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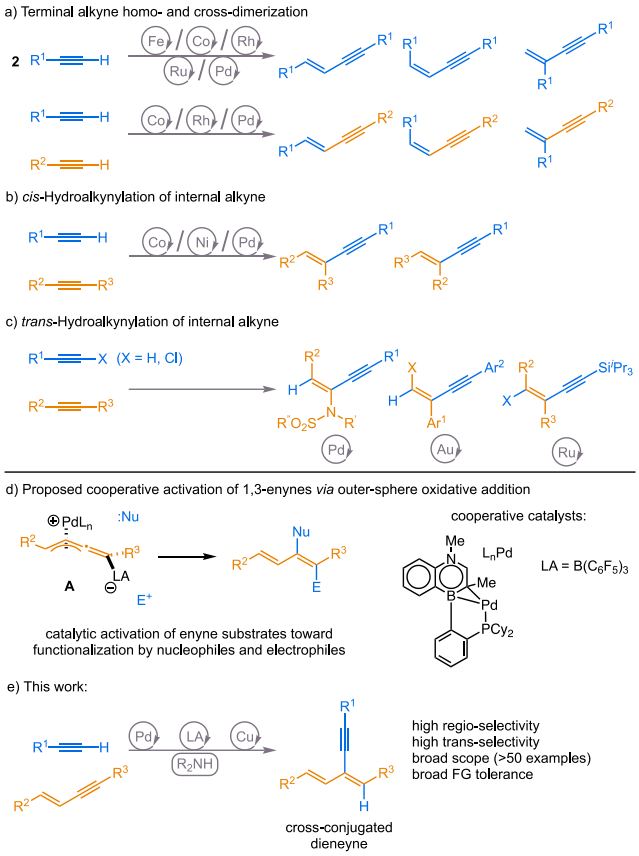
Supporting Information Placeholder

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,[1] functional materials[2] and complexity-building transformations.[3] To this end, significant advances have been achieved in terminal alkyne homo- and cross coupling[4,5] (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[6,4a] 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.[7] Recently, Lassaletta and coworkers developed a catalyst-counteranion-dependent Au-catalyzed divergent *trans*-hydroalkynylation of haloalkynes or *cis*-bromoalkynylation of terminal alkynes.[8] Another elegant work from Fürstner demonstrated that $[Cp^*RuCl]_4$ catalyzed the *trans*-addition of $^{i}Pr_3SiC{\equiv}CX$ (X =H, Cl) across internal alkynes.[9] Nevertheless, a broadly applicable *trans*-hydroalkynylation of internal alkynes with wide scope remains underdeveloped.

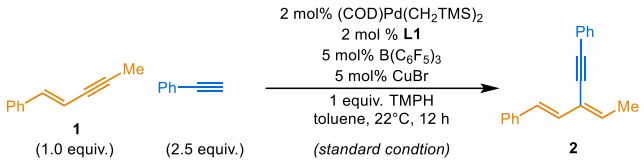
In our program to expand the chemical space in ligand design for applications in homogeneous catalysis through BN/CC isosterism,[10] we recently described *trans*-hydroboration,[11] *trans*-cyanoboration[12] and *cis*-carboboration of 1,3-enynes[13] catalyzed by a 1,4-azaborine biaryl phosphine(Senphos)-Pd complex. Mechanistic studies[14] support an unusual outer-sphere oxidative addition mechanism[15] where a Lewis acid (LA) activates a Pd(0)-enyne complex to form a zwitterionic Pd-π-allyl species (e.g., **A** in Scheme 1d).[16] Recently, we were able to crystallographically characterize an outer-sphere oxidative addition adduct where the LA is $B(C_6F_5)_3$.[17] Whereas in our reported borylative transformations the LA activator is employed in stoichiometric amounts as substrates, we hypothesized that a catalytic amount of LA[18] such as $B(C_6F_5)_3$ may enable a *general* and *selective* addition of nucleophiles and electrophiles across a 1,3-enyne via cooperative catalysis (Scheme 1d).[19] 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 diastereoslective, 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

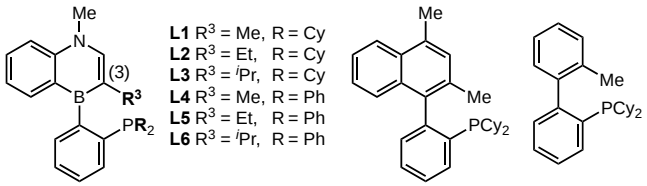


We selected 1,3-enyne **1** and phenylacetylene as model substrates for our reaction optimization efforts. We determined that a combination of catalytic amounts of Pd/**L1**, $B(C_6F_5)_3$, CuBr, and a stoichiometric amount of TMPH (2,2,6,6-tetramethylpiperidine) in toluene at room temperature was crucial 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[a]



Entry	Variation from standard condition	Yield (%)[b]	Selectivity[b]
1	none	88(84)[c]	>98:2
2	*without* [Pd]	<2	N.D.
3	*without* **L1**	<2	N.D.
4	*without* $B(C_6F_5)_3$	<2	N.D.
5	*without* CuBr	<2	N.D.
6	*without TMPH*	<2	N.D.
7	**L2** instead of **L1**	74	>98:2
8	**L3** instead of **L1**	9	>98:2
9	**L4** instead of **L1**	68	>98:2
10	**L5** instead of **L1**	61	>98:2
11	**L6** instead of **L1**	22	>98:2
12	**CC-L1** instead of **L1**	19	>98:2
13	**MePhos** instead of **L1**	13	>98:2



[a]Reaction performed at 0.4 mmol scale. See SI for detailed procedure. [b]Yield and selectivity was determined by ^{1}H NMR analysis of unpurified reaction mixture with CH_2Br_2 as the internal standard. Selectivity is defined as the ratio of title product over other isomers. [c]Yield of isolated product in parenthesis.

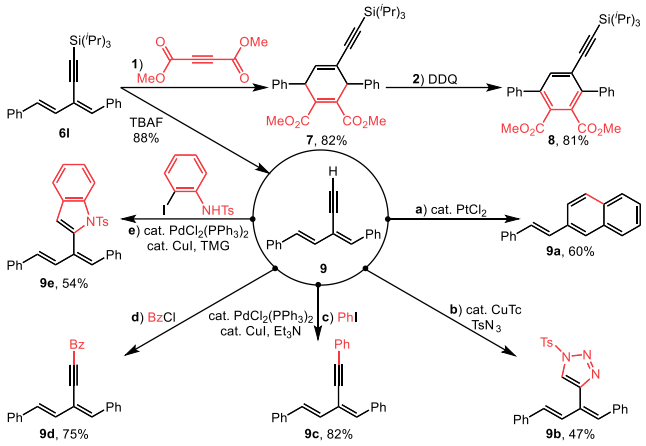
We then explored the ligand effect on this hydroalkynylation reaction. The use of a sterically more demanding ligand with a larger substituent on the C(3) position (e.g., R^3 = Et or ^{i}Pr) decreases the product yield (entries 7-8). When the R = Cy in Senphos is replaced with R = Ph, a reduction in yield is observed (entry 9 vs. entry 1). A similar detrimental effect of the increasing size of the R^3 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,[20] 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.[21]

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^2 (entries **6a-6g**). In addition to aryl groups, the R^2 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^3 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^3 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

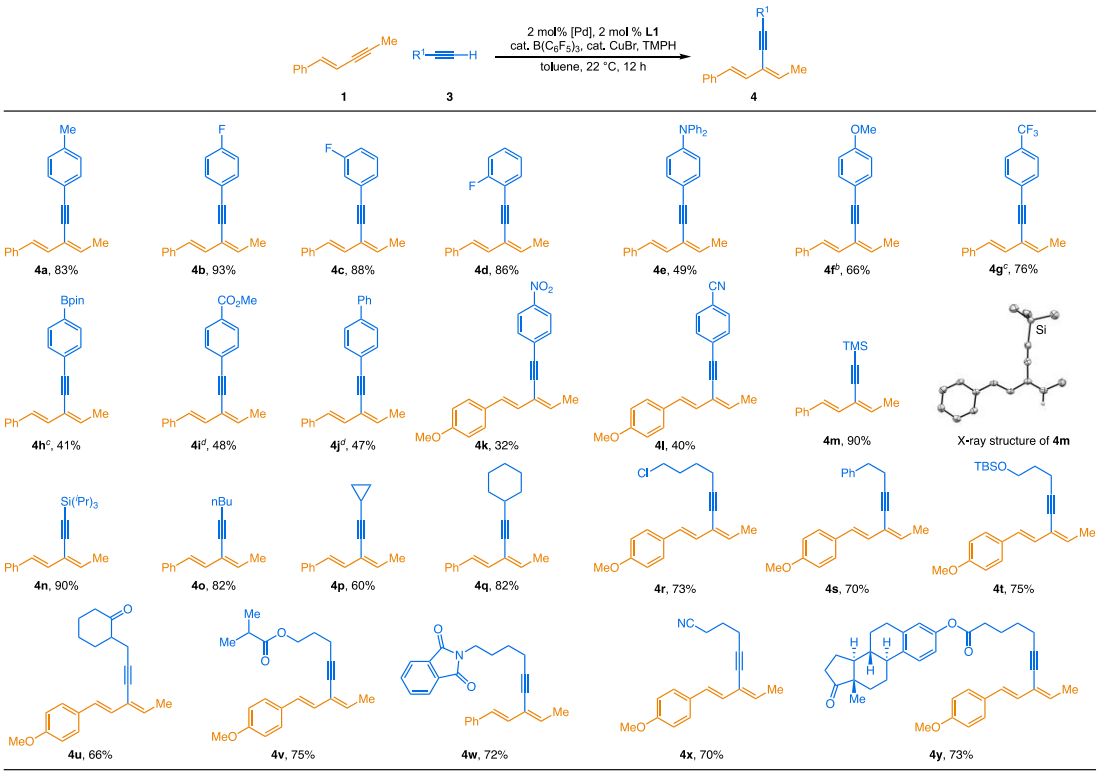
commercial drugs such as ibuprofen, isoxepac, naproxen afford the corresponding products **6w**-**6y** in high yield.

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[22] to give the arene product **8**.[23] 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 $PtCl_2$ catalyst.[24] In the presence of TsN_3 compound **9** generates triazole **9b** in a click reaction catalyzed by CuTc.[25] Furthermore, Sonogashira cross coupling of **9** with aryl and acyl electrophiles furnishes the corresponding products **9c**, **9d**, **9e**, respectively.[26]



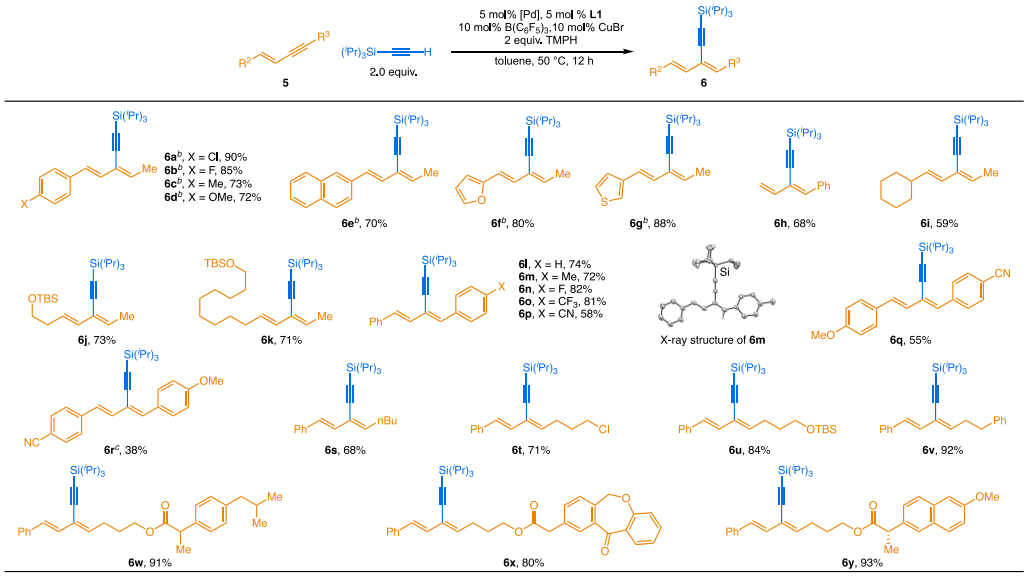
Scheme 2. Derivatization of Reaction Products.

Table 2. Reaction Scope of Terminal Alkynes. [a]



[a]Reaction condition: **1** (0.4 mmol), $(COD)Pd(CH_2TMS)_2$ (2 mol%), **L1** (2 mol%), for aryl alkynes **3a**-**3l**: **3** (1.0 mmol), $B(C_6F_5)_3$ (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), $B(C_6F_5)_3$ (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 ^1H NMR analysis of purified product. See SI for detailed procedure. [b]1.2 mmol 4-methoxyphenylacetylene was used. [c]24 h reaction time. [d]**1** (0.4 mmol), $(COD)Pd(CH_2TMS)_2$ (5 mol%), **L1** (5 mol%), $B(C_6F_5)_3$ (10 mol%), CuBr (5 mol%), TMPH (0.4 mmol), toluene (0.8 mL), 12 h, 50 °C.

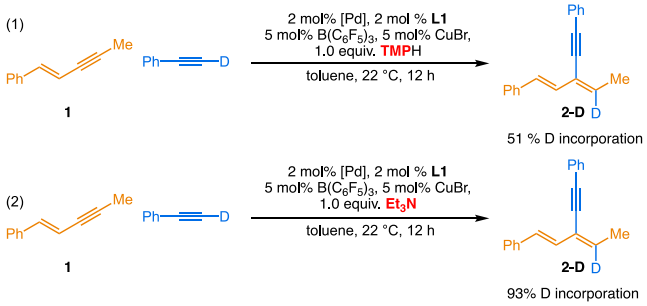
Table 3. Reaction Scope of Internal 1,3-Enynes. [a]



[a]Reaction condition: **5** (0.4 mmol), (triisopropylsilyl)acetylene (0.8mmol), (COD)Pd(CH_2TMS)$_2$ (5 mol%), **L1** (5 mol%), $B(C_6F_5)_3$ (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 ^{1}H NMR analysis of purified product. See SI for detailed procedure. [b]Standard conditions, except: (COD)Pd(CH_2TMS)$_2$ (2 mol%), **L1** (2 mol%), 22 °C. [c]Standard conditions, except: (COD)Pd(CH_2TMS)$_2$ (10 mol%), **L1** (10 mol%), $B(C_6F_5)_3$ (20 mol%), 24 h.

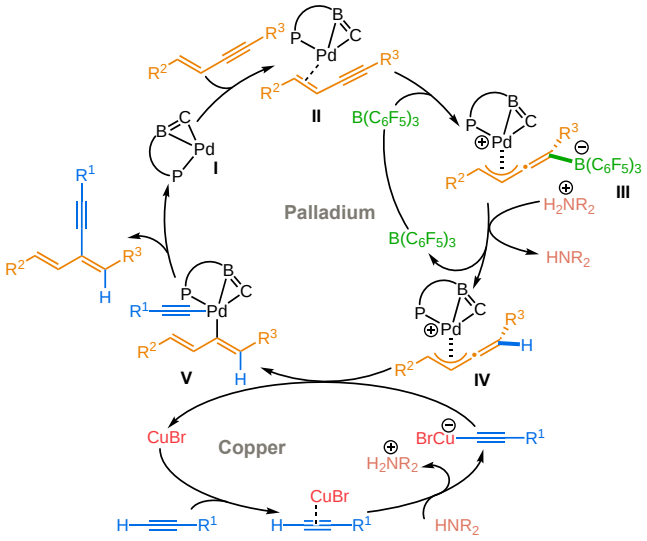
In preliminary labeling experiments we determined that 51% deuterium is incorporated into the product with deuterated phenylacetylene under standard conditions. With deuterated phenylacetylene in the presence of Et_3N (instead of TMPH), we observe 93% deuterium incorporation into the product (Scheme 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_2TMS)$_2$ and the Senphos ligand via reductive elimination,[27] which is then followed by the coordination of the enyne substrate to furnish complex **II**. The $B(C_6F_5)_3$ co-catalyst then activates the Pd(0)/enyne complex **II** to yield the outer-sphere oxidative addition adduct **III**. Complex **III** subsequently undergoes a protodeboronation[28] by an ammonium cation species (originating from a deprotonative activation of terminal alkyne in the Cu cycle to generate the Cu-alkynyl[29] species) to form **IV** with concomitant release of the $B(C_6F_5)_3$ co-catalyst. Transmetalation of the Cu-alkynl species (from Cu cycle) to **IV** affords intermediate **V**, which upon reductive elimination delivers the product and regenerates the Pd catalyst **I**.

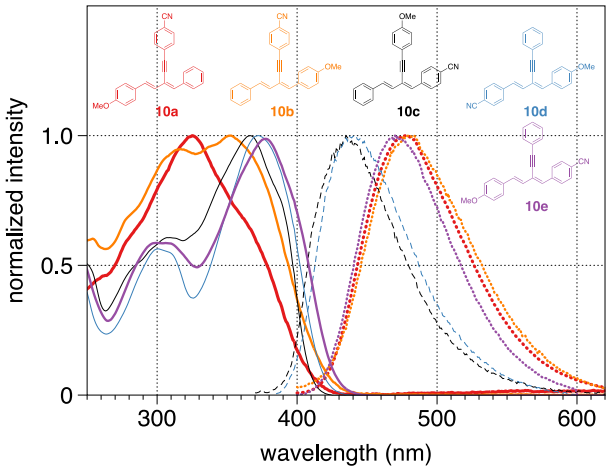
Scheme 4. Plausible Catalytic Cycle.



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

TD-DFT reveals that the lowest-energy absorption (λ_{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 π to π^* 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 λ_{em} for **10a**, **10b**, **10e** in CH_2Cl_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 CH_2Cl_2.[a]



Compound	λ_{abs}(nm) in CH_2Cl_2	λ_{em}(nm) in CH_2Cl_2	Φ in CH_2Cl_2
10a	360	477	0.28
10b	352	481	0.0037
10c	367	435	0.0041
10d	372	442	0.0022
10e	378	470	0.0037

[a]All data are independently measured in house at 1.0 x 10^{-5} M concentration to enable direct comparison. λ_{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 $B(C_6F_5)_3$ 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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