, triazolone derivatives have seen recent interests in their application in biologically active compounds. For example, researchers from China Pharmaceutical University reported a triazolone derivative **III** (H11), which shown potential as an anti-nonalcoholic steatohepatitis (anti-NASH) agent (Figure 2).[12] In addition, Ganetespib (**IV**) demonstrated significantly superior pharmacokinetic and safety profiles in a study reported in 2012, as Hsp90 inhibitor in cancer therapy.[13] The transformation shown in Table 2 is the first report of trazolone functionalization via photoredox chemistry to our knowledge.



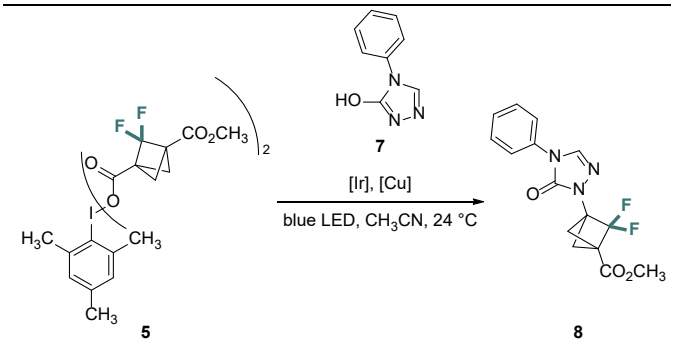
III (H11)
PPARα/δ agonist

IV (Ganetespib)
Hsp90 inhibitor

Figure 2. Biologically active compounds harboring triazolone core structures.

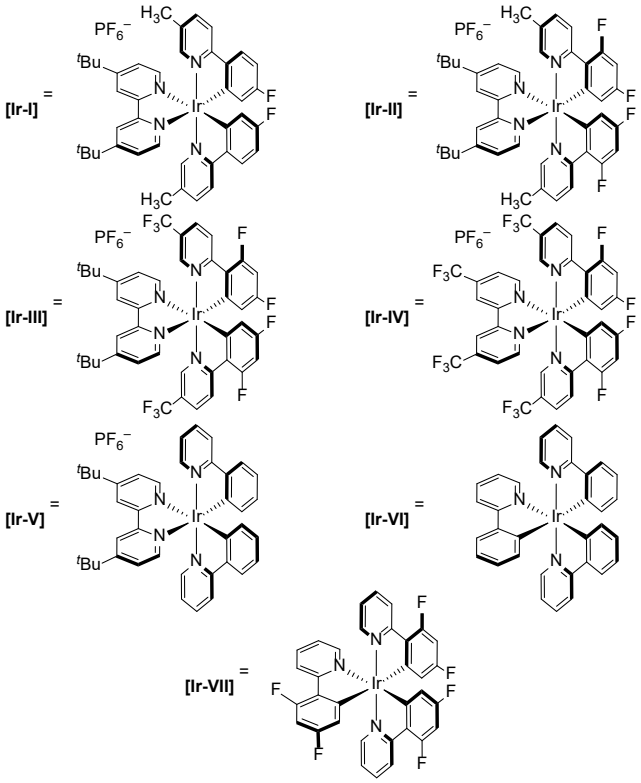
https://doi.org/10.26434/chemrxiv-2023-9nqnw **ORCID:** https://orcid.org/0000-0002-0713-2896

Table 2. Condition optimization of decarboxylative C-N coupling with triazolol **7**.[a]



entry	[Ir][b]	[Cu]	yield[c]
1	**[Ir-I]**	$Cu(acac)_2$	48%
2	**[Ir-II]**	$Cu(acac)_2$	36%
3	**[Ir-III]**	$Cu(acac)_2$	31%
4	**[Ir-IV]**	$Cu(acac)_2$	< 5%
5	**[Ir-V]**	$Cu(acac)_2$	78%
6	**[Ir-VI]**	$Cu(acac)_2$	55%
7	**[Ir-VII]**	$Cu(acac)_2$	67%
8	**[Ir-V]**	$Cu(CH_3CN)_4(PF_6)$	0%
9	**[Ir-V]**	Cu(TC)	0%
10	**[Ir-V]**	$Cu(dpm)_2$	25%
11	**[Ir-V]**	$Cu(tfacac)_2$	0%
12	**[Ir-V]**	$Cu(hfacac)_2$	0%

[a]Conditions: triazolol **7** (72.0 μmol, 1 equiv), hypervalent iodine **5** (144 μmol, 2.00 equiv), [Ir] (1.4 μmol, 2 mol%), [Cu] (36 μmol, 50 mol%), CH_3CN (0.1 M), 450 nm blue LED, 24 °C, 2.5 h; [b]List of iridium catalysts shown below; [c]Isolated yields.



Noticing that such photoredox decarboxylation process relies heavily on the matching of redox potentials of the iridium catalysts and the electrophile substrate, we examined a series of iridium catalysts first (entries 1-7). With increasing amounts of fluorinated substituents around the ligand of the iridium catalyst, we observed a decrease of the yield of **8** (entries 1-4). As a result, we decided to evaluate the catalyst that lacks all fluorinated substituents on the ligands. To our delight, **[Ir-V]** afforded 78% isolated yield of **8** (entry 5). We also examined tris[2-phenylpyridinato-C,N]iridium(III) (**[Ir-VI]**, entry 6, 55%) and tris[2-(2,4-difluorophenyl)pyridinato-C,N]iridium(III) (**[Ir-VII]**, entry 7, 67%) as the photoredox catalyst; however, neither of these catalysts provided superior results.

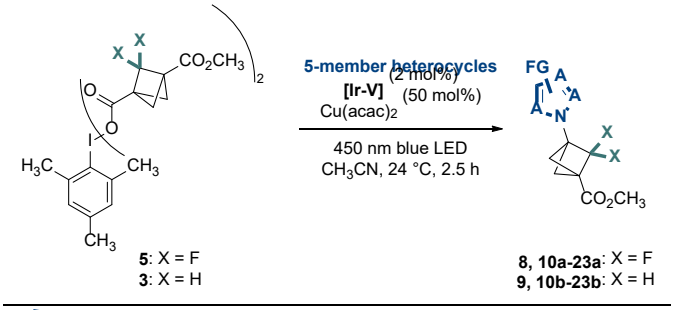
The effects of copper catalysts were also explored. Reexamining the copper(I) catalysts reaffirmed our earlier conclusion of its incompatibility with the BCP-F_2-derived hypervalent iodine **5** (entries 8-9, 0% yield). The we considered some other copper(II) β-diketonates. Increasing the steric bulk around the copper(II) center by employing copper(II) dipivaloylmethide [$Cu(dpm)_2$] was detrimental to the reaction process. Nevertheless, the desired product **8** was isolated in 25% yield (entry 10). The decarboxylative C-N coupling process was sensitive to the electronic environment around the copper(II) center. As shown in entries 11-12, fluorination of the β-diketone ligand prohibited the C-N coupling process, resulted in unproductive decompositions of the hypervalent iodine **5**. In addition to acetonitrile, we also examined other solvents, which did not provide superior results (not shown). Thus, we identified the most productive reaction conditions involve **[Ir-V]** as the photoredox catalyst, $Cu(acac)_2$ as the copper coupling catalyst with acetonitrile as the reaction solvent (entry 5).

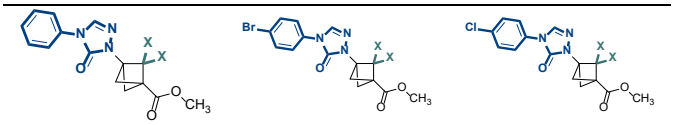
With the optimized conditions in hand, we expanded the substrate scope for the decarboxylative C-N coupling process. To demonstrate the divergent reactivities between BCP-F_2 and BCP analogues, we employed both **3** and **5** in our substrate exploration to provide head-to-head comparisons (Table 3).

We first examined a series of triazolol heterocycles. When coupling with triazolol **7**, the BCP-F_2 analogue **9a** was obtained in 78% isolated yields while the BCP analogue **9b** was isolated in 25% yield. The *para*-halo-derivatives of triazolols all provided synthetically useful yields for both the BCP-F_2 (**10a**, 95%; **11a**, 98%; **12a**, 74%) and BCP analogues (**10b**, 63%; **11b**, 55%; **12b**, 20%). Derivatives with *para*-methoxy and *para*-trifluoromethyl groups on the phenyl substituent of the triazolol heterocycle also yielded the desired products in 24-56% yields (for BCP-F_2 analogues: **13a**, 56%; **14a**, 48%; for BCP analogues: **13b**, 24%; **14b**, 37%). Installation of additional substituents on the triazolol heterocycle had profound impacts on the reaction productivity. While the additional methyl group yielded comparable results between the BCP-F_2 (**15a**, 62%) and the BCP analogues (**15b**, 67%). The additional phenyl substituents completely shut down the C-N coupling process providing no desired products with either BCP reagents (**16a**, 0%; **16b**, 0%). The piperidinyl triazolol analogues were afforded in 23% and 59% yields for the corresponding BCP-F_2 **17a** and BCP analogues **17b**, respectively.

To further showcase the possibility of applying this C-N coupling chemistry in broader scopes, we evaluated other five-membered heterocycles that are structurally closely

Table 3. Preliminary substrate scope for the decarboxylative C-N coupling with direct comparisons between BCP-F_2 and BCP analogues.[a]

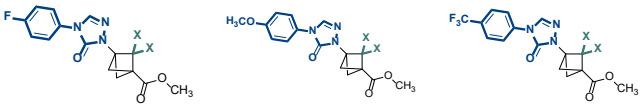




8: X = F, 78%
9: X = H, 25%

10a: X = F, 95%
10b: X = H, 63%

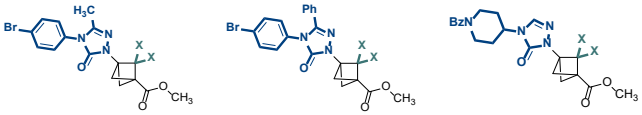
11a: X = F, 98%
11b: X = H, 55%



12a: X = F, 74%
12b: X = H, 20%

13a: X = F, 56%
13b: X = H, 24%

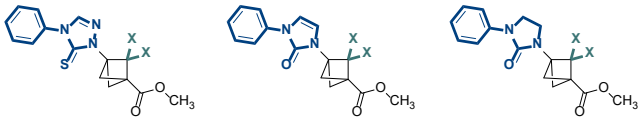
14a: X = F, 48%
14b: X = H, 37%



15a: X = F, 62%
15b: X = H, 67%

16a: X = F, 0%
16b: X = H, 0%

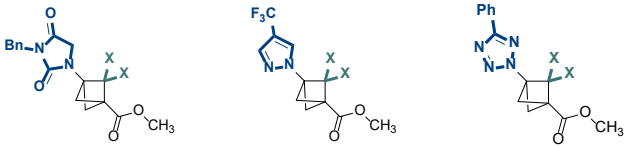
17a: X = F, 23%
17b: X = H, 59%



18a: X = F, < 5%
18b: X = H, 8%

19a: X = F, 0%
19b: X = H, 0%

20a: X = F, < 5%
20b: X = H, 32%



21a: X = F, 21%
21b: X = H, 15%

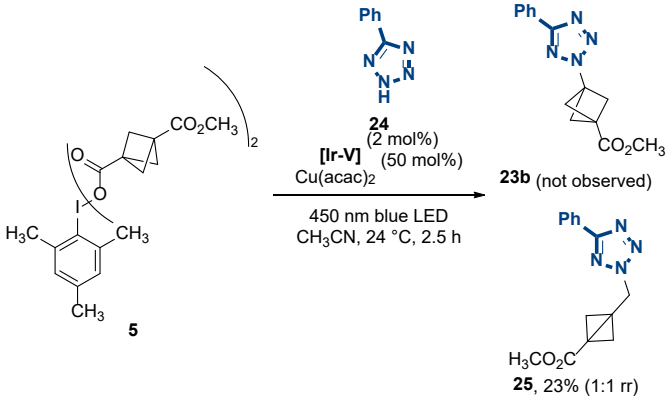
22a: X = F, 28%
22b: X = H, 0%

23a: X = F, 0%
23b: X = H, 0%[b]

[a]For details of reaction conditions, see *Experimental Section* and *Supporting information*. All yields are isolated yields; [b]Rearrangement products isolated.

related to the triazolol heterocycles. When using a 1,2,4-triazole-3-thiol derivative as the nucleophile, we only observed trace amounts of the desired BCP-F_2 product (**18a**, < 5%) and the corresponding BCP analogue **18b** was also only obtained in 8% isolated yield. Unfortunately, the imidazolol heterocycle was not a suitable substrate for the C-N coupling process for either the BCP-F_2 (**19a**, 0%) or BCP analogues (**19b**, 0%). To our delight, we found that the imidazolidinone heterocycle provided 32% isolated yield for the BCP analogue **20b**, while the corresponding BCP-F_2 analogue **20a** only yielded trace amounts of the desired product mass on LC-MS traces. Interestingly, the imidazol-diol heterocycle afforded productive C-N coupling processes for both cases, affording **21a** and **21b** in 21% and 15% isolated yields, respectively.

Significant differences in reactivities between **5** and **3** were observed in both of the pyrazole and tetrazole heterocycles. When using 4-(trifluoromethyl)-1*H*-pyrazole as the nucleophile, the C-N coupling afforded 28% isolated yields of **22a**, whereas the corresponding BCP analogue **22b** was not observed in LC-MS analyses. In the case of 5-phenyl-1*H*-tetrazole, the BCP-F_2-derived hypervalent iodine **5** was unproductive in the C-N coupling process (**23a**, 0%). In the case of the BCP-derived hypervalent iodine **3** provided **23b**, although the desired product **23b** was not observed, the rearranged by-product 25 was isolated in 23% yield with 1:1 regioisomeric ratio (rr, Scheme 3) with respect to *N*-1 versus *N*-2 alkylation. We speculated that this transformation may occur through an iodo-BCP or iodonium-BCP intermediate based on a recent publication by Mandler and coworkers from Bristol Myers Squibb.[14]

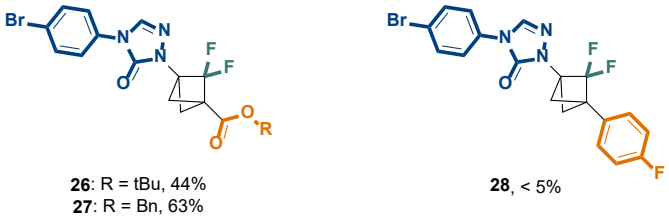


Scheme 3. The unexpected rearrangement product **25**.

Overall, the parent BCP-derived hypervalent iodine species **3** appears to demonstrate a broader substrate scope for the various heterocycles exemplified in our work, providing isolable amounts of desired products in 13 out of the 15 cases. The BCP-F_2-derived species **5** only provided isolable amounts of desired products in 10 out of the 15 cases. However, it is reasonable to conclude that the discovered reaction conditions, which are tailored to the reactivities of the BCP-F_2 derived hypervalent iodine **5**, might not be optimal for the corresponding BCP-derived hypervalent iodine **3**. This can be illustrated by the differences in isolated yields in various cases in Table 3. Additionally, considering the last six examples in Table 3, there appears to be reactivity differences between the putative 2,2-difluorobicyclo[1.1.1]pentyl radical and bicyclo[1.1.1]pentyl radical.

Understanding that the C1 bridge-head substituents profoundly influences the reactivities at the C3 bridge-head position, we also prepared three BCP-F_2-derived hypervalent iodine species varying the bridge-head substituents (Scheme 4). Both the *tert*-butyl ester and the benzyl ester analogues successfully provided the desired products **24** and **25** in 44% and 63% isolated yields, respectively. We attribute the lower yields to the decreased solubilities of the corresponding hypervalent iodine species. The heterogeneity of the reaction mixtures can impede light penetration and thusly promote unproductive decomposition pathways. However, the *para*-fluorophenyl analogue of the BCP-F_2-

derived hypervalent iodine species only provided traces amounts of the desired product mass in LC-MS traces of the reaction mixture (**26**, < 5%). This result further illustrates the "cross-talk" between the two bridge-head substitutions on each other's reactivity.



26: R = tBu, 44%
27: R = Bn, 63%

28, < 5%

Scheme 4. Further substrate scopes varying the substituents on the BCP-F_2 fragments.

To conclude, we report our efforts in optimizing the decarboxylative coupling using the BCP-F_2-derived bridgehead carboxylic acids. The iridium and copper co-catalyzed decarboxylative C-N coupling proceeds smoothly affording 0-98% isolated yields of the BCP-F_2 analogues. This is the first reported successful decarboxylative functionalization of BCP-F_2 derivatives via photoredox mechanism. During our substrate-scope exploration, we compared BCP-F_2- and BCP-derived hypervalent iodine species **5** and **3** in a head-to-head manner. Thusly, some overall trends and differences in their reactivities were observed. We continue to explore other decarboxylative functionalization strategies of the BCP-F_2 analogues. The mechanistic explanation of the divergent reactivities between the fluorinated BCPs and the non-fluorinated BCPs are also of interest to us.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.
Synthetic procedures and reproductions of NMR spectra for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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