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Enantioselective radical C–H amination for the synthesis of β-amino alcohols

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Asymmetric, radical C–H functionalizations are rare but powerful tools for solving modern synthetic challenges. Specifically, the enantio- and regioselective C–H amination of alcohols to access medicinally valuable chiral β-amino alcohols remains elusive. To solve this challenge, a radical relay chaperone strategy was designed, wherein an alcohol was transiently converted to an imidate radical that underwent intramolecular H-atom transfer (HAT). This regioselective HAT was also rendered enantioselective by harnessing energy transfer catalysis to mediate selective radical generation and interception by a chiral copper catalyst. The successful development of this multi-catalytic, asymmetric, radical C–H amination enabled broad access to chiral β-amino alcohols from a variety of alcohols containing alkyl, allyl, benzyl and propargyl C–H bonds. Mechanistic experiments revealed that triplet energy sensitization of a Cu-bound radical precursor facilitates catalyst-mediated HAT stereoselectivity, enabling the synthesis of several important classes of chiral β-amines by enantioselective, radical C–H amination.

Five of the six most commonly employed chemical reactions in the discovery of new medicines entail the construction of a C–N bond[1]. To supplement these classical methods for amination of preformed C–X bonds, modern synthetic efforts have focused on designing strategies for direct C–H amination[2,3]. To this end, aminations of aryl[4–6] and alkyl[7–9] C–H bonds have been developed. In the latter cases, stereochemical control of sp^3 C–H amination affords an added challenge, with rare solutions entailing nitrenes and heavy metals, porphyrins or enzymes[10–15]. Nonetheless, the synthesis of β-amino alcohols by enantio- and regioselective β-C–H amination remains an unsolved problem. Here, we report a new radical relay chaperone strategy, wherein an alcohol is transiently converted to an imidate radical[16] that enables intramolecular H-atom transfer (HAT)[17]. This regioselective 1,5-HAT[18,19] has now also been rendered enantioselective—a rare example for C–H amination—by harnessing energy transfer catalysis to mediate selective radical generation and interception by a chiral copper catalyst[20–22].

To selectively prepare chiral β-amino alcohols—a privileged motif in nature, medicine and catalysis—we sought to develop an enantio- and regioselective, radical C–H amination of alcohols, as shown in Fig. 1a. This strategy complements current methods to access vicinal amino alcohols that rely on the chiral pool (for example, amino acids), chiral auxiliaries (for example, imines) or multi-step conversion of chiral diols[23–25]. However, we were cognizant of the dearth of methods for stereoselective, radical C–H amination. In fact, asymmetric radical C–H functionalizations in general are rare, with pioneering solutions existing only for alkylation, arylation and deracemization[26–32]. Our analysis of this problem led us to propose that the challenge lies in the typical generation of radicals by non-selective H abstraction of weak C–H bonds (for example, benzylic and α-hetero), leading to radical chain processes that are difficult to render stereoselective—especially in the case of C–H amination[33]. We proposed that if these carbon radicals are instead mildly generated by intramolecular HAT from N-centred radicals, catalytic systems could be engineered to exercize complete regio- and stereoselective control over radical C–H amination.

Results and discussion

Design plan. In designing a HAT-mediated synthesis of chiral β-amino alcohols via radical C–H amination, we noted several challenges, as outlined in Fig. 1b. First, the α-C–H of an alcohol is weaker than the β- and γ-methylene C–H bonds (bond dissociation energy: 90 versus 98 kcal mol^{-1})[34]. We have shown that a radical relay chaperone strategy, wherein an alcohol is temporarily converted to an imidate radical, facilitates selective β-radical formation via 1,5-HAT to overcome this thermodynamic bias[16]. Yet, this approach has only been rendered racemic because of its reliance on non-selective, iodine atom transfer to generate and trap the requisite radicals. Alternatively, we envisioned that a chiral catalyst could mediate asymmetric C–H functionalization via an enantioselective HAT only if radical generation is dependent on the presence of a chiral catalyst, such as through a multi-catalytic, triplet sensitization mechanism. Moreover, the low barrier for inversion of alkyl radicals (0.5 kcal mol^{-1}; $>10^8$ s^{-1})[35] necessitates that this β-radical also be rapidly and stereoselectively trapped by the chiral catalyst. In this manner, and in contrast with concerted, nitrene insertion mechanisms, we envisioned that a radical-mediated approach could enable stereoselectivity by exercizing catalyst control over two elementary steps: (1) H-atom abstraction; and (2) alkyl radical trapping. We anticipated that catalytic stereocontrol over both of these radical-generating and -terminating events would provide highly enantioenriched β-amino alcohols.

Proposed mechanism. The chemo-, regio- and enantioselective radical C–H amination described herein is mediated by multiple catalysts working in concert to enable this valuable, asymmetric transformation via an energy transfer mechanism, as illustrated in Fig. 1c. In this strategy, an alcohol is converted to an oxime imidate by combination with a bench-stable imidoyl chloride chaperone prepared in two steps from H_2N–OPh[36]. This radical precursor is then coordinated by copper catalyst **A** bearing a chiral bisoxazoline ligand, as well as a chiral carboxylate, to generate Cu imidate complex **B**. Upon excitation with visible light, an Ir photocatalyst may

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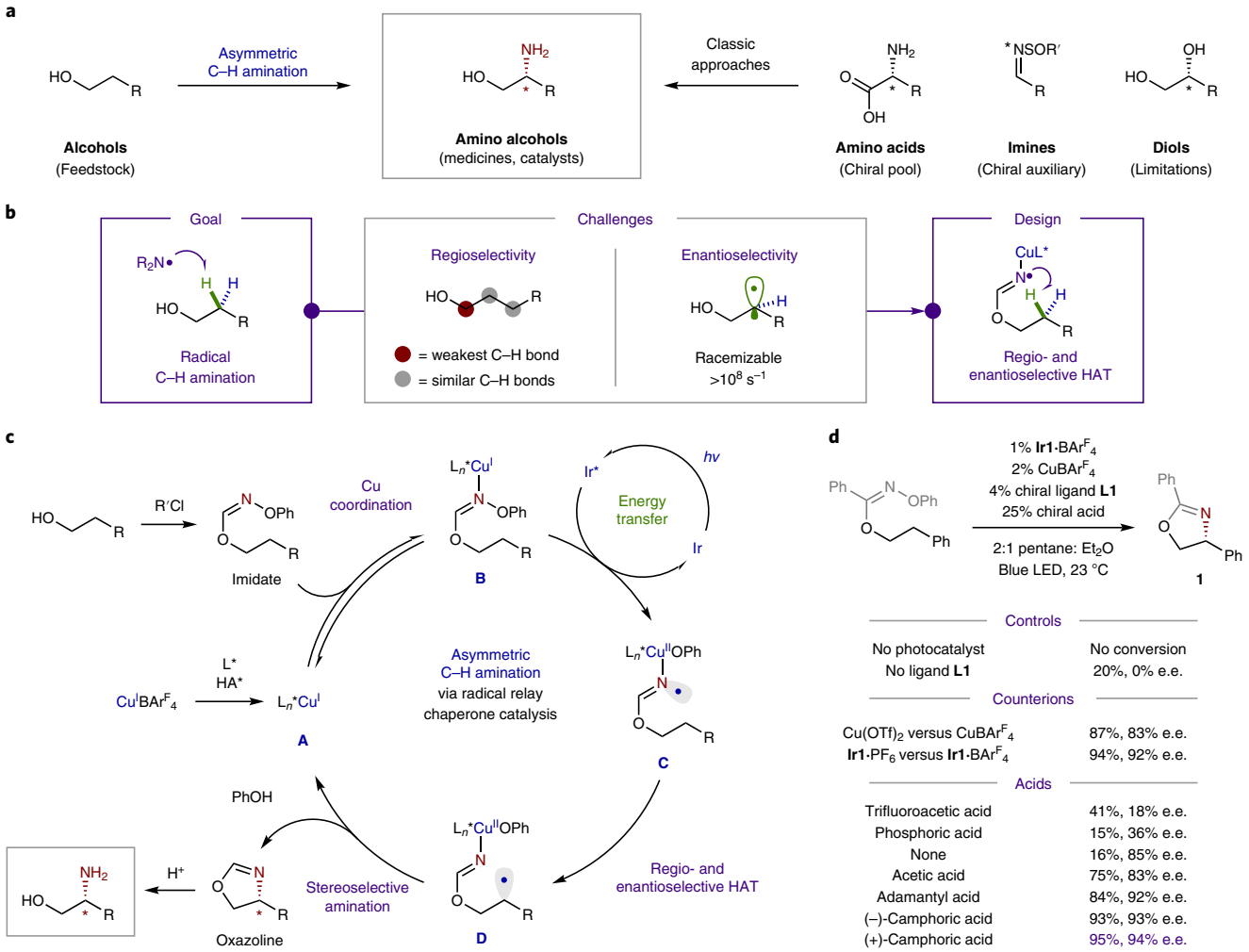
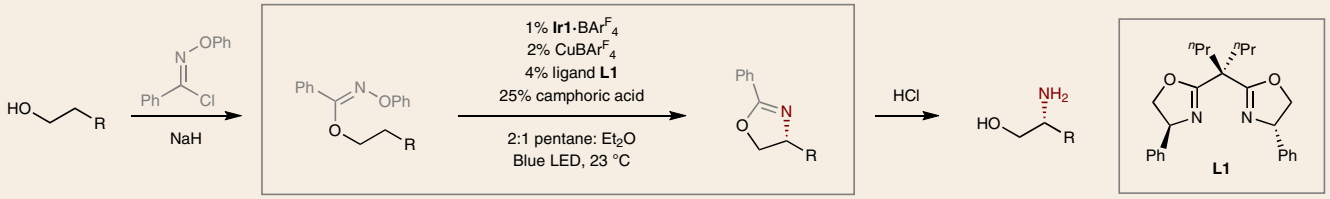


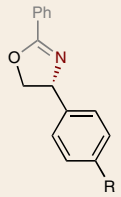
Fig. 1 | Design of a selective, radical C–H amination for the synthesis of β-amino alcohols. a, Radical C–H amination of cheap and abundant alcohols enables access to the privileged β-amino alcohol architecture, complementing classic approaches that are limited by the availability of chiral pool precursors (for example, amino acids) or stoichiometric chiral auxiliaries (for example, imines) or multi-step manipulation of chiral reagents (for example, diols). **b**, Dual challenges for a radical approach include selective formation and trapping of a transient radical intermediate. Specifically, β-regioselectivity is disfavoured compared with abstraction of the weaker α-C–H bond by an N-centred radical. Moreover, enantioselectivity is challenging to both control and retain in this process, as it may rapidly erode by radical epimerization. **c**, Proposed mechanism. Alcohol addition to an imidoyl chloride chaperone furnishes an oxime imidate, which binds to a chiral Cu catalyst. This complex then forms an N-centred radical via selective, triplet sensitization by an excited Ir photocatalyst. Regio- and enantioselective HAT, followed by stereoselective amination, affords a chiral oxazoline. Hydrolysis yields the enantioenriched β-amino alcohol. **d**, The development of this asymmetric β-C–H amination required a multi-catalytic strategy, wherein a photocatalyst selectively excites a chiral Cu catalyst complex when it is bound to an imidate-activated alcohol. Mechanistic probes illustrate the necessity of each component in ensuring the efficiency and selectivity of this radical C–H amination.

then sensitize this organocopper complex via an energy transfer mechanism[37], which generates N-centred radical **C** by triplet sensitization of the oxime N–O bond to enable a net photoinduced oxidative addition. The resulting chiral Cu-bound imidate radical **C** can undergo enantio- and regioselective HAT to afford chiral β-radical **D**. Amination may then occur with further stereocontrol by either: (1) diastereoselective metalation of the alkyl radical[38] and reductive elimination of the ensuing alkyl Cu(III) intermediate[39]; or (2) diastereoselective coupling of the radical within a Cu(II) complex[40]. Both pathways would afford enantioenriched oxazoline, along with PhOH and regenerated Cu catalyst **A**. Finally, acidic hydrolysis furnishes the chiral β-amino alcohol from this multi-catalytic radical relay mechanism.

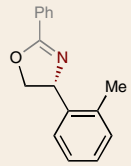
Reaction development. The execution of our design for asymmetric β-C–H amination, as shown in Fig. 1d, requires a multi-catalytic approach that includes chiral copper and acid co-catalysts working in concert with an energy transfer photocatalyst to selectively initiate and trap an intramolecular HAT mechanism. Specifically, the benzoic acid-derived oxime imidate of 2-phenyl ethanol was converted to chiral oxazoline **1** (95% yield; 94% e.e.) by combination of 1% **Ir1** photocatalyst (Ir{[dF(CF$_3$)ppy]$_2$dtbbpy}BAr$^F_4$), 2% CuBAr$^F_4$, 4% bisoxazoline ligand **L1** and 25% camphoric acid in a 2:1 mixture of pentane:Et$_2$O, with blue LED irradiation for 1 h. Although asymmetric, α-amido amination has been shown by direct photoexcitation of Cu carbazolides[40], neither Cu acetate **A** nor Cu imidate **B** absorbs visible light ($\lambda_{abs} > 400$ nm). Therefore, an external triplet sensitizer (**Ir1**) was used to mediate this reaction with blue LED irradiation. Control experiments confirmed that this photosensitizer was required (starting material is unconsumed without **Ir1**) and that other non-redox active, triplet sensitizers increased the reac-

Table 1 | Synthetic scope of alcohols in enantioselective, radical C–H amination

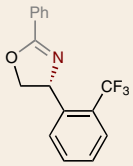




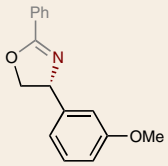
R = H, **1**, 80%, 94% e.e.
F, **2**, 98%, 93% e.e.
Cl, **3**, 87%, 94% e.e.
Br, **4**, 89%, 95% e.e.
I, **5**, 79%, 93% e.e.
Me, **6**, 89%, 91% e.e.
OMe, **7**, 80%, 84% e.e.
CF$_3$, **8**, 70%, 95% e.e.
OCF$_3$, **9**, 94%, 92% e.e.



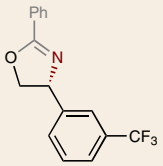
10, 95%, 91% e.e.



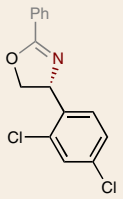
11, 81%, 97% e.e.



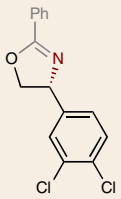
12, 79%, 93% e.e.



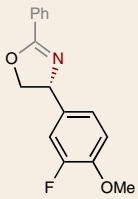
13, 85%, 91% e.e.



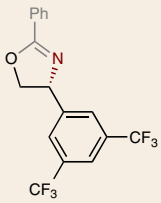
14, 88%, 98% e.e.



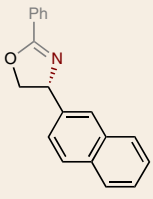
15, 87%, 93% e.e.



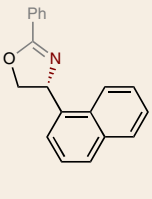
16, 90%, 89% e.e.



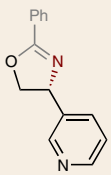
17, 79%, 80% e.e.



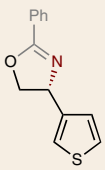
18, 92%, 93% e.e.



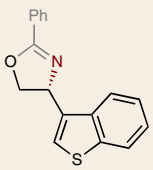
19, 99%, 94% e.e.



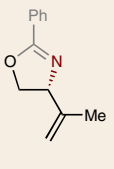
20, 65%, 82% e.e.



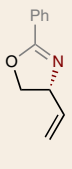
21, 83%, 90% e.e.



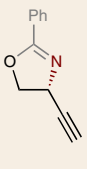
22, 92%, 95% e.e.



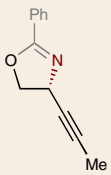
23, 82%, 94% e.e.



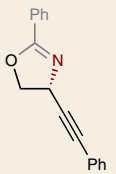
24, 80%, 83% e.e.



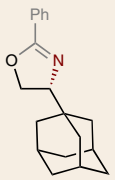
25, 99%, 89% e.e.



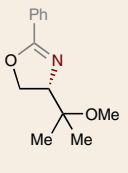
26, 96%, 83% e.e.



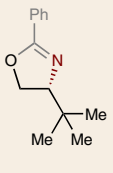
27, 89%, 83% e.e.



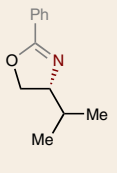
28, 36%, 89% e.e.



29, 47%, 94% e.e.



30, 86%, 88% e.e.



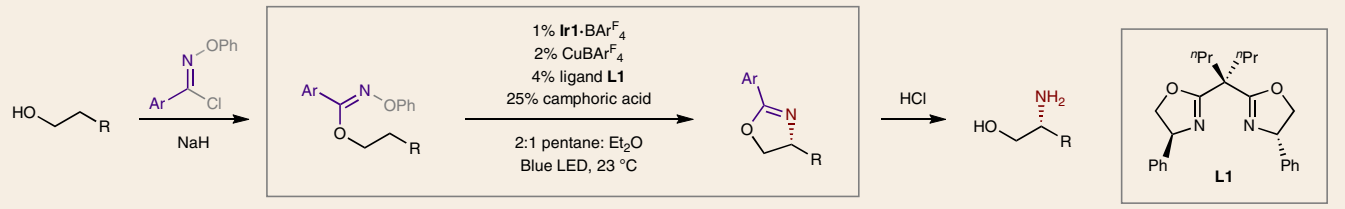
31, 50%, 79% e.e.

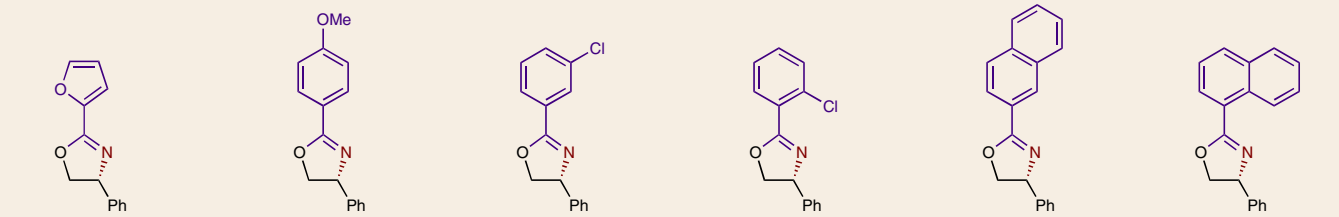
Conditions: 1% Ir{[dF(CF$_3$)ppy]$_2$dtbbpy}BAr$^F_4$, 2% CuBAr$^F_4$, 4% ligand **L1**, 25% camphoric acid and pentane:Et$_2$O (2:1) under blue LED irradiation at room temperature for 1h. See general procedure 3 in Supplementary Information section II for full experimental details. Isolated yield and e.e. values are indicated below each entry.

tion efficiency under ultraviolet irradiation (for example, naphthalene and xanthone; see Supplementary Information section VIII 'Mechanistic experiments'). Additionally, chiral ligand **L1** impacted both the reaction efficiency and selectivity (20% yield and 0% e.e. in its absence), and the BAr$^F_4$ counterion improved stereocontrol (83–94% e.e.)[41]. Finally, the acid co-catalyst played a pivotal role in controlling efficiency and selectivity. For example, acetic acid notably improved the yield relative to the absence of acid or the use of strong acids, whose anions were poorly coordinating (75% versus 16% yield). Notably, bulkier acids (for example, adamantyl or camphoric) afforded optimal efficiency (84–95% yield) and stereocontrol (92–94% e.e.). Together, these data indicate that a bulky—albeit not necessarily chiral—acid is required, probably to stabilize the higher oxidation state of Cu intermediates.

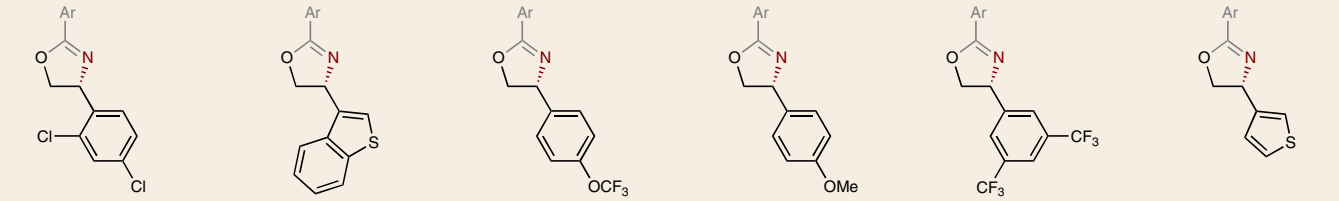
Synthetic scope. To probe the synthetic utility of this enantioselective β-C–H amination, we subjected a range of sterically and electronically diverse alcohols to this catalytic, radical relay sequence. As illustrated in Table 1, the HAT mechanism was robust and furnished β-amino variants of a wide range of *para*-substituted 2-aryl ethanols (**1**–**9**)—spanning Hammett σ_p constants of –0.3 (OMe) to +0.5 (CF$_3$)—with little effect on efficiency or selectivity (70–98%; up to 95% e.e.). Intrigued by the potential medicinal value of these

Table 2 | Synthetic scope and effect of chaperone in enantioselective, radical C–H amination





32, 56%, 97% e.e. | **33**, 75%, 94% e.e. | **34**, 99%, 93% e.e. | **35**, 49%, 98% e.e. | **36**, 64%, 94% e.e. | **37**, 80%, 97% e.e. versus **1**, 80%, 94% e.e.



Np: **38**, 64%, 99% e.e.
Ph: **14**, 88%, 98% e.e.

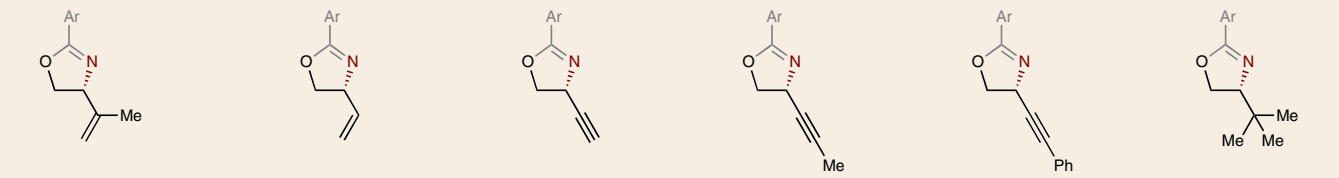
Np: **39**, 85%, 99% e.e.
Ph: **22**, 92%, 95% e.e.

Np: **40**, 77%, 97% e.e.
Ph: **9**, 94%, 92% e.e.

Np: **41**, 82%, 88% e.e.
Ph: **7**, 80%, 84% e.e.

Np: **42**, 65%, 97% e.e.
Ph: **17**, 79%, 80% e.e.

Np: **43**, 78%, 93% e.e.
Ph: **21**, 83%, 90% e.e.



Np: **44**, 82%, 94% e.e.
Ph: **23**, 82%, 94% e.e.

Np: **45**, 91%, 87% e.e.
Ph: **24**, 80%, 83% e.e.

Np: **46**, 87%, 91% e.e.
Ph: **25**, 99%, 89% e.e.

Np: **47**, 92%, 84% e.e.
Ph: **26**, 96%, 83% e.e.

Np: **48**, 96%, 90% e.e.
Ph: **27**, 89%, 83% e.e.

Np: **49**, 30%, 91% e.e.
Ph: **30**, 86%, 88% e.e.

Conditions: 1% Ir{[dF(CF$_3$)ppy]$_2$dtbbpy}BAr$^F_4$, 2% CuBAr$^F_4$, 4% ligand **L1**, 25% camphoric acid and pentane:Et$_2$O (2:1) under blue LED irradiation at room temperature for 1h. See general procedure 3 in Supplementary Information section II for full experimental details. Isolated yield and e.e. values are indicated below each entry. 1-naphthyl afforded improved enantioselectivity in many cases.
Np, 1-naphthyl; Ph, phenyl; Ar, aryl.

β-amino alcohols (for example, **7** is an isomeric analogue of the neurotransmitter octopamine, wherein the N and O atoms of the β-amino alcohol are inverted), we then explored various *ortho* and *meta* substitutions (**10**–**13**) as well as disubstituted arenes (**14**–**17**), which were also smoothly aminated. Similarly, alcohols containing polyaromatics (**18** and **19**) and heteroarenes (**20**–**22**) afforded β-C–H amination with high enantioselectivity.

Having established robust reactivity for benzylic C–H amination, we next probed this strategy for alcohols with stronger allylic, propargylic and aliphatic C–H bonds. In the allylic case, a more sterically encumbered 1,1-disubstituted alkene afforded greater enantioselectivity than a simple vinyl substituent (**23** (94% e.e.) versus **24** (83% e.e.)), although both were similarly efficient (80–82% yield). To our surprise, the smaller *sp*-hybridized substituent of propargylic alcohols also afforded β-C–H amination with high selectivity (**25**–**27**; 83–89% e.e.). The observation that the smallest ethynyl substituent afforded the greatest efficiency and selectivity among the trio suggests that these alkynes may interact with the Cu catalyst in an additional manner. With hopes of removing all such possible coordination from the substrate, we then probed a series of aliphatic alcohols bearing β-methylene units. Notably, simple 2-alkyl ethanols with large β-substituents afforded enantioselectivities as high as the 2-aryl ethanols (**28**–**30**; up to 94% e.e.), suggesting that the role of the aryl group is merely to act as a sterically repulsive, catalyst-recognition element. When the β-substituent size was decreased (for example, to an *i*Pr group), the stereoselectivity dropped (**31**; 79% e.e.), yet complete β-C–H regioselectivity remained intact as the kinetically favoured 1,5-HAT mechanism outcompeted 1,6-HAT of the weaker γ-tertiary C–H (Δ: 2 kcal mol^{-1})[34].

Having investigated the alcohol scope exclusively using simple benzimidate chaperones (derived from benzoyl chloride), we were interested in exploring the synthetic robustness of this β-C–H amination in accessing other chiral oxazolines. To this end, a variety of aryl imidates were prepared and subjected to the multi-catalytic sequence, as shown in Table 2. Interestingly, a smaller 3-furanyl substituent afforded unexpectedly high selectivity (**32**; 97% e.e.). Other arenes with stereoelectronically diverse substitution also afforded highly enantioenriched oxazolines (**33**–**35**; 93–98% e.e.), albeit with varying efficiency (49–99%). To our delight, we observed that a 1-naphthyl substituent (**37**) afforded similar efficiency to the Ph-imidate (80% in both cases), as well as boosting stereoselectivity (97% e.e. (versus 94% e.e. for **1**). To further investigate this effect, we

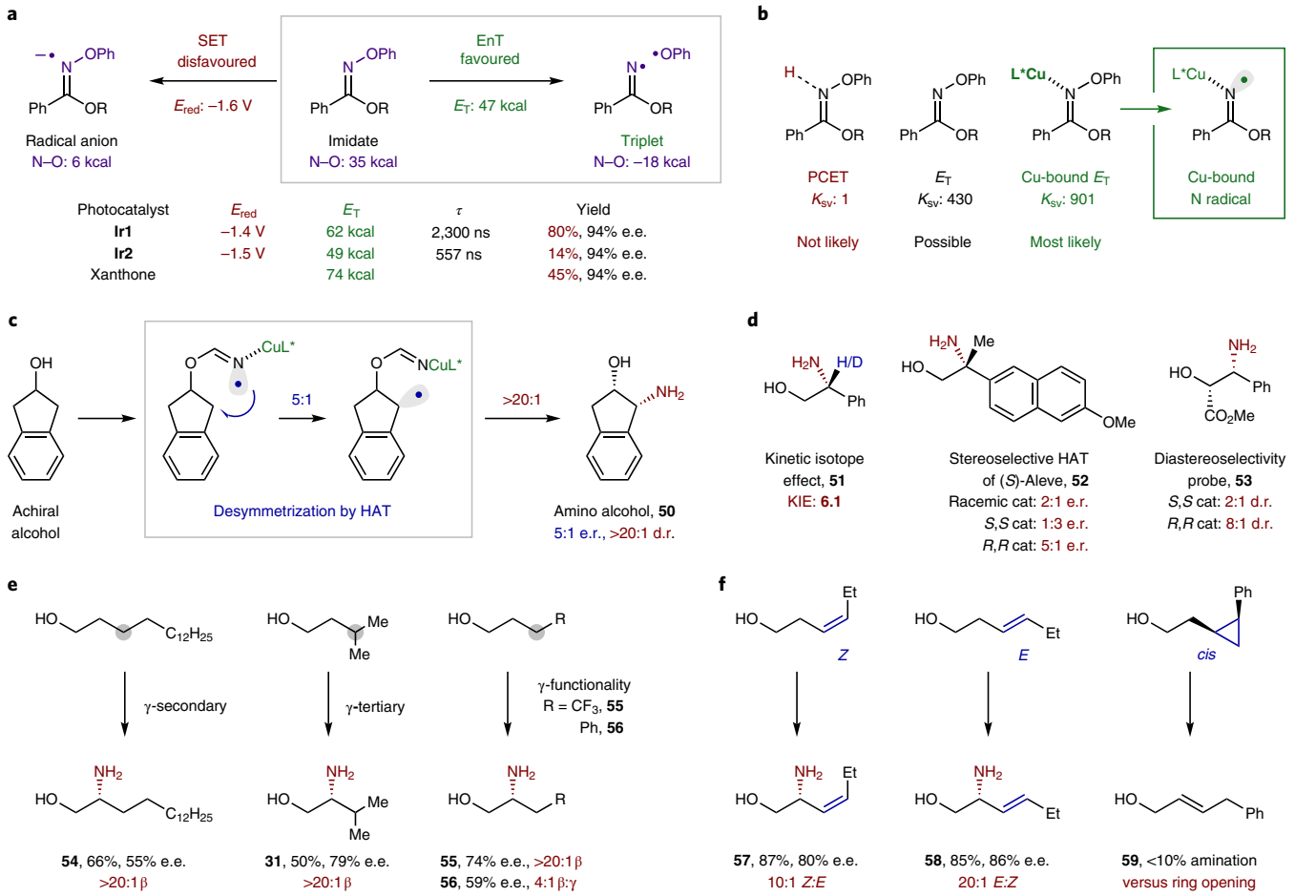


Fig. 2 | Mechanistic experiments. a, An energy transfer (EnT) pathway (versus single-electron transfer (SET)) is supported by cyclic voltammetry and density functional theory data. Specifically, a less reducing photocatalyst (**Ir1** versus **Ir2**) provides greater efficiency due to a higher triplet energy (E_T) and longer-lived excited state (τ). The triplet sensitizer xanthone also affords reactivity, indicating that the imidate triplet, which is computed to have a greatly weakened N–O bond, is the source of the N-centred radical. E_{red}, reduction potential. **b**, Photo-quenching experiments illustrate the favourability of Cu catalyst coordination during the triplet sensitization and subsequent N radical generation. **c**, Desymmetrization of a secondary alcohol demonstrates the ability of this Cu-bound N radical to discriminate among H atoms by enantioselective HAT (5:1 e.r.). High diastereoselectivity (>20:1 d.r.) illuminates the role of Cu radical trapping in further upgrading the high enantioselectivity observed for primary alcohols. **d**, A large KIE indicates HAT is the product-determining step. Stereoselectivity of the HAT was further probed with two chiral alcohols. Selectivity and efficiency are highly catalyst-dependent for both (*S*)-Aleve, which contains a β-stereocentre, as well as an enantioenriched secondary alcohol. cat, catalyst. **e**, A highly regioselective 1,5-HAT (>20:1 β) outcompetes 1,6-HAT even when much weaker γ-C–H bonds are present. r.r., regioisomeric ratio. **f**, Radical clocks indicate that radical trapping by Cu is more rapid than allyl radical isomerization, but slower than cyclopropyl ring opening.

probed the naphthyl imidates of a variety of alcohols from Table 1. In several cases, we observed near-complete enantiocontrol (**38**–**39**; 99% e.e.), with the improvement in enantioselectivity ranging from modest (**38**; Δ: 1% e.e.) to large (**42**; Δ: 17% e.e.). This effect was recapitulated for the vinyl-, alkynyl- and alkyl-substituted alcohols (**44**–**49**), which were boosted to >90% e.e. in many cases.

Mechanistic investigations. The rationale for the proposed mechanism illustrated in Fig. 1c is provided by a combination of data from cyclic voltammetry, as well as computational, photo-quenching, isotopic labelling, competition, desymmetrization and radical clock experiments, as shown in Fig. 2. Probing the role of the photocatalyst in radical initiation (Fig. 2a), we noted that a more strongly reducing Ir complex **Ir2** (−1.5 V; see Supplementary Information section VIII 'Mechanistic experiments' for details) was less efficient than a less reducing catalyst **Ir1** (−1.4 V) (14% versus 80% yield), which was surprising, given that the oxime imidate reduction potential is −1.6 V (all potentials versus the saturated calomel electrode)[36]. Yet, the more efficient complex (**Ir1**) has a notably higher triplet energy (62 versus 49 kcal mol^{-1}) and longer-lived excited state (2,300 versus 557 ns)[42], suggesting that energy transfer is more likely to be operative than an electron transfer pathway. Importantly, catalyst counterion effects (BAr^F_4 > PF_6 > OTf)—on both yield and enantioselectivity—were also observed, probably due to increased triplet energies or lifetimes, which may facilitate more efficient energy transfer[41]. Concerning the proposed mechanism of radical formation, photoinduced oxidative addition into the N–O bond of the oxime imidate was probably a result of its bond weakening. For example, upon catalytic triplet sensitization, the N–O bond of the triplet state was notably weaker than the ground state (−18 versus 35 kcal mol^{-1}), facilitating N–O scission (see Supplementary Information section IX 'Computational studies' for details).

The interaction of the excited Ir catalyst with the imidate was further investigated through Stern–Volmer quenching experiments (Fig. 2b). Since an acid co-catalyst was pivotal in obtaining high efficiency and selectivity (see Fig. 1d), a proton-coupled electron

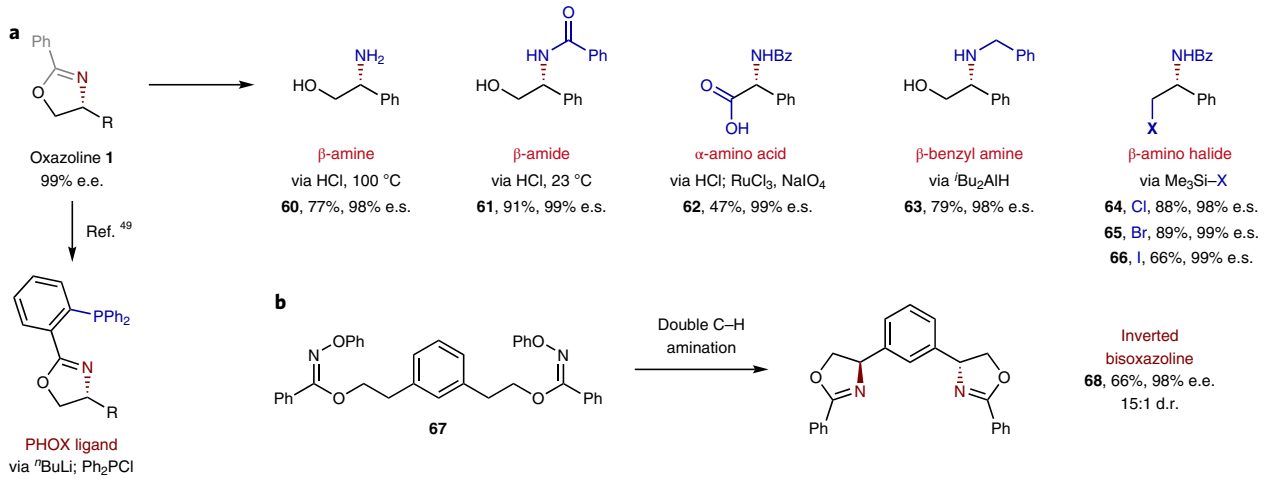


Fig. 3 | Synthetic applications. a, The enantioenriched oxazoline intermediate is rapidly converted to a family of valuable chiral products, including amino acids and β-amines, by acidic hydrolysis, oxidation, reduction or halide substitution. Reagents, yield and e.s. values are provided below each example (see Supplementary Information section VII 'Post-functionalization of oxazolines' for full details). Alternatively, directed lithiation and phosphinylation may afford access to phosphinooxazoline (PHOX) ligands[49]. **b**, Double C–H amination of a diol affords a new class of chiral catalysts.

transfer mechanism was first considered[18]. However, addition of acid to the imidate decreased quenching (K_{SV}: 1 versus 430), discounting the involvement of the Brønsted acid in radical generation. In contrast, addition of the copper catalyst increased quenching (K_{SV}: 901 versus 430), suggesting that the Cu-coordinated imidate is the most likely acceptor of triplet energy from the excited Ir photocatalyst. This Cu-bound energy transfer mechanism also explains the proximity of chiral information at the outset of radical generation to overcome racemic mechanisms, involving either energy transfer[43] or Cu catalysis[44], as well as to mediate a stereoselective HAT pathway.

To test the hypothesis that a Cu-bound N-centred radical mediates enantioselective HAT, we subjected an achiral secondary alcohol to the C–H amination (Fig. 2c). Given the likely irreversibility of the HAT, the observed desymmetrization (**50**; 5:1 e.r.) indicated that the coordinated chiral Cu is involved in promoting enantioselective HAT. The subsequent diastereoselectivity (>20:1 d.r.) illustrated the Cu catalyst's additional role in stereoselectively trapping this intermediate. The higher enantioselectivity observed for primary alcohols versus this secondary alcohol (see Tables 1 and 2) can be considered a result of these additive effects.

Further insight into the key HAT mechanism (Fig. 2d) was provided by a strong, primary kinetic isotope effect (KIE) observed in the intramolecular H/D competition (**51**; KIE: 6.1), which indicated that HAT is the product-determining step. To further test the likelihood of a stereoselective HAT, an enantiopure β-chiral alcohol derived from the non-steroidal anti-inflammatory drug (*S*)-Aleve was converted to β-amine **52**. A pronounced catalyst match/mismatch scenario was observed wherein the *S*,*S* catalyst afforded 1:3 e.r. while the *R*,*R* catalyst afforded 5:1 e.r., and the racemic catalyst afforded 2:1 e.r.—all with varying levels of efficiency (*R*,*R* > rac > *S*,*S*), indicating stereocontrol of both HAT and subsequent alkyl radical trapping. Likewise, subjecting an enantioenriched secondary alcohol as a diastereoselectivity probe, **53**, afforded between 2:1 d.r. (*S*,*S* catalyst) and 8:1 d.r. (*R*,*R* catalyst).

To probe the regioselectivity of the intramolecular HAT, several classes of alcohols were subjected to this amination (Fig. 2e). Notably, *n*-hexadecanol afforded a single β-aminated regioisomer (**54**) resulting from exclusive 1,5-HAT. Additionally, α-amination was not observed in any case, indicating that 1,5-HAT is highly favoured over 1,4-HAT despite an 8 kcal mol^{-1} weaker α-oxy C–H bond. To elucidate 1,5- versus 1,6-HAT regioselectivity, sterically and electronically diverse γ substituents—including those with weaker γ-C–H bonds—were investigated. However, β-selectivity (via 1,5-HAT) was exclusively observed (>20:1) for both γ-tertiary (**31**) and γ-CF_3 substituents (**55**). Even in the case of a 10 kcal mol^{-1} weaker γ-benzyl C–H bond, 4:1 β:γ regioselective amination was observed (**56**).

Since stereoselective C–H amination by HAT is much rarer than nitrene insertion, we wished to investigate whether these metal-bound nitrogen radicals behave more like radicals or nitrenes. If the former case were operative, we envisioned that a radical pathway could allow for catalyst stereocontrol over two steps (both HAT and alkyl radical trapping), rather than a single, C–H insertion step as in nitrene reactivity. Thus, a homoallylic alcohol was subjected to the amination (Fig. 2f). Interestingly, this probe exclusively afforded C–H amination (**57**–**58**; >85% yield; >80% e.e.) without any aziridination, as is sometimes observed in nitrene mechanisms[10,11,45]. Interestingly, a *Z*-alkene was tolerated, and only slightly isomerized (**57**; 10:1 *Z* from 20:1 *Z* starting material) despite a low inversion barrier for the allyl radical intermediate (15.7 kcal mol^{-1})[46], indicating that radical trapping by the Cu catalyst was rapid. As a control, an *E*-alkene completely retained its configuration (**58**; 20:1 *E*). As further evidence of a radical-mediated HAT mechanism, a β-cyclopropyl ring predominantly underwent ring opening or reduction (**59**), rather than C–H amination, unlike with Rh-nitrenes[11]. Combining these observations, we conclude that alkyl radical trapping by the Cu catalyst probably occurs at a rate between 10^8 s^{-1} (*t*Bu radical isomerization)[35] and 10^{11} s^{-1} (cyclopropyl ring opening)[47], which is rapid enough to retain (and enhance) chiral memory via diastereoselective catalyst coordination[38,48]. The large KIE (6.1) also contrasts with those observed for concerted C–H insertion by an Ir-nitrene (KIE: 1.5)[9]. Lastly, unlike nitrene-based methods that require azides or heterocyclic nitrene precursors[10–15], this Cu-catalysed radical relay strategy has the synthetic benefit of enabling C–H amination of ubiquitous alcohols via their readily available imidates.

Diversification of chiral products. Finally, the synthetic utility of this enantioselective β-C–H amination for accessing medicinally relevant motifs is illustrated in Fig. 3 via derivatization of oxazoline **1**. For example, subjecting **1** to HCl at 100 °C afforded free β-amino alcohol **60**, while hydrolysis with HCl at 23 °C afforded

β-benzamide **61**. This amide may then be oxidized by $RuCl_3/NaIO_4$ to α-amino acid **62**. Conversely, instead of an acidic work-up, double reduction by $^{i}Bu_2AlH$ at 0 °C yielded Bn-protected β-amine **63**, and C–O displacement by silyl halides ($Me_3Si–X$) afforded vicinal benzamide halides (**64**–**66**). Importantly, in each of these oxazoline derivatizations, the stereocentre was retained with greater than 98% e.s. Lastly, applying this method to streamlined access of privileged catalyst architectures, oxazoline may be selectively deprotonated with ^{n}BuLi, then quenched with Ph_2PCl, to afford phosphinooxazoline ligand[49]. Alternatively, the *bis*-imidate **67** of a *meta*-diol was converted to inverted bisoxazoline **68** (66% yield; 98% e.e.; 15:1 d.r.), providing rapid access to a new C_2 symmetric ligand class.

Conclusions

In summary, we expect that this enantio- and regioselective, radical β-C–H amination will streamline the synthesis of important molecules with the chiral, vicinal amino alcohol motif. Notably, this approach bypasses the use of chiral auxiliaries (imines) and chiral pool precursors (amino acids) and enables the enantioselective synthesis of several new β-amino alcohols. Moreover, this radical relay chaperone strategy will also enable the development of other classes of stereoselective C–H functionalization.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-020-0482-8.

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Methods

Enantioselective C–H amination. An oven-dried vial was charged with a stir bar, imidate (0.1 mmol) and (+)-camphoric acid (25 mol%). Catalyst solutions of **Ir1** (1 mol%), as well as $CuBAr^F_4$ (2 mol%) and **L1** (4 mol%) in Et_2O (see below for details) were added in a glove box. After dilution with pentane (4 ml), the vial was irradiated with a 455-nm blue LED for 1 h while cooling by fan. Upon completion, the reaction mixture was purified by column chromatography to afford the enantioenriched oxazoline. Further hydrolysis with HCl afforded the enantioenriched amino alcohol.

Preparation of catalyst solutions.
L1·CuBAr$^F_4$. A flame-dried flask was charged with a stir bar, $CuBAr^F_4$ (0.04 mmol) and **L1** (0.08 mmol) in a glove box. Et_2O (20 ml) was added and stirred at 23 °C for 1 h to afford a 0.002 M solution (1 ml was used in each experiment).

Ir1. A flame-dried flask was charged with **Ir{[dF(CF$_3$)ppy]$_2$dtbbpy}**BAr^F_4 photocatalyst (0.02 mmol) in a glove box. Et_2O (20 ml) was added to afford a 0.001 M solution (1 ml was used in each experiment).

Synthesis of imidate starting materials. A flame-dried flask was sequentially charged with a stir bar, alcohol (2 mmol), tetrahydrofuran (20 ml) and NaH (1.5 equiv.). After stirring for 1 h, imidoyl chloride (1.1 equiv.) was added and the resulting solution was further stirred. Upon complete consumption of alcohol, the reaction mixture was purified by column chromatography to afford the corresponding oxime imidate in 80–99% yields.

Data availability

The data that support the findings of this study are available within the article and its Supplementary Information files.

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Author contributions

K.M.N. designed and discovered the enantioselective C–H amination. K.M.N., E.A.W. and Z.Z. developed the optimized method. Z.Z. evaluated the synthetic scope. Z.Z. and L.M.S. performed the mechanistic experiments and derivatizations. A.D.C. performed the calculations. All authors contributed to writing the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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