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Nickel-Catalyzed Decarboxylative Cross-Coupling of Bicyclo[1.1.1]pentyl Radicals Enabled by Electron Donor–Acceptor Complex Photoactivation

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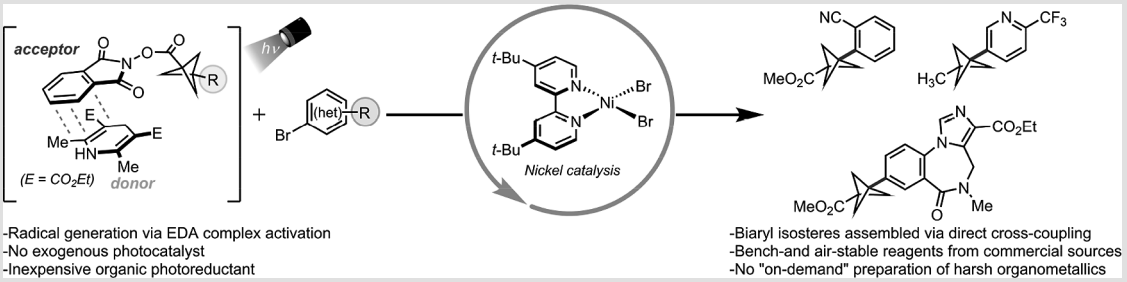

ABSTRACT: The use of bicyclo[1.1.1]pentanes (BCPs) as *para*-disubstituted aryl bioisosteres has gained considerable momentum in drug development programs. Carbon–carbon bond formation via transition-metal-mediated cross-coupling represents an attractive strategy to generate BCP–aryl compounds for late-stage functionalization, but these typically require reactive organometallics to prepare BCP nucleophiles on demand from [1.1.1]propellane. In this study, the synthesis and Ni-catalyzed functionalization of BCP redox-active esters with (hetero)aryl bromides via the action of a photoactive electron donor–acceptor complex are reported.

The operational ease of Pd-catalyzed $C(sp^2)–C(sp^2)$ coupling reactions along with the availability of coupling partners (in particular, arylboronates and aryl halides) has resulted in a bias toward biaryl-containing molecules in drug development programs.[1] These cross-coupling platforms have enabled the synthesis of diverse biaryl-containing drugs targeting a wide swath of therapeutic areas. However, considerable interest has developed in recent years to investigate sp^3-rich aryl isosteres in drug development programs.[2]

Of particular interest is the bicyclo[1.1.1]pentane (BCP) motif, which has been reported most commonly as a *p*-disubstituted aryl bioisostere but also as a *tert*-butyl or alkyne bioisostere, often imparting favorable pharmacokinetic properties, including improved aqueous solubility and membrane permeability.[3]

Although considerable advancements have been made in the synthesis of BCP-containing targets,[4−6] the methods available to forge BCP–aryl products via direct cross-coupling are somewhat limited. Szeimies and co-workers,[7] de Meijere and co-workers,[8] and Knochel and co-workers[9] have reported Kumada- and Negishi-type couplings between aryl halides and the corresponding BCP organometallic reagents (Figure 1A). Additionally, Kanazawa, Uchiyama, and co-workers[10] reported a Suzuki-type coupling using 1,3-difunctional silyl BCP boronates. Shortly after, the Walsh group, in collaboration with scientists at Merck,[11] disclosed the use of 1,3-difunctional benzylamine BCP boronates in Suzuki couplings (Figure 1B).

Leveraging a radical-based mechanism, Baran and co-workers[12] reported the cross-coupling of a single BCP redox-active ester (RAE) with Ph_2Zn. Anderson and co-workers, in collaboration with Pfizer,[13] then reported the iron-catalyzed Kumada coupling of various BCP iodides with aryl Grignard reagents (Figure 1C). In 2020, VanHeyst, Qi, and co-workers from Merck and WuXi engaged BCP trifluoroborate salts in Ni/photoredox dual cross-coupling and achieved modest to acceptable yields (Figure 1D).[14] Of note and particular pertinence to the results reported herein, the BCP trifluoroborate salts required preparation through a continuous flow photoborylation method from the corresponding *N*-(acyloxy)-phthalimide redox active esters (RAEs).[14,15]

Although BCP organometallic reagents perform well as cross-coupling partners, their applicability in late-stage functionalization is limited because of their functional group incompatibility and short-term stability. To address these

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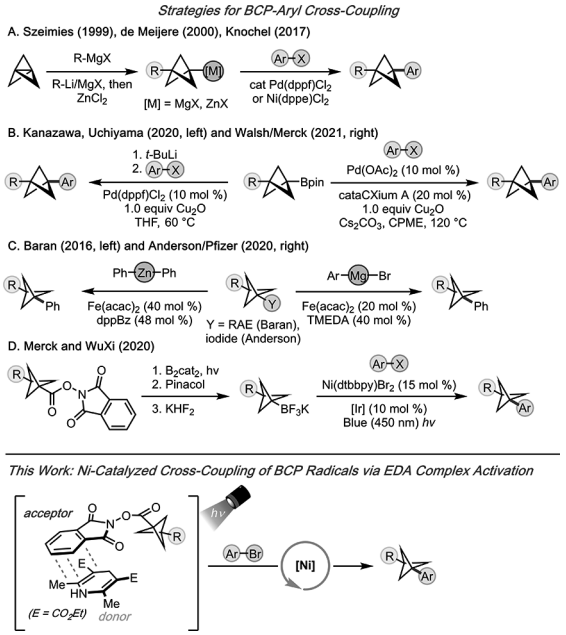

Figure 1. Comparison of two- and one-electron strategies to forge BCP−aryl cross-coupling products.

shortcomings, we envisioned employing bench stable, commercially available BCP carboxylic acid feedstocks under mild, Ni-catalyzed photochemical conditions.[16]

The initial goal was to use carboxylic acids directly in Ni/photoredox dual cross-coupling. Encouragingly, we established suitable conditions for the decarboxylation of a BCP carboxylate and verified that the resultant BCP radical engages in defluorinative alkylation with a trifluoromethyl-substituted alkene (Scheme S1A of the Supporting Information). However, adapting these conditions to Ni-catalyzed C−C bond formation with 4-bromobenzonitrile failed to generate the desired arylated BCP product.

Under dilute reaction conditions (0.025 M instead of 0.1 M), the corresponding BCP aryl ester was observed exclusively (Scheme S1B of the Supporting Information). This result can be rationalized by the high s character of the BCP−carboxylate bond ($\sim sp^{2.1}$),[6] resulting in a slower rate of decarboxylation, thus favoring an energy-transfer-dependent C−O coupling.[17,18]

These results motivated us to investigate the activation of BCP−*N*-(acyloxy)phthalimide RAEs, bench-stable solids that are readily prepared from the corresponding carboxylic acids via a quantitative Steglich esterification. These derivatives undergo decarboxylative radical fragmentation upon single-electron reduction[19] through photochemical strategies that are unavailable to the parent carboxylic acids.[20] In this vein, our group recently reported the nickel-catalyzed cross-coupling of primary- and secondary alkyl RAEs with (hetero)aryl halides using Hantzsch ester (HE) as a potent organic photoreductant.[20] The intermediacy of a photoactive electron donor−acceptor (EDA) complex[21−25] was envisioned to facilitate the generation and subsequent functionalization of BCP radicals in a Ni-catalyzed cross-electrophile paradigm, bypassing the need for preformed carbon nucleophiles as well as electron transfer events from exogenous photoredox catalysts. In addition, the developed protocol would provide a low barrier for practical implementation in medicinal chemistry settings.

Subsequently, we successfully adapted our previously reported conditions to the cross-coupling of a BCP RAE (1,3-dioxoisoindolin-2-yl bicyclo[1.1.1]pentane-1-carboxylate) with 4-((4-bromophenyl)sulfonyl)morpholine in modest yield (Table S1 of the Supporting Information). The addition of a mild base, such as $NaHCO_3$ or K_2HPO_4, improved the cross-coupling yield by diminishing the loss of the BCP radical to Minisci-type addition (**SI-21**) to Hantzsch pyridine, which is generated upon photoaromatization.

With suitable conditions established (see the Supporting Information for full optimization details), we proceeded to investigate the scope of aryl bromides amenable to the cross-coupling protocol (**1**−**16**, Scheme 1). In general, the best yields were obtained using aryl bromides bearing electron-withdrawing groups. Modest product formation was observed with electron-rich and electron-neutral aryl bromides because of competitive proto-debromination. Electrophilic and protic functional groups were well-tolerated (in contrast with cross-coupling methods based on organometallic reagents), including several synthetic handles found in substrates such as boronate **4**, chloride **5**, ester **7**, and amide **15**. Selected heteroaromatic bromides were accommodated and did not engage in Minisci-type side reactivity, giving modest to synthetically acceptable cross-coupling yields (**17**−**23**). Of particular note, pyridine **20** bears a 2-Cl handle for diversification via S_NAr, and the successful preparation of furan **23** was made possible by this net-reductive cross-electrophile platform. Importantly, these reductively and oxidatively sensitive systems are traditionally challenging structures in cross-couplings mediated by external photoredox catalysts, further underscoring the selectivity using the EDA paradigm. Finally, comparable reactivity was observed for product **16** using 3.3 mmol (1.0 g) of aryl bromide instead of 0.5 mmol.

In further investigations using 4-((4-bromophenyl)sulfonyl)-morpholine as a standard aryl bromide, the method was demonstrated to be amenable to a wide range of BCP RAEs with varying bridgehead substitutions (**24**−**31**). In particular, very few BCP−aryl compounds with amino-(**27**),[26−29] Cl-(**28**),[8] CF_3-(**29**),[30] CN-(**30**),[28] and F-(**33**)[31] bridgehead substitutions have been reported, and to our knowledge, none have been prepared via direct cross-coupling. Furthermore, the current method is proven to be more versatile than that of VanHeyst, Qi, and co-workers,[14] who were unsuccessful in employing NHBoc-, CF_3-, and CN-BCP trifluoroborates in Ni/photoredox cross-coupling. Finally, we underscored the utility of the method by engaging the BCP radical with several bromides bearing functionally dense, medicinally relevant structures (**37**−**44**). Under the developed conditions, late-stage functionalization of diverse scaffolds can be accomplished, including aryl chloride **37**, imidazole **38**, quinoline **42**, quinazoline **43**, and urea **44**. Notably, tertiary amines (**40** and **42**), often present in biologically active substances to modulate pharmacokinetic properties but typically susceptible to SET oxidation with traditional photoredox catalysts, can be accessed, albeit in low yields.[34]

To lend evidence for the intermediacy of an EDA complex, we measured ultraviolet/visible (UV/vis) absorption spectra for individual reaction components and mixtures thereof (Figure 2B). Although the RAE (violet line) and HE (golden line) absorb in the visible light region, they undergo a bathochromic shift (blue line) when combined, indicating the presence of charge-transfer aggregates. Indeed, the color

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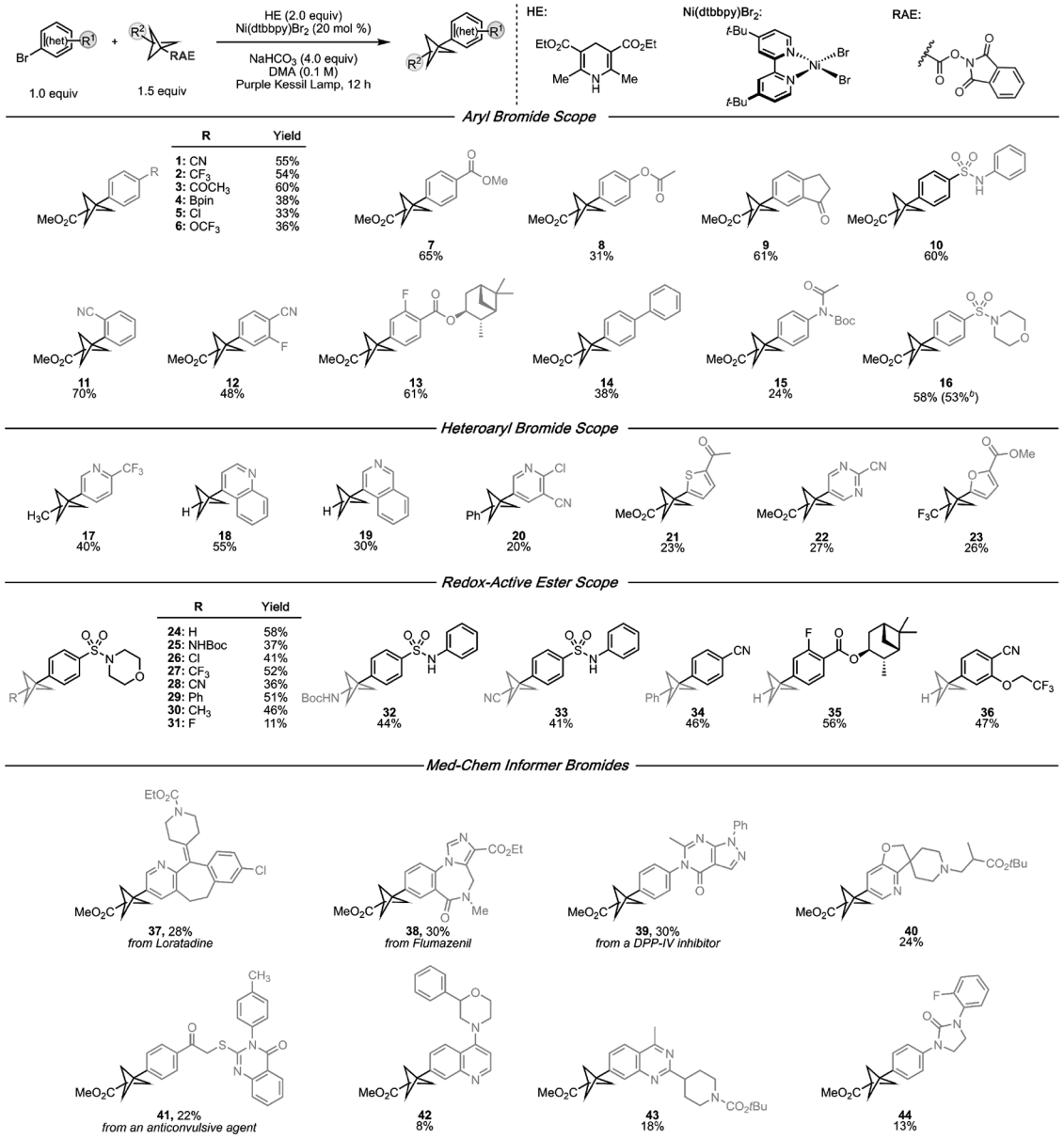
Scheme 1. Cross-Coupling Scope: Evaluation of BCP RAEs and (Hetero)aryl Bromides[a]



[a]Values refer to isolated yields. Unless otherwise noted, reactions were performed using ArBr (1 equiv, 0.5 mmol), RAE (1.5 equiv, 0.75 mmol), HE (2 equiv, 1.0 mmol), Ni(dtbbpy)Br_2 (20 mol %, 0.10 mmol), $NaHCO_3$ (4 equiv, 2.0 mmol), and dry, degassed DMA (5.0 mL). Irradiation was performed at room temperature using a 390 nm Kessil lamp with fan cooling. For Med-Chem Informer Bromides: ArBr (1 equiv, 0.25 mmol), RAE (1.5 equiv, 0.38 mmol), HE (2 equiv, 0.5 mmol), Ni(dtbbpy)Br_2 (20 mol %, 0.05 mmol), $NaHCO_3$ (4 equiv, 1.0 mmol), and dry degassed DMA (2.5 mL). [b]The reaction was performed using 3.3 mmol of ArBr (1.0 g).

change is apparent to the naked eye (Figure 2A). The association constant of the EDA complex and analysis via Job's method demonstrated a 1:1 molar stoichiometry (panels C and D of Figure 2).

With these results and with insight from our previous report,[20] we propose the following mechanism. Visible light excitation of the EDA complex triggers a single-electron transfer (SET) event from HE to the RAE, which fragments to generate phthalimidate, CO_2, and BCP radical **III**. This BCP radical is then captured by Ni^{II} oxidative addition complex II. Alternatively, the low-valent Ni^0 complex I could intercept BCP radical **III** and then undergo subsequent oxidative addition with the aryl bromide. Both pathways lead to Ni^{III} intermediate **IV**, which undergoes reductive elimination to furnish the cross-coupled product. Finally, photoexcited Hantzsch ester reduces Ni^I to the catalytically active Ni^0 species to close the cycle (Figure 3).

In conclusion, we have established a general route toward the synthesis of functionalized bicyclo[1.1.1]pentanes through Ni-catalyzed $C(sp^3)-C(sp^2)$ bond formation enabled by photoactive EDA complex activation. The developed cross-electrophile protocol evades the need for expensive transition-metal-based photoredox catalysts, preformed organometallics or boronate partners, and stoichiometric metal reductants. Under this photochemical paradigm, the generation of BCP radicals through direct visible-light excitation followed by subsequent cross-coupling with diverse (hetero)aryl halides is feasible. The commercial availability of carboxylic acids,

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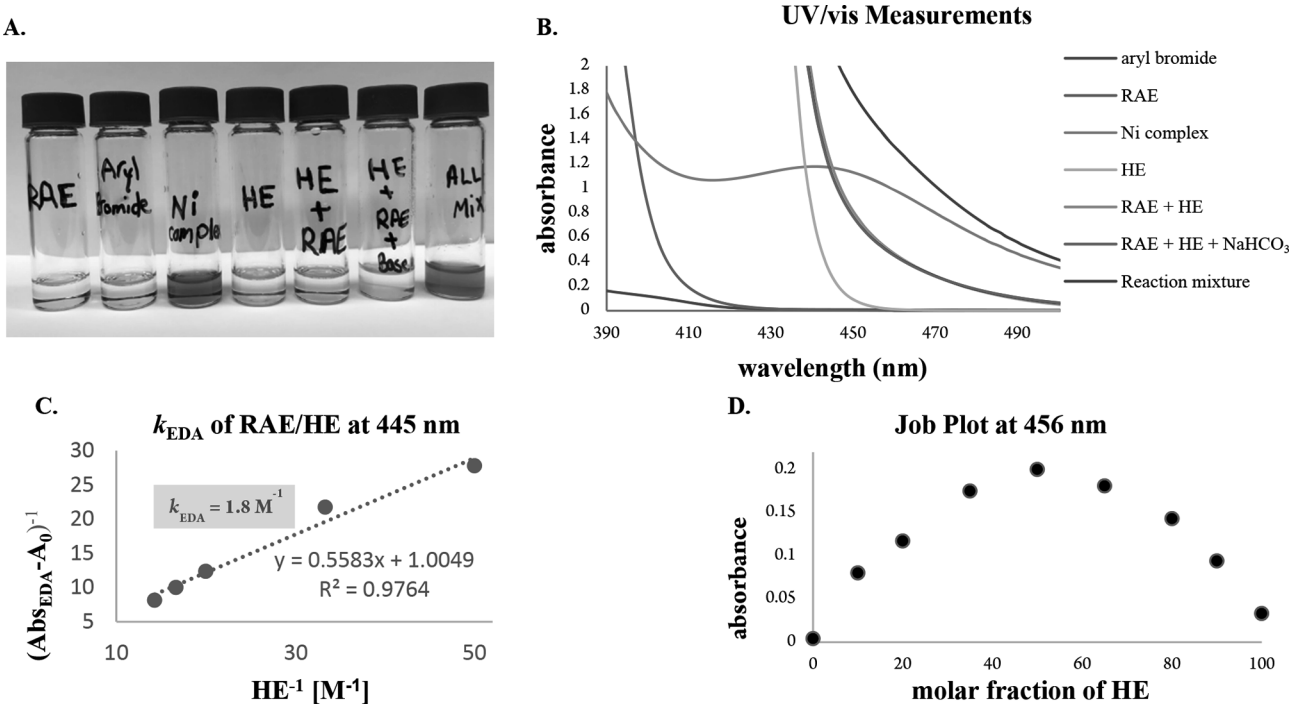

Figure 2. (A) Visual appearance of individual reaction components and mixtures thereof. (B) UV/vis absorption spectra measured in DMA (0.1 M). Aryl bromide, 4-((4-bromophenyl)sulfonyl)morpholine; RAE, 1,3-dioxoisoindolin-2-yl bicyclo[1.1.1]pentane-1-carboxylate; Ni complex, Ni(dtbbpy)Br_2; and HE, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. (C) Benesi−Hildebrand plot.[32] (D) Job plot[33] for a mixture of RAE and HE (0.2 M).

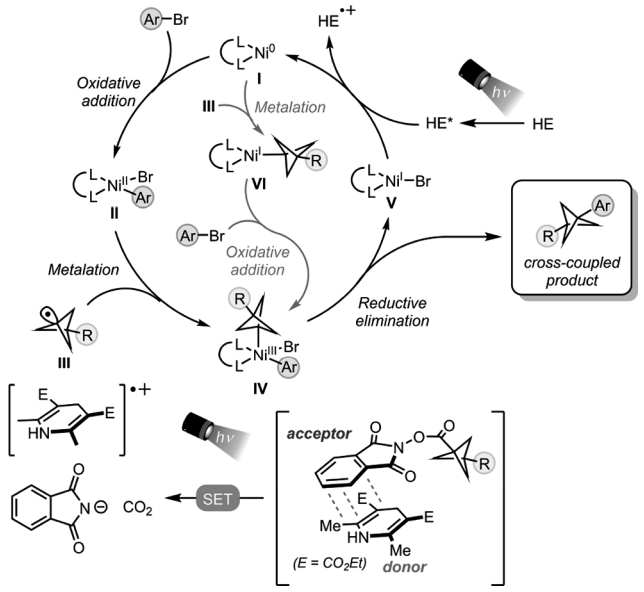

Figure 3. Proposed cross-coupling mechanism.

(hetero)aryl bromides, and HE enables the rapid assembly of diverse scaffolds. In addition, the mild reaction conditions facilitate late-stage modification of drug-like molecules with high functional group tolerance. Key spectroscopic studies highlight the necessity for EDA photoactivation for efficient BCP radical generation and subsequent functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01558.

Preparation of starting materials, optimization of cross-coupling and control studies, characterization data for products [nuclear magnetic resonance (NMR), infrared (IR), and mass spectrometry (MS)], mechanistic studies, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J. Med. Chem.* **2016**, *59*, 4385−4402.

(2) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(3) Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a ring on it: Application of small aliphatic rings in medicinal chemistry. *RSC Med. Chem.* **2021**, *12*, 448−471.

(4) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1−11.

(5) Grover, N.; Senge, M. O. Synthetic Advances in the C−H Activation of Rigid Scaffold Molecules. *Synthesis* **2020**, *52*, 3295−3325.

(6) Levin, M. D.; Kaszynski, P.; Michl, J. Bicyclo[1.1.1]pentanes, [n]Staffanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.02,5]pentanes. *Chem. Rev.* **2000**, *100*, 169−234.

(7) Daniel Rehm, J. D.; Ziemer, B.; Szeimies, G. A Facile Route to Bridgehead Disubstituted Bicyclo[1.1.1]pentanes Involving Palladium-Catalyzed Cross-Coupling Reactions. *Eur. J. Org. Chem.* **1999**, *1999*, 2079−2085.

(8) Messner, M.; Kozhushkov, S. I.; de Meijere, A. Nickel- and Palladium-Catalyzed Cross-Coupling Reactions at the Bridgehead of Bicyclo[1.1.1]pentane Derivatives—A Convenient Access to Liquid Crystalline Compounds Containing Bicyclo[1.1.1]pentane Moieties. *Eur. J. Org. Chem.* **2000**, *2000*, 1137−1155.

(9) Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of Bicyclo[1.1.1]pentane Bioisosteres of Internal Alkynes and para-Disubstituted Benzenes from [1.1.1]-Propellane. *Angew. Chem., Int. Ed.* **2017**, *56*, 12774−12777.

(10) Kondo, M.; Kanazawa, J.; Ichikawa, T.; Shimokawa, T.; Nagashima, Y.; Miyamoto, K.; Uchiyama, M. Silaboration of [1.1.1]Propellane: A Storable Feedstock for Bicyclo[1.1.1]pentane Derivatives. *Angew. Chem., Int. Ed.* **2020**, *59*, 1970−1974.

(11) Shelp, R.; Ciro, A.; Pu, Y.; Merchant, R. R.; Hughes, J. M. E.; Walsh, P. Strain-Release 2-Azaallyl Anion Addition/Borylation of [1.1.1]Propellane: Synthesis and Functionalization of Benzylamine Bicyclo[1.1.1]pentyl Boronates. *Chem. Sci.* **2021**, *12*, 7066−7072.

(12) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. Redox-Active Esters in Fe-Catalyzed C−C Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 11132−11135.

(13) Nugent, J.; Shire, B. R.; Caputo, D. F. J.; Pickford, H. D.; Nightingale, F.; Houlsby, I. T. T.; Mousseau, J. J.; Anderson, E. A. Synthesis of All-Carbon Disubstituted Bicyclo[1.1.1]pentanes by Iron-Catalyzed Kumada Cross-Coupling. *Angew. Chem., Int. Ed.* **2020**, *59*, 11866−11870.

(14) VanHeyst, M. D.; Qi, J.; Roecker, A. J.; Hughes, J. M. E.; Cheng, L.; Zhao, Z.; Yin, J. Continuous Flow-Enabled Synthesis of Bench-Stable Bicyclo[1.1.1]pentane Trifluoroborate Salts and Their Utilization in Metallaphotoredox Cross-Couplings. *Org. Lett.* **2020**, *22*, 1648−1654.

(15) Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. Photoinduced decarboxylative borylation of carboxylic acids. *Science* **2017**, *357*, 283−286.

(16) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **2014**, *345*, 437−440.

(17) Welin, E. R.; Le, C.; Arias-Rotondo, D. M.; McCusker, J. K.; MacMillan, D. W. C. Photosensitized, energy transfer-mediated organometallic catalysis through electronically excited nickel(II). *Science* **2017**, *355*, 380−385.

(18) Tian, L.; Till, N. A.; Kudisch, B.; MacMillan, D. W. C.; Scholes, G. D. Transient Absorption Spectroscopy Offers Mechanistic Insights for an Iridium/Nickel-Catalyzed C−O Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4555−4559.

(19) Niu, P.; Li, J.; Zhang, Y.; Huo, C. One-Electron Reduction of Redox-Active Esters to Generate Carbon-Centered Radicals. *Eur. J. Org. Chem.* **2020**, *2020*, 5801−5814.

(20) Kammer, L. M.; Badir, S. O.; Hu, R.-M.; Molander, G. A. Photoactive electron donor−acceptor complex platform for Ni-mediated C(sp3)−C(sp2) bond formation. *Chem. Sci.* **2021**, *12*, 5450−5457.

(21) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. Synthetic Methods Driven by the Photoactivity of Electron Donor−Acceptor Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 5461−5476.

(22) Pitre, S. P.; Allred, T. K.; Overman, L. E. Lewis Acid Activation of Fragment-Coupling Reactions of Tertiary Carbon Radicals Promoted by Visible-Light Irradiation of EDA Complexes. *Org. Lett.* **2021**, *23*, 1103−1106.

(23) Zheng, C.; Wang, G.-Z.; Shang, R. Catalyst-free Decarboxylation and Decarboxylative Giese Additions of Alkyl Carboxylates through Photoactivation of Electron Donor-Acceptor Complex. *Adv. Synth. Catal.* **2019**, *361*, 4500−4505.

(24) Yang, T.; Wei, Y.; Koh, M. J. Photoinduced Nickel-Catalyzed Deaminative Cross-Electrophile Coupling for C(sp2)−C(sp3) and C(sp3)−C(sp3) Bond Formation. *ACS Catal.* **2021**, *11*, 6519−6525.

(25) Zhang, J.; Li, Y.; Xu, R.; Chen, Y. Donor−Acceptor Complex Enables Alkoxyl Radical Generation for Metal-Free C(sp3)−C(sp3) Cleavage and Allylation/Alkenylation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12619−12623.

(26) Thirumoorthi, N. T.; Jia Shen, C.; Adsool, V. A. Expedient synthesis of 3-phenylbicyclo[1.1.1]pentan-1-amine via metal-free homolytic aromatic alkylation of benzene. *Chem. Commun.* **2015**, *51*, 3139−3142.

(27) Kanazawa, J.; Maeda, K.; Uchiyama, M. Radical Multicomponent Carboamination of [1.1.1]Propellane. *J. Am. Chem. Soc.* **2017**, *139*, 17791−17794.
(28) Applequist, D. E.; Renken, T. L.; Wheeler, J. W. Polar substituent effects in 1,3-disubstituted bicyclo[1.1.1]pentanes. *J. Org. Chem.* **1982**, *47*, 4985−4995.
(29) Kokhan, S. O.; Valter, Y. B.; Tymtsunik, A. V.; Komarov, I. V.; Grygorenko, O. O. Bicyclo[1.1.1]pentane-Derived Building Blocks for Click Chemistry. *Eur. J. Org. Chem.* **2017**, *2017*, 6450−6456.
(30) Adcock, J. L.; Gakh, A. A. Nucleophilic substitution in 1-substituted 3-iodobicyclo[1.1.1]pentanes. A new synthetic route to functionalized bicyclo[1.1.1]pentane derivatives. *J. Org. Chem.* **1992**, *57*, 6206−6210.
(31) Adcock, W.; Blokhin, A. V.; Elsey, G. M.; Head, N. H.; Krstic, A. R.; Levin, M. D.; Michl, J.; Munton, J.; Pinkhassik, E.; Robert, M.; Savéant, J.-M.; Shtarev, A.; Stibor, I. Manifestations of Bridgehead−Bridgehead Interactions in the Bicyclo[1.1.1]pentane Ring System. *J. Org. Chem.* **1999**, *64*, 2618−2625.
(32) Benesi, H. A.; Hildebrand, J. H. A Spectrophotometric Investigation of the Interaction of Iodine with Aromatic Hydrocarbons. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.
(33) Renny, J. S.; Tomasevich, L. L.; Tallmadge, E. H.; Collum, D. B. Method of Continuous Variations: Applications of Job Plots to the Study of Molecular Associations in Organometallic Chemistry. *Angew. Chem., Int. Ed.* **2013**, *52*, 11998−12013.
(34) Walker, D. K.; Jones, R. M.; Nedderman, A. N. R.; Wright, P. A. Primary, Secondary and Tertiary Amines and their Isosteres. In *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of Chemical Building Blocks on ADMET*; Smith, D. A., Ed.; Royal Society of Chemistry: London, U.K., 2010; Chapter 4, pp 168−209, DOI: 10.1039/9781849731102-00168.

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