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Trifluoroethanol-assisted asymmetric propargylic hydrazination to α-tertiary ethynylhydrazines enabled by sterically confined pyridinebisoxazolines

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We report the highly enantioselective Cu-catalyzed asymmetric propargylic substitution (APS) of α-tertiary propargylic electrophiles using hydrazines and hydroxylamines as a fruitful strategy to access multifunctional α-tertiary hydrazines or hydroxylamines. Using trifluoroethanol (TFE) as the solvent play a key role to decrease the nucleophilicity of hydrazines to suppress side reactions such as elimination, thus improve the yield and the enantioselectivity. NMR analysis and theoretical calculations suggest the formation of an H-bond adduct of TFE with hydrazide, stabilized by multiple H-bonding interactions, including C–F···H–N interaction. The sterically confined pyridinebisoxzolines (PYBOX), featuring a bulky benzylthio shielding group also contribute to the excellent enantioselectivity. Aryl- and aliphatic-ketone-derived α-ethynylalcohol carbonates, α-tertiary α-ethynyl epoxides, cyclic carbonates and and α-hydroxycarboxylates all are competent substrates to afford α-tertiary α-ethynylhydrazines with high structural diversity. The obtained products can be readily converted into various α-tertiary hydrazines and azacycles featuring an aza-quaternary stereocenter.

Chiral amines are ubiquitous in drugs, biological probes, and agrochemicals[1–7]. Their facile synthesis holds the key to future drug development. Hydrazine is a notable subclass of the amine family, and its derivatives constitute versatile synthetic intermediates for the synthesis of azacycles and prominent pharmacophores for drug design (Fig. 1a)[8–11]. For example, replacing the NH_2 group of methyldopa (used to treat high blood pressure) with a hydrazine group led to a different drug, carbidopa (used for Parkinson's disease), with a completely different pharmacology[12]. In addition, the N–N bond enables hydrazino acids to be used as aza-analogs of β-amino acids, allowing their application as backbone-extended peptidomimetics with a unique hydrazino turn structure[10,13]. With the chemical space associated with quaternary carbons emerging as an important element in drug discovery[14–19], chiral α-tertiary hydrazines have found increasing numbers of applications, as shown by the representative drugs and bioactive compounds in Fig. 1a[20–22]. Accordingly, it is important to develop efficient methods for the synthesis of diverse chiral α-tertiary hydrazines for medicinal research. Several strategies

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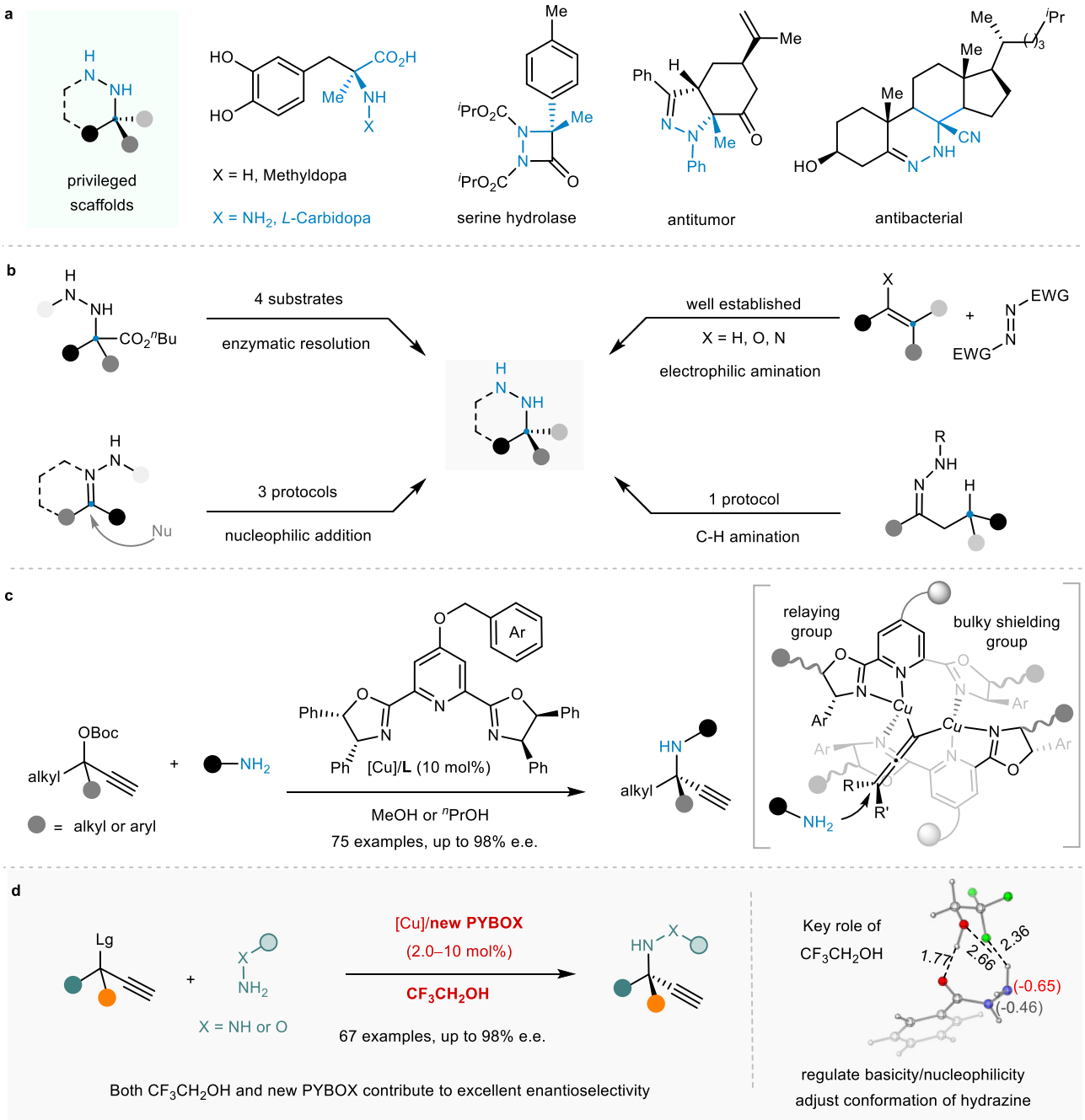

Fig. 1 | Working hypothesis. a Selected bioactive molecules containing chiral α-tertiary hydrazine. **b** Known strategies for catalytic asymmetric synthesis of α-tertiary hydrazine. **c** Our previous work on Cu-catalyzed asymmetric propargylic amination enabled by sterically confined PYBOX ligands. **d** This work, enantioselective propargylic hydrazination to generate α-tertiary ethynylhydrazines.

are known, including enzymatic resolution[23], the addition of nucleophiles to ketone hydrazones[24–26], electrophilic amination using azodicarboxylates[27,28] and C–H amination of methines[29] (Fig. 1b). These methods have been developed to varying degrees, but significant gaps remain in the scope of these methodologies. Thus, strategies to develop multifunctional chiral α-tertiary hydrazines as platform molecules are still highly desirable.

Since the seminal work of Nishibayashi, Hidai, Uemura, and coworkers[30], asymmetric propargylic substitution (APS) of propargylic alcohol derivatives has emerged as a powerful tool to construct multifunctional chiral synthons featuring an α-ethynyl group as a synthetic handle because its sp C–H bond and triple bond can undergo many diversifying reactions[31,32]. The APS of ketone-derived α-ethynyl alcohol derivatives using hydrazine derivatives would afford chiral α-tertiary α-ethynylhydrazines as a versatile synthetic platform from which to construct structurally diverse chiral hydrazines. However, this approach remains unexplored, although elegant APS of secondary α-ethynyl alcohol derivatives to give chiral 2-pyrazolines was achieved using *N*-phenylhydrazine[33], or to give chiral secondary α-ethynylhydrazines using hydrozones[34]. Two difficulties face the development of APS as a route to α-tertiary α-ethynylhydrazines. First, APS of simple ketone-derived α-ethynylalcohol derivatives to give fully substituted stereocenters remains undeveloped because the prochiral center in the key metal–allenylidene intermediate is separated from

the metal by three bonds[35–37]; thus, remote enantiofacial control is required to achieve excellent enantioselectivity[19,38,39]. Furthermore, a diminished chiral bias arises because of the similarities of the two substituents on the prochiral carbon. Second, because of the α-effect, the hydrazine derivatives are generally more nucleophilic than amines[40], which might lead to both side reactions such as elimination and poisoning of the metal catalyst by occupying the empty binding. Furthermore, the linear shape and dual reactive sites of hydrazine derivatives related to the N–N bond impose further requirements on the chiral catalysts to achieve excellent regio- and enantioselectivity via remote control. As a result, even racemic versions of APS of α-tertiary α-ethynylalcohol derivatives using hydrazines remain unexplored[41,42] despite the remarkable progress in the corresponding asymmetric propargylic amination reactions[43–54].

Recently, we developed a variety of sterically confined pyridinebisoxazoline (PYBOX) ligands featuring a bulky C4-shielding group on the pyridine to modify the electronic properties of the ligand and relay chiral information from the oxazoline ring. These ligands proved to be effective for asymmetric Cu-catalyzed alkyne-azide cycloaddition[55–57]. Particularly, those with both a C4-shielding and extra relaying groups on the 5-position of the oxazolines enabled a highly enantioselective Cu-catalyzed asymmetric propargylic amination (ACPA) of propargylic carbonates derived from simple aryl or aliphatic ketones (Fig. 1c)[52]. Theoretical studies suggest that the electron-donating benzyloxy group renders the ligands more Lewis basic and forms shorter N–Cu bonds, thereby increasing the contact regions of the chiral pocket and enhancing remote enantiofacial control (Fig. 1c). These results suggest the possibility of tuning the structure of such sterically confined PYBOX to address the aforementioned challenges in synthesizing α-tertiary α-ethynylhydrazines via APS. Herein, we report the PYBOX featuring a bulky C4 benzylthio shielding group that enables highly enantioselective APS of propargylic carbonates derived from both aliphatic and aryl ketones using hydrazides and hydroxylamines, with the assistance of trifluoroethanol (Fig. 1d).

Results

Reaction development

Given that the nature of the substituents greatly influences the nucleophilicity of hydrazines[40], we first evaluated the performance of various hydrazine derivatives in the APS of α-phenyl propargylic carbonate (**1a**) under previously developed conditions for the corresponding APS of anilines by using $CuCl_2 \cdot 2H_2O/L_6$ as the catalyst and MeOH as the solvent, with 1.0 equiv diisopropylethylamine (DIPEA)[52]. As expected, the structure of the hydrazine derivatives influenced the desired reaction significantly (Fig. 2a).

No desired product was obtained when hydrazine hydrochloride and acetyl hydrazine were used, with a large amount of carbonate **1a** recovered, accompanied by the elimination product enyne **4** and other unidentified byproducts. On the other hand, when *N*-benzyl or phenyl hydrazine, *p*-toluenesulfonyl hydrazine, or hydrazone was used, the carbonate **1a** was fully consumed, but no target product was detected; only enyne **4**, substitution byproduct **5**, and other unidentified products were observed. The fact that α-tertiary α-ethynyl alcohol derivatives can undergo an elimination reaction in the presence of a base is expected, but this may be aggravated by the use of hydrazine derivatives with strong nucleophilicity. It was found that without a chiral copper catalyst, no elimination occurred when stirring **1a** and DIPEA in MeOH at 0 °C for 48 h, but the presence of any tested hydrazine derivative shown in Fig. 2a led to obvious side reactions to yield enyne **4** and other unclarified byproducts, with 56–72% of carbonate **1a** being remained by GC analysis (see Table S5 of the Supplementary Information, SI). Fortunately, when benzoyl hydrazine **2a** was used, the desired α-tertiary α-ethynylhydrazine **3a** was obtained in 71% yield and 64% e.e., accompanied by a 29% yield of side products. It should be noted that, under the same conditions, the corresponding APS of **1a** using anilines generally gave the desired amines in over 80% yield and 90% e.e[52]. This difference clearly demonstrates that the efficient synthesis of α-tertiary α-ethynylhydrazines via APS is not as straightforward as it first appeared.

Subsequently, we examined other sterically confined PYBOX ligands to identify a suitable C4-shielding group to tune the electronic and steric properties of the catalyst to suppress side reactions while improving enantioselectivity (Fig. 2b). Indeed, the electronic properties of the C4 substituent affected the reaction significantly. As compared with unmodified ligand $\mathbf{L_1}$, which gave chiral hydrazine **3a** in 66% yield and 59% e.e., $\mathbf{L_2}$, with an electron-withdrawing chloro group, led to diminished e.e., whereas $\mathbf{L_3}$, with an electron-donating benzyloxy group, gave **3a** with an improved 64% e.e. Because sulfur has a lower electronegativity than oxygen and the C–S bond is longer than the C–O bond, we then designed ligand $\mathbf{L_4}$ with a benzylthio group for fine-tuning the catalyst properties and found that it afforded a higher e.e. of 73%. Further studies showed that with either the electron-rich 3,5-dimethoxylbenzylthio or electron-deficient 3,5-di(trifluoromethyl) benzylthio group, the corresponding ligands $\mathbf{L_5}$ and $\mathbf{L_7}$ both gave inferior results, but still afforded better e.e values than analogous $\mathbf{L_6}$ and $\mathbf{L_8}$ bearing a benzyloxy-type C4-shielding group. Nevertheless, $\mathbf{L_9}$, bearing a bulky C4 3,5-di-*tert*-butyl benzylthio group, afforded **3a** in slightly higher e.e. (77%) with similar yield.

These results justified developing sterically confined PYBOX ligands bearing a benzylthio-type group at C4 position. Notably, these C4 benzylthio-PYBOX ligands were readily prepared by a modified two-step procedure from easily available dicyanopyridine. For example, $\mathbf{L_9}$ can be obtained in an overall yield of 60% on a gram scale (for details, see Section 2 of SI). Next, to suppress E2 elimination, improve the yield, and enhance enantiofacial control, we examined the use of fluoroalkyl alcohols as solvents. Hexafluoroisopropanol (HFIP) and trifluoroethyl alcohol (TFE) are known to have unique properties that facilitate the synthesis of amines and azacycles[58–60], owing to their high polarity, enhanced Brøsted acidity, and capacity to stabilize carbocations better than the analogous nonfluorinated alcohols[61,62]. We considered that fluoroalkyl alcohols can form multiple H-bonding interactions with benzoyl hydrazine **2a** to modulate its basicity and/or nucleophilicity to suppress side elimination; furthermore, the resulting hydrazine-based H-bond adduct might have beneficial steric effects that would enhance enantiofacial discrimination. As anticipated, the use of fluoroalkyl alcohols as the solvent improved both the yield and the enantioselectivity substantially when ligand $\mathbf{L_9}$ was employed (Fig. 2c). The reaction in 2-fluoroethanol gave **3a** in obviously improved yield (87%) and e.e. (82%).

Better results were obtained when the solvent contained more fluorine atoms, with up to 93% yield and 90% e.e. achieved when TFE was used as the solvent. For comparison, the use of EtOH, ^{n}PrOH, or ^{n}BuOH as the solvent did not improve the outcome of the reaction, and the desired APS reaction proceeded poorly in common solvents as well (for details, see Section 3 of the SI). However, no reaction occurred when using HFIP as the solvent, possibly because its higher acidity led to irreversible protonation of **2a**; a similar finding that the epoxide ring-opening reaction with piperidine was inhibited by HFIP solvent was reported previously[63]. Further evaluating copper salts, bases, and temperature revealed that the reaction in TFE could be catalyzed by only 2.0 mol% of the $CuCl_2 \cdot 2H_2O/\mathbf{L_9}$ complex at −20 °C, in the presence of DABCO, to furnish α-ethynylhydrazine **3a** in 94% e.e. and 94% isolated yield.

Subsequently, NMR analysis and DFT calculations were conducted to establish the role of TFE. ^{13}C NMR analysis showed a distinct interaction between hydrazide **2a** and TFE. Upon adding TFE to a solution of **2a** in $CDCl_3$, the characteristic peak of the carbonyl group shifted downfield from 168.67 to 170.06 ppm. However, almost no change was observed in the same operation when EtOH was used as the solvent (Fig. 2d). ^{19}F NMR analysis also revealed a significant shift of

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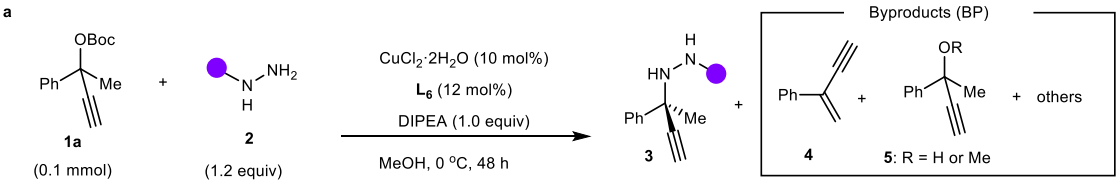
a

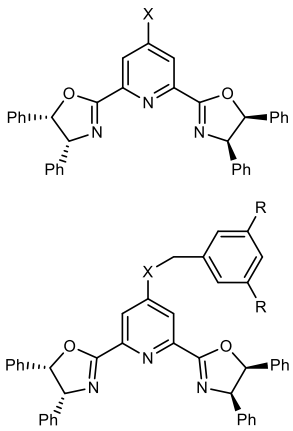


Influences of hydrazine derivatives[a]

	H_2N NH_2·HCl [b]	Bn N NH2 H	Ph N NH2 H	Ac N NH2 H	Ts N NH2 H	Ph N H N Ph	Bz N NH2 H **2a**
RSM of **1a**	78%	-	-	58%	-	-	-
Product **3**	-	-	-	-	-	-	71%, 64% e.e.
BP **4**	11%	57%	58%	26%	66%	82%	15%
BP **5**	-	15%	5%	-	10%	1%	-
Others	11%	28%	37%	16%	24%	17%	14%

b

Ligand effect (with **2a**)



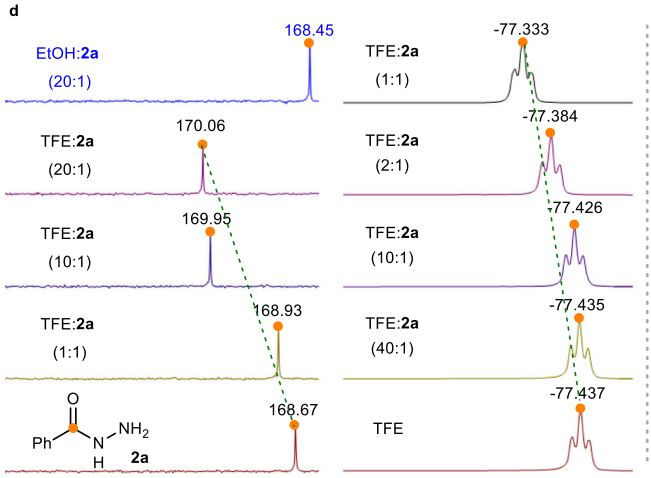
L	X	R	Yield (%)	e.e. (%)
L_1	H	-	66	59
L_2	Cl	-	62	49
L_3	OBn	-	62	64
L_4	SBn	-	64	73
L_5	S	OMe	70	70
L_6	O	OMe	71	64
L_7	S	CF_3	60	66
L_8	O	CF_3	62	62
L_9	S	^{t}Bu	66	77
L_{10}	O	^{t}Bu	64	72

c

Solvent effect (with L_9)

Alcohols	Yield (%)	e.e. (%)
MeOH	66%	77%
EtOH	72%	79%
^{n}PrOH	68%	66%
^{i}PrOH	65%	60%
^{n}BuOH	65%	64%
FCH_2CH_2OH	87%	82%
F_2CHCH_2OH	87%	87%
F_3CCH_2OH (TFE)	93%	90%
F_3CCH_2OH[c]	94%[d]	94%
HFIP	ND	-

d



e

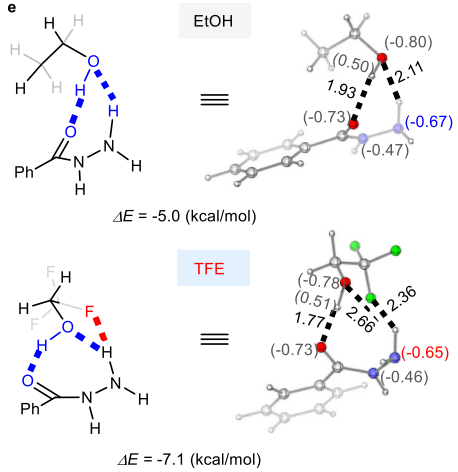


Fig. 2 | Reaction development. a Influences of hydrazine derivatives. **b** Effects of the ligands. **c** Effects of the solvent. Reagents and conditions: **1a** (0.10 mmol), **2** (0.12 mmol), $CuCl_2 \cdot 2H_2O$ (10 mol%), PYBOX ligand (12 mol%), DIPEA (1.0 equiv), solvent (1.0 mL), 0 °C, 48 h. NMR yield with 1,3,5-trimethoxybenzene as internal standard. The e.e. was determined by chiral HPLC analysis. **d** Left: ^{13}C NMR analysis for the interaction of TFE or EtOH with **2a**. Right: ^{19}F NMR study on the interaction of TFE with **2a**. **e** DFT calculations to examine the influence of the fluoro-atom on the interaction of alcohol with **2a**. The bond distances are given in angstroms and the natural bond oribital (NBO) charges are in parentheses. [a]Detected by GC analysis. [b]DIPEA (2.0 equiv). [c]$CuCl_2 \cdot 2H_2O$ (2.0 mol%), DABCO (1.0 equiv) in TFE at −20 °C. [d]Isolated yield. RSM: recovery of starting material. DIPEA diisopropylethylamine, TFE trifluoroethanol, BP byproduct, HFIP hexafluoroisopropanol.

the characteristic peak from −77.437 to −77.333 ppm upon titrating a solution of **2a** in CD_2Cl_2 against a solution of TFE in CD_2Cl_2. These results suggest that TFE forms stronger H-bonding interactions with hydrazine **2a** than EtOH. In addition to TFE being a better H-bond donor than EtOH, we wondered whether its C–F bond could serve as H-bond acceptor to form C–F···H–N interactions between TFE and **2a** to reinforce their binding, based on our interest in probing the influence of C–F···H–X interactions in organic reactions[64–68], as well as reports from other groups[69–75]. This hypothesis was supported by DFT calculations (Fig. 2e). It was found that by changing from EtOH to mono-, di-, and trifluoroethanol, the binding energy (ΔE) between **2a** and the alcohol increased gradually from −5.0 to −7.1 kcal/mol, indicating the formation of a more stable complex (for details, see Section 9 of the SI). In the case of TFE, the calculations revealed that O–H···O = C interactions between the hydroxyl group of TFE and the carbonyl group of **2a** (bond length 1.77 Å; bond angle of O–H···O = C, 162.9°), along with the H-bonding interactions between the NH_2 group of **2a** and the oxygen of TFE (bond length 2.66 Å; bond angle of N–H···O–C, 126.1°), formed a seven-membered ring. Meanwhile, effective C–F···H–N interactions between TFE and the NH_2 group of **2a** (bond length 2.36 Å; bond angle of N–H···F–C, 128.0°) were observed, given that the sum of the van der Waals radii of hydrogen and fluorine atoms is approximately 2.55 Å. Such nonclassical H-bonding interactions between hydrazide **2a** and mono- and difluoroethyl alcohol were also suggested by the DFT calculations (for details, see Section 9 of the SI). These studies cast light on the beneficial influence of TFE on the reaction. The effective H-bonding interactions between TFE and **2a** both regulate the basicity and/or nucleophilicity of **2a** to suppress competitive side reactions and confine the rotation of the N–N bond. This adjusts the conformation of **2a** to a more favorable orientation to attack Cu–allenylidene intermediate for better enantiofacial discrimination.

Although HFIP and TFE are among the most common oxo-halogenated unconventional solvents to facilitate organic reactions[61,62], to our knowledge, the correlation between their extraordinary reactivity-enabling character and the potential of their C–F bonds as H-bond acceptors has not been previously proposed. We believe our studies will bring insights into these nonclassical interactions, which can be leveraged to facilitate selective organic reactions by using fluoroalkyl alcohols as the reaction media.

Substrate scope

With the optimized conditions in hand, we examined the generality of the APS of α-tertiary α-ethynylalcohol derivatives using hydrazines (Fig. 3). Gratifyingly, propargylic carbonates derived from both aryl and aliphatic ketones worked well to give the desired chiral α-tertiary ethynylhydrazines in good to excellent yields and e.e. values. First, alkyl aryl ketone-derived α-tertiary α-ethynylalcohol carbonates were evaluated. Various α-phenyl propargylic carbonates reacted smoothly with benzoyl hydrazine **2a** to give the desired chiral ethynylhydrazines **3a**–**m** in 85–96% yield with 84–94% e.e., irrespective of the nature and position of the substituents on the phenyl group. Acetonaphthone-derived carbonate also worked well to give **3n** in 93% yield with 90% e.e. Carbonates bearing ethyl, *n*-propyl, or *n*-butyl were also viable substrates, delivering the corresponding chiral α-ethynylhydrazines **3o**–**q** in high yield and e.e. values. Subsequently, the performance of challenging aliphatic-ketone-derived α-ethynyl carbonates was investigated. A range of benzylacetone-derived propargylic carbonates reacted smoothly with hydrazide **2a** to afford the corresponding α-alkyl α-ethynylhydrazines **3r**–**u** in 80%–92% yield with 84–91% e.e., irrespective of the electron-donating or -withdrawing nature of the substituent on the phenyl group. 2-Naphthyl, 3-indolyl, 3-benzothienyl, and 2-furanyl substituted carbonates were also viable substrates, yielding the corresponding hydrazines **3v**–**y** in 84–92% yield with 86–97% e.e. Notably, linear aliphatic carbonates bearing an alkene moiety also worked well to furnish chiral hydrazines **3z**–**ab** in 87–90% yield with 90% e.e. Heptanone-derived carbonate gave the corresponding product **3ac** in 78% yield with moderate e.e. The use of a range of substituted benzoyl hydrazines was then examined. The electronic nature of phenyl substituents had little impact on the hydrazination using carbonate **1a**, giving the desired hydrazines **3ad**–**ai** in 78–99% yield with 92–94% e.e. Hydrizines with 1-naphthyl, 2-naphthyl, 3-indolyl, or piperonyl reacted smoothly, giving **3aj**–**am** in 88–95% yield with 91–95% e.e.

Encouraged by the excellent enantioselectivity achieved in the APS of α-tertiary α-ethynyl carbonates and hydrazides, we attempted to extend the reaction using hydroxylamines as the nucleophile for the synthesis of optically active α-tertiary ethynylhydroxylamines; these are multifunctional building blocks that are used to access chiral α-tertiary hydroxylamines, which are prominent structural motifs in pharmaceutically active compounds that are difficult to synthesize[76–78]. Gratifyingly, the APS of *O*-benzylhydroxylamine **6a** with various benzylacetone-derived propargylic carbonates proceeded well to yield the chiral hydroxylamines **7a**–**d** in 73–80% yield with 90–92% e.e. Carbonates bearing 2-naphthyl, 2-furanyl, 3-benzothienyl, and 3-indolyl readily afforded the desired products **7e**–**h** in 78–85% yield with 75–94% e.e. Hydroxylamines bearing benzyl or allyl substituents were also tolerated, allowing access to hydroxylamines **7i**–**k** in 61–75% yield with 91–94% e.e. However, α-aryl carbonates afforded the desired products in moderate yield and e.e., as shown by the synthesis of **7 l** (65% yield, 52% e.e.).

To demonstrate further the capacity of the C4 benzylthio-PYBOX ligands, we then examined the Cu-catalyzed propargylic hydrazination using α-tertiary α-ethynyl epoxides[36], cyclic carbonates[37,38], and α-hydroxycarboxylates[40]. These propargylic electrophiles have been widely used in amination reactions, but their propargylic hydrazination remains undeveloped. We envisioned that this approach could provide pathways to access chiral β-hydrazino alcohols or α-hydrazino acids, which are valuable targets for medicinal research. As shown in Fig. 4, α-aryl epoxides reacted well with benzoyl hydrazines to afford the desired β-hydrazino alcohols **8a**–**f** in 70–80% yield with 86–93% e.e. A variety of α-aryl cyclic carbonates also readily reacted with benzoyl hydrazine **2a** to give the corresponding α-aryl β-hydrazino alcohols **8a**–**i** in 77–90% yield with 92–98% e.e. Furthermore, both α-aryl and α-alkyl α-ketoester derived α-ethynyl carbonates were also suitable, delivering chiral α-tertiary α-hydrazino acid esters **8j**–**n** in up to 85% yield and 90% e.e.

Application explorations

Having established the highly enantioselective propargylic hydrazination, its synthetic utility was further explored (Fig. 5). First, the scalability of this protocol was shown by the facile access to 1.2 g of chiral α-tertiary α-ethynylhydrazine (*S*)–**3a** by using 2.0 mol% chiral catalyst under the optimized conditions, without erosion of enantioselectivity. Leveraging the ethynyl or hydrazine groups as synthetic handles enabled diversity-oriented synthesis based on **3a** to be achieved; this allowed the construction of structurally diverse α-tertiary hydrazines and azacycles that are difficult to access by previous protocols. For example, the Au-catalyzed intramolecular hydroamination led to chiral cyclic hydrazine **9** in an 82% yield. Starting from **3a** and isocyanate, a sequential nucleophilic addition and base-mediated cyclization process afforded imidazolidinone **10** in 79% yield, and a tandem nucleophilic addition and Au-catalyzed cyclization sequence unexpectedly delivered chiral oxadiazole **11** in 75% yield. Furthermore, taking advantage of the ethynyl group, it was possible to merge the resulting α-tertiary α-ethynylhydrazines for late-stage modification of drugs and bioactive compounds, as shown by a CuAAC, which enabled the effective fusion of a zidovudine fragment (a drug commonly used in the treatment of AIDS-related syndromes and HIV infection), leading to compound **12**, bearing a triazole moiety, in a

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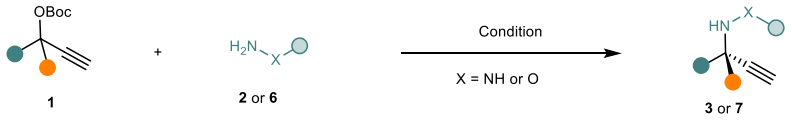
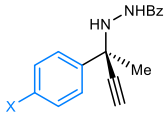
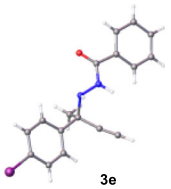


α-aryl propargylic esters (condition A)



3a, X = H, 94%, 94% e.e.
3b, X = F, 92%, 90% e.e.
3c, X = Cl, 92%, 92% e.e.
3d, X = Br, 96%, 92% e.e.
3e, X = I, 95%, 94% e.e.
3f, X = CF_3, 85%, 91% e.e.
3g, X = Me, 87%, 88% e.e.
3h, X = Ph, 87%, 90% e.e.



3e
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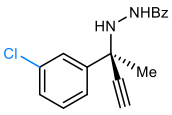
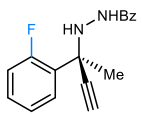
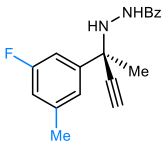


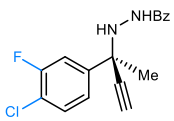
3i, 92%, 86% e.e.



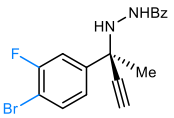
3j, 87%, 84% e.e.



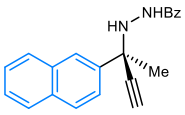
3k, 85%, 86% e.e.



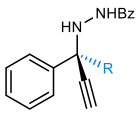
3l, 93%, 87% e.e.



3m, 90%, 90% e.e.

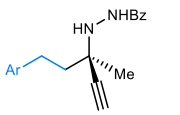


3n, 93%, 90% e.e.

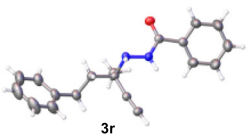


3o, R = Et, 84%, 80% e.e.
3p, R = ^{n}Pr, 86%, 74% e.e.
3q, R = ^{n}Bu, 80%, 78% e.e.

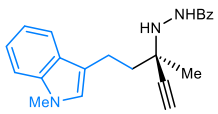
α-alkyl propargylic esters (condition B)



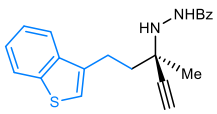
3r, Ar = Ph, 90%, 90% e.e.
3s, Ar = 4-MeC_6H_4, 80%, 91% e.e.
3t, Ar = 3-MeC_6H_4, 84%, 90% e.e.
3u, Ar = 4-BrC_6H_4, 92%, 84% e.e.
3v, Ar = 2-naphthyl, 84%, 91% e.e.



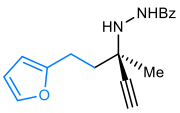
3r
CCDC: 2389394



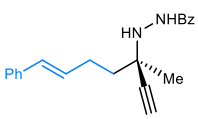
3w, 87%, 97% e.e.



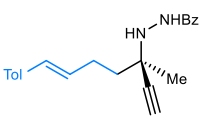
3x, 92%, 94% e.e.



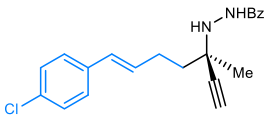
3y, 84%, 86% e.e.



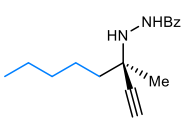
3z, 89%, 90% e.e.



3aa, 90%, 90% e.e.

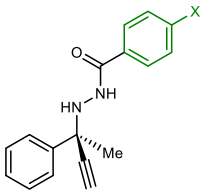


3ab, 87%, 90% e.e.

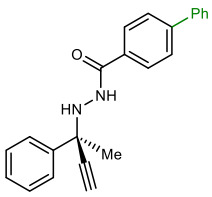


3ac, 78%, 46% e.e.

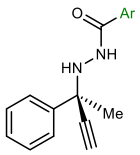
scope of hydrazines (condition A)



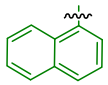
3ad, X = F, 99%, 92% e.e.
3ae, X = Br, 96%, 92% e.e.
3af, X = Me, 80%, 94% e.e.
3ag, X = ^{t}Bu, 91%, 93% e.e.
3ah, X = OMe, 78%, 94% e.e.



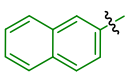
3ai, 92%, 93% e.e.



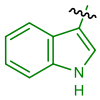
Ar =



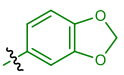
3aj, 95%, 91% e.e.



3ak, 93%, 95% e.e.

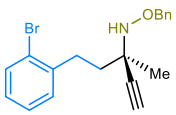


3al, 88%, 94% e.e.

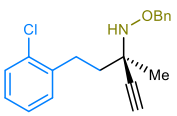


3am, 90%, 94% e.e.

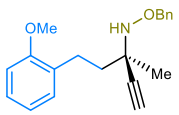
scope of hydroxylamines (condition C)



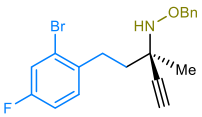
7a, 75%, 92% e.e.



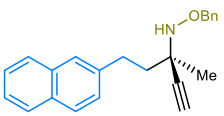
7b, 76%, 92% e.e.



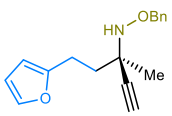
7c, 73%, 91% e.e.



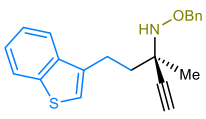
7d, 80%, 90% e.e.



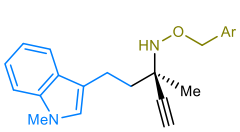
7e, 85%, 75% e.e.



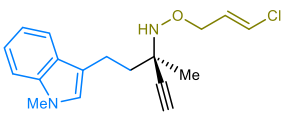
7f, 80%, 83% e.e.



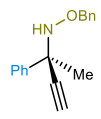
7g, 83%, 91% e.e.



7h, Ar = Ph, 78%, 94% e.e.
7i, Ar = 4-FC_6H_4, 67%, 94% e.e.
7j, Ar = 4-MeOC_6H_4, 61%, 93% e.e.



7k, 75%, 91% e.e.



7l, 65%, 53% e.e.

Fig. 3 | Scope of reaction with propargylic carbonates. Conditions **A**: α-aryl propargylic ester **1** (0.2 mmol), hydrazide **2** (0.24 mmol), $CuCl_2{\cdot}2H_2O$ (2.0 mol%), $\mathbf{L_9}$ (2.4 mol%), DABCO (0.2 mmol), CF_3CH_2OH (2.0 mL), −20 °C, 2 days. Conditions **B**: α-alkyl propargylic ester **1** (0.2 mmol), hydrazide **2** (0.24 mmol), $CuBr_2$ (10 mol%), $\mathbf{L_8}$ (12 mol%), DABCO (0.1 mmol), CF_3CH_2OH (2.0 mL), −20 °C, 2 days. Conditions **C**: propargylic ester **1** (0.2 mmol), hydroxylamine **6** (0.24 mmol), $CuBr_2$ (10 mol%), $\mathbf{L_8}$ (12 mol%), *N*,*N*-dimethylpiperazine (0.8 mmol), ^{n}PrOH (2.0 mL), −20 °C, 4 days. Isolated yield. The e.e values were determined by chiral HPLC analysis. The absolute configuration of (*S*)−**3e** and (*R*)−**3r** was determined by X-ray analysis, for detail see Section 10 of the SI.

https://doi.org/10.1038/s41467-025-59845-5

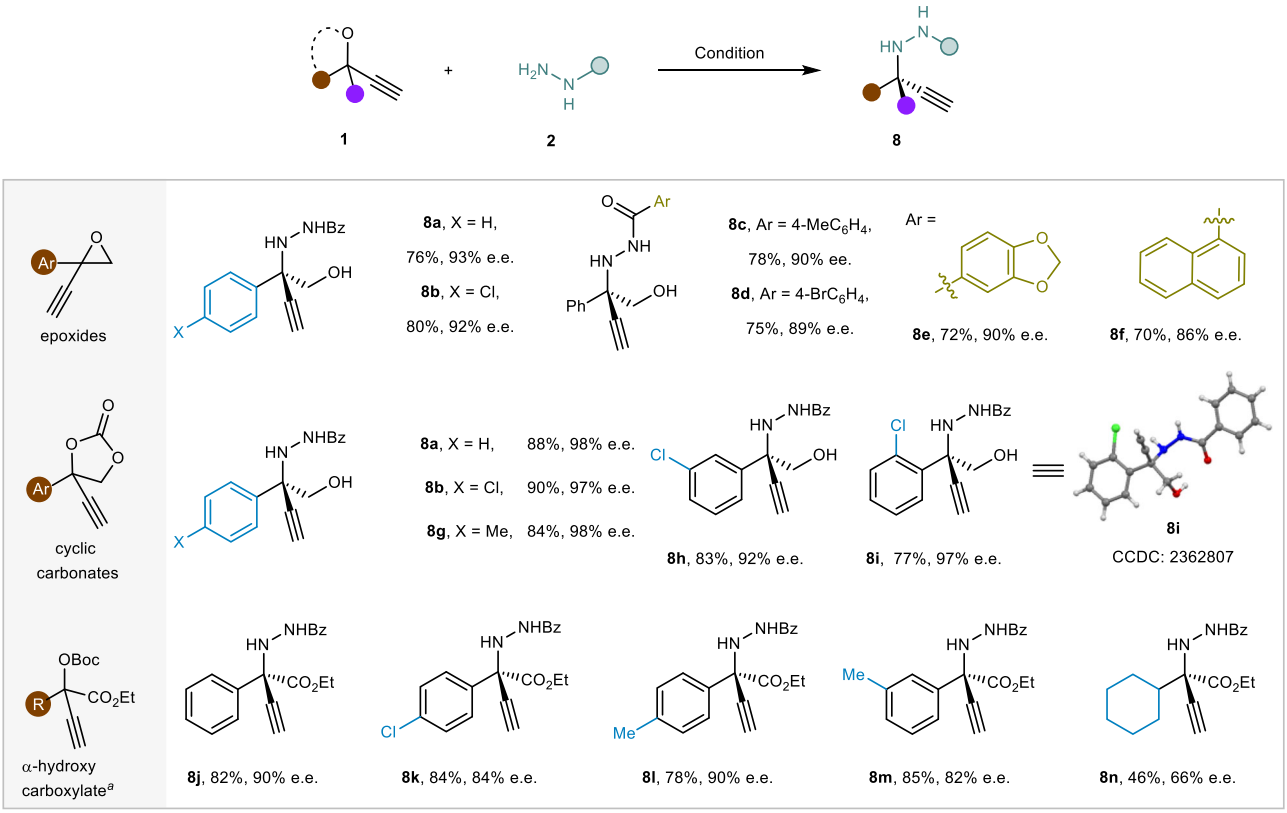


Fig. 4 | Scope of reaction with epoxides, cyclic carbonates and α-hydroxycarboxylate. Reaction conditions: **1** (0.2 mmol), hydrazide **2** (0.24 mmol), $CuCl_2{\cdot}2H_2O$ (10 mol%), $\mathbf{L_9}$ (12 mol%), DABCO (0.2 mmol), CF_3CH_2OH (2.0 mL), −20 °C, 2 days. [a]$\mathbf{L_{13}}$ was used; for details see Section 6 of the SI. Isolated yield. The e.e. values were determined by chiral HPLC analysis. The absolute configuration of (*S*)−**8i** was determined by X-ray analysis. The absolute configuration of (*S*)−**8j** was determined by converting the ester group into a hydroxymethyl group and comparing the optical rotation value with that of the (*S*)−**8a**.

remarkable 99% yield and >20:1 dr. Gratifyingly, the selective hydrogenation of the alkyne moiety mediated by Pd/C or Lindlar catalyst afforded α-ethyl hydrazine **13** or α-vinyl hydrazine **14** in 90% and 89% yield, respectively. The Sonogashira coupling gave chiral hydrazine **15** in 83% yield with 94% e.e.

Interestingly, the Cu-catalyzed propargylic hydrazination can be further coupled with an Ag-catalyzed carboxylative cyclization (CC) for tandem synthesis of chiral 2-oxazolidinones using CO_2 as a C1 synthon. Based on our recently reported tandem ACPA/CC reactions[79], we further developed a similar tandem propargylic hydrazination/CC sequence using a modified condition, paving way to chiral 5-methylidene-2-oxazolidinones **16** bearing αza-quaternary stereocenters in 83%−87% e.e., slightly lower than that of the corresponding chiral α-tertiary ethynylhydrazines. It is worth mentioning that optically active 2-oxazolidinones are privileged scaffolds in drugs and bioactive compounds, but methods to those bearing an aza-quaternary stereocenter are rare[80], despite incorporating a fully substituted carbon might significantly enhance the pharmaceutical properties of bioactive compounds[14].

Mechanistic studies

Mechanistic studies were conducted to probe the beneficial role of the C4 benzylthio group of the ligands in the highly enantioselective Cu-catalyzed propargylic hydrazination (Fig. 6). First, single crystals of complexes formed from $CuCl_2 \cdot 2H_2O$ with unmodified ligand $\mathbf{L_1}$ or benzylthio-PYBOX $\mathbf{L_9}$ were obtained. Comparative analysis revealed that the Cu−N distances in complex Cu(II)/$\mathbf{L_9}$ were substantially shorter than those in the complex Cu(II)/$\mathbf{L_1}$ (1.992, 1.922, and 1.969 Å vs. 2.033, 1.995, and 2.025 Å, respectively), as shown in Fig. 6a. These data showed that the electron-donating C4 benzylthio group enhanced the Lewis basicity of the PYBOX ligand, thereby strengthening the binding of $\mathbf{L_9}$ to Cu(II). This analysis is consistent with our previous theoretical calculations that in the key Cu(I)-allenylidene intermediates, PYBOX ligand L_3 (featuring a C4 benzyloxy group) formed shorter Cu−N bonds than unmodified ligand L_1. Therefore, we believe the role of the electron-donating C4 benzylthio group was to enhance the Lewis basicity of the ligands to form shorter Cu−N bonds, which, in turn, led to the formation of a more congested chiral pocket. In addition, the sterically hindered C4 benzylthio group could interact with the two relaying phenyls at the 5-position of the oxazolines, leading to a more confined chiral environment. Consequently, the electronic and steric effects of the C4 benzylthio group have a concerted effect that reinforces the remote enantiofacial control during the nucleophilic attack of hydrazide **2** to the Cu−allenylidene intermediate.

To obtain more information on the reactive chiral copper species involved in the reaction, the e.e. value of PYBOX $\mathbf{L_9}$ versus that of α-ethynylhydrazine **3a** was examined. The data exhibited a pronounced positive nonlinear effect (NLE), which implied that more than one chiral ligand might be involved in the stereoselective amination step (Fig. 6b). Investigations into the Cu/$\mathbf{L_9}$ stoichiometric ratio further demonstrated that the optimal catalytic performance occurred at a ratio near 1:1.2 (Fig. 6c), supporting the hypothesis of a dicopper complex stabilized by two chiral ligands as the active species. Additionally, UV-vis spectroscopy of the reaction mixture under standard conditions with $CuCl_2{\cdot}2H_2O$/$\mathbf{L_9}$ displayed nearly identical absorption profiles to that with CuCl/$\mathbf{L_9}$ (Fig. 6d), suggesting the dominance of a Cu(I)-ligand complex rather than a Cu(II) species in the catalytic cycle,

https://doi.org/10.1038/s41467-025-59845-5

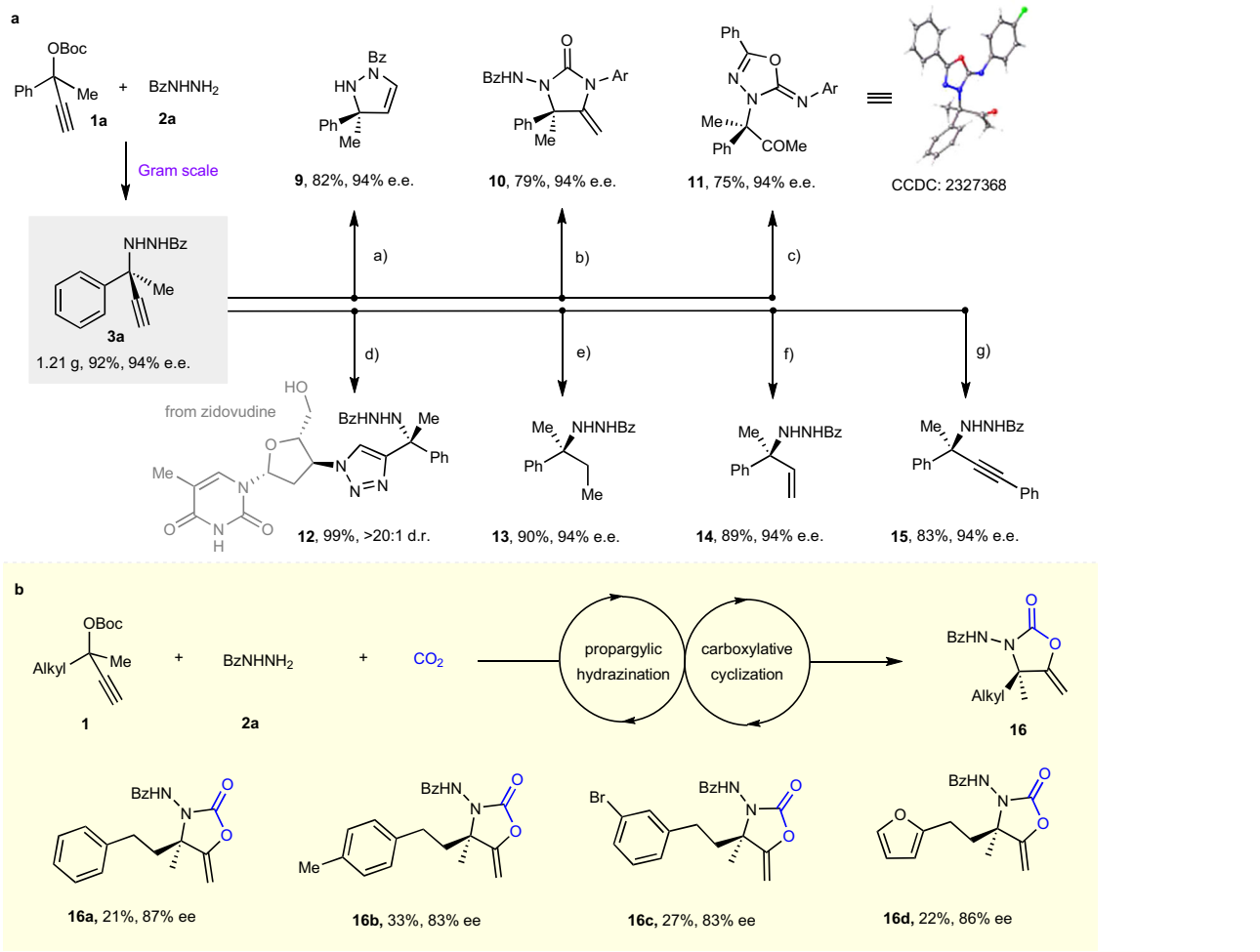


Fig. 5 | Application explorations. a Product elaboration: Reaction conditions: (a) Ph_3PAuCl (20 mol%), MeOH, 50 °C, 8 h; (b) 4-fluorophenyl isocyanate (1.0 equiv), Et_2O, 4 h, then NaOMe (2.0 equiv), MeOH, 50 °C, 2 h, Ar = 4-FC_6H_4; (c) 4-fluorophenyl isocyanate (1.0 equiv), Et_2O, 4 h, then Ph_3PAuCl (5.0 mol%), MeOH, 50 °C, 24 h, Ar = 4-FC_6H_4; (d) zidovudine (1.0 equiv), $CuSO_4 \cdot 5H_2O$ (10 mol%), sodium ascorbate (20 mol%), $^tBuOH/H_2O$ (1:1, v/v), rt, 4 h; (e) Pd/C (10 mol% Pd), H_2 (1.0 atm), MeOH (1.0 mL), 50 °C, 6 h; (f) Lindlar catalyst (10 mol% Pd), quinoline (2.0 equiv), H_2 (1.0 atm), EtOAc, rt, 10 min; (g) $Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), PhI (1.5 equiv), Et_3N (10 equiv), DMF, 55 °C, 3 h. Isolated yield. The e.e. values were determined by chiral HPLC analysis. **b** Tandem reaction: The propargylic hydrazination/carboxylative cyclization sequence. For hydrazination step: according to standard condition; For carboxylative cyclization step: AgOTs (50 mol%), 1,3-diphenylguanidine (1.2 equiv), CO_2 (3.0 MPa) at 25 °C for 72 h. Isolated yield. The e.e. values were determined by chiral HPLC analysis.

which was further supported by EPR spectroscopy experiments (for details, see Section 9 of the SI).

Based on these results and our previously established working model for the benzyloxy-PYBOX-enabled Cu-catalyzed propargylic amination, DFT calculations were performed to study the possible transition states (TSs) for the formation of chiral **3a** catalyzed by benzylthio-PYBOX $\mathbf{L_4}$. Initially, the possible TSs in the absence of TFE were examined. As shown in Fig. 6e, in the optimized TS-$\mathbf{L_4}$-*S* for the major (*S*)−**3a**, two key stabilizing interactions could be identified: the π−π stacking interaction between the phenyl group of **1a** and the 4-phenyl group of the oxazoline ring in ligand $\mathbf{L_4}$, as well as the C−H/π interaction involving the phenyl group of **1a** and the phenyl group of the benzylthio moiety. In contrast, the optimized TS-$\mathbf{L_4}$-*R* corresponding to the minor (*R*)−**3a** enantiomer lacked these stabilizing interactions and exhibited destabilizing steric repulsion between the methyl group of **1a** and the phenyl group of $\mathbf{L_4}$, resulting in a 2.3 kcal/mol higher free energy.

Next, the optimized TSs in the presence of TFE, incorporating H-bonding interactions, were studied based on the established **2a**-TFE interaction model. As shown in Fig. 6f, the H-bonding-induced spatial constraint between **2a** and TFE enhances the favorable π−π stacking interactions in TS- $\mathbf{L_4}$/TFE-*S*-1 while exacerbating unfavorable steric repulsions in TS-$\mathbf{L_4}$/TFE-*R*-1. This is evidenced by the shorter Ph···Ph distances in TS-$\mathbf{L_4}$/TFE-*S*-1 (3.83 Å) compared to TS-$\mathbf{L_4}$-*S* (3.91 Å), and more pronounced repulsive interactions between the methyl group of **1a** and the phenyl group of $\mathbf{L_4}$ in TS-$\mathbf{L_4}$/TFE-*R*-1 (2.23 Å) versus TS-$\mathbf{L_4}$-*R* (2.26 Å). Consequently, DFT calculations revealed a substantial free-energy gap (3.7 kcal/mol) between transition states TS-$\mathbf{L_4}$/TFE-*S*-1 and TS-$\mathbf{L_4}$/TFE-*R*-1, matched well with experimental results. These theoretical results indicate that the H-bonding interactions between TFE and **2a** plays an important role in achieving the excellent enantioselectivity through two complementary mechanisms: stabilizing π−π interactions in the *S*-type transition state and exacerbating steric repulsion between the methyl group of **1a** and the phenyl group of $\mathbf{L_4}$ in the *R*-type transition state.

Discussion

We have developed a highly enantioselective Cu-catalyzed APS of α-tertiary propargylic electrophiles using hydrazides and hydroxylamines, enabled by the sterically confined PYBOX ligands featuring a C4 benzylthio group. The scope of the propargylic electrophiles was broad, with suitable substrates including not only

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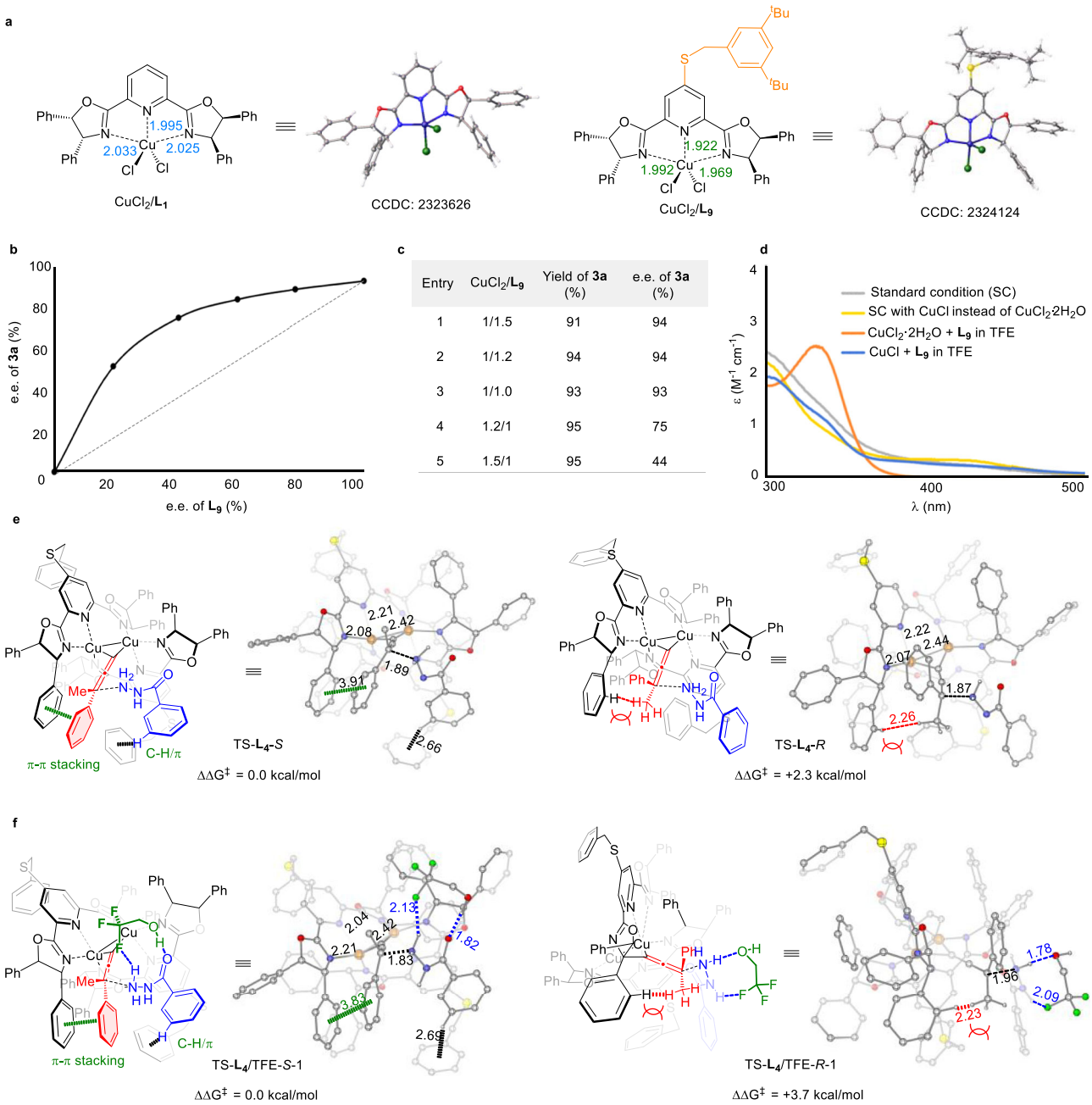

Fig. 6 | Mechanistic studies. a X-ray structure of $CuCl_2$/L_1 and $CuCl_2$/L_9. **b** Nonlinear effects of the e.e. values of ligand L_9 and product **3a**. **c** Variations of $CuCl_2$/L_9 ratios of propargylic hydrazination of **1a** and **2a**. NMR yield. **d** UV–vis spectroscopy experiments with Cu complexes. **e** DFT calculations of the optimized structures for TS modes to chiral **3a** catalyzed by benzylthio–PYBOX L_4 in the absence of TFE. **f** DFT calculations of the optimized structures in the presence of TFE.

aryl- and aliphatic-ketone-derived α-ethynylalcohol carbonates, but also α-tertiary α-ethynyl substituted epoxides, cyclic carbonates, and α-hydroxycarboxylates. To our knowledge, no previous report can achieve highly enantioselective APS reaction with such a broad scope of α-tertiary propargylic electrophiles. The use of TFE as the solvent played an important role in suppressing side reactions, leading to increased yield and improved enantioselectivity. As suggested by NMR analysis and theoretical calculations, this beneficial effect is believed to originate from the formation of a H-bond adduct between the TFE and the hydrazide, which is stabilized by multiple H-bonding interactions, including C–F···H–N interactions, which is a reactivity-enabling characteristic of fluoroalkyl alcohols that has previously been overlooked. This research also highlights the potential of our sterically confined PYBOX ligands in developing other APS reactions. X-ray crystallographic analysis of the $CuCl_2$/L_1 and $CuCl_2$/L_9 complexes as well as theoretical calculations revealed that the C4 benzylthio group increased the congestion of the chiral pocket, leading to increased remote enantiofacial control. This approach facilitates the synthesis of α-tertiary α-ethynylhydrazines and α-ethynylhydroxylamines with high structural diversity. The multifunctional chiral α-tertiary α-ethynylhydrazines that are generated provide versatile platform molecules that can undergo various diversifying transformations. We believe that our method should attract the interest of researchers in medicinal, agrochemical, and materials science.

Methods

General procedure for the synthesis of chiral α-tertiary propargylhydrazines **3** and **8**. To a 5 mL vial equipped with a screw-cap were added $CuCl_2 \cdot 2H_2O$ or $CuBr_2$ (0.004 or 0.02 mmol, 2.0 or 10 mol%) and PYBOX ligand $\mathbf{L_8}$ or $\mathbf{L_9}$ (0.0048 or 0.024 mmol, 2.4 or 12 mol%), followed by 2.0 mL of anhydrous CF_3CH_2OH. The solution was stirred at 40 °C for 2.0 h, and then propargylic esters **1** (0.2 mmol, 1.0 equiv) was added. After cooling the mixture to −20 °C for 0.5 h, DABCO (0.1 or 0.2 mmol, 0.5 or 1.0 equiv) was added, and the mixture was continued to stir at −20 °C for another 0.5 h, following by the addition of hydrazides **2** (0.24 mmol, 1.2 equiv). The resulting mixture was stirred at −20 °C for 2 days till almost full conversion of **1** by TLC analysis, and then quickly passed through a short column to remove copper catalyst using EtOAc as the eluent. The thus obtained solution was concentrated under reduced pressure, and the residue was directly subjected to column chromatography purification using petroleum ether/EtOAc (10:1 to 3:1, v/v) as the eluent, to afford the desired chiral α-tertiary α-ethynylhydrazines **3** and **8**.

Data availability

Materials and methods, detailed optimization studies, experimental procedures, mechanistic studies, NMR spectra and computational data are available in the Supplementary Information. Source data are present. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers **3e** (CCDC 2326713), **3r** (CCDC 2389394), **8i** (CCDC 2362807), **11** (CCDC 2327368), $CuCl_2/\mathbf{L_1}$ (CCDC 2323626) and $CuCl_2/\mathbf{L_9}$ (CCDC 2324124). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. The Cartesian coordinates of the optimized transition states are recorded in Supplementary Data 1. All source data in support of the findings of this study are available within the Article and its Supplementary Information or from the corresponding author upon request.

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Author contributions

J.Z. and F.Z. conceived the idea; Y.G. performed the experiments, collected and analyzed the data; Z. Z., H. L., T. W., M. J., N. F., P. P. and H. W. prepared the starting materials; X.W. performed the DFT calculation studies; F.Z. and J.Z. directed the project and co-wrote the manuscript.

Competing interests

The authors declare no competing interest.

Additional information

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