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

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Supporting Information Placeholder

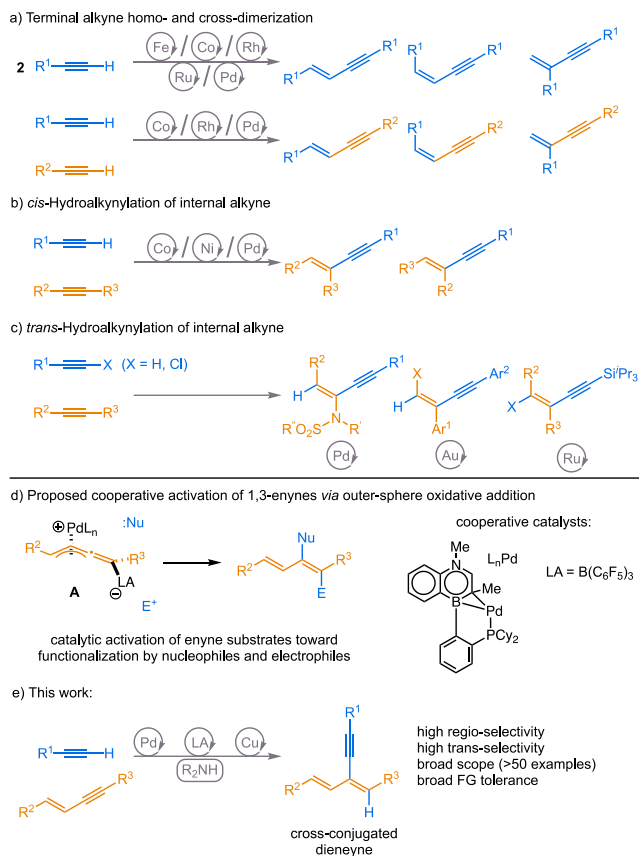
ABSTRACT: A cooperative catalyst system involving Pd(0)/Senphos complex, tris(pentafluorophenyl)borane, copper bromide, and an amine base, is demonstrated to catalyze *trans*-hydroalkynylation of internal 1,3-enynes. For the first time, a Lewis acid catalyst is shown to promote the reaction involving 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,¹ functional materials² 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*₂RuCl]₄ catalyzed the *trans*-addition of ^tPr₃SiC≡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*-cyanoboration¹² and *cis*-carboration of 1,3-enynes¹³ catalyzed by a 1,4-azaborine biaryl phosphine(Senphos)-Pd complex. Mechanistic studies¹⁴ support an unusual outer-sphere oxidative addition mechanism¹⁵ where a Lewis acid (LA)

activates a Pd(0)-enynne 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(C₆F₅)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 LA¹⁸ such as B(C₆F₅)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 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.

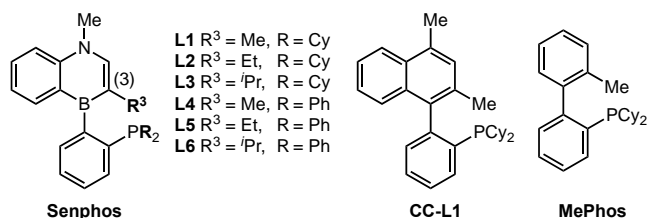
Scheme 1. Transition Metal-Catalyzed Hydroalkynylation of Alkynes



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(C₆F₅)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 ₆ F 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



^aReaction performed at 0.4 mmol scale. See SI for detailed procedure.
^bYield and selectivity was determined by ¹H NMR analysis of unpurified reaction mixture with CH₂Br₂ as the internal standard. Selectivity is defined as the ratio of title product over other isomers. ^cYield 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., R³ = Et or ⁱPr) 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 R³ 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 R² (entries **6a-6g**). In addition to aryl groups, the R² 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 R³ 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 R³ 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 oxidized²² 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 PtCl₂ catalyst.²⁴ In the presence of TsN₃ 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.

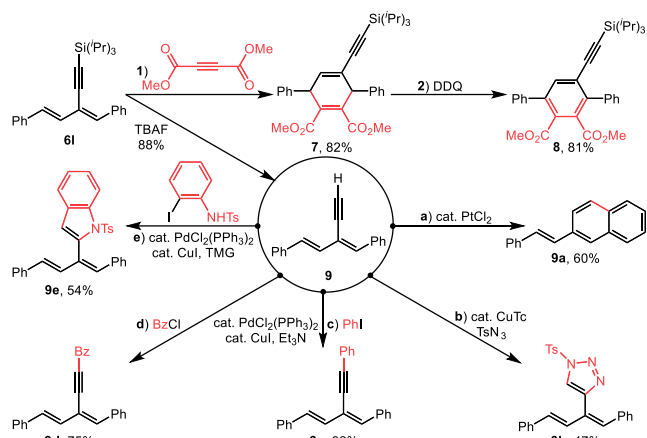
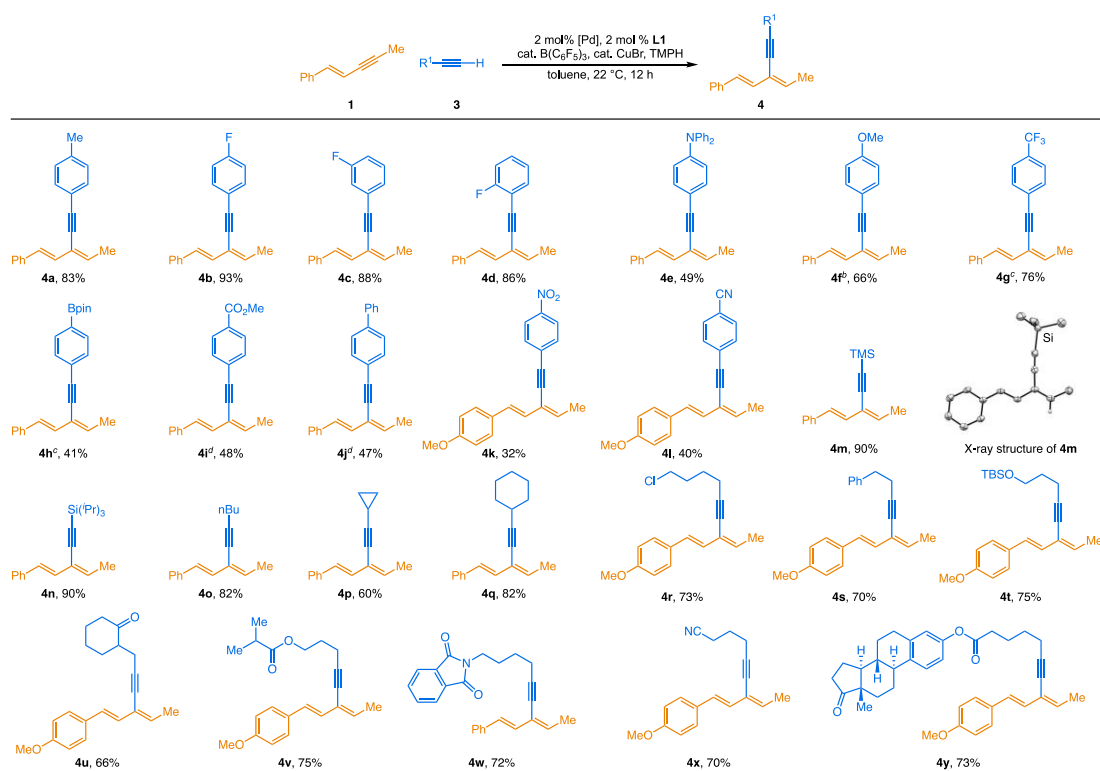
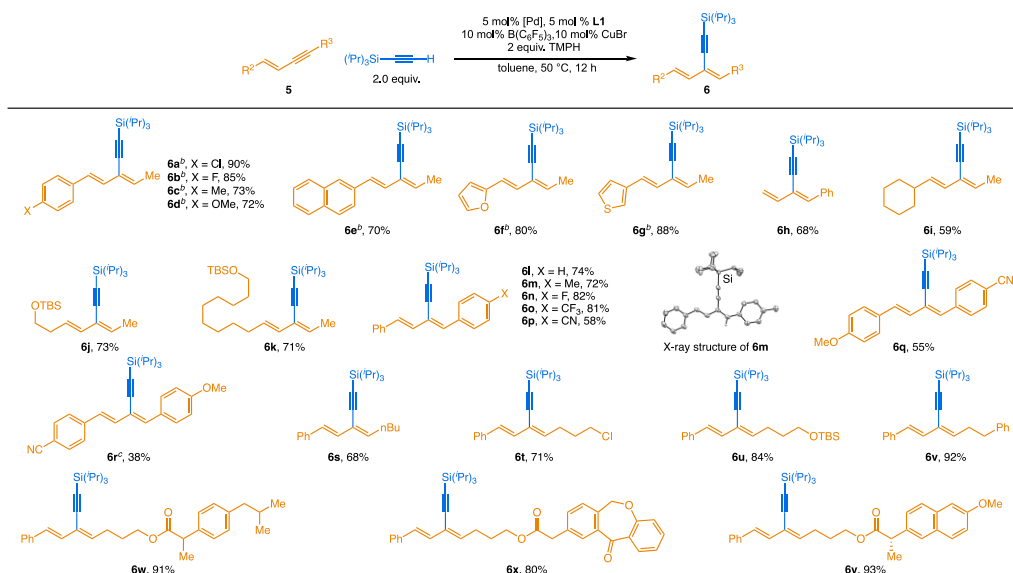


Table 2. Reaction Scope of Terminal Alkynes.^a



^aReaction condition: **1** (0.4 mmol), (COD)Pd(CH₂TMS)₂ (2 mol%), **L1** (2 mol%), for aryl alkynes **3a-3l**: **3** (1.0 mmol), B(C₆F₅)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(C₆F₅)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. ^b1.2 mmol 4-methoxyphenylacetylene was used. ^c24 h reaction time. ^d**1** (0.4 mmol), (COD)Pd(CH₂TMS)₂ (5 mol%), **L1** (5 mol%), B(C₆F₅)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



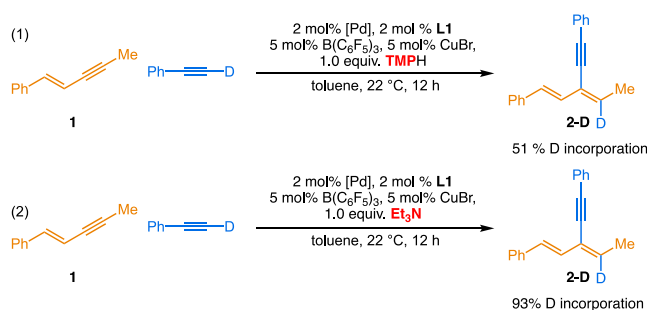
^aReaction condition: **5** (0.4 mmol), (triisopropylsilyl)acetylene (0.8 mmol), (COD)Pd(CH₂TMS)₂ (5 mol%), **L1** (5 mol%), B(C₆F₅)₃ (10 mol%), CuBr (10 mol%), TMPH (0.8 mmol), toluene (0.6 mL), 50 °C, 12 h, unless otherwise noted. Yields of isolated product are reported as an average of two runs. Selectivity is determined by ¹H NMR analysis of purified product. See SI for detailed procedure.

^bStandard conditions, except: (COD)Pd(CH₂TMS)₂ (2 mol%), **L1** (2 mol%), 22 °C.

^cStandard conditions, except: (COD)Pd(CH₂TMS)₂ (10 mol%), **L1** (10 mol%), B(C₆F₅)₃ (20 mol%), 24 h.

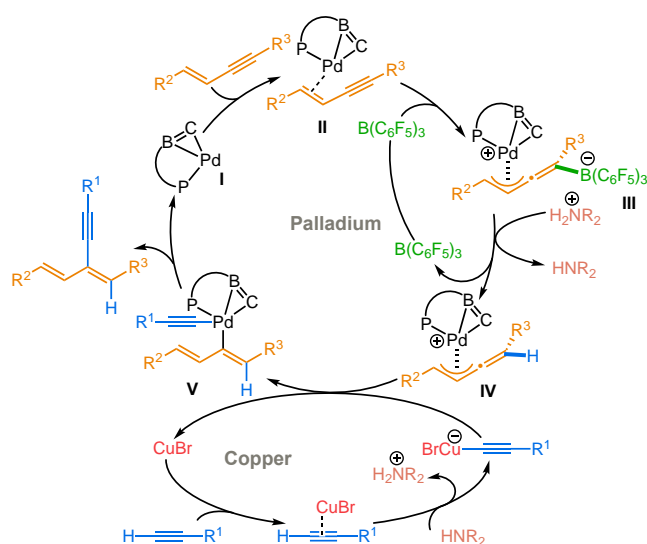
In preliminary labeling experiments we determined that 51% deuterium is incorporated into the product with deuterated phenylacetylene under standard conditions. With deuterated phenylacetylene in the presence of Et₃N (instead of TMPH), we observe 93% deuterium incorporation into the product (Scheme 3). 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(CH₂TMS)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(C₆F₅)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 protodeboronation²⁸ by an ammonium cation species (originating from a deprotonative activation of terminal alkyne in the Cu cycle to generate the Cu-alkynyl²⁹ species) to form **IV** with concomitant release of the B(C₆F₅)₃ 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**.

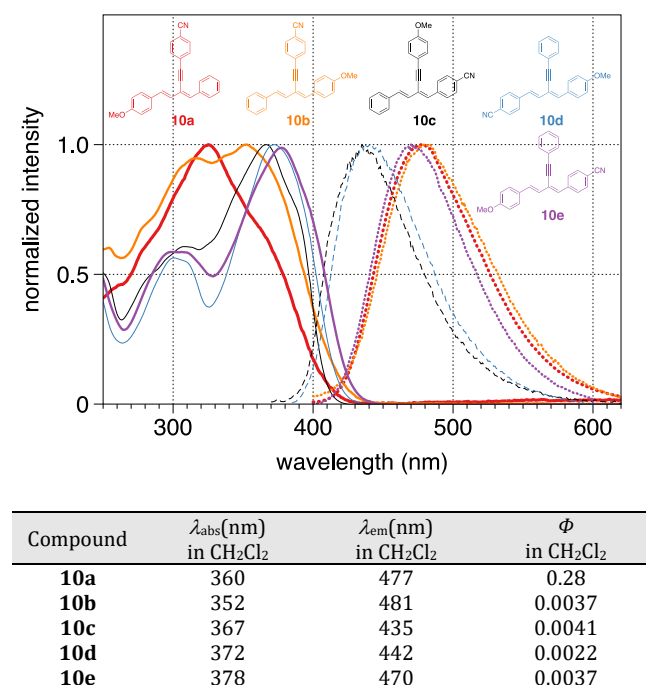
Scheme 4. Plausible Catalytic Cycle.



Using our methodology, we were able to prepare a library of donor/acceptor substituted cross-conjugated³⁰ dienynes **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 ($\phi = 28\%$) 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) level³³ (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



^aAll data are independently measured in house at 1.0×10^{-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 $\text{B}(\text{C}_6\text{F}_5)_3$ 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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REFERENCES

- (1) (a) Goldberg, I. H., Mechanism of Neocarzinostatin Action: Role of DNA Microstructure in Determination of Chemistry of Bistranded Oxidative Damage. *Acc. Chem. Res.* **1991**, *24*, 191-198. (b) Nicolaou, K. C.; Dai, W. M., Chemistry and Biology of the Eneidyne Anticancer Antibiotics. *Angew. Chem., Int. Ed.* **1991**, *30*, 1387-1416. (c) Nicolaou, K. C.; Dai, W. M.; Tsay, S. C.; Estevez, V. A.; Wrasidlo, W., Designed enediyne: A new class of DNA-cleaving molecules with potent and selective anticancer activity. *Science* **1992**, *256*, 1172-1178. (d) Rudi, A.; Schleyer, M.; Kashman, Y., Clathrulins A and B, two novel nitrogen-containing metabolites from the sponge *Clathrina* aff. *reticulum*. *J. Nat. Prod.* **2000**, *63*, 1434-1436. (e) Fontana, A.; D'Ippolito, G.; D'Souza, L.; Mollo, E.; Parameswaram, P. S.; Cimino, G., New acetogenin peroxides from the Indian sponge *Acarinus bicladotylota*. *J. Nat. Prod.* **2001**, *64*, 131-133. (f) Schaus, S. E.; Cavalieri, D.; Myers, A. G., Gene transcription analysis of *Saccharomyces cerevisiae* exposed to neocarzinostatin protein-chromophore complex reveals evidence of DNA damage, a potential mechanism of resistance, and consequences of prolonged exposure. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 11075-11080. (g) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D., Asymmetric total syntheses of (+)-3-(Z)-laureatin and (+)-3-(Z)-isolaureatin by "lone pair-lone pair interaction-controlled" isomerization. *J. Am. Chem. Soc.* **2007**, *129*, 2269-2274.
- (2) (a) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z., π -conjugated aromatic enynes as a single-emitting component for white electroluminescence. *J. Am. Chem. Soc.* **2006**, *128*, 5592-5593. (b) Chen, G.; Wang, L.; Thompson, D. W.; Zhao, Y., Highly π -extended TTF analogues with a conjugated macrocyclic enyne core. *Org. Lett.* **2008**, *10*, 657-660. (c) Liu, C. P.; Newby, J. J.; Müller, C. W.; Lee, H. D.; Zwieter, T. S., Spectroscopic characterization of structural isomers of naphthalene: (E)- and (Z)-phenylvinylacetylene. *J. Phys. Chem. A* **2008**, *112*, 9454-9466.
- (3) Bao, X.; Ren, J.; Yang, Y.; Ye, X.; Wang, B.; Wang, H., 2-Activated 1,3-enynes in enantioselective synthesis. *Org. Biomol. Chem.* **2020**, *18*, 7977-7986.
- (4) (a) Trost, B. M.; Masters, J. T., Transition metal-catalyzed couplings of alkynes to 1,3-enynes: modern methods and synthetic applications. *Chem. Soc. Rev.* **2016**, *45*, 2212-2238. (b) Zhou, Y.; Zhang, Y.; Wang, J., Recent advances in transition-metal-catalyzed synthesis of conjugated enynes. *Org. Biomol. Chem.* **2016**, *14*, 6638-6650. (c) Weber, S. M.; Hilt, G., Late 3d Metal-Catalyzed (Cross-) Dimerization of Terminal and Internal Alkynes. *Front. Chem.* **2021**, *9*.
- (5) (a) Trost, B. M.; Chan, C.; Ruhter, G., Metal-Mediated Approach to Enynes. *J. Am. Chem. Soc.* **1987**, *109*, 3486-3487. (b) Bianchini, C.; Zanobini, F.; Frediani, P.; Albinati, A., A Ru(II) Enynyl Complex Mediates the Catalytic Dimerization of 1-Alkynes to Z-1,4-Disubstituted Enynes. *J. Am. Chem. Soc.* **1991**, *113*, 5453-5454. (c) Rubina, M.; Gevorgyan, V., Can agostic interaction affect regiochemistry of carbopalladation? Reverse regioselectivity in the palladium-catalyzed dimerization of aryl acetylenes. *J. Am. Chem. Soc.* **2001**, *123*, 11107-11108. (d) Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T., Novel Z-selective head-to-head dimerization of terminal alkynes catalyzed by lanthanide half-metalocene complexes. *J. Am. Chem. Soc.* **2003**, *125*, 1184-1185. (e) Jahier, C.; Zatulochnaya, O. V.; Zvyagintsev, N. V.; Ananikov, V. P.; Gevorgyan, V., General and selective head-to-head dimerization of terminal alkynes proceeding via hypopalladation pathway. *Org. Lett.* **2012**, *14*, 2846-2849. (f) Chen, T.; Guo, C.; Goto, M.; Han, L. B., A Brønsted acid-catalyzed generation of palladium complexes: Efficient head-to-tail dimerization of alkynes. *Chem. Commun.* **2013**, *49*, 7498-7500. (g) Xu, C.; Du, W.; Zeng, Y.; Dai, B.; Guo, H., Reactivity switch enabled by counterion: Highly chemoselective dimerization and hydration of terminal alkynes. *Org. Lett.* **2014**, *16*, 948-951. (h) Zatulochnaya, O. V.; Gordeev, E. G.; Jahier, C.; Ananikov, V. P.; Gevorgyan, V., Carboxylate switch between hydro- and carbopalladation pathways in regiodivergent dimerization of alkynes. *Chem. - Eur. J.* **2014**, *20*, 9578-9588. (i) Chen, L.; Regan, M.; Mack, J., The Choice Is Yours: Using Liquid-Assisted Grinding to Choose between Products in the Palladium-Catalyzed Dimerization of Terminal Alkynes. *ACS Catal.* **2016**, *6*, 868-872. (j) Storey, C. M.; Gyton, M. R.; Andrew, R. E.; Chaplin, A. B., Terminal Alkyne Coupling Reactions through a Ring: Mechanistic Insights and Regiochemical Switching. *Angew. Chem., Int. Ed.* **2018**, *57*, 12003-12006. (k) Galiana-Cameo, M.; Urriolabeitia, A.; Barenas, E.; Passarelli, V.; Pérez-Torrente, J. J.; Di Giuseppe, A.; Polo, V.; Castarlenas, R., Metal-Ligand Cooperative Proton Transfer as an Efficient Trigger for Rhodium-NHC-Pyridonato Catalyzed gem-Specific Alkyne Dimerization. *ACS Catal.* **2021**, *11*, 7553-7567. (l) Pfeffer, C.; Wannemacher, N.; Frey, W.; Peters, R., Stereo- and regioselective dimerization of alkynes to enynes by bimetallic syn-carbopalladation. *ACS Catal.* **2021**, *11*, 5496-5505. (m) Weber, S.; Veiros, L. F.; Kirchner, K., Selective Manganese-Catalyzed Dimerization and Cross-Coupling of Terminal Alkynes. *ACS Catal.* **2021**, *11*, 6474-6483. (n) Guo, H.; Zhang, S.; Li, Y.; Yu, X.; Feng, X.; Yamamoto, Y.; Bao, M., Palladium-Catalyzed Tail-to-Tail Reductive Dimerization of Terminal Alkynes to 2,3-Dibranching Butadienes. *Angew. Chem., Int. Ed.* **2022**, *61*, e202116870.
- (6) (a) Matsuyama, N.; Tsurugi, H.; Satoh, T.; Miura, M., Ligand-Controlled Cross-Dimerization and -Trimerization of Alkynes under Nickel Catalysis. *Adv. Synth. Catal.* **2008**, *350*, 2274-2278. (b) Sakurada, T.; Sugiyama, Y.-k.; Okamoto, S., Cobalt-Catalyzed Cross Addition of Silylacetylenes to Internal Alkynes. *J. Org. Chem.* **2013**, *78*, 3583-3591.
- (7) Liu, G.; Kong, W.; Che, J.; Zhu, G., Palladium-Catalyzed Cross Addition of Terminal Alkynes to Aryl Ynamides: An Unusual trans-Hydroalkynylation Reaction. *Adv. Synth. Catal.* **2014**, *356*, 3314-3318.
- (8) García-Fernández, P. D.; Iglesias-Sigüenza, J.; Rivero-Jerez, P. S.; Díez, E.; Gómez-Bengoa, E.; Fernández, R.; Lassaletta, J. M., Au-Catalyzed Hydroalkynylation of Haloalkynes. *J. Am. Chem. Soc.* **2020**, *142*, 16082-16089.
- (9) Barsu, N.; Leutzsch, M.; Fürstner, A., Ruthenium-Catalyzed trans-Hydroalkynylation and trans-Chloroalkynylation of Internal Alkynes. *J. Am. Chem. Soc.* **2020**, *142*, 18746-18752.
- (10) Giustra, Z. X.; Liu, S.-Y., The State of the Art in Azaborine Chemistry: New Synthetic Methods and Applications. *J. Am. Chem. Soc.* **2018**, *140*, 1184-1194.
- (11) Xu, S.; Zhang, Y.; Li, B.; Liu, S.-Y., Site-Selective and Stereoselective trans-Hydroboration of 1,3-Enynes Catalyzed by 1,4-Azaborine-Based Phosphine-Pd Complex. *J. Am. Chem. Soc.* **2016**, *138*, 14566-14569.
- (12) Zhang, Y.; Li, B.; Liu, S.-Y., Pd-Senphos Catalyzed trans-Selective Cyanoboration of 1,3-Enynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 15928-15932.
- (13) Wang, Z.; Wu, J.; Lamine, W.; Li, B.; Sotiropoulos, J.-M.; Chrostowska, A.; Miqueu, K.; Liu, S.-Y., C-Boron Enolates Enable Palladium Catalyzed Carboboration of Internal 1,3-Enynes. *Angew. Chem., Int. Ed.* **2021**, *60*, 21231-21236.
- (14) (a) Yang, Y.; Jiang, J.; Yu, H.; Shi, J., Mechanism and Origin of the Stereoselectivity in the Palladium-Catalyzed trans Hydroboration of Internal 1,3-Enynes with an Azaborine-Based Phosphine Ligand. *Chem. - Eur. J.* **2018**, *24*, 178-186. (b) Wang, Z.; Lamine, W.; Miqueu, K.; Liu, S.-Y., A Syn Outer-Sphere Oxidative Addition: The Reaction Mechanism in Pd/Senphos-Catalyzed Carboboration of 1,3-Enynes. *ChemRxiv DOI*: 10.26434/chemrxiv-2022-g3qng.
- (15) For related catalytic reactions involving a proposed outersphere oxidative addition step, see: (a) Tsukamoto, H.; Konno, T.; Ito, K.; Doi, T., Palladium(0)-Lithium Iodide Co-catalyzed Asymmetric Hydroalkylation of Conjugated Enynes with Pronucleophiles Leading to 1,3-Disubstituted Allenes. *Org. Lett.* **2019**, *21*, 6811-6814. (b) Xiao, B. X.; Jiang, B.; Yan, R. J.; Zhu, J. X.; Xie, K.; Gao, X. Y.; Ouyang, Q.; Du, W.; Chen, Y. C., A Palladium Complex as an Asymmetric pi-Lewis Base Catalyst for Activating 1,3-Dienes. *J. Am. Chem. Soc.* **2021**, *143*, 4809-4816.
- (16) (a) Trost, B. M.; Van Vranken, D. L., Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395-422. (b) Trost, B. M.; Crawley, M. L., Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921-2944. (c) Trost, B. M., Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem.* **2004**, *69*, 5813-5837.
- (17) Zhang, Y.; Wang, Z.; Lamine, W.; Xu, S.; Chrostowska, A.; Miqueu, K.; Liu, S.-Y., Mechanism of Pd/Senphos-Catalyzed trans-Hydroboration of 1,3-Enynes: Experimental and Computational Evidence in Support of the Unusual Outer-Sphere Oxidative Addition Pathway. *ChemRxiv DOI*: 10.26434/chemrxiv-2022-cmzdf.
- (18) Becica, J.; Dobreiner, G. E., The roles of Lewis acidic additives in organotransition metal catalysis. *Org. Biomol. Chem.* **2019**, *17*, 2055-2069.
- (19) (a) Sancheti, S. P.; Urvashi; Shah, M. P.; Patil, N. T., Ternary Catalysis: A Stepping Stone toward Multicatalysis. *ACS Catal.* **2020**, *10*, 3462-3489. (b) Martínez, S.; Veth, L.; Lainer, B.; Dydio, P., Challenges and Opportunities in Multicatalysis. *ACS Catal.* **2021**, *11*, 3891-3915.
- (20) Surry, D. S.; Buchwald, S. L., Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338-6361.
- (21) Xu, S.; Haeffner, F.; Li, B.; Zakharov, L. N.; Liu, S.-Y., Monobenzofused 1,4-Azaborines: Synthesis, Characterization, and Discovery of a Unique Coordination Mode. *Angew. Chem., Int. Ed.* **2014**, *53*, 6795-6799.
- (22) For an overview of DDQ as an oxidant, see: Alsharif, M. A.; Raja, Q. A.; Majeed, N. A.; Jassas, R. S.; Alsimaree, A. A.; Sadiq, A.; Naeem, N.; Mughal, E. U.; Alsantali, R. I.; Moussa, Z.; Ahmed, S. A., DDQ as a

versatile and easily recyclable oxidant: a systematic review. *RSC Advances* **2021**, *11*, 29826-29858.

(23) Kotha, S.; Chavan, A. S., Design and Synthesis of Benzosultine-sulfone as a *o*-Xylylene Precursor via Cross-ene Metathesis and Rongalite: Further Expansion to Polycyclics via Regioselective Diels–Alder Reaction. *J. Org. Chem.* **2010**, *75*, 4319-4322.

(24) (a) Mamane, V.; Hannen, P.; Fürstner, A., Synthesis of Phenanthrenes and Polycyclic Heteroarenes by Transition-Metal Catalyzed Cycloisomerization Reactions. *Chem. Eur. J.* **2004**, *10*, 4556-4575. (b) Kang, D.; Kim, J.; Oh, S.; Lee, P. H., Synthesis of Naphthalenes via Platinum-Catalyzed Hydroarylation of Aryl Enynes. *Org. Lett.* **2012**, *14*, 5636-5639.

(25) Raushel, J.; Fokin, V. V., Efficient Synthesis of 1-Sulfonyl-1,2,3-triazoles. *Org. Lett.* **2010**, *12*, 4952-4955.

(26) (a) Chinchilla, R.; Nájera, C., The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874-922. (b) Chinchilla, R.; Nájera, C., Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084-5121.

(27) Takahashi, R.; Kubota, K.; Ito, H., Air- and moisture-stable Xantphos-ligated palladium dialkyl complex as a precatalyst for cross-coupling reactions. *Chem. Commun.* **2020**, *56*, 407-410.

(28) Tamke, S.; Qu, Z. W.; Sitte, N. A.; Florke, U.; Grimme, S.; Paradies, J., Frustrated Lewis Pair-Catalyzed Cycloisomerization of 1,5-Enynes via a 5-endo-dig Cyclization/Protodeborylation Sequence. *Angew. Chem., Int. Ed.* **2016**, *55*, 4336-4339.

(29) (a) M. Mykhalichko, B.; N. Temkin, O.; G. Mys'kiv, M., Polynuclear complexes of copper(I) halides: coordination chemistry and catalytic transformations of alkynes. *Russ. Chem. Rev.* **2000**, *69*, 957-984. (b)

Zuidema, E.; Bolm, C., Sub-Mol % catalyst loading and ligand-acceleration in the coppercatalyzed coupling of aryl iodides and terminal alkynes. *Chem. - Eur. J.* **2010**, *16*, 4181-4185. (c) Nishihara, Y.; Saito, D.; Inoue, E.; Okada, Y.; Miyazaki, M.; Inoue, Y.; Takagi, K., Palladium- and base-free synthesis of conjugated ynones by cross-coupling reactions of alkynylboronates with acid chlorides mediated by CuCl. *Tetrahedron Lett.* **2010**, *51*, 306-308. (d) Zou, L. H.; Johansson, A. J.; Zuidema, E.; Bolm, C., Mechanistic insights into copper-catalyzed sonogashira-hagihara-type cross-coupling reactions: Sub-mol % catalyst loadings and ligand effects. *Chem. - Eur. J.* **2013**, *19*, 8144-8152. (e) Lin, C. X.; Zhu, J. F.; Li, Q. S.; Ao, L. H.; Jin, Y. J.; Xu, F. B.; Hu, F. Z.; Yuan, Y. F., 2,5-Bis(2-(diphenylphosphino)phenyl)-1,3,4-oxadiazole ligands and their Cu(I) complexes for Sonogashira coupling reaction. *Appl. Organomet. Chem.* **2014**, *28*, 298-303. (f) Liu, L. L.; Wu, Y.; Wang, Z.; Zhu, J.; Zhao, Y., Mechanistic insight into the copper-catalyzed phosphorylation of terminal alkynes: A combined theoretical and experimental study. *J. Org. Chem.* **2014**, *79*, 6816-6822. (g) Ahammed, S.; Kundu, D.; Ranu, B. C., Cu-Catalyzed Fe-Driven Csp–Csp and Csp–Csp² Cross-Coupling: An Access to 1,3-Diynes and 1,3-Enynes. *J. Org. Chem.* **2014**, *79*, 7391-7398.

(30) For an overview, see: (a) Phelan, N. F.; Orchin, M., Cross conjugation. *J. Chem. Educ.* **1968**, *45*, 633. (b) Limacher, P. A.; Lüthi, H. P., Cross-conjugation. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2011**, *1*, 477-486. (c) Hosoya, H., Cross-Conjugation at the Heart of Understanding the Electronic Theory of Organic Chemistry. *Curr. Org. Chem.* **2015**, *19*, 293-310. (d) Hopf, H.; Sherburn, M. S., *Cross Conjugation: Modern Dendralene, Radialene and Fulvene Chemistry*. John Wiley & Sons: 2016. (e) Gu, J.; Wu, W.; Stuyver, T.; Danovich, D.; Hoffmann, R.; Tsuji, Y.; Shaik, S., Cross Conjugation in Polyenes and Related Hydrocarbons: What Can Be Learned from Valence Bond Theory about Single-Molecule Conductance? *J. Am. Chem. Soc.* **2019**, *141*, 6030-6047. (f) Gholami, M.; Tykwinski, R. R., Oligomeric and Polymeric Systems with a Cross-conjugated p-Framework. *Chem. Rev.* **2006**, *106*, 4997-5027.

(31) For the synthesis and reactivity studies of the parental compound, 2-ethynyl-1,3-butadiene, see: (a) Bader, H.; Hopf, H.; Jäger, H., 2-Ethynyl-1,3-Butadien – Ein Neues Dien für die Diels-Alder-Reaktion. *Chem. Ber.* **1989**, *1193*-1198. (b) Hopf, H.; Jäger, H.; Ernst, L., On the Chemical Behavior of 2-Ethynyl-1,3-butadiene. *Liebigs Ann.* **1996**, *815*-824.

(32) For studies of the related cross-conjugated enediyne (Y-enynes), see: (a) Tykwinski, R. R.; Zhao, Y., Cross-Conjugated Oligo(enynes). *Synlett*, **2002**, *12*, 1939-1953. (b) Kaafarani, B. R.; Wex, B.; Strehmel, B.; Neckers, D. C., Structural Concept for Fluorinated Y-Enynes with Solvatochromic Properties. *Photochem. Photobiol. Sci.*, **2002**, *1*, 942-950. (c) Zhao, Y.; Ciulei, S. C.; Tykwinski, R. R., The Effects of π -Acceptor and π -Donor Substitution in Cross-conjugated Enynes. *Tetrahedron Lett.* **2001**, *42*, 7721-7723.

(33) Gaussian09, RevisionD.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino,

B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, Williams, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian Inc., Wallingford, CT, 2009.