pubs.acs.org/OrgLett

## Regioselective Radical Borylation of $\alpha,\beta$ -Unsaturated Esters and Related Compounds by Visible Light Irradiation with an Organic Photocatalyst

Guosong Li,<sup>§</sup> Guanwang Huang,<sup>§</sup> Ruixia Sun, Dennis P. Curran,<sup>\*</sup> and Wen Dai<sup>\*</sup>



L igated  $\alpha$ - and  $\beta$ -boryl carbonyl compounds are air stable and easily handled. In these molecules, the ligated boryl group and the carbonyl group can be independently manipulated, and this opens paths to selective transformations that are useful in a variety of fields.<sup>1</sup> Ligated boryl carbonyl compounds are typically either boronate derivatives of *N*methyliminodiacetic acid (MIDA)<sup>1</sup> or borane complexes with amines, phosphines, or N-heterocyclic carbene (NHC).<sup>2–5</sup>

B–H bond insertion reactions of ligated boranes and  $\alpha$ diazocarbonyl compounds provided the first straightforward route to make ligated  $\alpha$ -boryl carbonyl compounds in the borane oxidation state, and these reactions can be catalyzed by Rh, Cu, and even genetically engineered enzymes (Scheme 1a).<sup>2</sup> Wang has made *a*-NHC-boryl carbonyl compounds by regioselective radical hydroboration of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds with NHC-boranes (Scheme 1b).<sup>3</sup> This reaction is initiated by AIBN and aided by a thiol hydrogen atom transfer (HAT) catalyst. We have made various  $\alpha$ -NHC-boryl ketones by radical reactions of alkenyl triflates and NHCboranes in the presence of diisopropyl ethyl amine (Scheme 1c).<sup>4</sup> Most recently, Zhu described a photoredox method to construct  $\beta$ -NHC-boryl imides using an iridium-based photocatalyst and thiol as the HAT catalyst (Scheme 1d).<sup>5</sup>

These valuable methods have attendant limitations.  $\alpha$ -Diazocarbonyl compounds and alkenyl triflates need to be synthesized and can be unstable (triflates) and even hazardous (diazo carbonyls). Methods require expensive metal catalysts or combine high-energy initiators with large amounts (20–50 mol %) of a thiol to aid hydrogen atom transfer. Substrate limitations also constrain applicability. For example, the alkenyl triflate (Scheme 1c) only provides ketones, while the route to

Scheme 1. Methods for Synthesis of Stable Boryl Carbonyl Compounds



 $\beta$ -boryl compounds (Scheme 1d) is currently limited to imides. Accordingly, practical methods of broad scope are needed.

 Received:
 April 15, 2021

 Published:
 May 18, 2021



Letter



Other reactions of NHC-boranes that are induced by visible light and a metal photocatalyst include 1,4-hydroborations of electron-poor aromatic rings,<sup>6,7</sup> homolytic substitutions of fluorine atoms in various settings,<sup>6,8,9</sup> arylboration and hydroboration of fluorinated alkenes,<sup>8</sup> and hydroboration of imines.<sup>10</sup> In addition to a metal catalyst, all these reactions require other additives including bases and thiols.

Predating all this recent work, Lacôte and Lalevée reported in 2012 the first examples of generation of NHC-boryl radicals by visible light.<sup>11</sup> They described soft polymerization of acylates with NHC-boranes and acridine orange. Since then, organic photocatalysts (dyes) have seen little use in small molecule reactions of NHC-boranes. The hydroboration reactions of Zhu succeeded with an iridium photocatalyst but failed with eosin Y and **4-CzIPN** (see Table S1 for structure).<sup>5</sup> Wu reported a few successful defluoroborylation reactions with **4-CzIPN**, but conditions with Ir photocatalysts were much preferred.<sup>6</sup>

We have discovered that visible-light irradiation of unsaturated carbonyl compounds or nitriles, NHC-boranes, and a small amount of photocatalyst 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4-DPAIPN) regioselectively delivers either  $\alpha$ - or  $\beta$ -NHC-boryl functionalized compounds, depending on the substrate structure (Scheme 2). The starting

# Scheme 2. Strategy for the Synthesis of Boryl Functionalized Molecules



materials are structurally diverse and readily accessible, and the scope is broad. The conditions are mild and metal-free, and no base, cocatalyst, or other additive is needed.

We chose ethyl cinnamate 1a and 1,3-dimethylimidazoyl-2ylidine borane  $2^{12}$  as pilot reaction partners, and Table S1 (see the Supporting Information (SI)) shows the results of an assortment of preliminary reactions. In the first experiment, irradiation of a room temperature acetonitrile solution of 1a, 2 (2 equiv), and the photocatalyst 3-DPAFIPN<sup>13</sup> (10 mol %) with a 30 W blue light-emitting diode (LED) for 12 h provided  $\alpha$ -boryl ester 3a in 56% isolated yield (entry 1). No product was produced in the absence of the light or photocatalyst (entries 2 and 3). Next, we reduced the amount of borane and found that 1.1 equiv gave about the same yield as 2 equiv (entries 4 and 5). Among the various photocatalysts tested (4-DPAIPN, 4-CzIPN, 4-CzPN, 5-CzBN, eosin Y, and DCN, entries 6-11), 4-DPAIPN gave the best yield (99% NMR, 82% isolated, entry 6).<sup>14</sup> Decreasing the catalyst loading to 5 mol % resulted in a moderate decrease in yield (94% NMR, 79% isolated, entry 12), whereas increasing the amount of catalyst gave about the same yield (entry 13). Finally, decreasing the reaction time from 12 to 8 h did not change the yield, while a further decrease to 5 h gave a moderate reduction (compare entries 6, 14, and 15).

Based on these results, we selected the conditions of entry 14 (10% mol 4-DPAIPN, 8 h, rt) as standard for the ensuing study of scope.

We next studied the scope with respect to the alkene compounds, and Scheme 3 shows results of reactions of various  $\beta$ -aryl- $\alpha$ , $\beta$ -unsaturated esters, lactones, amides, nitriles, and ketones. A variety of  $\beta$ -phenyl- $\alpha$ , $\beta$ -unsaturated esters smoothly underwent regioselective hydroboration to afford  $\alpha$ boryl- $\beta$ -phenyl esters, regardless of the electronic nature of the substituents on the aromatic ring (see **3b**-**3k**).  $\beta$ -Heteroaryl- $\alpha$ , $\beta$ -unsaturated esters with pyridine, thiophene, or quinoline rings were also viable substrates, delivering the corresponding  $\alpha$ -addition products in moderate yields (**3l**-**3n**). Hydroboration of two cumarins worked well to give *a*-boryl lactones **3o** and **3p**.

In contrast,  $\alpha,\beta$ -unsaturated esters bearing an additional ester or cyano group at  $\alpha$ -position led exclusively to  $\beta$ -addition products in excellent yield (3q-3t). When  $\alpha,\beta$ -unsaturated esters containing an additional methyl group at  $\alpha$ -position were subjected to this protocol, the  $\beta$ -addition pathway continued to predominate, giving stereoisomeric  $\beta$ -addition products  $3u-\beta$  and  $3u-\beta'$  in 62% combined yield with an 8% yield of  $\alpha$ -addition product  $3u-\alpha$ . The change in regioselectivity is probably caused by synergistic steric and electronic effects of the added substituent. The steric effect disfavors  $\alpha$ addition. When a second electron-withdrawing group is added at the  $\alpha$ -position, the nucleophilicity of the NHC-boryl radical takes over and  $\beta$ -selectivity is favorable.

All the reactions in the scope study were conducted on 0.2 mmol scale. To test the scalability, we conducted a reaction with 1.00 g (5.8 mmol) of 1a and 2 (674 mg, 1.1 equiv) under the standard conditions. This provided 1.26 g of 3a, and the yield (78%) is comparable to the small-scale experiment (83%, Table S1, entry 14) (see the SI).

Next, we examined alternatives to esters as activating groups. Pleasingly, representative  $\alpha$ , $\beta$ -unsaturated amides gave  $\alpha$ -boryl amides in good yields (3v-3z). Notably, several  $\beta$ -aryl- $\alpha$ , $\beta$ -unsaturated nitriles and a ketone also underwent the  $\alpha$ -additions affording the  $\alpha$ -NHC-boryl products (3aa-3af). However, cinnamic acid and cinnamaldehyde were inert to the hydroboration process and did not provide the boryl carbonyl compounds.

The  $\beta$ -aryl group in these substrates stabilizes the adduct radical by resonance, thereby promoting  $\alpha$ -addition. In contrast,  $\beta$ -addition might be favored due to the strong nucleophilicity of NHC-boryl radical if this group is absent. To test this notion, we next studied the reactions to  $\beta$ -alkyl- $\alpha_{\beta}\beta$ unsaturated carbonyl compounds (Scheme 4). Indeed, a wide range of  $\beta$ -alkyl- $\alpha$ , $\beta$ -unsaturated esters and lactones were suitable substrates and underwent  $\beta$ -addition, giving solely  $\beta$ boryl esters and lactones in generally good yields (3ag-3an). Increasing the steric effect on the  $\beta$ -carbon, such as ethyl 3methylcrotonate, failed to give the desired hydroboration product. Interestingly, ethyl acrylate, which is easily polymerized by NHC-boryl radicals,<sup>11</sup> was hydroborated to provide the  $\beta$ -NHC-boryl ester **3ao** in good yield. Reactions of  $\beta$ -alkyl- $\alpha_{,\beta}$ -unsaturated amides were also highly  $\beta$ -selective, albeit with moderate yields (3ap-3ar). Finally, a  $\beta$ -alkyl- $\alpha$ , $\beta$ -unsaturated nitrile also afforded the  $\beta$ -boryl nitrile in good yield (3as).

Scheme 5 summarizes experiments aimed at providing mechanistic information. In radical-blocking experiments, reactions of 1a and 2 were conducted under standard conditions in the presence of 2,2,6,6-tetramethyl-1-piperidinyl oxyl (TEMPO) as a radical scavenger. When 4 equiv of TEMPO were used, the yield of  $\alpha$ -boryl ester 3a was decreased to 20%. When 6 equiv of TEMPO were used, 3a was not



Scheme 3. Scope of Photocatalytic Radical Borylation of  $\beta$ -Aryl- $\alpha$ , $\beta$ -unsaturated Esters, Lactones, Amides, Nitriles, and Ketones<sup>*a*,*b*</sup>

<sup>a</sup>Standard conditions: alkene 1 (0.2 mmol), 2 (0.22 mmol), 4-DPAIPN (10 mol %), MeCN (2 mL), rt, 30 W blue LEDs, 8 h. <sup>b</sup>The yield was determined by <sup>11</sup>B-NMR, and isolated yield is given in parentheses. <sup>c</sup>16 h. <sup>d</sup>24 h. <sup>e</sup>72 h.

formed. In both experiments adduct **15** was detected by HRMS. These results suggest that an NHC-boryl radical pathway is involved but that the reaction is not a radical chain (only small amounts of TEMPO are needed to inhibit chains).

Deuteration experiments were performed to learn the source of the new hydrogen atom, the three possibilities being the solvent, the NHC-borane, or water from undried solvent. There was no deuterium in product **3a** when the reaction was performed in CD<sub>3</sub>CN, so the solvent is not the source of the hydrogen atom. When **2** was replaced with **2**- $d_3$ , 25% deuterium incorporation was found at the benzylic position of the product **3a**- $d_2$ /**3a**- $d_3$ . When the reaction was performed with unlabeled **2** and 15 equiv of D<sub>2</sub>O, the product **3a**/**3a**- $d_1$ contained a single deuterium (95%) at the benzylic position. These results show that the source of the hydrogen atom on carbon is a proton, which can come from either residual water or the NHC-borane (Scheme Sb).

Taken together, results support a photoredox catalysis mechanism as outlined in Scheme 6. The organic photocatalyst PC absorbs a photon to give an excited state  $PC^{*,15}$  which is quenched by NHC-BH<sub>3</sub> to generate the photocatalyst radical PC<sup>-•</sup> and radical cation **16**. Subsequent deprotonation of the

radical cation **16** produces the NHC-boryl radical. In this way, a hydrogen atom from the NHC-borane is incorporated into the proton pool with residual water.

Next, the oxidatively generated the NHC-boryl radical undergoes addition to the electron-deficient alkenes. For the  $\beta$ aryl substituted alkene, the NHC-boryl radical undergoes  $\alpha$ addition, giving radical intermediate 17. For the  $\beta$ -alkyl substituted alkene, addition occurs at the  $\beta$ -carbon to generate radical intermediate 18. Both intermediates 17 and 18 are then quickly reduced by PC<sup>-•</sup> to the corresponding anions 19 and 20 with the concurrent regeneration of the photocatalyst PC, thus completing the photocatalytic cycle.<sup>16</sup> Protonation of these anions provides the hydroboration products.

In summary, we have developed a photoredox radical hydroboration of electron-deficient alkenes with NHC-boranes that uses only an organocatalyst. The substrate scope is broad, and a wide variety of stable  $\alpha$ - or  $\beta$ -boryl esters, amides, ketones, and nitriles are formed in good yields. The  $\alpha/\beta$  regioselectivity is high and is dictated by the substituents of the alkene component. Neither reaction component is used in excess, the conditions are mild, and both the reaction and purification protocols are convenient.

Scheme 4. Scope of Photocatalytic Radical  $\beta$ -Borylation with  $\beta$ -Alkyl- $\alpha$ , $\beta$ -unsaturated Esters, Lactones, Amides, and Nitriles<sup>*a*,*b*</sup>



<sup>a</sup>Standard conditions: alkene 1 (0.2 mmol), 2a (0.22 mmol), 4-DPAIPN (10 mol %), MeCN (2 mL), rt, 30 W blue LEDs, 8 h. <sup>b</sup>The yield was determined by <sup>11</sup>B-NMR, and isolated yield is given in parentheses. <sup>c</sup>24 h. <sup>d</sup>16 h. <sup>e</sup>2a (0.30 mmol), 16 h. <sup>f</sup>72 h. <sup>g</sup>48 h.

#### Scheme 5. Mechanistic Experiments



Compared to other recent hydroboration reactions with NHC-boranes, this method has a broader scope.<sup>5,6</sup> In addition, it does not require a metal catalyst and has no other additives besides the organocatalyst itself. The method directly delivers

## Scheme 6. Proposed Mechanistic for Radical Borylation of Alkenes with NHC-Boranes



NHC-boryl radicals from NHC-boranes. This opens the way for further development of visible-light-driven radical borylation reactions, thereby enabling the unique features of NHC-boranes to be used in new transformations.

## ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01270.

Experimental, compound characterization, and copies of spectra (PDF)

#### AUTHOR INFORMATION

#### **Corresponding Authors**

- Dennis P. Curran Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15208, United States; orcid.org/0000-0001-9644-7728; Email: curran@ pitt.edu
- Wen Dai Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; o orcid.org/ 0000-0002-9098-5215; Email: daiwen@dicp.ac.cn

#### Authors

- **Guosong Li** Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
- **Guanwang Huang** Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
- Ruixia Sun Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01270

#### **Author Contributions**

<sup>§</sup>G.L. and G.H. contributed equally.

#### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Financial support from Dalian Institute of Chemical Physics and the National Natural Science Foundation of China (21773232) is acknowledged.

### REFERENCES

(1) (a) He, Z.; Zajdlik, A.; Yudin, A. K. Air-and moisture-stable amphoteric molecules: enabling reagents in synthesis. *Acc. Chem. Res.* **2014**, 47, 1029. (b) Diaz, D. B.; Scully, C. C.; Liew, S. K.; Adachi, S.; Trinchera, P.; St. Denis, J. D.; Yudin, A. K. Synthesis of aminoboronic acid derivatives from amines and am-photeric boryl carbonyl compounds. *Angew. Chem., Int. Ed.* **2016**, 55, 12659. (c) Bai, J.; Burke, L. D.; Shea, K. J. BH<sub>3</sub>-catalyzed oligomerization of ethyl diazoacetate: the role of C-boron enolates. *J. Am. Chem. Soc.* **2007**, *129*, 4981. (d) Caskey, S. R.; Stewart, M. H.; Johnson, M. J.; Kampf, J. W. Carbon–carbon bond formation at a neutral terminal carbido ligand: generation of cyclopropenylidene and vinylidene com-plexes. *Angew. Chem., Int. Ed.* **2006**, *45*, 7422.

(2) (a) Li, X.; Curran, D. P. Insertion of reactive rhodium carbenes into boron-hydrogen bonds of stable N-heterocyclic carbene boranes. J. Am. Chem. Soc. 2013, 135, 12076. (b) Chen, D.; Zhang, X.; Qi, W.-Y.; Xu, B.; Xu, M.-H. Rhodium (I)-catalyzed asymmetric carbene insertion into B-H bonds: highly enantioselective access to functionalized organobo-ranes. J. Am. Chem. Soc. 2015, 137, 5268. (c) Cheng, Q.-Q.; Zhu, S.-F.; Zhang, Y.-Z.; Xie, X.-L.; Zhou, Q.-L. Copper-catalyzed B-H bond insertion reaction: a highly efficient and enantioselective C-B bond-forming reaction with amine-borane and phosphine-borane adducts. J. Am. Chem. Soc. 2013, 135, 14094. (d) Kan, S. J.; Huang, X.; Gumulya, Y.; Chen, K.; Arnold, F. H. Genetically programmed chiral organoborane synthesis. Nature 2017, 552, 132.

(3) (a) Ren, S. C.; Zhang, F.-L.; Xu, A.-Q.; Yang, Y.; Zheng, M.; Zhou, X.; Fu, Y.; Wang, Y.-F. Regioselective radical  $\alpha$ -borylation of  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds for direct synthesis of  $\alpha$ borylcarbonyl molecules. *Nat. Commun.* **2019**, *10*, 1934. (b) Huang, Y.-S.; Wang, J.; Zheng, W.-X.; Zhang, F.-L.; Yu, Y.-J.; Zheng, M.; Zhou, X.; Wang, Y.-F. Regioselective radical hydroboration of electron-deficient alkenes: ssynthesis of  $\alpha$ -boryl functionalized molecules. *Chem. Commun.* **2019**, *55*, 11904.

(4) Dai, W.; Geib, S. J.; Curran, D. P. Facile Synthesis of  $\alpha$ -N-heterocyclic carbene-boryl ketones from N-heterocyclic carbene-boranes and alkenyl triflates. *J. Am. Chem. Soc.* **2019**, *141*, 12355.

(5) Zhu, C.; Dong, J.; Liu, X.; Gao, L.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Photoredox-controlled  $\beta$ -regioselective radical hydroboration of activated alkenes with NHC-boranes. *Angew. Chem., Int. Ed.* **2020**, *59*, 12817.

(6) Xu, W.; Jiang, H.; Leng, J.; Ong, H. W.; Wu, J. Visible-lightinduced selective defluoroborylation of polyfluoroarenes, gemdifluoroalkenes, and trifluoromethylal-kenes. *Angew. Chem., Int. Ed.* **2020**, 59, 4009.

(7) Dai, W. E. N.; Geib, S. J.; Curran, D. P. 1,4-Hydroboration reactions of electron-poor aromatic rings by N-heterocyclic carbene boranes. J. Am. Chem. Soc. **2020**, 142, 6261.

(8) Qi, J.; Zhang, F.-L.; Jin, J.-K.; Zhao, Q.; Li, B.; Liu, L. X.; Wang, Y. F. New Radical borylation pathways for organoboron synthesis enabled by photoredox catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 12876.

(9) Xia, P. J.; Song, D.; Ye, Z. P.; Hu, Y. Z.; Xiao, J. A.; Xiang, H. Y.; Chen, X. Q.; Yang, H. Photoinduced single-electron transfer as an enabling principle in the radical borylation of alkenes with NHCborane. *Angew. Chem., Int. Ed.* **2020**, *59*, 6706. (10) Zhou, N.; Yuan, X. A.; Zhao, Y.; Xie, J.; Zhu, C. Synergistic photoredox catalysis and organocatalysis for inverse hydroboration of imines. *Angew. Chem., Int. Ed.* **2018**, *57*, 3990.

(11) Telitel, S.; Schweizer, S.; Morlet-Savary, F.; Graff, B.; Tschamber, T.; Blanchard, N.; Fouassier, J. P.; Lelli, M.; Lacôte, E.; Lalevée, J. Soft photopolymerizations initiated by dye-sensitized formation of NHC-boryl radicals under visible light. *Macromolecules* **2013**, *46*, 43.

(12) Gardner, S.; Kawamoto, T.; Curran, D. P. 1,3-dimethylimidazoyl-2-ylidene borane. Org. Synth. 2016, 92, 342.

(13) Flynn, A. R.; McDaniel, K.; Hughes, M.; Vogt, D.; Jui, N. T. Hydroarylation of arenes via reductive radical-polar crossover. J. Am. Chem. Soc. 2020, 142, 9163.

(14) (a) Lu, J.; Pattengale, B.; Liu, Q.; Yang, S.; Shi, W.; Li, S.; Huang, J.; Zhang, J. Donor-acceptor fluorophores for energytransfer-mediated photocatalysis. J. Am. Chem. Soc. 2018, 140, 13719. (b) Xu, W.; Wang, W.; Liu, T.; Xie, J.; Zhu, C. Late-stage trifluoromethylthiolation of benzylic C-H bonds. Nat. Commun. 2019, 10, 4867. (c) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. Chem. Rev. 2016, 116, 10075.

(15) (a) McAtee, R. C.; McClain, E. J.; Stephenson, C. R. Illuminating photoredox catalysis. *Trends Chem.* 2019, *1*, 111.
(b) Sap, J. B.; Straathof, N. J.; Knauber, T.; Meyer, C. F.; Médebielle, M.; Buglioni, L.; Genicot, C.; Trabanco, A. s. A.; Noël, T.; Am Ende, C. W.; Gouverneur, V. Organophotoredox Hydrodefluorination of Trifluoromethylarenes with Translational Applicability to Drug Discovery. *J. Am. Chem. Soc.* 2020, 142, 9181.

(16) Sim, B.; Griller, D.; Wayner, D. Reduction potentials for substituted benzyl radicals: pKa values for the corresponding toluenes. J. Am. Chem. Soc. **1989**, 111, 754. (b) Luo, J.; Zhang, J. Donor-acceptor fluorophores for visible-light-promoted organic synthesis: Photoredox/Ni dual catalytic C(sp3)-Cs(sp2) cross-coupling. ACS Catal. **2016**, 6, 873. (c) Fu, Q.; Bo, Z.-Y.; Ye, J.-H.; Ju, T.; Huang, H.; Liao, L.-L.; Yu, D.-G. Transition metal-free phosphonocarboxylation of alkenes with carbon dioxide via visible-light photoredox catalysis. Nat. Commun. **2019**, 10, 3592.