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Enantioselective Intermolecular Aminoalkynylation of Styrenes via Copper-Catalyzed Radical Relay

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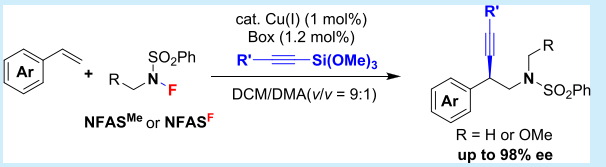
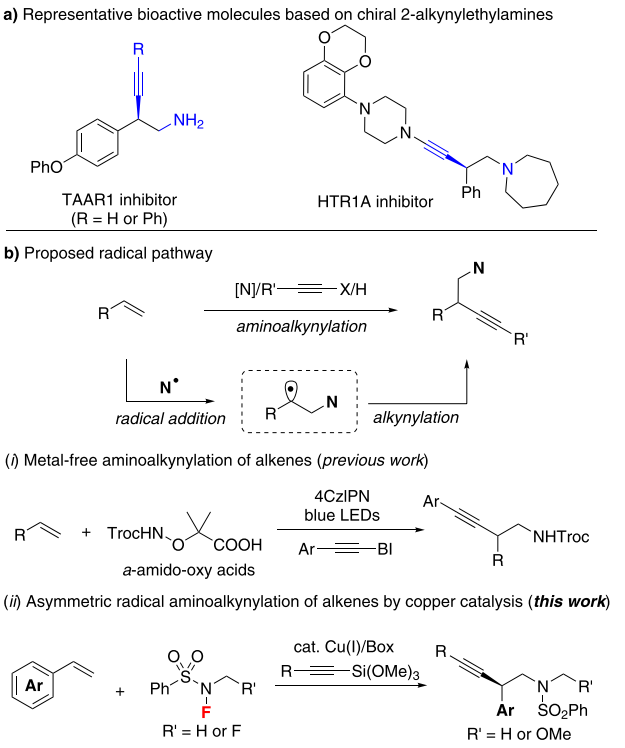
ABSTRACT: A novel copper-catalyzed intermolecular aminoalkynylation of alkenes through a radical relay process has been developed in this work, in which *N*-fluoro-*N*-alkylsulfonamides (NFASs) are used as nitrogen-centered radical precursors and alkynyltrimethoxysilanes as alkynylating reagents. This method presents an efficient and straightforward approach to various enantioenriched 2-alkynyl-2-arylethylamines in good yields with excellent enantioselectivity, and these products can be readily converted into a series of synthetically useful chiral terminal alkynes, allenes, alkenes, amines, amino acids, and N-heterocycles.



2-Alkynylamines are frequently found in natural products and therapeutics, such as trace amine-associated receptor 1 (TAAR1) inhibitors, dopamine β-hydroxylase (DBH), and 5-hydroxytyptamine reportor 1a inhibitor (HTR1A) (Scheme 1a).[1,2] In addition, 2-alkynylethylamines are also regarded as valuable and versatile building blocks for the synthesis of amines, amino acids, N-heterocycles, and so on.[3] Therefore, chemists have directed considerable effort toward their synthesis, and aminoalkynylation of alkenes serves as a prevalent and powerful tool for their synthesis. In the past decade, transition-metal-catalyzed *intramolecular* aminoalkynylation of alkenes has been developed by the groups of Waser,[4] Bower,[5] Wang,[6] and Han,[7] where ethynylbenziodoxolone (EBX) reagents or bromoacetylenes were employed as alkynylating reagents.[8] Nevertheless, *intermolecular* aminoalkynylation of alkenes remains elusive. Very recently, an elegant intermolecular aminoalkynylation of alkenes via a radical pathway under metal-free conditions was demonstrated by Studer and co-workers, in which Troc-protected α-amidocarboxylic acids were employed as nitrogen-centered radical precursors and EBX reagents were used as the resulting carbon-centered radical acceptors (Scheme 1b, *i*).[9] Despite these advances, to the best of our knowledge there have been no documented examples of such asymmetric variants to date, presumably because of the highly reactive carbon-centered radicals. Herein we communicate the first enantioselective intermolecular radical aminoalkynylation of styrenes via a copper-catalyzed radical relay process, providing easy access to structurally diverse 2-alkynyl-2-arylethylamines in good yields with excellent enantioselectivities under very mild reaction conditions (Scheme 1b, *ii*).

As part of our continuous interest in asymmetric radical transformations (ARTs),[10] we have disclosed a series of

Scheme 1. Representative Bioactive Molecules and Asymmetric Radical Aminoalkynylation of Alkenes



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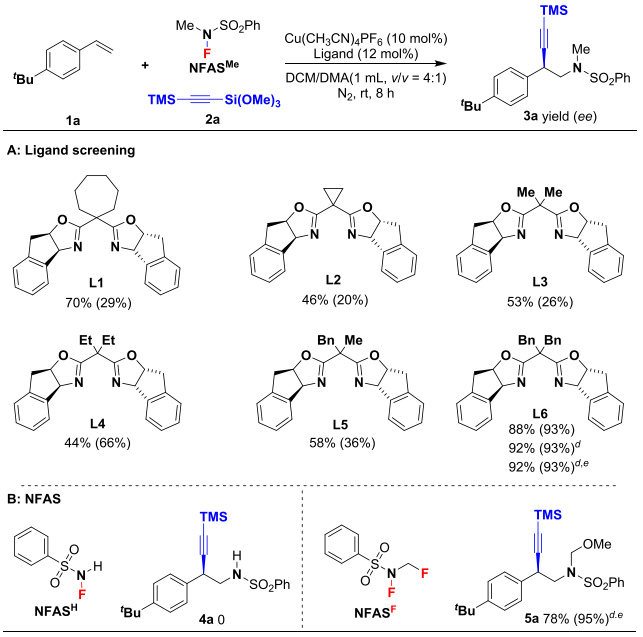
enantioselective cyanation[11]/arylation[12] reactions of benzylic and/or allylic radicals via a Cu-catalyzed radical relay process, providing easy access to enantioenriched alkylnitriles and 1,1-diarylmethane derivatives. Very recently, asymmetric alkynylation of benzylic radicals was also developed by the use of alkynyltrimethoxysilanes as suitable alkynylating reagents,[13] which encouraged us to investigate the asymmetric aminoalkynylation of styrenes. Therefore, we speculated that if the benzylic radicals generated by N-centered radical (NCR) addition to alkenes could be captured by the highly reactive chiral (L*)Cu^{II}–alkynyl species, enantioselective intermolecular aminoalkynylation of alkenes could be realized (Scheme 1b, *ii*).

To test the above-mentioned hypothesis, we examined the reaction of 4-*tert*-butylstyrene (**1a**) with alkynyltrimethoxysilane **2a** under our previously reported asymmetric aminoarylation conditions[12b] using *N*-methyl-*N*-fluorobenzenesulfonylamide ($NFAS^{Me}$) as the NCR precursor. To our delight, when the chiral bis(oxazoline) (Box) ligand **L1** was employed in combination with $Cu(CH_3CN)_4PF_6$, the reaction indeed provided the desired product **3a** in 70% yield with 29% ee (Scheme 2A). Encouraged by this result, a series of Box ligands were then screened. Compared with **L1**, ligand **L2** bearing a geminal three-membered ring gave **3a** in a lower yield (46%) and enantioselectivity (20% ee). For the acyclic substituted Box ligands, **L4** bearing *gem*-diethyl groups exhibited better enantioselectivity than **L3** with *gem*-dimethyl groups, while **L6** bearing *gem*-dibenzyl groups performed the best, giving the desired product **3a** in 88% yield with 93% ee. Furthermore, increasing the ratio of dichloromethane (DCM) to *N*,*N*-dimethylacetamide (DMA) from 4:1 to 9:1 led to a slightly better yield of **3a** (92%) without loss of enantioselectivity (93% ee). It is noteworthy that the reaction still proceeded smoothly without loss of reaction efficiency and enantioselectivity in the presence of only 1 mol % $Cu(CH_3CN)_4PF_6$ and 1.2 mol % **L6**, although the reaction time was prolonged from 8 to 16 h. Moreover, because of the synthetic utility of RNHTs, $NFAS^{H}$ was used as the NCR precursor for the asymmetric aminoalkynylation; unfortunately, the desired product **4a** was not detected (Scheme 2B). During the synthesis of $NFAS^{Me}$, an unexpected N–F reagent, $NFAS^{F}$, was produced by overfluorination of the *N*-methyl group. Gratifyingly, $NFAS^{F}$ also performed very well in the reaction, and the fluoromethyl group in $NFAS^{F}$ was simultaneously converted into the methoxymethyl group, affording the product **5a** in 78% yield with 95% ee. **5a** could easily be further converted to **4a** by removal of the methoxy group under mild reaction conditions (see Scheme 7).

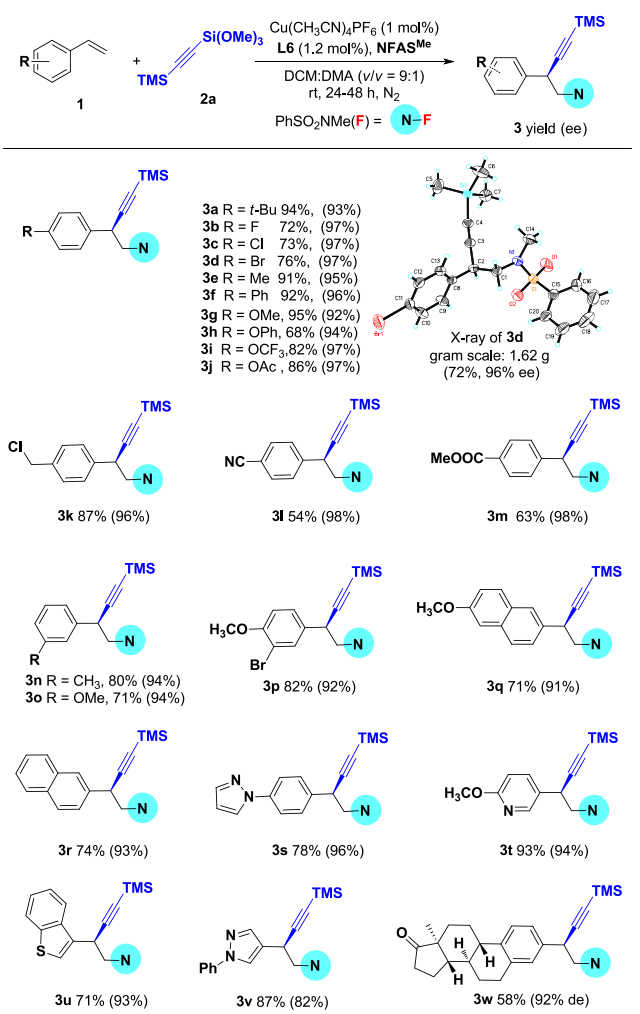
With the optimized reaction conditions, we next explored the substrate scope of styrenes using $NFAS^{Me}$. As shown in Scheme 3, the reaction seems quite general with respect to the electronic nature of substituents on the aromatic ring of styrene at C3 or C4, affording the desired aminoalkynylation products **3a**–**p** in good to excellent yields (54–95%) with excellent enantiose-

Scheme 2. Optimization of the Reaction Conditions[a,b,c]



[a]Unless otherwise noted, the reactions were run on a 0.1 mmol scale with $Cu(CH_3CN)_4PF_6$ (10 mol %), ligand (12 mol %), **1a** (0.1 mmol), **2a** (0.15 mmol), and $NFAS^{Me}$ (0.12 mmol). [b]^{1}H NMR yields of **3a** obtained using CH_2Br_2 as an internal standard are reported. [c]Enantiomeric excess was determined by HPLC on a chiral stationary phase. [d]DCM:DMA (1 mL, 9:1 v/v). [e]$Cu(CH_3CN)_4PF_6$ (1 mol %) and ligand (1.2 mol %) were used for the reaction for 16 h.

Scheme 3. Scope of Alkenes Using $NFAS^{Me}$[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $NFAS^{Me}$ (0.24 mmol), **2a** (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (1 mol %), and **L6** (1.2 mol %) in DCM/DMA mixed solvent (2 mL). [b]Isolated yields are reported; ee values were determined by HPLC on a chiral stationary phase.

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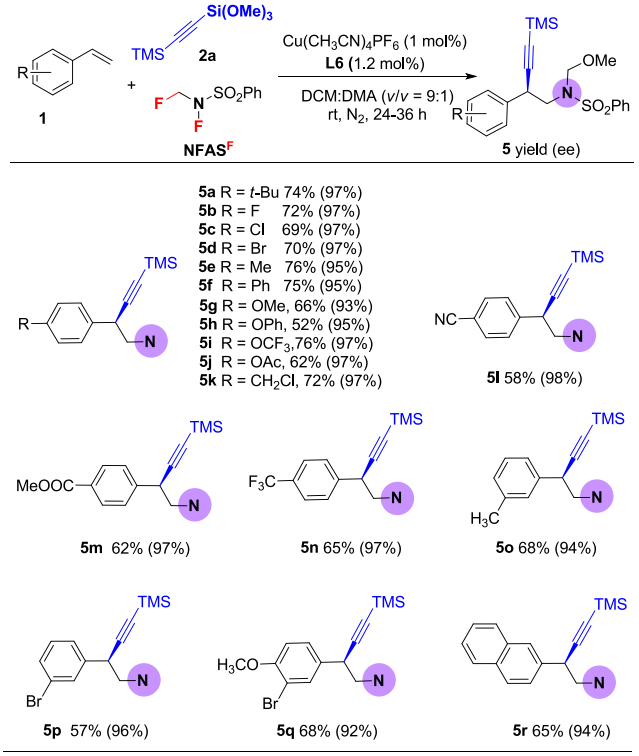
lectivities (92−98% ee). Notably, a wide variety of functional groups such as halogen, ether, ester, and nitrile were compatible with the current conditions. In addition, the aryl framework could be extended to a naphthalene-derived system (**3q** and **3r**). Furthermore, vinylarenes bearing various heteroarenes, such as pyrazole (**3s**, **3v**), pyridine (**3t**), and benzothiophene (**3u**), were suitable, affording the corresponding products in good to excellent yields (71−93%) with excellent enantioselectivities (82−96% ee). Importantly, the reaction of a substrate derived from estrone proceeded smoothly to deliver the desired product **3w** in 58% yield with 92% de. The reaction of 4-bromostyrene could be conducted on a gram scale (5 mmol) to provide 1.62 g of the desired product **3d** in 72% yield with 96% ee, and the absolute configuration of (*S*)-**3d** was unambiguously determined by X-ray diffraction analysis.

In addition, the substrate scope of alkenes using NFAS^{F} was also examined (Scheme 4). Similar to the above-shown

Scheme 4. Scope of Alkenes Using NFAS^{F}[a,b]

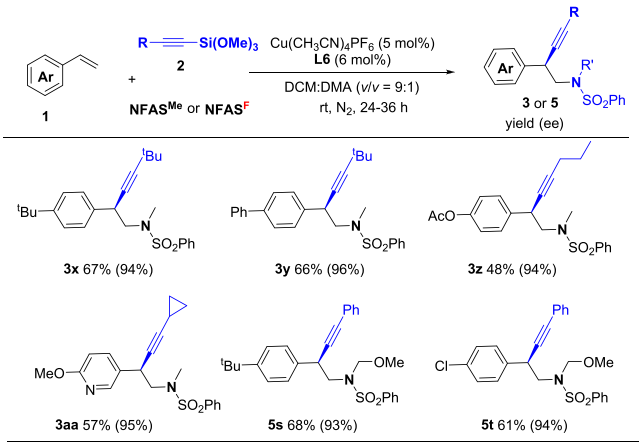


[a]Reaction conditions: **1** (0.2 mmol), NFAS^{F} (0.24 mmol), **2a** (0.4 mmol), Cu(CH$_3$CN)$_4$PF$_6$ (1 mol %), and **L6** (1.2 mol %) in DCM/DMA (2 mL). [b]Isolated yields are reported; ee values were determined by HPLC on a chiral stationary phase.

reactions, styrenes bearing either electron-rich or electron-deficient substituents on the aryl ring at C3 or C4 were suitable for the reaction, providing the desired products **5a−r** in good yields (52−76%) with excellent enantioselectivities (92−98% ee). Again, various functional groups such as halogen, ether, trifluoromethoxy, ester, and nitrile were well-tolerated under the mild conditions.

Moreover, a wide array of alkynylating reagents with different substituents on the C−C triple bond, such as ^{t}Bu, ^{n}Pr, cyclopropyl, and phenyl groups, were applied to the asymmetric aminoalkynylation of styrenes using either NFAS^{Me} or NFAS^{F} as the NCR precursor. Compared with the reactivity of **2a**, these alkynyl reagents proved to be good candidates but were slightly less active. As shown in Scheme 5, the reactions proceeded

Scheme 5. Scope of Alkynylating Reagents[a,b]

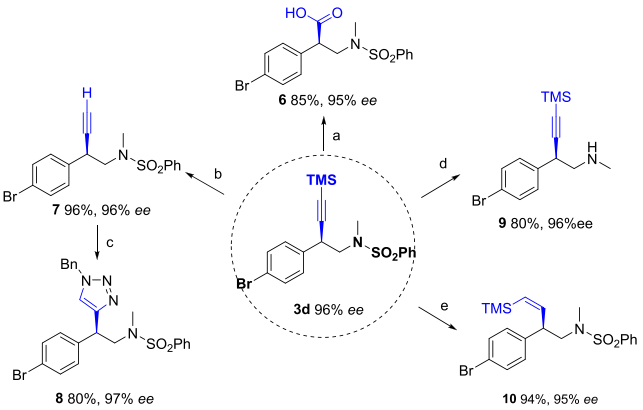


[a]All of the reactions were run on a 0.2 mmol scale with **1** (0.2 mmol), NFAS^{Me} or NFAS^{F} (0.24 mmol), alkyne **2** (0.4 mmol), Cu(CH$_3$CN)$_4$PF$_6$ (5 mol %), and **L6** (6 mol %). [b]Isolated yields are reported; ee values were determined by HPLC on a chiral stationary phase

smoothly using a catalyst loading of 5 mol % and yielded the corresponding aminoalkynylation products **3x−aa**, **5s**, and **5t** in moderate to good yields (48−68%) with excellent enantioselectivities (93−96% ee).

To demonstrate the potential synthetic utility of our present method, further transformations of the aminoalkynylation products were surveyed (Scheme 6). Oxidation of the alkynyl

Scheme 6. Product Transformations[a]



[a]Reaction conditions: (a) RuCl$_3$ (5 mol %), NaIO$_4$ (4.0 equiv), rt, 2 h. (b) Cu(OAc)$_2$ (10 mol %), NaAsc (0.2 equiv), ^{t}BuOH/H$_2$O (1:1 v/v), rt, 24 h. (c) NH$_4$F (8 equiv) in MeOH, rt, 12 h. (d) SmI$_2$ (6 equiv), H$_2$O (3.0 equiv), and Et$_3$N (2 equiv) in THF. (e) DIBAL-H (4.0 equiv) in Et$_2$O, rt, 48 h.

moiety of **3d** provided easy access to *β*-amino acid **6** in 85% yield with 95% ee (Scheme 6a).[14] Upon exposure to NH$_4$F, the C−Si bond in **3d** was successfully cleaved to afford terminal alkyne **7** in 96% yield with 96% ee (Scheme 6b), and **7** could be further transformed into 1,2,3-triazole **8** in 80% yield with 97% ee by a click reaction (Scheme 6c).[15] It is noteworthy that the sulfonyl group in the aminoalkynylation products could be removed in

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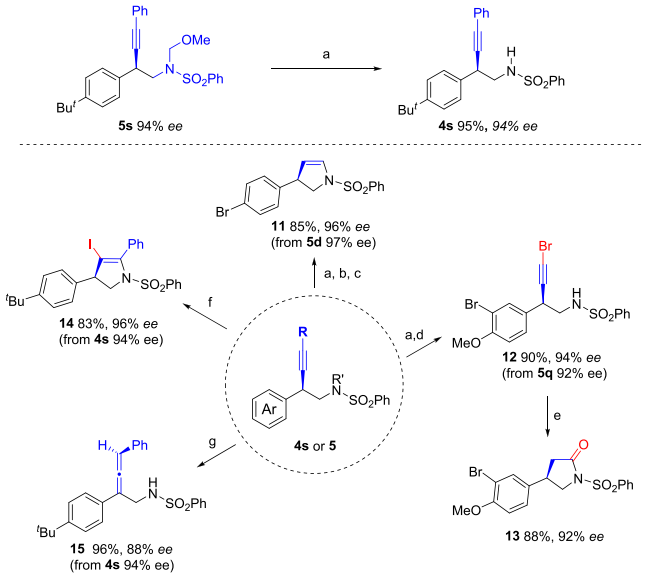
the presence of $SmI_2/H_2O/Et_3N$ to furnish secondary alkylamine **9** in 80% yield with 96% ee (Scheme 6d).[16] Moreover, the C−C triple bond could be reduced with diisobutylaluminum hydride (DIBAL-H) to deliver the (*Z*)-alkene in 94% yield with 95% ee (Scheme 6e).[17]

More importantly, the aminoalkynylation products could be converted into various chiral heterocyclic motifs that commonly exist in therapeutics and natural products (Scheme 7). Upon

Scheme 7. Synthetic Applications[a]



[a]Reaction conditions: (a) Conc. HCl in MeCN, rt, 2 h. (b) NH_4F (8 equiv) in MeOH, rt, 12 h. (c) AgOAc (10 mol %) in CH_2Cl_2, 40 °C, 18 h. (d) $AgNO_3$ (10 mol %), NBS (1.2 equiv), and H_2O (3 equiv) in acetone, rt, 2 h. (e) $Hg(OTf)_2$ (20 mol %), H_2O (3.0 equiv), rt, 18 h. (f) I_2 (3 equiv), K_2CO_3 (3 equiv), and AgOAc (3 equiv) in CH_3CN, 0 °C, 12 h. (g) TBD (20 mol %) in THF, rt, 48 h.

treatment of **5s** with concentrated hydrochloric acid, the methoxymethyl (MOM) N-protecting group could be easily removed to give secondary sulfonamide **4s** in 95% yield with 94% ee. Sulfonamide **5d** could be transformed into 2,3-dihydropyrrole **11** in 85% overall yield over three steps with 96% ee through sequential MOM deprotection, desilylation, and silver(I)-catalyzed cyclization.[18] After MOM deprotection of **5q**, direct bromination of the alkynyl-TMS group using *N*-bromosuccinimide (NBS) enabled access to **12** in 90% yield with 94% ee. In the presence of $Hg(OTf)_2$ and water, **12** could be readily transformed into lactam **13** in 88% yield with 92% ee.[19] In addition, iodocyclization of sulfonamide **4s** led to the formation of iodopyrroline **14** in 83% yield with 96% ee.[20] Moreover, **4s** could be isomerized to allene **15** in 96% yield with 88% ee by the use of triazabicyclodecene (TBD) as a catalyst.[21]

In conclusion, we have developed the first copper-catalyzed enantioselective intermolecular aminoalkynylation of styrenes via a radical relay process, which provides easy access to 2-alkynylethylamines in good yields with excellent enantioselectivities. The reaction displays a wide substrate scope, high functional group tolerance, and mild conditions. In addition, the aminoalkynylation products can be easily converted into a wide variety of synthetically useful chiral synthons, such as terminal alkynes, (*Z*)-alkenes, allenes, amines, bromoalkynes, carboxylic acids, and heterocycles, making the method particularly useful. Further applications of this strategy are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03826.

General considerations, synthesis and characterization of alkynyl silanes and N−F reagents, general procedure for the asymmetric aminoalkynylation of alkenes, further transformations of products, new compound characterization, and single-crystal X-ray diffraction data for **3d** (PDF)

NMR spectra of substrates and products and HPLC analysis of products (PDF)

FAIR data, including the primary NMR FID files, for compounds **2c**, **2d**, **3a−z**, **3aa**, **4s**, **5a−t**, **6−15**, and NFAS-F (ZIP)

Accession Codes

CCDC 2010759 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 1995. (b) *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (c) *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, Germany, 2014.

(2) (a) Kruse, L. I.; Kaiser, C.; DeWolf, W. E.; Chambers, P. A.; Goodhart, P. J.; Ezekiel, M.; Ohlstein, E. H. beta.-Substituted Phenethylamines as High-affinity Mechanism-based Inhibitors of Dopamine beta.-hydroxylase. *J. Med. Chem.* **1988**, *31*, 704. (b) Tan, E. S.; Miyakawa, M.; Bunzow, J. R.; Grandy, D. K.; Scanlan, T. S. Exploring the Structure-Activity Relationship of the Ethylamine Portion of 3-Iodothyronamine for Rat and Mouse Trace Amine-Associated Receptor 1. *J. Med. Chem.* **2007**, *50*, 2787. (c) Glase, S.; Jaen, J. C.; Smith, S. J.; Wise, L. D. (Warner-Lambert Co.). Substituted piperazines as central nervous system agents. US 5270312 A, 1993. (d) Girijavallabhan, V. M.; Chen, L.; Dai, C.; Feltz, R. J.; Firmansjah, L.; Li, D.; Kim, S. H.; Kozlowski, J. A.; Lavey, B. J.; et al. Novel TNF-α Converting enzyme (TACE) Inhibitors as Potential Treatment for Inflammatory Diseases. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7283.

(3) Lopchuk, J. M. Five-Membered Ring Systems: Pyrroles and Benzo Analogs. *Prog. Heterocycl. Chem.* **2017**, *29*, 183.

(4) (a) Orcel, U.; Waser, J. One-Pot Three-Component Synthesis of Vicinal Diamines via In Situ Aminal Formation and Carboamination. *Angew. Chem., Int. Ed.* **2016**, *55*, 12881. (b) Orcel, U.; Waser, J. Palladium-Catalyzed Vicinal Amino Alcohols Synthesis from Allyl Amines by In Situ Tether Formation and Carboetherification. *Angew. Chem., Int. Ed.* **2015**, *54*, 5250. (c) Orcel, U.; Waser, J. In situ tether Formation from Amines and Alcohols Enabling Highly Selective Tsuji-Trost allylation and olefin functionalization. *Chem. Sci.* **2017**, *8*, 32. (d) Nicolai, S.; Piemontesi, C.; Waser, J. A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of (±)-Trachelanthamidine. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680.

(5) Faulkner, A.; Scott, J. S.; Bower, J. F. An Umpolung Approach to Alkene Carboamination: Palladium Catalyzed 1,2-Amino-Acylation, -Carboxylation, -Arylation, -Vinylation, and -Alkynylation. *J. Am. Chem. Soc.* **2015**, *137*, 7224.

(6) Shen, K.; Wang, Q. Copper-catalyzed Aminoalkynylation of Alkenes with Hypervalent Iodine Reagents. *Chem. Sci.* **2017**, *8*, 8265.

(7) Han, W.-J.; Wang, Y.-R.; Zhang, J.-W.; Chen, F.; Zhou, B.; Han, B. Cu-Catalyzed Oxyalkynylation and Aminoalkynylation of Unactivated Alkenes: Synthesis of Alkynyl-Featured Isoxazolines and Cyclic Nitrones. *Org. Lett.* **2018**, *20*, 2960.

(8) For more examples of asymmetric alkynylation reactions, see: (a) Li, Z.; Li, C.-J. Catalytic Enantioselective Alkynylation of Prochiral sp^3 C−H Bonds Adjacent to a Nitrogen Atom. *Org. Lett.* **2004**, *6*, 4997. (b) Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. Highly Enantioselective Catalytic Cross-Dehydrogenative Coupling of *N*-Carbamoyl Tetrahydroisoquinolines and Terminal Alkynes. *Org. Lett.* **2015**, *17*, 1684. (c) Huang, T.; Liu, X.; Lang, J.; Xu, J.; Lin, L.; Feng, X. Asymmetric Aerobic Oxidative Cross-Coupling of Tetrahydroisoquinolines with Alkynes. *ACS Catal.* **2017**, *7*, 5654. (d) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. Enantioselective Double Manipulation of Tetrahydroisoquinolines with Terminal Alkynes and Aldehydes under Copper(I) Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 277. (e) Han, Y.-Q.; Ding, Y.; Zhou, T.; Yan, S.-Y.; Song, H.; Shi, B.-F. Pd(II)-Catalyzed Enantioselective Alkynylation of Unbiased Methylene C(sp^3)−H Bonds Using 3,3′-Fluorinated-BINOL as a Chiral Ligand. *J. Am. Chem. Soc.* **2019**, *141*, 4558.

(9) Jiang, H.; Studer, A. Transition-Metal-Free Three-Component Radical 1,2-Amidoalkynylation of Unactivated Alkenes. *Chem. - Eur. J.* **2018**, *25*, 516.

(10) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036.

(11) For asymmetric cyanation, see: (a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective Cyanation of Benzylic C−H Bonds via Copper-Catalyzed Radical Relay. *Science* **2016**, *353*, 1014. (b) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process. *J. Am. Chem. Soc.* **2016**, *138*, 15547. (c) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. Site-Specific Allylic C−H Bond Functionalization with a Copper-Bound *N*-Centered Radical. *Nature* **2019**, *574*, 516. (d) Lu, F.-D.; Liu, D.; Zhu, L.; Lu, L.-Q.; Yang, Q.; Zhou, Q.-Q.; Wei, Y.; Lan, Y.; Xiao, W.-J. Asymmetric Propargylic Radical Cyanation Enabled by Dual Organophotoredox and Copper Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 6167. (e) Cheng, Z.; Chen, P.; Liu, G. Enantioselective Cyanation of Remote C−H Bonds via Cooperative Photoredox Catalysis and Copper Catalysis. *Huaxue Xuebao* **2019**, *77*, 856.

(12) For asymmetric arylation, see: (a) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2904. (b) Wang, D.; Wu, L.; Wang, F.; Wan, X.; Chen, P.; Lin, Z.; Liu, G. Asymmetric Copper-Catalyzed Intermolecular Aminoarylation of Styrenes: Efficient Access to Optical 2,2-Diarylethylamines. *J. Am. Chem. Soc.* **2017**, *139*, 6811. (c) Wu, L.; Wang, F.; Chen, P.; Liu, G. Enantioselective Construction of Quaternary All-Carbon Centers via Copper-Catalyzed Arylation of Tertiary Carbon-Centered Radicals. *J. Am. Chem. Soc.* **2019**, *141*, 1887. (d) Zhang, W.; Wu, L.; Chen, P.; Liu, G. Enantioselective Arylation of Benzylic C−H bonds by Copper-Catalyzed Radical Relay. *Angew. Chem., Int. Ed.* **2019**, *58*, 6425. (e) Zhang, Z.; Stateman, L. M.; Nagib, D. A. δ C−H (hetero)arylation via Cu-catalyzed radical relay. *Chem. Sci.* **2019**, *10*, 1207.

(13) For asymmetric alkynylation, see: (a) Fu, L.; Zhou, S.; Wan, X.; Chen, P.; Liu, G. Enantioselective Trifluoromethyl-alkynylation of Alkenes via Copper-Catalyzed Radical Relay. *J. Am. Chem. Soc.* **2018**, *140*, 10965. (b) Fu, L.; Zhang, Z.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Copper-Catalyzed Alkynylation of Benzylic C−H Bonds via Radical Relay. *J. Am. Chem. Soc.* **2020**, *142*, 12493. (c) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. A General Asymmetric Copper-Catalyzed Sonogashira C(sp^3)-C(sp) Coupling. *Nat. Chem.* **2019**, *11*, 1158. (d) Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Asymmetric Radical 1,2-Carboalkynylation of Alkenes with Alkyl Halides and Terminal Alkynes. *J. Am. Chem. Soc.* **2020**, *142*, 9501. (e) Mo, X.; Chen, B.; Zhang, G. Copper-Catalyzed Enantioselective Sonogashira Type Coupling of Alkynes with α-Bromoamides. *Angew. Chem., Int. Ed.* **2020**, *59*, 13998−14002.

(14) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. A Greatly Improved Procedure for Ruthenium Tetroxide Catalyzed Oxidations of Organic Compounds. *J. Org. Chem.* **1981**, *46*, 3936. (b) An, D. K.; Okamoto, S.; Sato, F. Synthesis of Chiral Alkynes Having 2H or Halogen at the Secondary or Tertiary Propargylic Stereogenic Center by Hydrolysis and Halogenolysis of Optically Active Allenyltitaniums having Axial Chirality. *Tetrahedron Lett.* **1998**, *39*, 4555.

(15) Menendez, C.; Gau, S.; Lherbet, C.; Rodriguez, F.; Inard, C.; Pasca, M. R.; Baltas, M. Synthesis and Biological Activities of Triazole Derivatives as Inhibitors of InhA and Antituberculosis Agents. *Eur. J. Med. Chem.* **2011**, *46*, 5524.

https://dx.doi.org/10.1021/acs.orglett.0c03826
Org. Lett. XXXX, XXX, XXX−XXX

(16) Ankner, T.; Hilmersson, G. Instantaneous Deprotection of Tosylamides and Esters with SmI_2/Amine/Water. *Org. Lett.* **2009**, *11*, 503.
(17) Sidera, M.; Costa, A. M.; Vilarrasa, J. Iododesilylation of TIPS-, TBDPS-, and TBS-Substituted Alkenes in Connection with the Synthesis of Amphidinolides B/D. *Org. Lett.* **2011**, *13*, 4934.
(18) Yuan, H.; Guo, Z.; Luo, T. Synthesis of (+)-Lysergol and Its Analogues To Assess Serotonin Receptor Activity. *Org. Lett.* **2017**, *19*, 624.
(19) Kiran Kumar, Y.; Ranjith Kumar, G.; Sridhar Reddy, M. Hg/Pt-Catalyzed Conversion of Bromo Alkynamines/alkynols to Saturated and Unsaturated γ-butyrolactams/lactones via Intramolecular Electrophilic Cyclization. *Org. Biomol. Chem.* **2016**, *14*, 1252.
(20) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. A Convenient and Efficient Ring-opening Reaction of Aziridines with Acetylenes and Synthesis of Dihydropyrroles. *Tetrahedron* **2005**, *61*, 9586.
(21) Cui, X.-Y.; Ge, Y.; Tan, S. M.; Jiang, H.; Tan, D.; Lu, Y.; Lee, R.; Tan, C.-H. (Guanidine)copper Complex-Catalyzed Enantioselective Dynamic Kinetic Allylic Alkynylation under Biphasic Condition. *J. Am. Chem. Soc.* **2018**, *140*, 8448.

https://dx.doi.org/10.1021/acs.orglett.0c03826
Org. Lett. XXXX, XXX, XXX−XXX