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Metalloradical approach for concurrent control in intermolecular radical allylic C–H amination

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Although they offer great potentials, the high reactivity and diverse pathways of radical chemistry pose difficult problems for applications in organic synthesis. In addition to the differentiation of multiple competing pathways, the control of various selectivities in radical reactions presents both formidable challenges and great opportunities. To regulate chemoselectivity and regioselectivity, as well as diastereoselectivity and enantioselectivity, calls for the formulation of conceptually new approaches and fundamentally different governing principles. Here we show that Co(II)-based metalloradical catalysis enables the radical chemoselective intermolecular amination of allylic C–H bonds through the employment of modularly designed D_2-symmetric chiral amidoporphyrins with a tunable pocket-like environment as the supporting ligand. The reaction exhibits a remarkable convergence of regioselectivity, diastereoselectivity and enantioselectivity in a single catalytic operation. In addition to demonstrating the unique opportunities of metalloradical catalysis in controlling homolytic radical reactions, the Co(II)-catalysed convergent C–H amination offers a route to synthesize valuable chiral α-tertiary amines directly from an isomeric mixture of alkenes.

Allylic radicals are extensively explored as versatile intermediates for chemical synthesis[1,2]. As a textbook example, the Wohl–Ziegler reaction represents a classic process for the radical functionalization of allylic C–H bonds that involves delocalized allylic radicals as the key intermediates[3,4]. This type of radical process entails the activation of allylic C–H bonds by a radical initiator ($R_i^{\bullet}$) via hydrogen-atom abstraction (HAA) to generate allylic radical intermediates and a subsequent new bond formation via X-atom abstraction (XAA) from atom donor X–Y to deliver the functionalized product, as exemplified by the combination of the initial HAA and consecutive Br-atom abstraction in radical allylic C–H bromination[5,6]. This classic organic free radical pathway (HAA–XAA) for allylic radical C–H functionalization, however, faces the long-standing challenge of controlling the regioselectivity associated with both the HAA and XAA steps, which typically generates a regioisomeric mixture of products (Fig. 1a). Further challenges arise from additional selectivity issues, and include (1) control of the chemoselectivity of HAA over competing radical addition to C=C π bonds, (2) control of the (*E*)/(*Z*)-diastereoselectivity of the resulting C=C bonds and (3) control of the enantioselectivity of the newly generated stereogenic centres. To address these challenging issues calls for the formulation of conceptually new approaches and fundamentally different governing principles[7–9]. One potential solution to address the issue of multiselectivities is the introduction of α-metallorganic radicals $L_nM–X^{\bullet}$, a class of metal-stabilized organic radicals such as the α-metalloaminyl radicals $L_nM–N\dot{R}$ and α-metalloalkyl radicals $L_nM–\dot{C}R_2$, to replace free organic radicals $R_i^{\bullet}$ (Fig. 1b). In this metallorganic radical approach, the metal-supported organic radicals $L_nM–X^{\bullet}$, which are no longer 'free' because of a bonding interaction with the metal centre and steric protection by the supporting ligand, could potentially undergo chemoselective HAA from allylic C–H bonds with the possibility to

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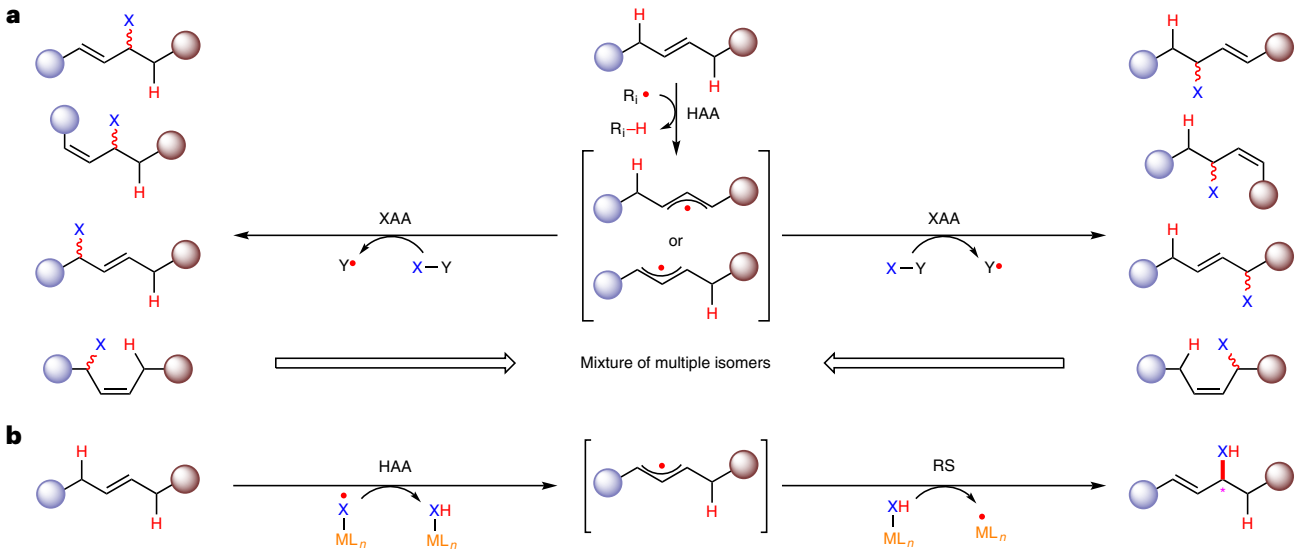

Fig. 1 | Radical pathways for direct functionalization of allylic C–H bonds: challenges, opportunities and solution. a, Organic free radical pathway involving HAA and XAA. This classic HAA–XAA pathway for allylic radical C–H functionalization faces the longstanding challenge to control multiple selectivities associated with both steps, which typically generate an isomeric mixture of products. **b**, Metallorganic radical pathway HAA–RS. This proposed HAA–RS pathway, which is based on the introduction of α-metallorganic radicals L_nM–X• to replace free organic radicals, may offer a potential solution to address the challenging issue of multiselectivities, and possibly form the product as a single enantiomer.

control the regioselectivity, and so lead to the selective formation of allylic radicals with the concomitant generation of L_nM–XH, such as metal amides L_nM–NHR and metal alkyls L_nM–CHR_2. Given that M–X (X = NR or CR_2) bonds are typically weaker than C–X bonds, it is feasible for the resulting allylic radicals and initially formed L_nM–XH to undergo a subsequent radical substitution (RS), which leads to an allylic C–H functionalization. This otherwise inherently difficult RS process would be further facilitated for the case in which a stable metalloradical $L_nM^{\bullet}$ is generated. In addition to the potential control of regioselectivity and (*E*)/(*Z*)-selectivity, this metallorganic radical pathway (HAA–RS) could be rendered as a catalytic process for allylic C–H functionalization with the possible control of diastereoselectivity and enantioselectivity, assuming that L_nM–X• could be catalytically generated from $L_nM^{\bullet}$.

Among considerable efforts to develop selective radical reactions[10–13], metalloradical catalysis (MRC) represents a fundamentally different approach by exploiting metalloradical complexes as open-shell catalysts for the catalytic generation of metal-stabilized organic radicals as key intermediates to control the reactivity and selectivity of radical processes[14–20]. In this respect, Co(II) complexes of porphyrins as stable 15e-metalloradicals have been demonstrated as a type of open-shell catalyst that can homolytically activate organic azides to generate α-Co(III)-aminyl radicals as key intermediates for catalytic reactions that involve nitrogen-centred radicals[21]. With the support of modularly designed D_2-symmetric chiral amidoporphyrins as a versatile ligand platform, Co(II)-based MRC was recently applied to develop an enantioselective radical process for the intermolecular benzylic C–H amination of carboxylic esters with organic azides[22]. Given the importance of chiral allylic amines in stereoselective organic synthesis[23], we were attracted by the possibility to develop a catalytic radical process for asymmetric intermolecular amination of allylic C–H bonds via a Co(II)-based metalloradical catalyst that involves the aforementioned HAA–RS pathway (Fig. 1b). Specifically, we envisioned a catalytic pathway for the allylic C–H amination of trisubstituted alkene **2** with organic azide **1** by Co(II)-metalloradical catalysts to selectively produce chiral α-tertiary allylic amines **3** that consist of the initial metalloradical activation of azide **1** to generate α-Co(III)-aminyl radical **I**, subsequent HAA from the allylic C–H bonds of alkene **2** by radical intermediate **I** and final RS of Co(III)–amido complex ^{b}**II** by allylic radical ^{a}**II** in the resulting ∞-Co(III)-alkyl radical intermediate **II** (Fig. 2a). In addition to inherent issues related to intermolecular radical processes[22], this proposed catalytic process presented extra challenges associated with the concurrent control of multiple selectivities. First, it would involve the issue of controlling chemoselectivity between the desired amination of allylic C–H bonds and the competitive aziridination of the C=C bonds[24]. Additionally, the control of regioselectivity would be implicated in the RS step between the secondary and tertiary allylic sites of the delocalized allylic radical ^{a}**II**. Furthermore, a concern would be the issue of (*E*)/(*Z*)-selectivity during the formation of the new alkene in the product, especially for the case of allylic C–H amination of multisubstituted alkenes. Finally, what elements could be exploited to control the enantioselectivity as well as the regioselectivity of the final RS step for C–N bond formation? Inspired by our recent success in the development of an intermolecular reaction for an enantioselective benzylic C–H amination[22], we hoped to address these and related issues through the discovery of a tailored Co(II)-metalloradical catalyst by fine-tuning the steric, electronic and chiral environment of a D_2-symmetric chiral amidoporphyrin ligand. The key strategy would be to utilize a network of non-covalent weak interactions as attractive but reversible forces to bind, position and orient the substrates and subsequent intermediates inside the pocket of the ligand environment for a concurrent control of the multiple selectivities. These challenges aside, the proposed stepwise radical mechanism could offer a unique opportunity to achieve allylic C–H amination by directly employing a mixture of allylic isomers, such as constitutional, (*E*)/(*Z*) and enantiomeric isomers, as starting materials as they would all converge to the same intermediate of the delocalized allylic radical ^{a}**II** after HAA (Fig. 2b). In addition to the appealing fundamental challenge, this type of substrate convergence could have attractive practical consequences as the preparation of the allylic substrates, especially those with multisubstituents, in an isomeric pure form is often difficult if not impossible. If the aforementioned challenges could be successfully addressed through catalyst development, this unique opportunity might be harnessed and lead to the creation of a radical process for allylic C–H amination that enables highly convergent syntheses of valuable chiral α-tertiary allylic amines in a single enantiomeric form from an isomeric mixture of alkenes.

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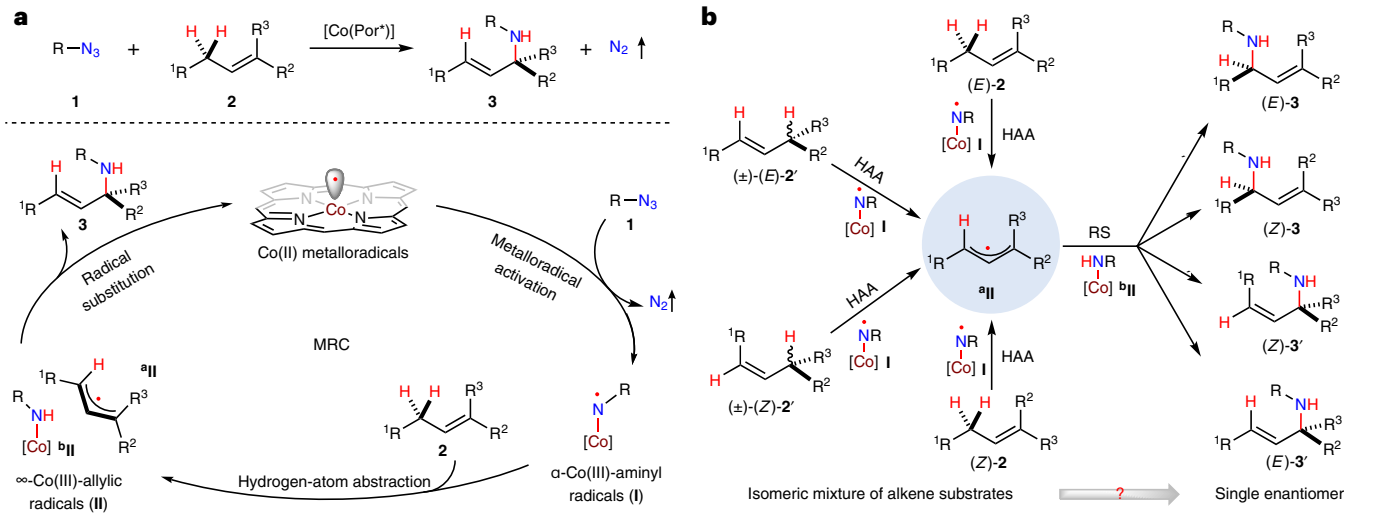

Fig. 2 | Convergent radical amination of allylic C–H bonds with organic azides via Co(II)-based MRC. a, Targeted catalytic reaction for allylic C–H amination of trisubstituted alkenes **2** with organic azides **1** to produce chiral α-tertiary allylic amines **3**. The proposed mechanism consists of an initial metalloradical activation of azide **1** by a Co(II) metalloradical catalyst to generate α-Co(III)-aminyl radical **I**, subsequent HAA from the allylic C–H bonds of alkene **2** by radical intermediate **I** and final RS of the Co(III)–amido complex ^{b}**II** by allylic radical ^{a}**II** in the resulting ∞-Co(III)-alkyl radical **II**. **b**, Proposed concurrent convergence of multiselectivities. The proposed mechanism via a Co(II)-based MRC could offer an opportunity to achieve allylic C–H amination by directly employing a mixture of allylic isomers, such as constitutional, (*E*)/(*Z*) and enantiomeric isomers, as starting materials as they would all converge to the same allylic radical intermediate ^{a}**II** after HAA. Por, porphyrin.

Catalytic intermolecular amination of allylic C–H bonds represents an attractive approach for the stereoselective synthesis of chiral allylic amines[25]. Existing examples include catalytic amination systems that involve *π*-allyl metal complexes for nucleophilic attack with amines[26–31], metallonitrenes for C–H insertion[32–36], heteroene reactions followed by rearrangement[37–40], photocatalytic methods[41,42] and electrochemical methods[43]. Although they represent significant advances, these existing catalytic systems experience issues such as alkene transposition, competing aziridination or lack of control in regioselectivity and enantioselectivity. Two important exceptions are the Ru-based catalytic system by Katsuki and co-workers for symmetric allylic amination via nitrene C–H insertion[32] and the two-step heteroene–rearrangement protocol of Tambar and co-workers for asymmetric allylic amination with the concurrent control of regioselectivity and (*E*)/(*Z*)-selectivity[39,40]. Given that neutral radicals typically react under mild conditions at a fast rate and with a high degree of tolerance towards the electronic properties of substrates, allylic C–H amination systems that involve radical intermediates are expected to enjoy a higher reactivity and broader substrate scope in comparison with those of the existing ionic systems. Guided by the mechanistic principles of Co(II)-based MRC, we here report a catalytic radical system for intermolecular allylic C–H amination with organic azides that enables the effective control of multiple selectivities. Specifically, we describe the development of a Co(II)-based metalloradical system that can activate fluoroaryl azides for the chemoselective amination of allylic C–H bonds with a concurrent convergence of regioselectivity, (*E*)/(*Z*)-selectivity and enantioselectivity. Among the practical attributes, the Co(II)-catalysed allylic C–H amination can directly use an isomeric mixture of alkenes for the stereoselective synthesis of chiral α-tertiary allylic amines, which have been showcased as valuable intermediates for different synthetic applications. At a fundamental level, we demonstrate the principle of incorporating non-covalent attractive interactions in ligand design to address various selectivity issues in catalytic radical reactions.

Results and discussion

At the onset of this study, we selected the allylic C–H amination of trisubstituted olefin (*E*)-**2a** with aryl azide **1a** as the model reaction by using different Co(II)-metalloradical catalysts to test the proposed radical amination via Co(II)-MRC (Table 1). When the simple metalloradical catalyst [Co(**P1**)] (**P1** = tetraphenylporphyrin) was used (Table 1, entry 1), it was found that the catalytic amination reaction of (*E*)-**2a** with azide **1a** resulted in a mixture of four products: α-tertiary amine (*E*)-**3aa** in a 22% yield, α-secondary amine (*E*)-**4aa** in a 47% yield, α-secondary amine (*Z*)-**4aa** in an 8% yield and imine **5aa** in a 10% yield. In striking contrast, the use of first-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = ChenPhyrin) gave rise to α-tertiary amine (*E*)-**3aa** as the only product in a near qualitative yield (99%) with a high enantioselectivity (82% e.e.) (Table 1, entry 2). The dramatic difference in product distribution between the catalytic reactions by [Co(**P1**)] and [Co(**P2**)] is attributed to the presence of multiple hydrogen bonding and other non-covalent attractive interactions between the cyclopropanecarboxyamide units in [Co(**P2**)] and the substrates that cooperatively stabilize and orientate the Co(III)–amido complex ^{b}**II** and allylic radical ^{a}**II** in the resulting ∞-Co(III)-alkyl radical intermediate **II** towards the desired C–N bond formation via RS. Surprisingly, second-generation chiral metalloradical catalyst [Co(**P3**)] (**P3** = 2,6-DiPhS-QingPhyrin), previously shown to be the optimal catalyst for benzylic C–H amination[22], was found to be completely ineffective in catalysing the reaction, presumably due to the steric hindrance of the catalyst (Table 1, entry 3). Like the catalytic reaction of (*E*)-**2a**, the same notable ligand effect on the reactivity and product selectivity was also observed in the Co(II)-catalysed allylic C–H amination reactions of (*Z*)-**2a** (Table 1, entries 4–6) as well as (±)-(*E*)-**2a′** (Table 1, entries 7–9) with azide **1a**. These results suggest that the RS should be both the regio- and enantiodetermining step in this metalloradical-catalysed allylic C–H amination. The fact that the catalytic reactions of (*E*)-**2a**, (*Z*)-**2a** and (±)-(*E*)-**2a′** with azide **1a** and [Co(**P2**)] all led to the exclusive formation of α-tertiary amine (*E*)-**3aa** in excellent yields with high enantioselectivities pointed to the feasibility of using a mixture of olefin isomers **2a** as the starting materials for a catalytic allylic C–H amination. In addition to revealing the fundamental principles and unique features of MRC, this type of convergence could have practical significance as the preparation of multisubstituted alkenes in an isomeric pure form is often difficult if not impossible. Indeed, when a mixture of olefin isomers (*E*)-**2a**, (*Z*)-**2a** and (±)-(*E*)-**2a′**, which

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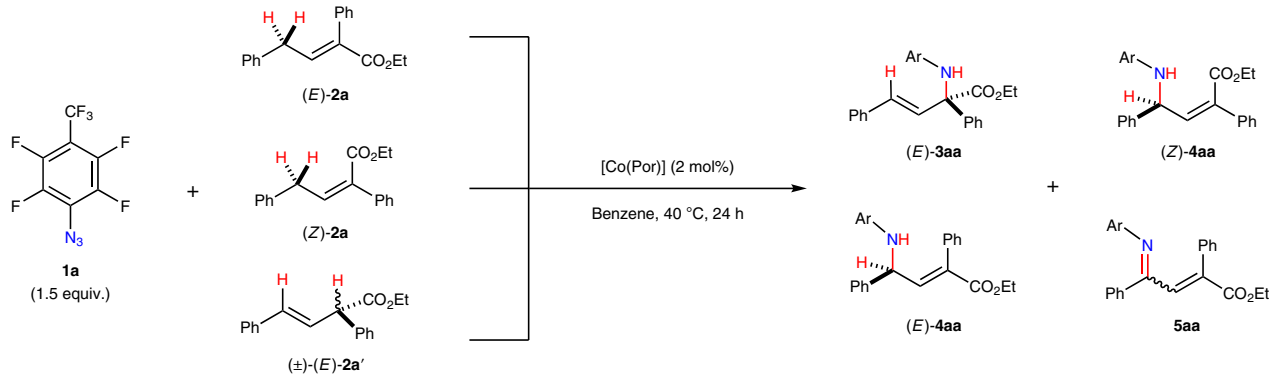
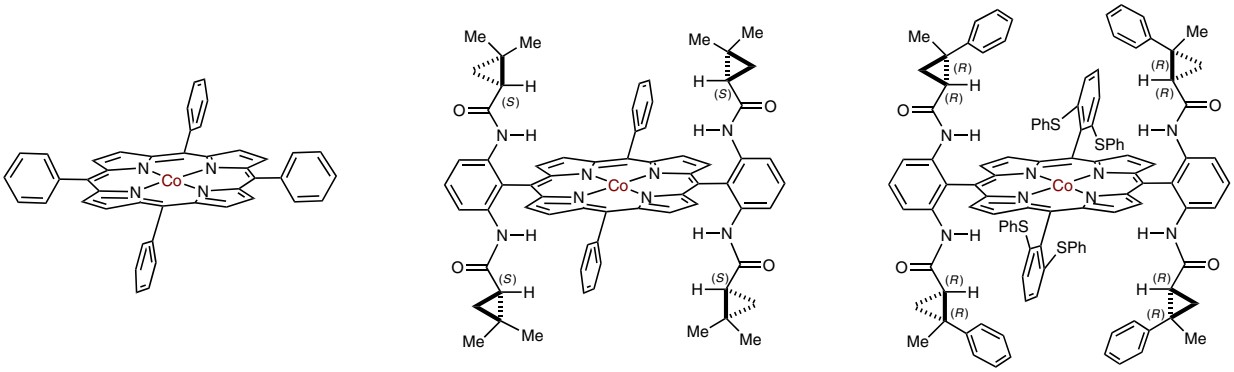
Table 1 | Ligand effect on the Co(II)-based catalytic system for convergent allylic C–H amination of trisubstituted olefin 2a with aryl azide 1a



Entry	Substrate	Catalyst	Conversion (%)	Yield (%) (*E*)-**3aa**	Yield (%) (*E*)-**4aa**	Yield (%) (*Z*)-**4aa**	Yield (%) 5**aa**	e.e. (%) (*E*)-**3aa**
1	(*E*)-**2a**	[Co(**P1**)]	99	22	47	8	10	–
2	(*E*)-**2a**	[Co(**P2**)]	99	99	0	0	0	82
3	(*E*)-**2a**	[Co(**P3**)]	0	0	0	0	0	–
4	(*Z*)-**2a**	[Co(**P1**)]	99	22	46	4	16	–
5	(*Z*)-**2a**	[Co(**P2**)]	99	99	0	0	0	82
6	(*Z*)-**2a**	[Co(**P3**)]	0	0	0	0	0	–
7	(±)-(*E*)-**2a**′	[Co(**P1**)]	99	24	43	9	16	–
8	(±)-(*E*)-**2a**′	[Co(**P2**)]	99	99	0	0	0	82
9	(±)-(*E*)-**2a**′	[Co(**P3**)]	0	0	0	0	0	–



[Co(**P1**)] [Co(**P2**)] [Co(**P3**)]

See Supplementary Section 4 for experimental details. Conversions and yields based on ^{1}H NMR analysis of the crude reaction mixture. e.e. determined by chiral HPLC.

were readily prepared by the Horner–Wadsworth–Emmons reaction, were directly used as the substrate for [Co(**P2**)]-catalysed amination with azide **1a**, it gave the desired α-tertiary amine (*E*)-**3aa** in 99% yield with 82% e.e. (Table 2), which demonstrates a concurrent control of multiple convergences and selectivities in the catalytic process. As in the case of [Co(**P2**)], the catalytic reactions by other metalloradical catalysts ([Co(**P4**)], [Co(**P5**)], [Co(**P6**)] and [Co(**P7**)], Co(II) complexes of D_2-symmetric chiral amidoporphyrins with varied steric, electronic and chiral environments, all gave α-tertiary amine (*E*)-**3aa** as the only product but in varied yields and with different enantioselectivities. Together, these results indicate a predominant role of the chiral cyclopropanecarboxyamide units in the control of the regioselectivity. After systematic evaluation of the reaction parameters (see Supplementary Table 1 for details), α-tertiary allylic amine (*E*)-**3aa** could be produced in an 82% isolated yield with 92% e.e. directly from the mixture of the olefin isomers when the reaction was performed in fluorobenzene at 4 °C using 4 mol% [Co(**P2**)] as the catalyst.

Under the optimized conditions, the substrate scope of [Co(**P2**)]-catalysed convergent allylic C–H amination was evaluated by employing different alkenes **2** with azide **1a** as the representative nitrogen source (Table 3). As demonstrated for alkene **2a**, all alkenes **2** were directly used as substrates in a mixture of isomers, (*E*)-**2**, (*Z*)-**2** and (±)-(*E*)-**2′**, except substrates (*E*)-**2l**, (*E*)-**2m** and (*E*)-**2o**, which were prepared in an isomerically pure form. As for alkene **2a**, the derivatives bearing substituents with varied electronic properties at the aryl group, such as –OMe, –OCF_3, –F and –Cl, were suitable for the Co(II)-based catalytic process to afford the corresponding α-tertiary amino acid esters **3aa**–**3af** in high yields with excellent enantioselectivities. It is worth mentioning that the catalytic amination process could be readily scaled up, as demonstrated by the synthesis of α-tertiary amine acid ester **3aa** in an 83% yield with a 91% e.e. on a 2.0 mmol scale. Additionally, this convergent allylic amination system with [Co(**P2**)] was shown to tolerate heterocyclic functionalities, as exemplified by the highly asymmetric synthesis of α-tertiary amino acid esters that

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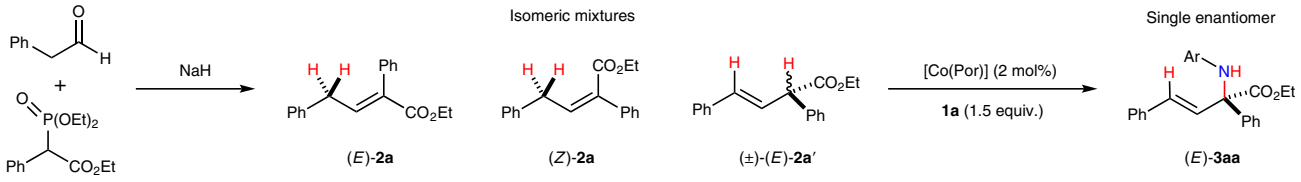
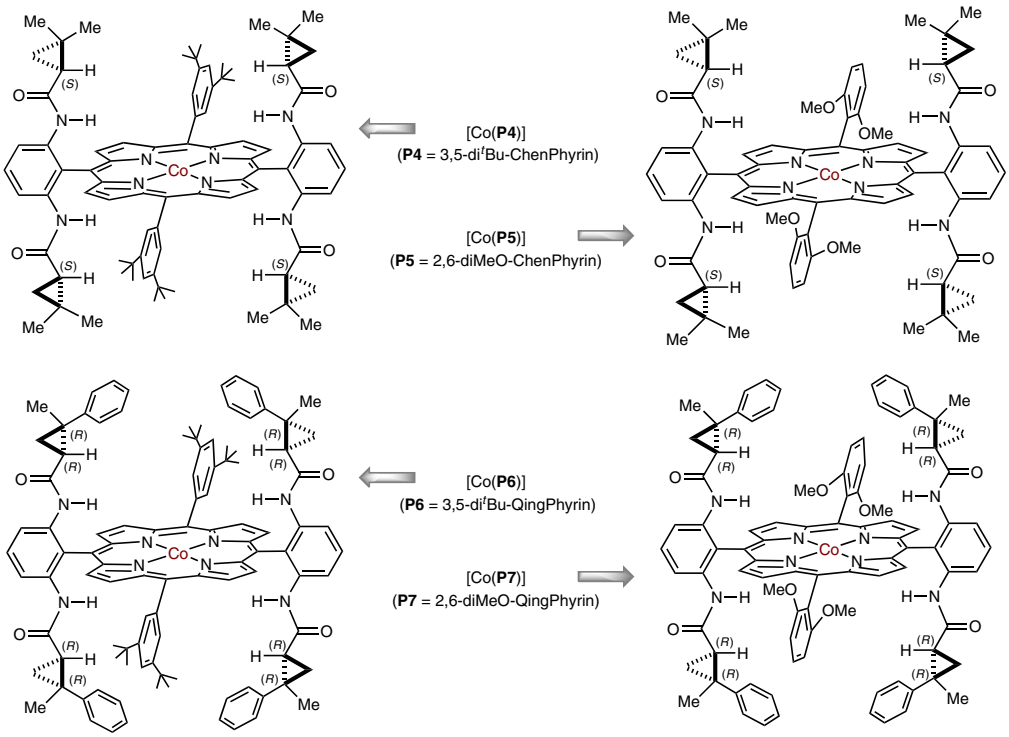
Table 2 | Ligand effect on a Co(II)-based catalytic system for convergent allylic C–H amination of olefin 2a as an isomeric mixture with aryl azide 1a





Exclusive regioselectivity	
Catalyst	(*E*)-**3aa**
[Co(**P2**)]	99% yield; 82% e.e.
[Co(**P4**)]	80% yield; 64% e.e.
[Co(**P5**)]	8% yield; 66% e.e.
[Co(**P6**)]	59% yield; 40% e.e.
[Co(**P7**)]	10% yield; 46% e.e.
[Co(**P2**)][a]	82% yield; 92% e.e.

See Supplementary Sections 4 and 5 for experimental details. [a]The reaction was carried out with **1a** (0.15 mmol) and **2a** (0.10 mmol) by [Co(**P2**)] (4 mol%) in fluorobenzene (0.5 ml) at 4 °C for 72 h in the presence of 4 Å molecular sieves. Isolated yields. See Supplementary Table 1 for details of the reaction condition optimizations.

contained indole (**3ag**), benzofuran (**3ah**), dihydrobenzofuran (**3ai**) and benzothiophene (**3aj**) moieties. In addition to the synthesis of **3ak** bearing the naphthyl group, this Co(II)-catalysed amination system could be further applied to synthesize α-tertiary amino acid esters that contained other extended aromatic units, such as the conjugated enyne (**3al**) and diene (**3am**) in moderate yields with high enantioselectivities. Besides ethyl esters, this catalytic system was also applicable for the productive formation of α-tertiary amino acid methyl ester **3an** and thioester **3ao**. Furthermore, chiral α-tertiary amino ketones, which included heteroaryl ketones, could also be synthesized through the Co(II)-based convergent allylic C–H amination, as shown with the asymmetric synthesis of **3ap**–**3ar** in moderate to excellent yields with high enantioselectivities. Other than chiral α-tertiary amino carbonyl compounds with an α-phenyl group, **3aa**–**3ar**, [Co(**P2**)] was also effective in catalysing the asymmetric synthesis of chiral α-tertiary amino carbonyl compounds with different α-aryl groups, such as **3as** and **3at**. However, the catalyst was found to insufficiently control enantioselectivity for the asymmetric synthesis of chiral α-tertiary amino carbonyl compounds with α-alkyl groups. For example, [Co(**P2**)] could catalyse the formation of α-tertiary amino acid esters **3au**–**3aw**, which bear –Me, –Et and –Bn groups, respectively, in good-to-high yields but with poor enantioselectivities. Intriguingly, the second-generation chiral metalloradical catalyst [Co(**P3**)], which was incapable of catalysing the formation of **3aa**, was found to be much superior for the asymmetric synthesis of **3au**–**3aw** with high enantioselectivities, albeit in relatively lower yields. The superiority of [Co(**P3**)] over [Co(**P2**)] for the asymmetric synthesis of chiral α-tertiary amino carbonyl compounds with α-alkyl substituents was further demonstrated for the productive construction of α-tertiary amines **3ax**–**3aaa** that contain cyclic ketones of varied ring sizes with high enantioselectivities.

We then investigated the scope of aryl azides for [Co(**P2**)]-catalysed convergent allylic C–H amination by using an isomeric mixture of alkenes, (*E*)-**2a**, (*Z*)-**2a** and (±)-(*E*)-**2a′**, as the standard substrate. In addition to the representative *para*-CF_3-substituted 2,3,5,6-tetrafluorophenyl azide (**1a**), analogues that bear other *para*-substituents, such as –CO_2Me (**1b**), –F (**1c**) and –Br (**1d**), could all be used as effective nitrogen-based metalloradicophiles for the Co(II)-based amination to furnish the corresponding α-tertiary amino acid esters **3ba**–**3da** in excellent yields with high enantioselectivities. Interestingly, [Co(**P2**)] could effectively activate 4-tetrafluoropyridinyl azide (**1e**) for a highly enantioselective C–H amination to generate α-tertiary amino acid ester **3ea** in an excellent yield with a high enantioselectivity without complication from the potential coordination of the pyridine unit to the cobalt centre. Tetrafluorophenyl azide (**1f**) also proved to be a suitable aminating reagent for the catalytic process, as it delivered **3fa** in a high yield with high enantioselectivity. Additionally, a variety of trifluorophenyl and difluorophenyl azides, such as **1g**–**1l**, worked well in the catalytic system and led to the asymmetric synthesis of fluorinated chiral α-tertiary amines **3ga**–**3la** in high yields with high

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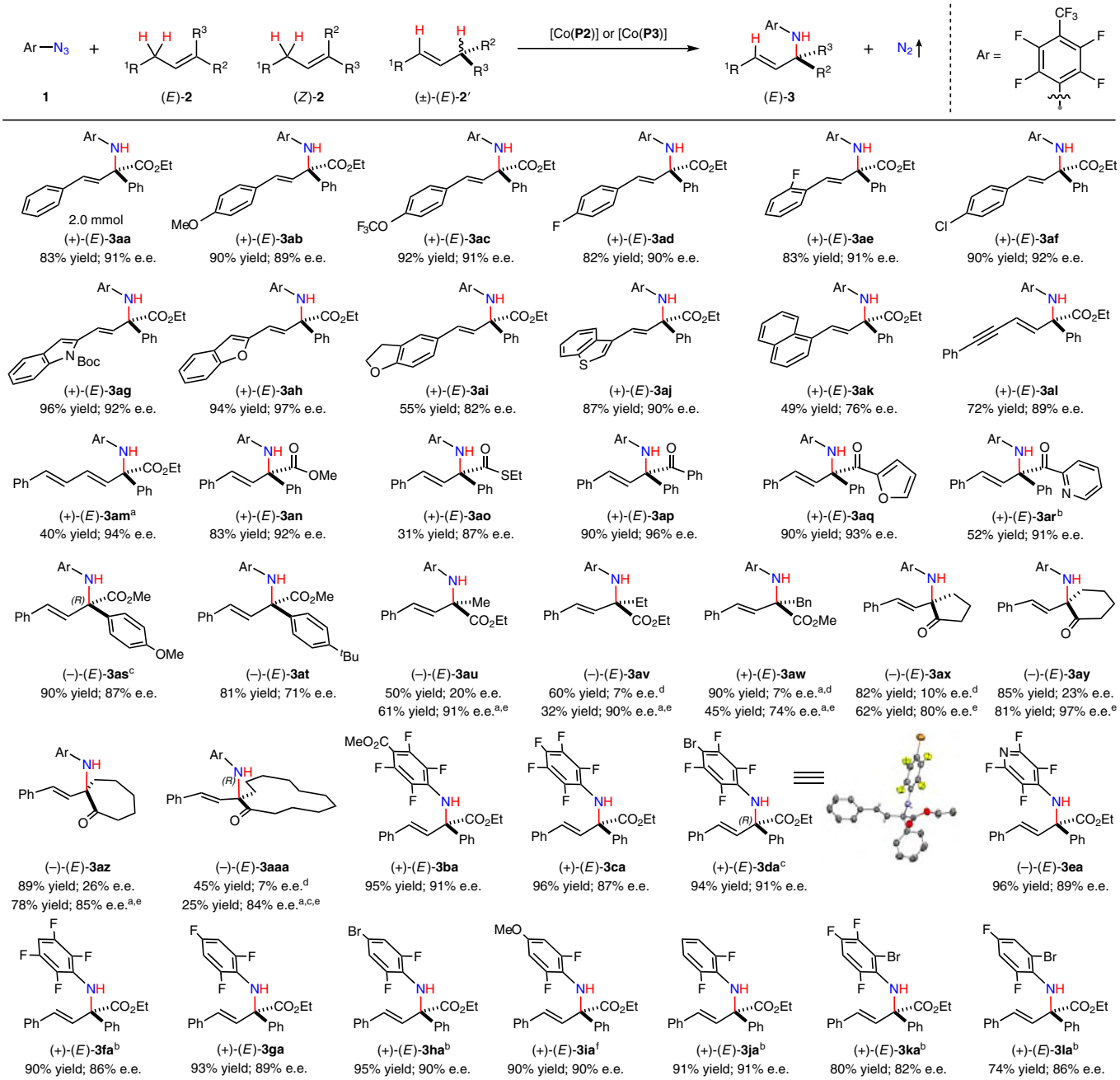
Table 3 | Substrate scope of Co(II)-catalysed convergent amination of allylic C–H bonds with organic azides



Unless otherwise noted, the reactions were carried out with **1** (0.15 mmol) and **2** (0.10 mmol) by [Co(**P2**)] (4 mol%) in fluorobenzene (0.5 ml) at 4 °C for 72 h in the presence of 4 Å molecular sieves. Isolated yields. e.e. determined by chiral HPLC. [a]Minor regioisomers were observed. [b]Performed with **1** (0.20 mmol) at room temperature. [c]Absolute configuration determined by X-ray crystallography. [d]Performed at 40 °C. [e]Performed with [Co(**P3**)] (2 mol%) in hexane (0.5 ml) at 40 °C for 72 h. [f]Performed with **1** (0.40 mmol) at 4 °C.

enantioselectivities, which may find applications as pharmaceuticals and agrochemicals as well as in materials science[44]. Note that in all these cases no competitive aziridination occurred under the reaction conditions[24]. For all the α-tertiary amine products, the α-vinyl units were determined to exclusively have an (*E*)-configuration. The absolute configurations of the newly generated stereogenic centres in products **3as**, **3aaa** and **3da** were all established as (*R*) by X-ray crystallography. The absolute configurations in all the other products were accordingly assigned as (*R*) by analogy.

Combined experimental and computational studies were carried out to comprehend the underlying mechanism and the origin of convergence and selectivity in the Co(II)-based catalytic system for intermolecular allylic C–H amination (Fig. 3). To study the kinetic isotope effect (KIE) of the allylic C–H amination, (*E*)-**2a** and (*E*)-**2a**-d_2 were used as substrates for a direct competition reaction with azide **1a** at 40 °C using [Co(**P2**)] as the catalyst (Fig. 3a). The reaction produced a mixture of C–H amination products **3aa** and **3aa**-d_2 in a 90% combined yield. The KIE (k_H/k_D) value was determined to be 8.8 by ^{1}H-NMR analysis of the product mixture. This high value of competitive primary KIE, which is similar to that of Co(II)-catalysed intermolecular benzylic C–H amination[22], agrees well with the proposed C–H bond cleavage via HAA by α-Co(III)-aminyl radical intermediate **I**. To provide evidence for the formation of ∞-Co(III)-alkyl radical intermediate **II** from HAA of the allylic C–H bond by the initially generated α-Co(III)-aminyl radical intermediate **I** during the catalytic process, TEMPO was added to the catalytic reaction of (*E*)-**2a** with azide **1a** by [Co(**P2**)] for the direct

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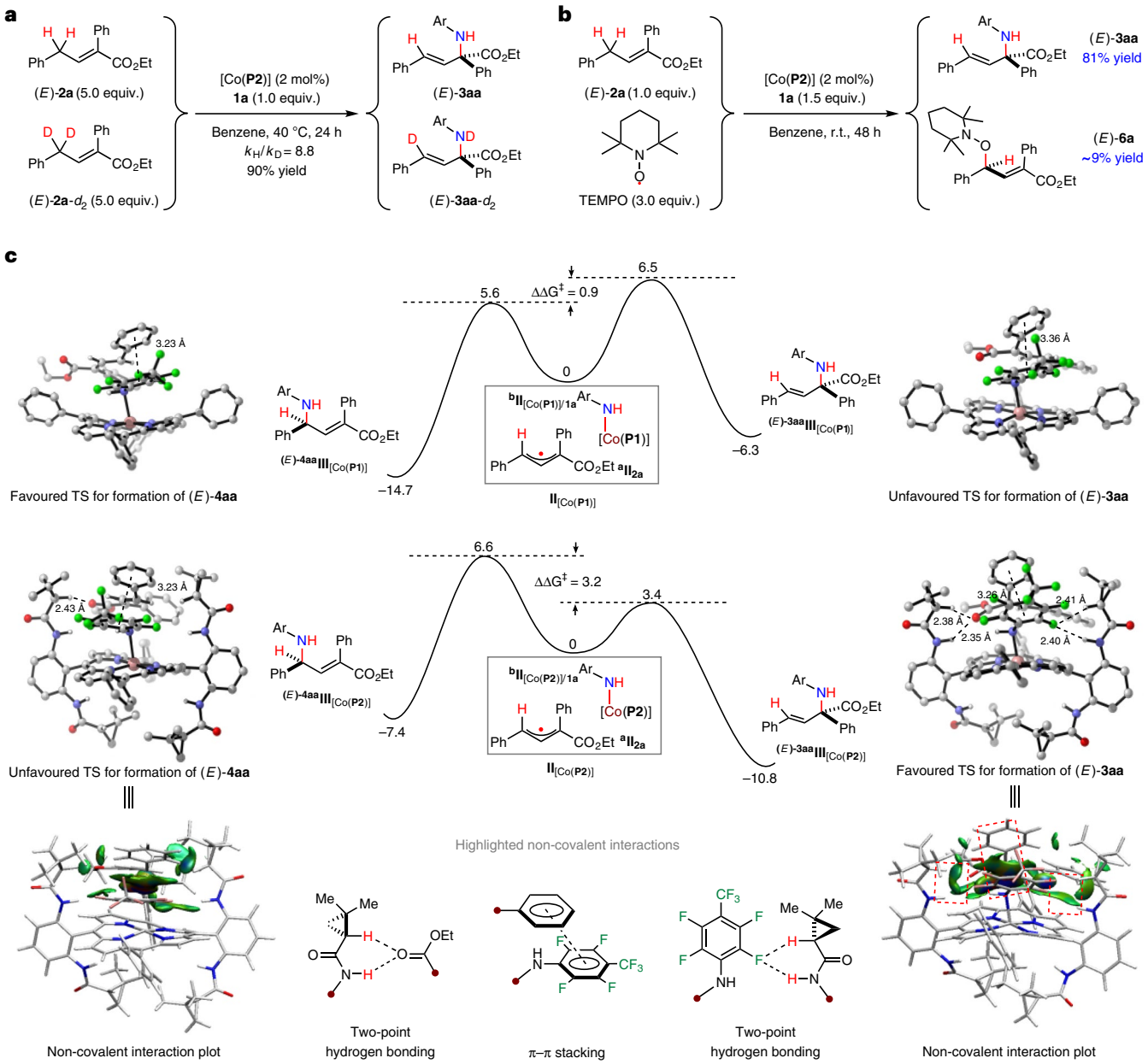

Fig. 3 | Mechanistic studies on the Co(II)-based metalloradical system for convergent amination of allylic C–H bonds. a, Measurement of the KIE. The high degree of the competitive primary KIE is consistent with the proposed step of C–H bond cleavage via intermolecular HAA by the α-Co(III)-aminyl radical intermediate **I**. **b**, Trapping of the allylic radical intermediate by TEMPO. The observation of TEMPO-trapped product **6a** provides evidence for the existence of the ∞-Co(III)-allylic radical intermediate **II** from HAA of the allylic C–H bond by the initially generated α-Co(III)-aminyl radical intermediate **I** during the catalytic process. **c**, DFT study of the ligand effect on the regioselectivity of Co(II)-catalysed allylic C–H amination. Top: difference in energy barriers ($\Delta\Delta G^{\ddagger}$) for RS at the two allylic radical sites by [Co(**P1**)]. Bottom: difference in energy barriers ($\Delta\Delta G^{\ddagger}$) for RS at the two allylic radical sites by [Co(**P2**)]. The NCI plot clearly indicates multiple NCIs, such as two-point hydrogen-bonding interactions and π–π stackings that exist in the TS. DFT calculations (all values in kcal mol^{-1}) were performed at the SMD(Benzene)-BP86-D3(BJ)/def2TZVP//BP86-D3(BJ)/def2SVP level of theory. r.t., room temperature.

trapping of allylic radical ^{a}**II** (Fig. 3b). Remarkably, α-tertiary amine **3aa** was still produced as the major product (81% yield) even in the presence of excess TEMPO (3.0 equiv.), which indicates facile C–N bond formation via a subsequent RS within the pocket-like environment of the catalyst. Concomitantly, the reaction also produced compound **6a** as a minor product (~9% yield), which was evidently generated from C–O bond formation through trapping of allylic radical intermediate ^{a}**II** by TEMPO at the original carbon site of HAA. The different regioselectivities for the formation of **6a** from **3aa** further indicates the effectiveness of metalloradical catalyst [Co(**P2**)] in controlling the course of the radical process.

To elucidate the structures of the catalytic intermediates and associated energetics, density functional theory (DFT) calculations were performed for the allylic C–H amination reaction of (*E*)-**2a** with azide **1a** by both [Co(**P1**)] and [Co(**P2**)] (Fig. 3c). In addition to providing detailed pictures of the intermediates and related transition states (TS), the DFT calculations revealed that both catalytic processes by [Co(**P1**)] and [Co(**P2**)] have low activation barriers (see Supplementary Section 9 for details), which are consistent with the fact that both catalysts were effective in catalysing the reaction under mild conditions. In addition to the formation of the α-tertiary amine (*E*)-**3aa**, further DFT calculations were conducted to examine the catalytic pathway that leads to

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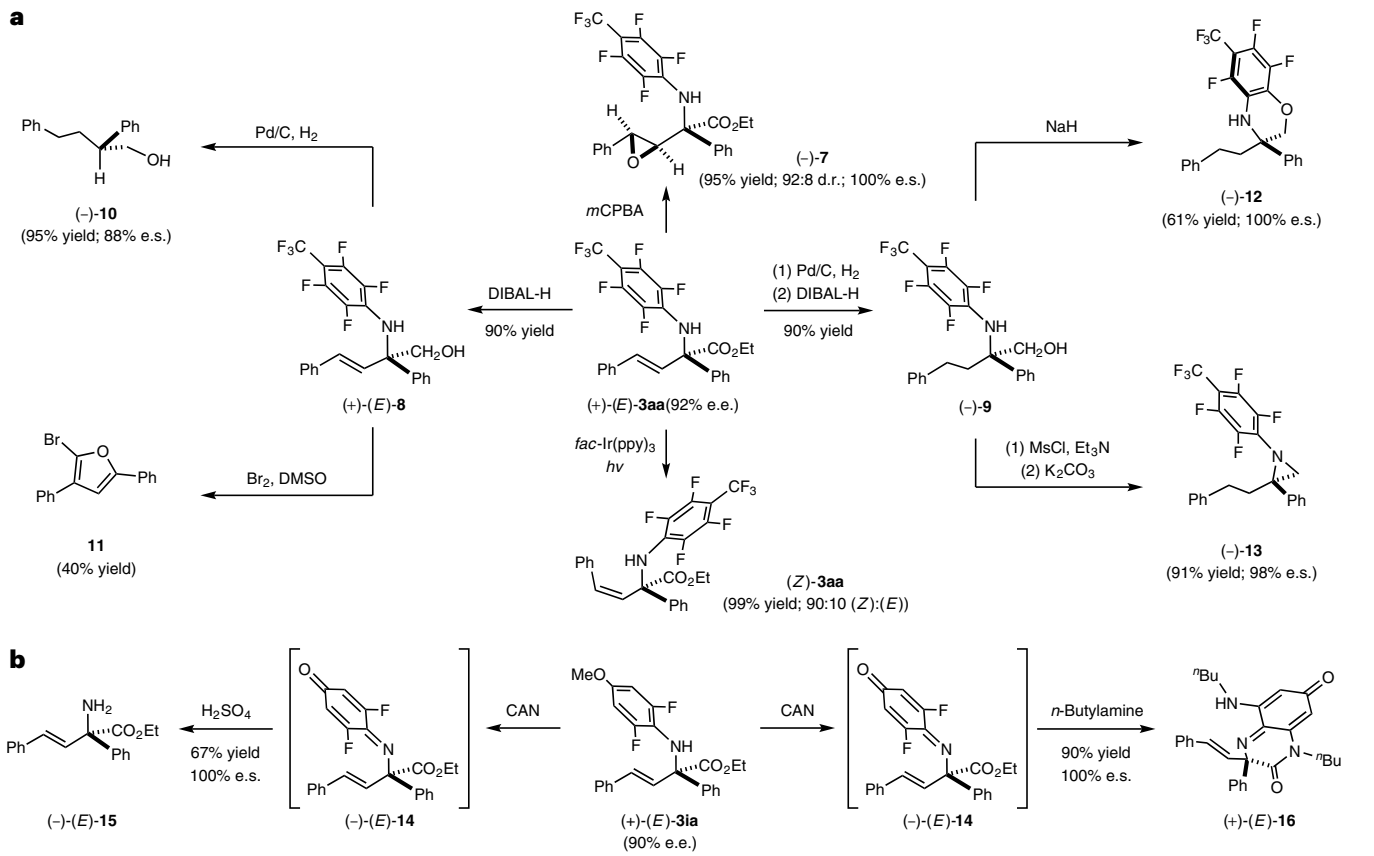

Fig. 4 | Synthetic applications of the resulting chiral α-tertiary amines from Co(II)-catalysed allylic C–H amination. a, Stereoselective conversion of the enantioenriched α-tertiary amino acid ester (*E*)-**3aa** to epoxide-containing amino acid ester **7** by epoxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA); to amino alcohol (*E*)-**8** by reduction with DIBAL-H; this could be further converted into chiral alcohol **10** by hydrogenation on Pd/C and to trisubstituted furan **11** by bromoetherification, followed by double elimination and subsequent bromination; to fully reduced amino alcohol **9** by reduction with dihydrogen on Pd/C and followed with DIBAL-H, which could be further converted into benzomorpholine **12** by intramolecular nucleophilic substitution and to aziridine **13** by treatment with MsCl followed by intramolecular nucleophilic substitution; to (*Z*)-**3aa** by photocatalytic isomerization. **b**, Stereoselective conversion of α-tertiary amino acid ester (*E*)-**3ia** to give unprotected α-tertiary amino acid ester (*E*)-**15** by oxidation with CAN via the *p*-quinonimide intermediate (*E*)-**14** and to *N*-heterocycle (*E*)-**16** by oxidation with CAN followed by reaction with *n*-butylamine.

the α-secondary amine (*E*)-**4aa** by both [Co(**P1**)] and [Co(**P2**)] for the purpose of understanding the regioselectivity. When [Co(**P1**)] is the catalyst, the calculations revealed that the difference in energy barriers ($\Delta\Delta G^{\ddagger}$) for RS of the ∞-Co(III)-alkyl radical intermediate **II** at the two allylic radical sites is 0.9 kcal mol^{-1} in favour of the formation of (*E*)-**4aa** (Fig. 3c). Interestingly, the use of [Co(**P2**)] as the catalyst increases the $\Delta\Delta G^{\ddagger}$ value to 3.2 kcal mol^{-1} and switches the preference towards the formation of (*E*)-**3aa**. The computed $\Delta\Delta G^{\ddagger}$ values are closely in line with the experimental results on the difference in regioselectivity between the two catalysts (Table 1). As illustrated by the non-covalent interaction (NCI) plots of the DFT-optimized transition-state structures, there exist two unique two-point hydrogen-bonding interactions in the TS that lead to the formation of the α-tertiary amine (*E*)-**3aa**: (1) a N–H···O=C and C–H···O=C two-point hydrogen bond between one cyclopropanecarboxyamide unit of the catalyst [Co(**P2**)] and the carbonyl group in the allylic radical component $^{a}\mathbf{II}_{\mathbf{2a}}$ and (2) a N–H···F–Ar and C–H···F–Ar two-point hydrogen bond between another cyclopropanecarboxyamide unit of the catalyst [Co(**P2**)] and the fluoroaryl group in the Co(III)–amido component $^{b}\mathbf{II}_{[\mathbf{Co(P2)}]/\mathbf{1a}}$ (Fig. 3c; see Supplementary Section 9 for details). However, it is also apparent from the NCI plot that both of the two-point hydrogen bonding interactions are absent or significantly weakened in the unfavoured TS that leads to the formation of the α-secondary amine (*E*)-**4aa**. Together with the hydrogen-bonding interactions, the other non-covalent attractive interactions, such as π–π stacking between the fluorophenyl group in the Co(III)–amido component $^{b}\mathbf{II}_{[\mathbf{Co(P2)}]/\mathbf{1a}}$ and the phenyl substituent in the allylic component $^{a}\mathbf{II}_{\mathbf{2a}}$ may also contribute to the overall control of the observed regioselectivity though they exist in both of the TS. Evidently, it is the network of multiple attractive NCIs that holds the two reacting substrates in proximity and orients them in proper conformations within the pocket of the catalyst to facilitate the C–N bond formation with an effective control of the regioselectivity while inducing a high asymmetry.

Given that chiral α-tertiary amines are attractive structural motifs for the research and development of bioactive molecules and pharmaceuticals[45], the resulting enantioenriched α-tertiary amino acid esters from the Co(II)-catalysed allylic C–H amination, which bear multiple functionalities, may serve as useful intermediates for a variety of synthetic applications. To this end, enantioenriched α-tertiary amino acid ester (*E*)-**3aa** (92% e.e.) was used as a representative α-tertiary amino acid ester to explore further the stereoselective transformations (Fig. 4a). For example, the alkene unit in (*E*)-**3aa** could be stereoselectively epoxidized with *meta*-chloroperoxybenzoic acid at room temperature to form the three-membered cyclic ether with the creation of two additional stereogenic centres to furnish α-tertiary amino acid ester **7** in a high yield (95%) with a high diastereoselectivity (92:8) and complete retention of the original enantiopurity. In view of the diverse ring-opening reactions of epoxide functionality with different nucleophiles, compound **7** may serve as a valuable precursor for the stereoselective synthesis of α,β,γ-trifunctional amino acids that bear three contiguous stereogenic centres. As another example, the ester functionality in (*E*)-**3aa** could

be selectively reduced to primary alcohol with diisobutylaluminium hydride (DIBAL-H) with the preservation of the alkene unit to afford the amino alcohol (*E*)-**8** in a 90% yield. Alternatively, the alkene unit and the ester functionality in (*E*)-**3aa** could efficiently undergo consecutive reduction reactions when treated with dihydrogen on Pd/C followed by DIBAL-H to provide the fully reduced amino alcohol **9** in a 90% yield. Both amino alcohols **8** and **9** were shown to serve as valuable intermediates for further transformations. For example, it was discovered that the olefinic amino alcohol (*E*)-**8** underwent a catalytic hydrogenation reaction on Pd/C to effectively reduce the alkene unit while simultaneously cleaving the C–N bond, which generated chiral alcohol **10** in a high yield (95%) with some loss of the original enantiopurity (88% e.s.). The hydroxyl group seems to be essential to this unusual C–N bond cleavage process under hydrogenolysis as it probably served as a metal-binding site to facilitate the activation of the C–N bond by the Pd centre. As another unexpected outcome of the attempt to construct a tetrahydrofuran core via intramolecular bromoetherification of the olefinic amino alcohol (*E*)-**8** under the condition of bromine and dimethylsulfoxide (DMSO), trisubstituted furan **11** was instead obtained in a 40% yield, which presumably resulted from double elimination of the initially formed brominated tetrahydrofuran intermediate and subsequent bromination of the resulting furan. As an example of further transformations with saturated amino alcohol **9**, it was found that one of the two *ortho*-aryl fluorides could undergo an intramolecular nucleophilic substitution reaction with the primary hydroxyl group in the presence of NaH for the construction of a biologically interesting fused six-membered morpholine structure, which generated chiral benzomorpholine **12** in a moderate yield (61%) with complete enantiospecificity (100% e.s.). As a different type of intramolecular nucleophilic substitution reaction of the amino alcohol **9**, a synthetically versatile three-membered *N*-heterocyclic structure could be efficiently constructed by an initial treatment with methanesulfonyl chloride (MsCl)–Et_3N and then with K_2CO_3 to produce chiral aziridine **13** in a high yield (91% for two steps) with an almost full reservation of the original optical purity (98% e.s.). Although the Co(II)-based metalloradical system for stereoconvergent allylic C–H amination produced enantioenriched α-tertiary amino acid esters **3** as (*E*)-diastereomers only, it was also shown that the (*Z*)-diastereomers could be generated from the resulting (*E*)-diastereomers by photocatalytic isomerization[46]. For example, (*E*)-**3aa** could efficiently undergo photocatalytic isomerization with the use of *fac*-Ir(ppy)$_3$ as the photocatalyst to afford (*Z*)-**3aa** in a near quantitative yield (99%) with a high diastereoselectivity (90:10 (*Z*):(*E*)).

Given that α-tertiary-α-aryl amino acids and their derivatives have found important applications as modifiers of peptide conformations and associated bioactivities in addition to serving as precursors to other bioactive molecules[47,48], it is desirable for the *N*-fluoroaryl groups in the resulting enantioenriched α-tertiary amino acid esters **3** from the Co(II)-catalysed allylic C–H amination to be removed to form the corresponding α-tertiary amine esters with a primary amine functionality for further transformations. To this end, substantial efforts were made to deprotect the *N*-fluoroaryl group for the preparation of the synthetically challenging unprotected chiral amino acid esters[49]. As the outcome of the efforts, it was found that the *N*-2,6-difluoro-4-methoxyphenyl group in enantioenriched (*E*)-**3ia** (90% e.e.) could be oxidized with ceric ammonium nitrate (CAN) to provide *p*-quinonimide intermediate (*E*)-**14**, which could undergo in situ acidic hydrolysis to afford the corresponding unprotected α-tertiary amino acid ester (*E*)-**15** in a 67% yield without loss of enantiopurity (100% e.s.) (Fig. 4b). In addition to the deprotection through acidic hydrolysis, it was shown that *p*-quinonimide (*E*)-**14** could function as a valuable intermediate for other further transformations, as showcased by its in situ reaction with *n*-butylamine for the stereoselective synthesis of *N*-heterocycle **16** in a high yield (90% for two steps) with complete retention of the original enantiopurity (100% e.s.). Presumably, *N*-heterocycle **16** was formed through first the nucleophilic substitution of the C–F bond in *p*-quinonimide by *n*-butylamine through a combination of addition and elimination, followed by lactamization with the ester.

Conclusion

In summary, we have demonstrated a catalytic approach via MRC for the concurrent control of multiple convergences and selectivities in a radical reaction. As stable 15e-metalloradical catalysts, Co(II) complexes of porphyrins were shown to have the capability of catalysing intermolecular allylic C–H amination with aryl azides. With the support of the D_2-symmetric chiral amidoporphyrin ChenPhyrin as the ligand, the Co(II)-based metalloradical system can homolytically activate a diverse array of fluoroaryl azides for the radical amination of allylic C–H bonds in a wide range of trisubstituted alkenes under mild conditions, which leads to a stereoselective synthesis of valuable α-tertiary amino acid derivatives in high yields. In addition to outstanding chemoselectivity and regioselectivity, the Co(II)-catalysed radical allylic C–H amination enables the concurrent control of diastereoselectivity and enantioselectivity while exhibiting a remarkable level of multiple stereochemical convergences at the same time. As a result, the catalytic C–H amination methodology can directly employ an isomeric mixture of alkenes as the substrates, an unusual feature that may have significant practical implications. The key to the success in concurrently controlling multiple convergences and selectivities of the radical process lies in judicious catalyst development to maximize the non-covalent attractive interactions with the reacting substrates through fine-tuning the cavity-like environment of the modularly designed D_2-symmetric chiral amidoporphyrin ligand platform. With the introduction of MRC, the formidable challenges associated with controlling the reactivity and selectivity of a radical reaction can be translated into a solvable problem of catalyst design and development. It is our hope that this work will stimulate further research interest in applying MRC to harness the untapped potential of homolytic radical chemistry for the development of new synthetic tool.

Online content

Any methods, additional references, Nature Portfolio 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/s41557-022-01119-4.

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Methods

In a typical procedure for intermolecular amination of allylic C–H bonds, an oven-dried Schlenk tube was charged with [Co(**P2**)] (**P2** = ChenPhyrin) (4 mol%, 4.6 mg) and 4 Å sieves. The Schlenk tube was then evacuated and backfilled with nitrogen three times. Azide **1** (0.15 mmol, 1.5 equiv.), an isomeric mixture or pure isomer **2** (0.10 mmol, 1.0 equiv.) and fluorobenzene (0.5 ml) were added under nitrogen. The tube was purged with nitrogen and then stirred at 4 °C for 72 h. After completion of the reaction, the reaction mixture was purified via flash chromatography on silica gel. The fractions that contained the product were collected and concentrated by rotary evaporation to afford the purified compound.

Data availability

All the data that support the findings of this study, which include experimental procedures and compound characterization, are available within the paper and its Supplementary Information. CIF crystallographic data files and xys coordinates of the optimized structures are available as Supplementary Data. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2160224 (**3as**), 2160223 (**3aaa**) and 2160225 (**3da**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

P.X. conducted the experiments. J.X. conducted the DFT calculations. D.-S.W. assisted the project. X.P.Z. conceived the work and directed the project. P.X. and X.P.Z. designed the experiments. P.X. and X.P.Z. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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