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S. J. Connon, M. O. Senge *et al.*
Conformational control of nonplanar free base porphyrins: towards bifunctional catalysts of tunable basicity

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Direct photochemical cross-coupling between aliphatic acids and BF_3K salts

Zhuming Sun, Bingqing Tang, Kevin K.-C. Liu and Hugh Y. Zhu*[a]

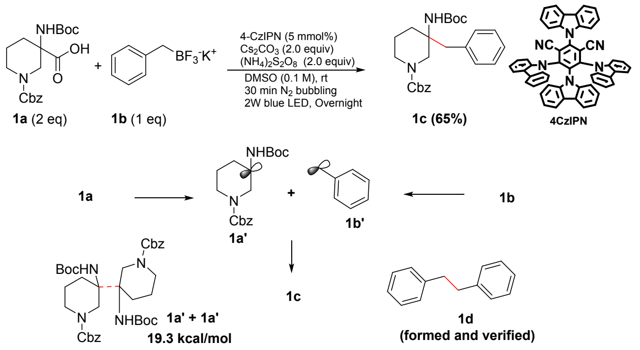
We describe a novel photoredox hetero-coupling reaction of two C (sp^3) radicals from aliphatic acids or BF_3K salts. The kinetic differences in radical persistence provide cross-selectivity, using an organic photoredox catalyst and an oxidant with visible light. This method exhibits broad scope, including several examples constructing sterically hindered C(sp^3)-C(sp^3) bonds.

Carbon radical-based chemistry has flourished in recent years.[1] Numerous publications have demonstrated the prowess of dual photoredox/Ni catalysis protocols in constructing C(sp^3)-C(sp^2) bonds.[2] C(sp^3)-C(sp^3) bonds could be formed through C(sp^3) radical addition to π systems (Giese coupling).[3] In theory, matching persistent radicals with kinetically transient radicals may facilitate synthetically useful hetero-couplings.[4] In a seminal demonstration of this concept, MacMillan attributed the high efficiency of α-amino C-H arylation to persistent aryl anion radicals C(sp^2) coupling with transient C(sp^3) α-amino radicals.[5] MacMillan's laboratory subsequently reported synthesizing a variety of β-amino ether products through C(sp^3)-C(sp^3) coupling using a photoredox-hydrogen atom transfer (HAT) system, in which both radical coupling partners formed at the same rate within the same "redox-neutral" cycle.[6] Other studies promoted radical cross-couplings by adding external reducing agents.[7] These impressive results spur development of novel photoredox chemistry.

We sought to investigate direct photochemical C(sp^3)-C(sp^3) radical coupling reactions using readily available precursors, such as carboxylic acids and alkyltrifluoroborate salts. We proposed generating two C(sp^3) radicals in a decoupled manner with a common photoredox catalyst, to enable hetero-coupling a persistent radical (PR) with a transient radical (TR), in the presence of a stoichiometric oxidant to recycle reduced photoredox catalyst.

In our separate study, we reported that the C(sp^3) radical generated from commercially available amino acid **1a** directly reacted with a number of sp^2 aromatic substrates.[8] We reasoned that the resulting **1a'** had persistent radical character due to hyperconjugation from neighboring heteroatoms and steric hindrance. *In silico* calculation of 19.3 kcal/mol for the central bond of a **1a'**-**1a'** dimer predicted a low propensity for self-dimerization (Scheme 1).[9]

To extend these results in the current study, we observed that the benzyl radical **1b'** was readily generated from benzylic BF_3K salt **1b** under the same photoredox conditions using 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), forming the dimeric bibenzyl **1d**.[4a,10,11] With the addition of persulfate salts as oxidant,[12] carboxylic acid **1a** directly coupled with **1b** in good yield, consistent with a reaction of persistent radical **1a'** with transient radical **1b'**.[13] Product **1c** was isolated in 65% yield (based on **1b**, 0.3 mmol) under our optimized conditions [4CzIPN (5 mmol%), acid **1a** (2 equiv), Cs_2CO_3 (2 equiv), $(NH_4)_2S_2O_8$ (2 equiv), DMSO solvent, 2W blue LED reactor).[14] We also isolated bibenzyl **1d** (~15% consumption of **1b**), but did not detect a homodimer from **1a'**. Considering the transient nature of the radicals and their diffusion controlled kinetics, the relatively high 65% yield was consistent with the low propensity of **1a'** dimerization. To our best knowledge, this is the first report of direct coupling of C (sp^3)–C (sp^3) between a carboxylic acid and an organotrifluoroborate salt.



Scheme 1. Optimized conditions for radical cross-coupling in a model system, and a mechanistic proposition.

Next, we explored the scope of carboxylic acid substrates using benzyl trifluoroborate **1b** as the TR precursor (figure 1). In the case of **2a** with a quaternary acid starting material, the yield was slightly

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[a] Novartis Institute for Biomedical Research, 4218 Jinke Road, Pudong, Shanghai, China. E-mail: hughzhu@hotmail.com

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lower than its *N*-Boc amino acid counterpart **1a**, suggesting a diminished stabilizing effect from only one β-amino group. Other cyclic amino acids gave yields ranging from 39% to 67% (**2b-g**), exhibiting tolerance for several *N*-protecting groups (**2d-f**). Secondary radicals from acids with α-heteroatoms such as pipecolic acid (**2i**), tetrahydropyran-2-carboxylic acid (**2j**) and proline (**2k**) all successfully coupled with **1b**. The scope further expanded to the lactam from pyroglutamic acid (**2l**) and the acyclic amino acids *N*-Boc alanine and phenylalanine (**2h**, **2m-n**). Other functional groups such as alcohols, phenols, and electrophilic alkenes were tolerated, as Nateglinide, Enoxolone or *N*-Boc methyldopa afforded good yields (**2o-q**). We consistently observed minimal amount of dimer **1d** (~10%) and little or no PR dimers. For the preparations of **2i** and **2k**, the yields substantially increased with 4 equivalents of cesium carbonate. The additional loading of base promoting carboxylate anion formation may maintain a higher concentration of persistent radical, to complete more effectively with transient radical dimerization.

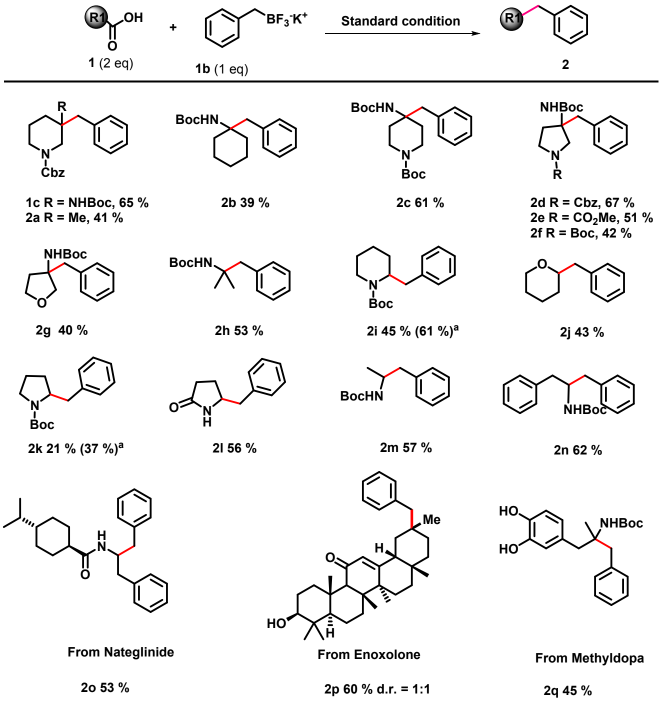

Figure 1. Coupling between different acids **1** and **1b**. All isolated yields calculated on BF$_3$K salt. No e.e. detected. [a] Cs$_2$CO$_3$ (4 equiv) was used.

Other BF$_3$K salts were then surveyed (figure 2). As expected, electron-donating substituents generally gave better yields, as observed with 4-OMe benzyl radicals (**3a, 3e, 3f**). Methyl substituted benzyl BF$_3$K salts also coupled with piperidine carboxylic acid (**3b-d**) and pyrrolidine carboxylic acid (**3g-i**). The yield arising from the methoxymethyl BF$_3$K salt under standard conditions nearly doubled with 4 equivalents of Cs$_2$CO$_3$ (**3j**).

A variety of carboxylic acids were effective precursors for the transient radical component, significantly broadening the scope of coupling partners due to the greater availability of carboxylic acids. Halogenated phenylacetic acids gave acceptable yields (**4a-b**, figure 3). Acids containing other aryl and heteroaryl groups such as pyrimidine (**4c**), pyrazine (**4d**), triazole (**4e**), phenol (**4g**), phenol ethers (**4f** and **4h**) and pyridines (**4i-k**) were all compatible. Adjusting the stoichiometry of the PR:TR precursor ratio from 2:1 to 1:2 improved yields in some cases (**4h**, **4j**, **4l-m**, **4o** & **4r**). However, only **4o** showed a boost in yield with additional Cs$_2$CO$_3$. Transient secondary radical derived from acids also afforded cross-coupling products (**4p-r**). This acid-to-acid hetero-coupling worked for other "PR" precursors as well **(4s-t, 5a-b)**. Even *N*-protected α-amino acids served as coupling partners, albeit in lower yields (**5c-5e**).

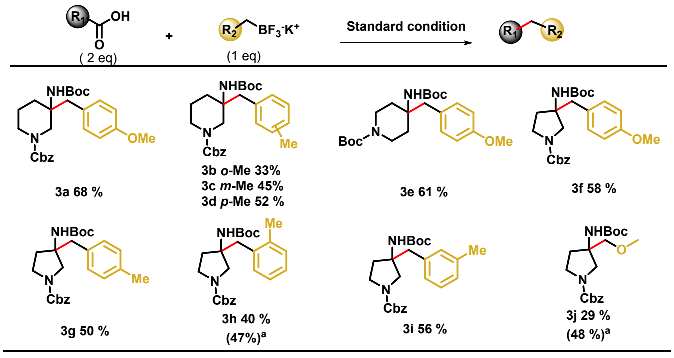

Figure 2. Coupling between various acids and different BF$_3$K salts. All isolated yields calculated based on BF$_3$K salt. No e.e. detected. [a] Cs$_2$CO$_3$ (4 equiv) was used.

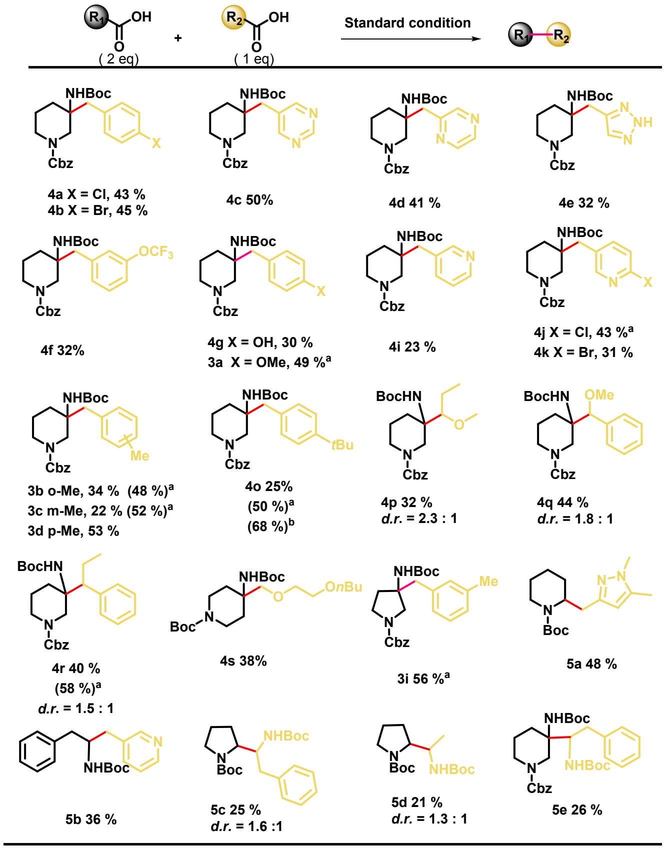

Figure 3. Coupling between two acids. All isolated yields (calculated based on R$_2$CO$_2$H if not noted). No e.e. detected. [a] R$_1$CO$_2$H : R$_2$CO$_2$H = 1: 2. Yield calculated based on R$_1$CO$_2$H [b] Cs$_2$CO$_3$ (4 equiv) was used.

We observed some nuance between acid-BF$_3$K and acid-acid coupling reactions. In acid-BF$_3$K couplings, significant amounts of dimers from TR precursors were isolated, whereas from acid-acid couplings, these dimers were seldom detected, suggesting a lower concentration of transient radicals in acid-acid couplings. This also explained the yield boosts using two equivalents of the TR-precursor carboxylic acids (figure 3). On the contrary, increase in the equivalents of persistent radical precursor along with additional base may increase the yields in our acid-BF$_3$K couplings. These observations reflect the complexity of kinetic control, and possibly other side reactions that we have not yet characterized.

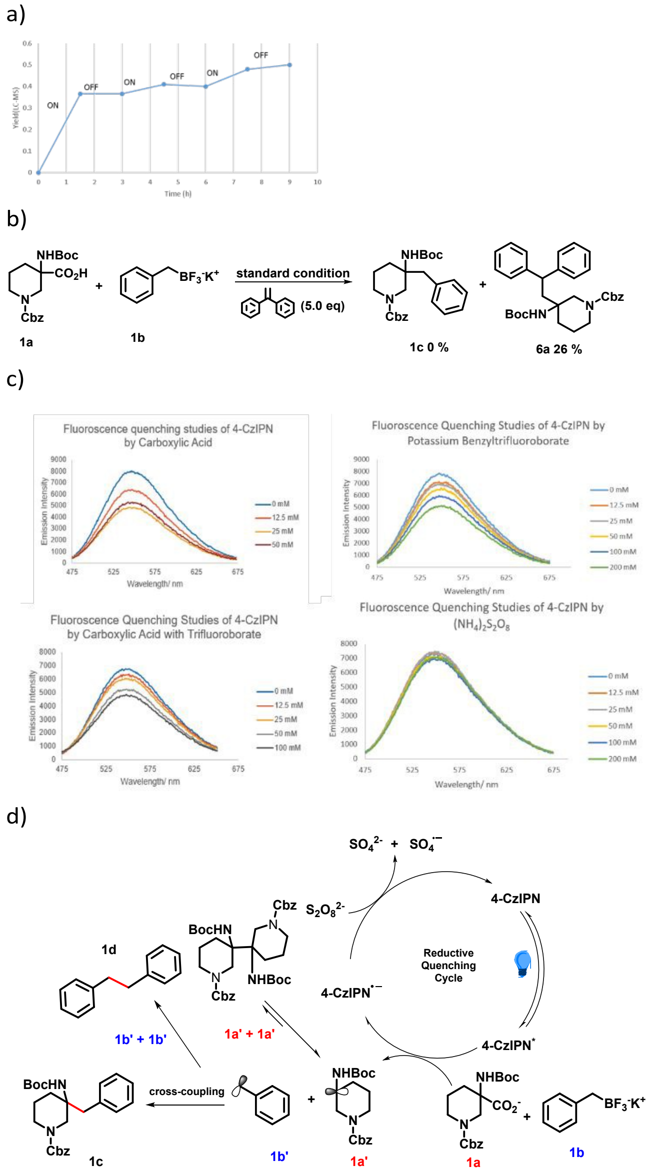

Figure 4. ^{a} Light on-off experiment. ^{b} Radical trapping experiment. ^{c} Fluorescent quenching experiment. ^{d} Proposed reaction mechanism.

Light on-off experiments on our model **1a** and **1b** reaction demonstrated the light-dependency of this reaction (figure 5, a). In addition to forming bibenzyl **1d** as the self-dimer of **1b'**, we isolated the adduct **6a** arising from trapping the PR radical **1a'** with 1,1-diphenylethylene (figure 5, b), consistent with a radical mechanism. In fluorescent quenching experiment, carboxylic acids or BF$_3$K salts reduced the 4CzIPN*-4CzIPN fluorescent signal, whereas $S_2O_8^{2-}$ had no effect (figure 5, c).[15] Based on this, we proposed a catalytic cycle (figure 5, d). Irradiation transformed 4CzIPN into its long-lived excited-state 4CzIPN*, which acted as a strong oxidant ($E_{1/2}PC^*/PC^- = +1.35$ V vs SCE) to convert **1a** carboxylate anion and **1b** into the respective radicals **1a'** and **1b'**. The reduced radical anion 4CzIPN$^{\bullet-}$ was subsequently oxidized by persulfate, regenerating ground state 4CzIPN.

As traditional methods are often unsuitable for constructing hindered carbon-carbon bonds, we attempted tetrasubstituted tertiary C(sp^3) and quaternary C(sp^3) couplings (figure 5). The simple access to these congested structures further exemplified the value of our photoredox strategy. For our general interest in drug discovery, practical incorporation of C(sp^3) may improve selectivity and physicochemical properties of prospective drug candidates.[16]

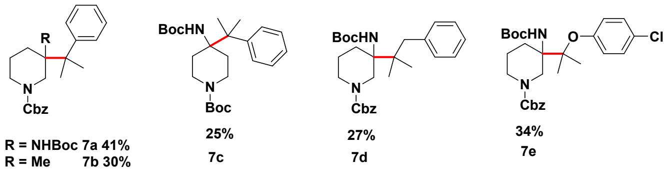

Figure 5. Examples of tetrasubstituted tertiary and quaternary carbon bond formations from acid-acid couplings (all isolated yields).

In conclusion, this novel C(sp^3)-C(sp^3) coupling reaction exhibits relatively broad substrate scope and reasonably good isolated yields, under mild conditions with simple operations. This method uses inexpensive low-toxicity organic photoredox catalysts and abundantly available carboxylic acid starting materials.[17] By directly enabling single-step access to under-explored chemical spaces, this method may find applications in natural product synthesis and drug discovery. Due to the complex nature of the kinetic conditions, these results warrant additional experimentation and theoretical studies, including evaluation of other photoredox catalysts, flow chemistry for better kinetic control, and/or extensions to chiral induction.

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Conflicts of interest

There are no conflicts to declare.

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