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# *trans*-Hydroalkynylation of Internal 1,3-Enynes Enabled by Cooperative Catalysis

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## Supporting Information Placeholder

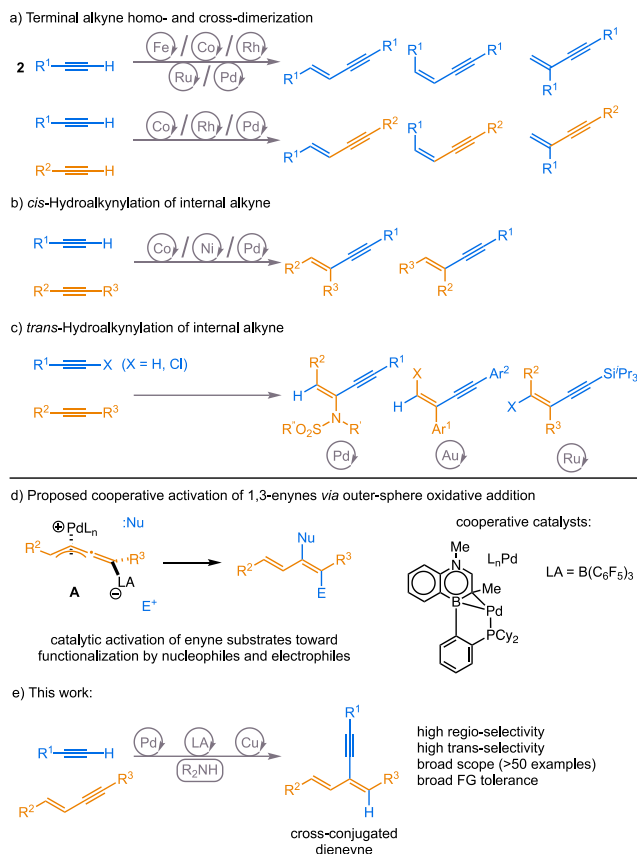
**ABSTRACT:** A cooperative catalyst system involving Pd(0)/Senphos complex, tris(pentafluorophenyl)borane, copper bromide, and an amine base, is demonstrated to catalyze *trans*-hydroalkynylation of internal 1,3-enynes. For the first time, a Lewis acid catalyst is shown to promote the reaction involving the emerging outer-sphere oxidative reaction step. The resulting cross-conjugated dieneynes are versatile synthons for organic synthesis and their characterization reveals distinct photophysical properties depending on the positioning of the donor/acceptor substituents along the conjugation path.

Hydroalkynylation, i.e., the net addition of terminal alkyne to an alkyne unit, is an atom-economical and straightforward approach to 1,3-enynes and related conjugated molecules which are widely exploited in bioactive molecules,<sup>1</sup> functional materials<sup>2</sup> and complexity-building transformations.<sup>3</sup> To this end, significant advances have been achieved in terminal alkyne homo- and cross coupling<sup>4,5</sup> (Scheme 1a). However, the hydroalkynylation of an internal alkyne has been more challenging due to the competing homodimerization, oligomerization and cyclotrimerization of either starting materials as well as regio- and diastereoselectivity issues when unsymmetrical internal alkynes are used. So far, a few stereoselective hydroalkynylation<sup>6,4a</sup> of internal alkynes (Scheme 1b) have been reported, with *trans*-selective examples being particularly rare (Scheme 1c). In 2014, Zhu et al. reported the first example of Pd-catalyzed *trans*-addition terminal alkyne to N-sulfonyl ynamides.<sup>7</sup> Recently, Lassaletta and coworkers developed a catalyst-counteranion-dependent Au-catalyzed divergent *trans*-hydroalkynylation of haloalkynes or *cis*-bromoalkynylation of terminal alkynes.<sup>8</sup> Another elegant work from Fürstner demonstrated that [Cp\*RuCl]<sub>4</sub> catalyzed the *trans*-addition of *t*-Pr<sub>3</sub>SiC≡CX (X =H, Cl) across internal alkynes.<sup>9</sup> Nevertheless, a broadly applicable *trans*-hydroalkynylation of internal alkynes with wide scope remains underdeveloped.

In our program to expand the chemical space in ligand design for applications in homogeneous catalysis through BN/CC isosterism,<sup>10</sup> we recently described *trans*-hydroboration,<sup>11</sup> *trans*-cyanoboration<sup>12</sup> and *cis*-carboboration of 1,3-enynes<sup>13</sup> catalyzed by a 1,4-azaborine biaryl phosphine (Senphos)-Pd complex. Mechanistic studies<sup>14</sup> support an unusual outer-sphere oxidative addition mechanism<sup>15</sup> where a Lewis acid (LA)

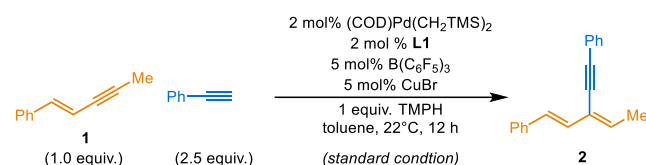
activates a Pd(0)-enyn complex to form a zwitterionic Pd- $\pi$ -allyl species (e.g., **A** in Scheme 1d).<sup>16</sup> Recently, we were able to crystallographically characterize an outer-sphere oxidative addition adduct where the LA is B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>.<sup>17</sup> Whereas in our reported borylative transformations the LA activator is employed in stoichiometric amounts as substrates, we hypothesized that a catalytic amount of LA<sup>18</sup> such as B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> may enable a *general* and *selective* addition of nucleophiles and electrophiles across a 1,3-enyn via cooperative catalysis (Scheme 1d).<sup>19</sup> In this communication, we present the successful development of the Pd/Senphos-catalyzed *trans*-selective hydroalkynylation of internal 1,3-enynes in the presence of Lewis acid and copper co-catalysts and an amine base (Scheme 1e). The nucleophile in this work is proposed to be the Cu-alkynyl species and the electrophile is a proton. Our catalytic transformation is site-, regio-, and diastereoselective, exhibits broad scope and functional group tolerance, and is an atom-economic and simple method to access the family of cross-conjugated dieneynes. A library of donor/acceptor-substituted derivatives could be readily prepared and characterized by UV-Vis absorption and emission spectroscopy.

## Scheme 1. Transition Metal-Catalyzed Hydroalkynylation of Alkynes

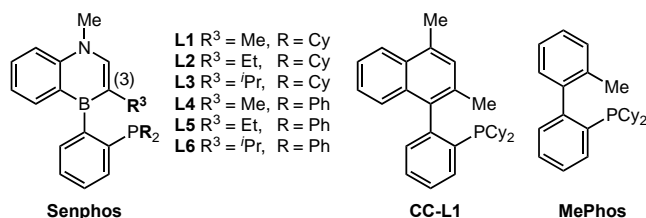


We selected 1,3-enyne **1** and phenylacetylene as model substrates for our reaction optimization efforts. We determined that a combination of catalytic amounts of Pd/**L1**, B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, CuBr, and a stoichiometric amount of TMPH (2,2,6,6-tetramethylpiperidine) in toluene at room temperature was crucial to obtain the desired product **2**. When any of the catalysts or the TMPH was absent under otherwise identical conditions, the desired hydroalkynylation reaction did not proceed (Table 1, entries 1-6).

**Table 1. Control Experiment and Ligand Survey of Internal 1,3-enyne *trans*-Hydroalkynylation<sup>a</sup>**



Entry	Variation from standard condition	Yield (%) <sup>b</sup>	Selectivity <sup>b</sup>
1	none	88(84) <sup>c</sup>	>98:2
2	without [Pd]	<2	N.D.
3	without <b>L1</b>	<2	N.D.
4	without B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	<2	N.D.
5	without CuBr	<2	N.D.
6	without TMPH	<2	N.D.
7	<b>L2</b> instead of <b>L1</b>	74	>98:2
8	<b>L3</b> instead of <b>L1</b>	9	>98:2
9	<b>L4</b> instead of <b>L1</b>	68	>98:2
10	<b>L5</b> instead of <b>L1</b>	61	>98:2
11	<b>L6</b> instead of <b>L1</b>	22	>98:2
12	<b>CC-L1</b> instead of <b>L1</b>	19	>98:2
13	<b>MePhos</b> instead of <b>L1</b>	13	>98:2



<sup>a</sup>Reaction performed at 0.4 mmol scale. See SI for detailed procedure.  
<sup>b</sup>Yield and selectivity was determined by <sup>1</sup>H NMR analysis of unpurified reaction mixture with CH<sub>2</sub>Br<sub>2</sub> as the internal standard. Selectivity is defined as the ratio of title product over other isomers. <sup>c</sup>Yield of isolated product in parenthesis.

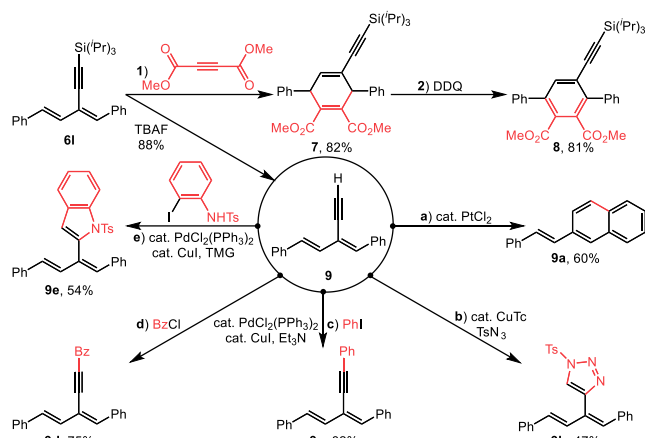
We then explored the ligand effect on this hydroalkynylation reaction. The use of a sterically more demanding ligand with a larger substituent on the C(3) position (e.g., R<sup>3</sup> = Et or <sup>i</sup>Pr) decreases the product yield (entries 7-8). When the R = Cy in Senphos is replaced with R = Ph, a reduction in yield is observed (entry 9 vs. entry 1). A similar detrimental effect of the increasing size of the R<sup>3</sup> substituent is also observed for the arylphosphine (R = Ph) ligand series (entries 9-11). We also determined that the performances of the corresponding carbonaceous ligand **CC-L1** and the commercially available structurally related analogue **MePhos**,<sup>20</sup> are significantly inferior to Senphos **L1** (entries 12-13 vs. entry 1), highlighting the distinct electronic structure features of the Senphos ligands enabling this transformation.<sup>21</sup>

The hydroalkynylation proved to be quite general; a broad range of terminal alkynes serve as suitable substrates, affording the corresponding *trans*-addition product exclusively (Table 2). Various aryl alkynes (entries **4a-4l**) bearing electron-donating or electron-withdrawing groups can readily participate in this reaction to afford product in moderate to good yield. Compatible functional groups include fluoro (entries **4b-d**), tertiary amine (entry **4e**), methoxy (entry **4f**), trifluoromethyl (entry **4g**), pinacolborato (entry **4h**), ester (entry **4i**), nitro (entry **4k**) and cyano (entry **4l**) groups. In addition, silyl acetylenes (entries **4m** and **4n**) and terminal aliphatic alkynes (entries **4o-4y**) of different carbon chain length containing primary chloride (entry **4r**), silyl ether (entry **4t**), ketone (entry **4u**), ester (entry **4v**), phthalimide (entry **4w**), nitrile (entry **4x**) and estrone moiety (entry **4y**) are well accepted. We have obtained the X-ray crystal structure of **4m**, thus unambiguously establishing the connectivity and the diastereoselectivity of the reaction product. For ease of purification, a more polar enyne was used as a reactant in some cases (entries **4k**, **4l**, **4r-4y**).

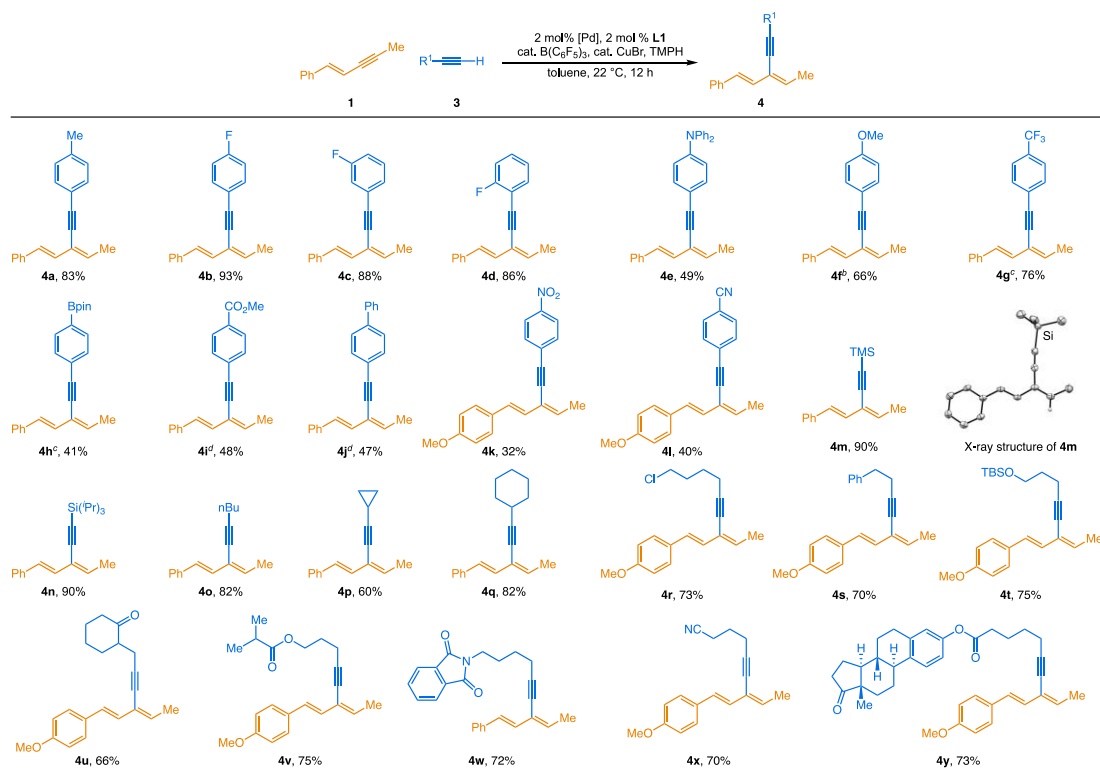
We also evaluated the scope with respect to internal 1,3-enynes, and we were pleased to find broad applicability of the optimized reaction conditions and exclusive *trans*-selectivity of the reaction products (Table 3). For example, the reaction is insensitive to an array of electronically different aryl group on the alkene position R<sup>2</sup> (entries **6a-6g**). In addition to aryl groups, the R<sup>2</sup> position also tolerates H (entry **6h**) and alkyl substituents (entries **6i-6k**), albeit requiring slightly forcing conditions. The reaction is also compatible with various diaryl 1,3-enyne substrates bearing electronically diverse aryl groups at the R<sup>3</sup> position (entries **6l-6r**). The regio- and stereochemistry of the hydroalkynylation of a representative diaryl 1,3-enyne substrate is established by an X-ray structure of the product **6m**. In addition to Me and aryl groups at the R<sup>3</sup> position, enynes with longer chain alkyl groups (entry **6s**) and those bearing functional groups (entries **6t-6y**) are also suitable substrates. We also note that 1,3-enynes derived from

commercial drugs such as ibuprofen, isoxepac, naproxen afford the corresponding products **6w–6y** in high yield. The hydroalkynylation products are versatile building blocks in organic synthesis. As shown in Scheme 2, the conjugated diene unit of **6l** can participate in a Diels-Alder reaction to produce intermediate **7**, which can be oxidized<sup>22</sup> to give the arene product **8**.<sup>23</sup> In the presence of TBAF, desilylation of **6l** proceeds smoothly to afford terminal alkyne **9**. Building block **9** cycloisomerizes to the corresponding naphthalene derivative **9a** in the presence of PtCl<sub>2</sub> catalyst.<sup>24</sup> In the presence of TsN<sub>3</sub> compound **9** generates triazole **9b** in a click reaction catalyzed by CuTc.<sup>25</sup> Furthermore, Sonogashira cross coupling of **9** with aryl and acyl electrophiles furnishes the corresponding products **9c**, **9d**, **9e**, respectively.<sup>26</sup>

**Scheme 2. Derivatization of Reaction Products.**

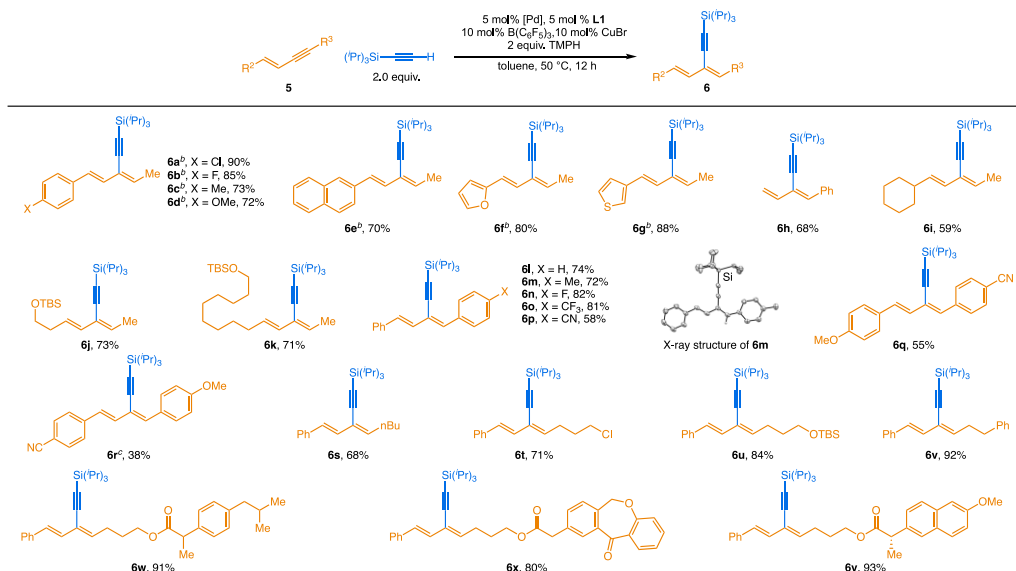


**Table 2. Reaction Scope of Terminal Alkynes.<sup>a</sup>**



<sup>a</sup>Reaction condition: **1** (0.4 mmol), (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> (2 mol%), **L1** (2 mol%), for aryl alkynes **3a–3l**: **3** (1.0 mmol), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (5 mol%), CuBr (5 mol%), TMPH (0.4 mmol), toluene (0.8 mL), 22 °C, 12 h; for alkyl alkynes **3m–3y**: **3** (0.8 mmol), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (10 mol%), CuBr (10 mol%), TMPH (0.8 mmol), toluene (0.6 mL), 22 °C, 12 h, unless otherwise noted. Yields of isolated product are reported as an average of two runs. Selectivity is determined by <sup>1</sup>H NMR analysis of purified product. See SI for detailed procedure. <sup>b</sup>1.2 mmol 4-methoxyphenylacetylene was used. <sup>c</sup>24 h reaction time. <sup>d</sup>**1** (0.4 mmol), (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> (5 mol%), **L1** (5 mol%), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (10 mol%), CuBr (5 mol%), TMPH (0.4 mmol), toluene (0.8 mL), 12 h, 50 °C.

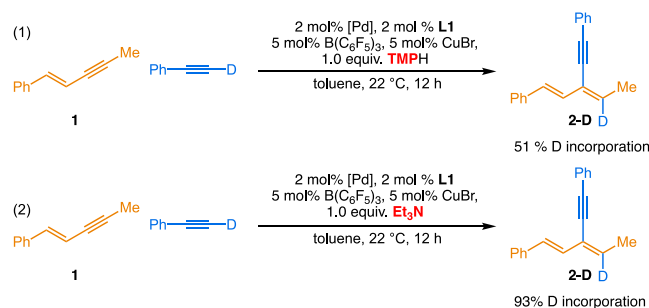
**Table 3. Reaction Scope of Internal 1,3-Enynes.<sup>a</sup>**



<sup>a</sup>Reaction condition: **5** (0.4 mmol), (triisopropylsilyl)acetylene (0.8 mmol), (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> (5 mol%), **L1** (5 mol%), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (10 mol%), CuBr (10 mol%), TMPH (0.8 mmol), toluene (0.6 mL), 50 °C, 12 h, unless otherwise noted. Yields of isolated product are reported as an average of two runs. Selectivity is determined by <sup>1</sup>H NMR analysis of purified product. See SI for detailed procedure.  
<sup>b</sup>Standard conditions, except: (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> (2 mol%), **L1** (2 mol%), 22 °C. <sup>c</sup>Standard conditions, except: (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> (10 mol%), **L1** (10 mol%), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (20 mol%), 24 h.

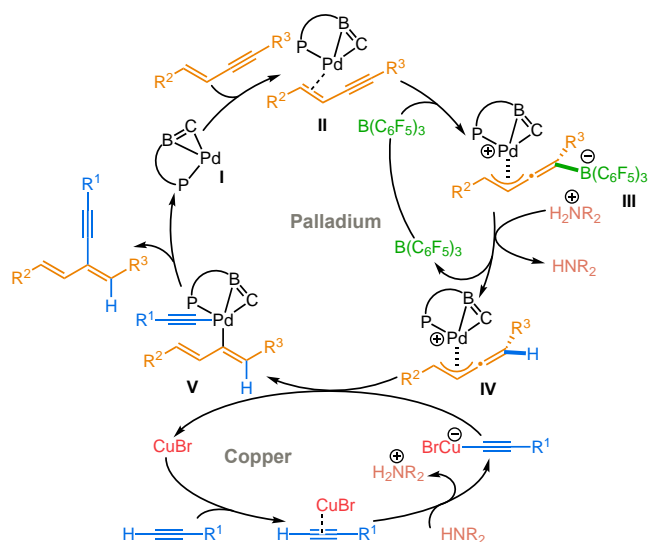
In preliminary labeling experiments we determined that 51% deuterium is incorporated into the product with deuterated phenylacetylene under standard conditions. With deuterated phenylacetylene in the presence of Et<sub>3</sub>N (instead of TMPH), we observe 93% deuterium incorporation into the product (Scheme 3). These observations from the deuterium labeling experiments are consistent with the amine serving as a proton shuttle to deliver the proton to the activated enyne.

### Scheme 3. Deuterium Labeling Studies.



Scheme 4 illustrates a plausible mechanism for the hydroalkynylation reaction. The active Pd(0)/Senphos complex **I** is generated from the catalyst precursor (COD)Pd(CH<sub>2</sub>TMS)<sub>2</sub> and the Senphos ligand via reductive elimination,<sup>27</sup> which is then followed by the coordination of the enyne substrate to furnish complex **II**. The B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> co-catalyst then activates the Pd(0)/enyne complex **II** to yield the outersphere oxidative addition adduct **III**. Complex **III** subsequently undergoes a protodeboronation<sup>28</sup> by an ammonium cation species (originating from a deprotonative activation of terminal alkyne in the Cu cycle to generate the Cu-alkynyl<sup>29</sup> species) to form **IV** with concomitant release of the B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> co-catalyst. Transmetalation of the Cu-alkynyl species (from Cu cycle) to **IV** affords intermediate **V**, which upon reductive elimination delivers the product and regenerates the Pd catalyst **I**.

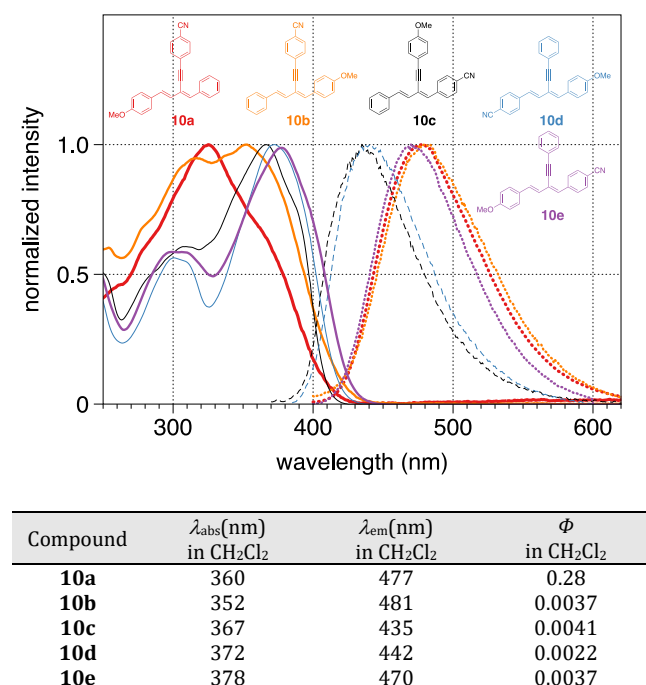
### Scheme 4. Plausible Catalytic Cycle.



Using our methodology, we were able to prepare a library of donor/acceptor substituted cross-conjugated<sup>30</sup> dienynes **10a-e**<sup>31</sup> and characterize their photophysical properties.<sup>32</sup> As can be seen from Figure 1, the isomeric compounds **10a-e** display a relatively narrower  $\lambda_{\text{abs}}$  range (352 - 378 nm) than the  $\lambda_{\text{em}}$  range (435 - 481 nm). Compounds **10a**, **10b**, **10e** exhibit a bathochromically shifted  $\lambda_{\text{em}}$  compared to compounds **10c** and **10d**. Among the investigated compounds, **10a** stands out as the molecule featuring the highest quantum yield ( $\Phi$  = 28%) and as the only structure where its lowest energy transition ( $\lambda_{\text{abs}}$  = 360 nm) does not have the strongest extinction coefficient. Electronic structure and TD-DFT calculations at wB97XD/6-311G(d,p) level<sup>33</sup> (see Supporting Information for details) support the experimental observations.

TD-DFT reveals that the lowest-energy absorption ( $\lambda_{\text{abs}}$ ) is mostly derived from HOMO-LUMO transition for all compounds. Consistent with experimental data, the transition to the second excited state for **10a** is predicted to have a larger oscillator strength than the transition to the first excited state. From the computed electronic structure calculations, the HOMO-LUMO transitions have more charge transfer character for compounds **10a**, **10b**, **10e** whereas for compounds **10c** and **10d** the first excited state is more consistent with a  $\pi$  to  $\pi^*$  transition. The distinct electronic structure differences of these frontier orbitals and the stronger charge transfer character may be responsible for the observed bathochromic shift in  $\lambda_{\text{em}}$  for **10a**, **10b**, **10e** in  $\text{CH}_2\text{Cl}_2$  vs. **10c** and **10d**. It is worth noting that **10a** is the only structure investigated where the donor and acceptor placement involves a cross-conjugated path.

**Figure 1. Normalized Absorption and Emission Spectra and Photophysical Data of 10a-10e in  $\text{CH}_2\text{Cl}_2$ .<sup>a</sup>**



<sup>a</sup>All data are independently measured in house at  $1.0 \times 10^{-5}$  M concentration to enable direct comparison.  $\lambda_{\text{abs}}$  is defined as the wavelength of the lowest energy electronic transition. Quantum yield was determined through comparative method with quinine sulfate as standard.

In summary, we have developed a highly selective *trans*-hydroalkynylation reaction of internal 1,3-enynes with broad scope and functional group tolerance. In developing the reaction, we demonstrate for the first time that catalytic amounts of Lewis acids such as  $\text{B}(\text{C}_6\text{F}_5)_3$  can be deployed to promote a reaction involving an outer-sphere oxidative reaction step. The resulting cross-conjugated dieneynes serve as versatile building block for a variety of conjugated reaction products. In addition, the facile access to a library of isomeric donor/acceptor substituted dieneynes reveals distinct photophysical properties depending on the positioning of the donor/acceptor substituents along the conjugation path. Overall, the unorthodox reactivity pattern exhibited by this reaction should serve as a general platform to other hydrofunctionalizations of unsaturated compounds, which is a subject of current efforts in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, computational and crystallographic information (PDF)

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### Notes

The authors declare no competing financial interests.

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