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Expedited synthesis of α-amino acids by single-step enantioselective α-amination of carboxylic acids

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The conversion of C–H bonds to C–N bonds offers a sustainable and economical strategy for the synthesis of nitrogen-containing compounds. However, challenges regarding the control of regio- and stereoselectivity currently limit the broad applicability of intermolecular C(sp^3)–H amination reactions. We address these restrictions by directed nitrene-mediated C–H insertion using a metal-coordinating functional group. We report a highly stereocontrolled, iron-catalysed direct α-amination of abundant carboxylic acid feedstock molecules. The method provides in a single step high-value *N*-Boc-protected α-monosubstituted and α,α-disubstituted α-amino acids, which can then be immediately used for applications including solution- and solid-phase peptide synthesis. This method fulfils important aspects of sustainability by being highly step efficient and utilizing non-toxic, Earth-abundant iron as the catalytic metal.

Amines are some of the most prevalent functional groups found in natural molecules and pharmaceuticals[1,2]. As such, the demand for economical and sustainable synthetic methods for the introduction of amino groups remains strong and growing. The direct replacement of a hydrogen by an amine functionality[3] through transition metal-catalysed, nitrene-mediated intermolecular C–H amination represents an attractive and highly step-efficient solution[4–7]. However, despite the considerable research efforts that have been focused on this area, the abundance of C–H bonds in organic molecules typically poses a formidable regioselectivity challenge for intermolecular C–H aminations. Furthermore, control of stereoselectivity is often difficult to achieve for the outer-sphere C–N bond formation step in which the substrate is not bound to the metal (Fig. 1a). These two aspects currently limit the broad applicability of stereocontrolled nitrene-mediated intermolecular C(sp^3)–H aminations in synthetic chemistry.

Directed C–H activation by transition metal catalysis has proven to be a powerful tool for addressing the regio- and stereoselectivity issues confronted in C–H functionalizations such as the amination of non-activated C(sp^3)–H bonds[8]. Directed C–H amination exploits a metal-coordinating directing group for site-selective activation of a specific C–H bond, usually by the formation of a metallacycle intermediate, followed by reaction of the metal–carbon bond with an external or metal-bound nitrogen species. The sustainability of these methods, however, is often diminished by the reliance on noble metals, such as Pd, Ru, Rh and Ir, for inducing cyclometalation. In a different mechanistic manifold, directed C(sp^3)–H amination could be achieved through nitrene insertion into C–H bonds without the preceding formation of a C–M bond, where M is a metal (Fig. 1b). Surprisingly, this mechanistic scheme is rarely explored and has only been realized non-racemically through hydrogen bond-mediated catalysis[9,10] and in racemic reactions through high-valence iridium[11] and rhodium[12] nitrene intermediates, and not in a catalytic asymmetric manner.

We intended to achieve asymmetric intermolecular C(sp^3)–H amination through directed C(sp^3)–H nitrene insertion. Specifically, we envisioned that carboxylic acids might be suitable directing groups for regioselective and stereocontrolled nitrene-mediated C–H aminations to directly convert abundant feedstock carboxylic acids into highly valuable non-racemic chiral α-amino acids bearing unnatural side chains, which are sought-after synthetic building blocks due to their modulated chemical, physical and pharmaceutical properties[13–18] (Fig. 1c). Direct α-amination of carboxylic acids has rare precedents and is highly challenging, in contrast with the well-established α-amination of aldehydes,

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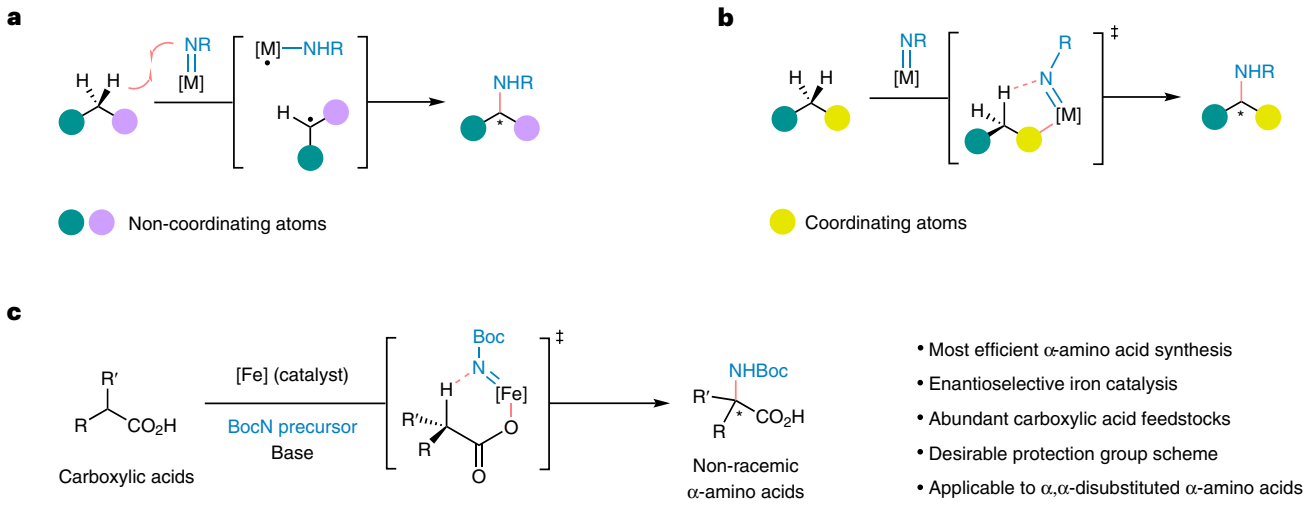

Fig. 1 | Reaction design for catalytic asymmetric C(sp^3)–H α-aminations. **a**, Non-directed asymmetric intermolecular C(sp^3)–H nitrene insertion via the outer-sphere mechanism (well developed). **b**, Directed asymmetric intermolecular C(sp^3)–H nitrene insertion amination using metal-coordinating functional groups (rare precedents). **c**, This work. Intermolecular iron-catalysed directed α-C(sp^3)–H nitrene insertion of carboxylic acids. The asterisks indicate the chiral centre. Boc, *tert*-butyloxycarbonyl; [M], metal catalyst; [Fe], iron catalyst.

ketones, 1,3-dicarbonyl compounds, esters and some carboxylic acid surrogates[19–21]. This can be attributed to both the acidity of the carboxylic acid moiety and the typically high pK_a value of the α-hydrogen. In 1972, Yamada et al.[22] was the first to report the preparation of α-amino acids from carboxylic acids by a one-pot procedure through double deprotonation followed by reaction with *O*-methylhydroxylamine. However, this method requires a strong base and provides only racemic products. In 2012, Smith and colleagues[23] reported the enantioselective organocatalytic α-amination of carboxylic acids with *N*-aryl-*N*-aroyldiazenes in a one-pot, two-step procedure via in situ-generated acid anhydrides. This method is limited to the synthesis of *N*-aryl-α-glycine derivatives after SmI_2-induced cleavage of the initially obtained hydrazides. In 2019, Shimizu and colleagues[24] introduced a boron-catalysed α-hydrazination of carboxylic acids with diisopropyl azodicarboxylate. In one example, the presence of a chiral ligand provided modest enantioselectivity (45% enantiomeric excess (e.e.)). Unfortunately, converting the α-hydrazino into an amino group required harsh reaction conditions.

Herein, we report a previously elusive stereocontrolled intermolecular one-step α-C(sp^3)–H amination to afford high-value *N*-protected chiral α-amino acids. Our method refrains from multi-step synthetic sequences or inconvenient starting materials. Instead, it utilizes abundant carboxylic acid feedstock, sustainable and Earth-abundant iron catalysis and the popular *tert*-butyloxycarbonyl (Boc)-protecting group, which does not require a subsequent step-intensive exchange of the protection group. These characteristics render this method highly attractive for the expedited synthesis of α-monosubstituted and α,α-disubstituted α-amino acids.

Results and discussion

Initial experiments and optimization

We initially selected phenylacetic acid (**PAA**) as our model substrate. (*R*,*R*)-[$FeCl_2$(BIP)], bearing a bis-benzimidazole ligand with a chiral 2,2′-bipyrrolidine backbone (BIP) and two labile chloride ligands (hereafter referred to as (*R*,*R*)-**FeBIP**) was chosen as the catalyst as it was recently identified by us as an excellent catalyst for a 1,3-migratory nitrene insertion[25] (Table 1). We envisioned that the coordination of the deprotonated **PAA** and the simultaneous formation of an iron nitrenoid might trigger a nitrene-mediated amination of the α-C(sp^3)–H bond to form phenylglycine via a cyclic transition state with potentially high regio- and stereocontrol (Fig. 1c). As the choice of protecting group would be crucial for later applications, we elected to use the Boc group, one of the most commonly employed *N*-protecting groups in amino acid chemistry[26].

We proceeded to explore the suitability of *N*-Boc-protected carbamates with various leaving groups at the nitrogen (BocNH-X; X = leaving group) as nitrene precursors[27–33]. While no conversion was observed with benzoate as the leaving group (entry 1), sulfonates provided more encouraging results. With toluenesulfonate as the leaving group, the desired *N*-Boc-protected phenylglycine was formed with 29% NMR spectroscopy yield and 91% e.e. after 20 h at −15 °C in an incomplete conversion (entry 2). An isopropyl sulfonate leaving group did not perform significantly better (entry 3). The best results were obtained with mesylate (Ms) as the leaving group. Subjecting **PAA** to (*R*,*R*)-**FeBIP** (8 mol%), BocNHOMs (2 equiv.) and piperidine (4 equiv.) in 1,2-dichlorobenzene (*o*-DCB) at −15 °C provided *N*-Boc-protected (*S*)-phenylglycine (**1**) in 78% NMR spectroscopy yield (77% isolated yield) with 93% e.e. (entry 4). Bases such as K_2CO_3 (entry 5) or Et_3N (entry 6) afforded inferior results. Other solvents, including dichloromethane or acetonitrile, led to decreased yields and enantioselectivities (entries 7 and 8). It is worth noting that higher temperatures also provided diminished yields (entries 9 and 10), presumably due to a Lossen-type rearrangement of BocNHOMs induced by the base at elevated temperatures[29]. Less favourable results were also obtained when using an excess of aminating reagent to drive conversion to completion, which resulted in a decreased yield due to oxidative decomposition of the amino acid product (compare entries 4 and 11) (see also Supplementary Information section 'Oxidative decomposition of α-amino acids under reaction conditions' for details).

Finally, two popular related chiral iron catalysts featuring tetradentate *N*4-donor ligands were tested for comparison and displayed inferior results. The bis-pyridine complex (*R*,*R*)-**Fe1** (ref. [34]) provided *R*-configurated **1** in a significantly lower yield and with significantly lower enantioselectivity (20% yield with 48% e.e.; entry 12), while the bis-benzimidazole diacetonitrile iron complex (*R*,*R*)-**Fe2** (ref. [35]), which is prepared from (*R*,*R*)-**FeBIP** by silver-promoted ligand exchange, provided comparable enantioselectivity but a significantly decreased yield (entry 13). These results confirm the benefit of both the benzimidazole and chloride ligands of the **FeBIP** catalyst scaffold.

Substrate scope

With optimized reaction conditions in hand, we next investigated the substrate scope for this protocol (**1**–**49**) (Table 2). The reaction

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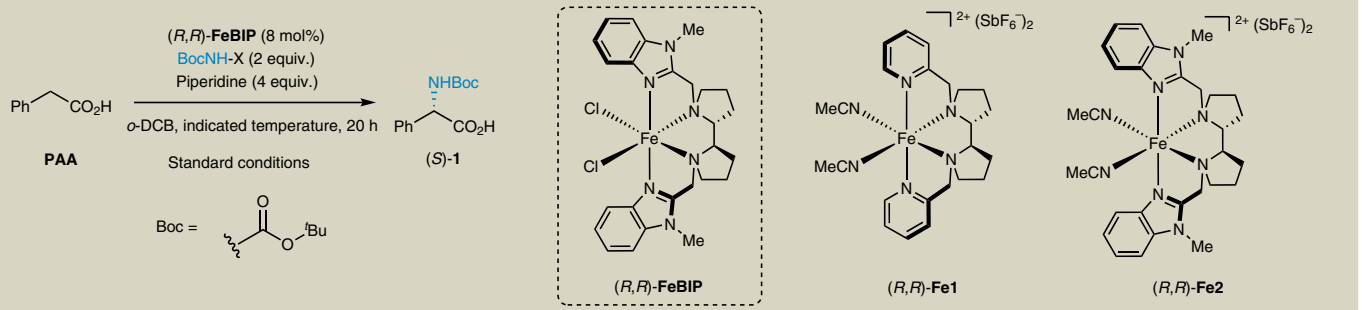
Table 1 | Initial experiments and optimization of reaction conditions



Entry	Leaving group	Reaction conditions[a]	Temperature (°C)	Conversion (%)[b]	Yield (%)[b]	e.e. (%)[c]
1	OBz	Standard conditions	−15	0	–	–
2	OTs	Standard conditions	−15	35	29	91 (*S*)
3	$OSO_2{}^iPr$	Standard conditions	−15	44	31	93 (*S*)
4	OMs	Standard conditions	−15	90	78 (77)[d]	93 (*S*)
5	OMs	K_2CO_3 as base	−15	31	7	93 (*S*)
6	OMs	Et_3N as base	−15	38	28	91 (*S*)
7	OMs	CH_2Cl_2 as solvent	−15	67	46	86 (*S*)
8	OMs	CH_3CN as solvent	−15	33	15	72 (*S*)
9	OMs	Standard conditions	0	74	58	90 (*S*)
10	OMs	Standard conditions	25	56	46	80 (*S*)
11	OMs	Standard conditions[e]	−15	91	70	93 (*S*)
12	OMs	(*R*,*R*)-**Fe1** as catalyst	−15	69	20	48 (*R*)
13	OMs	(*R*,*R*)-**Fe2** as catalyst	−15	83	69	93 (*S*)

[a]Deviations from standard conditions are shown. Standard conditions: **PAA** (27.2 mg; 0.2 mmol), BocNHOMs (84.5 mg; 0.4 mmol; 2 equiv.), piperidine (82 µl; 0.8 mmol; 4 equiv.) and (*R*,*R*)-**FeBIP** (8.9 mg; 8 mol%) in *o*-DCB (2 ml) were stirred under an N_2 atmosphere at the indicated temperature for 20 h. [b]Conversion and yield were determined by ^1H NMR spectroscopy analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by high-performance liquid chromatography analysis on chiral stationary phases. The major configuration of **1** is provided in parentheses. [d]Isolated yield provided in parentheses. [e]Reaction performed with BocNHOMs (3 equiv.) and piperidine (5 equiv.). OBz, benzoate; OMs, methansulfonate; OTs, toluensulfonate.

tolerated a wide range of electron-donating and electron-withdrawing substituents on the aromatic ring of the PAA substrate, including methyl (**2**–**4**), *tert*-butyl (**5**), phenyl (**6**), methoxy (**7**), fluorine (**8**), chlorine (**9**), azide (**10**), trifluoromethyl (**11**), methoxycarbonyl (**12**), 3,5-dimethyl (**13**), 1,3-dioxole (**14**) and 3,4,5-trimethoxy (**15**). The important unnatural arylglycine[36] products **2**–**15** were obtained in satisfactory yields (49–78%) and with 85–94% e.e. Benzannulated (**16** and **17**) and heteroaromatic arylglycines (**18**–**20**) could also be readily prepared using this method (44–64% yield; 74–93% e.e.). It is worth mentioning that for α-aryl amino acids **11**, **12** and **20**, as well as α-alkyl amino acids **21**–**28**, using dichloromethane as the solvent instead of *o*-DCB afforded higher yields. Even more gratifyingly, our synthetic protocol also proved effective for aliphatic carboxylic acids with non-activated C(sp^3)–H bonds, which represent a long-standing challenge in intermolecular asymmetric C–H amination[4,6,7]. The non-racemic α-amino acids **21**–**25**, containing primary alkyl substituents, were successfully obtained in 30–55% yield and with 87–91% e.e. Intriguingly, using the mirror-imaged iron complex (*S*,*S*)-**FeBIP** as a catalyst, the reaction provides convenient access to D-configured α-amino acids with proteinogenic side chains, such as Boc-D-leucine (**26**). For sterically hindered substrates such as 2-cyclohexylacetic acid and 3,3-dimethylbutanoic acid, the desired products **27** and **28** were obtained in more modest yields of 40 and 21%, respectively, but with satisfactory e.e. values. For aliphatic side chains (**21**–**28**), where regioisomeric amination might occur, α-amino acid products were exclusively observed. However, electronically activating the β-C–H position can lead to competing formation of β-amino acids (see the Supplementary Information section '1,5-HAT vs. 1,6-HAT for amination of 3-phenylpropionic acid' for details). Finally, it is noteworthy that for reactions that provided low to moderate yields, the remaining mass balance constitutes mainly intact starting material, while minor side products result from overoxidation. Furthermore, the reaction is also applicable to the Troc (2,2,2-trichloroethoxycarbonyl) protection group. For example, *N*-Troc-protected (*S*)-phenylglycine (**1′**) was obtained in 72% yield and with 94% e.e.

Next, we applied our protocol to the synthesis of α,α-disubstituted α-amino acids, which are distinguished by their restricted conformational flexibility, increased lipophilicity and metabolic stability, as well as increased resistance towards racemization[37,38]. Most existing synthetic routes rely on electrophlic α-alkylation of amino acid enolate equivalents. While aminations of α-branched carbonyl compounds have been achieved mainly by electrophilic hydrazinations of enolates with azidocarboxylates, the subsequent cleavage of the hydrazides to the target amines requires harsh conditions[39–41]. We envisioned applying our direct amination protocol to α-branched carboxylic acids, which would provide a general and rapid synthetic method for accessing non-racemic α,α-disubstituted α-amino acids that has to date been elusive. Indeed, when we reacted racemic α-branched carboxylic acids with BocNHOMs under iron catalysis, the tertiary α-C–H was aminated in a stereocontrolled fashion to afford the desired products in high yields and with high enantioselectivities. For example, *N*-Boc-protected α,α-disubstituted α-amino acids containing one α-methyl and one α-aryl group were synthesized in 68–89% yield and with 79–91%

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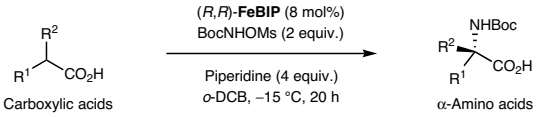
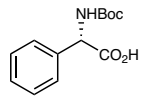
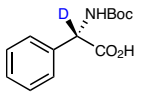
Table 2 | Substrate scope for the α-amination of carboxylic acids



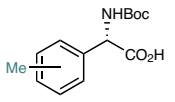
α-Aryl amino acids



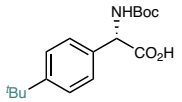
1, 77%, 93% e.e.
1'[a] (Troc instead of Boc): 72%, 94% e.e.



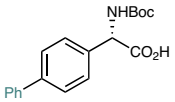
1-*d*[b,c]
72%, 94% e.e.



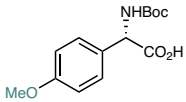
2 (*para*), 63%, 93% e.e.
3 (*meta*), 72%, 92% e.e.
4[b] (*ortho*), 68%, 94% e.e.



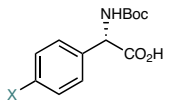
5
78%, 92% e.e.



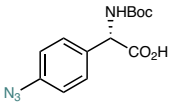
6
53%, 91% e.e.



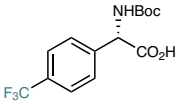
7
50%, 93% e.e.



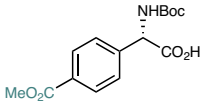
8 (X = F), 56%, 93% e.e.
9 (X = Cl), 49%, 92% e.e.



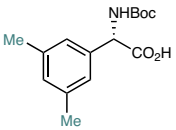
10
54%, 93% e.e.



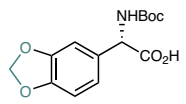
11[d]
60%, 85% e.e.



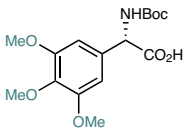
12[d]
62%, 86% e.e.



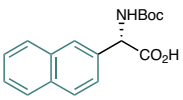
13
70%, 93% e.e.



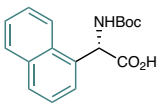
14
55%, 93% e.e.



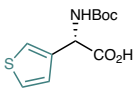
15
52%, 90% e.e.



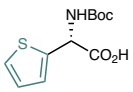
16
62%, 91% e.e.



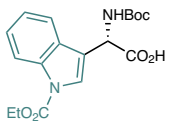
17[b]
64%, 84% e.e.



18
44%, 93% e.e.

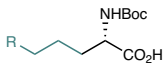


19
48%, 90% e.e.

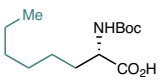


20[d]
44%, 74% e.e.

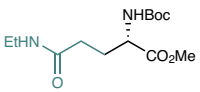
α-Alkyl amino acids



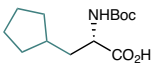
21[d,e] (R = Ph), 55%, 87% e.e.
22[d,e] (R = N_3), 46%, 91% e.e.



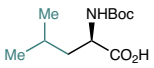
23[d,e]
51%, 88% e.e.



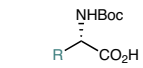
24[d,e,f]
30%, 89% e.e.



25[d,e]
52%, 89% e.e.

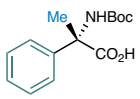


26[d,e,g]
42%, 89% e.e.

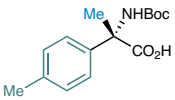


27[d,e] (R = Cy), 40%, 90% e.e.
28[d,e] (R = ^{t}Bu), 21%, 89% e.e.

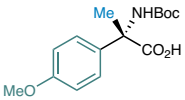
α,α-Disubstituted amino acids



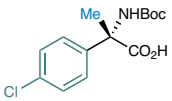
29[b,c,h]
89%, 91% e.e.



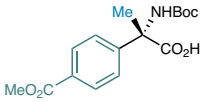
30[b,c,h]
80%, 91% e.e.



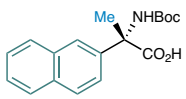
31[b,c,h]
79%, 79% e.e.



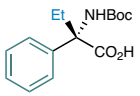
32[b,c,h]
81%, 89% e.e.



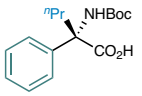
33[b,c,h]
72%, 90% e.e.



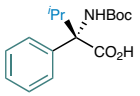
34[b,c,h]
68%, 91% e.e.



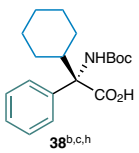
35[b,c,h]
85%, 93% e.e.



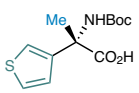
36[b,c,h]
76%, 93% e.e.



37[b,c,h]
64%, 93% e.e.



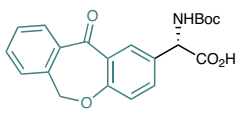
38[b,c,h]
59%, 94% e.e.



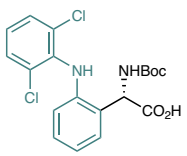
39[b,c,h]
45%, 88% e.e.

40[b,c,d,h] (R = ^{n}Bu), 34%, 23% e.e.
41[b,c,d,h] (R = Cy), 43%, 43% e.e.

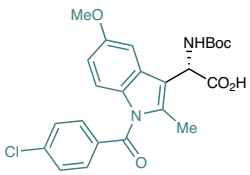
Late-stage C–H aminations



42[b] (from isoxepac)
59%, 90% e.e.



43 (from diclofenac)
37%, 83% e.e.



44[b] (from indomethacin)
75%, 70% e.e.

45[d,e] (from lithocholic acid)
43%, 23/1 d.r.

46[d,e] (from *d*-desthiobiotin)
40%, 21/1 d.r.

47[b,c,h] (from ibuprofen)
87%, 91% e.e.

48[b,c,h] (from ketoprofen)
88%, 90% e.e.

49[b,c,h] (from naproxen)
65%, 85% e.e.

Cy, cyclohexyl; d.r., diastereomeric ratio; TBS, *tert*-butyldimethylsilyl; Troc, 2,2,2-trichloroethoxycarbonyl. [a]Reaction conditions for **1'**: 1 mol% (*R*,*R*)-**FeBIP**, 1.5 equiv. TrocNHOMs and 2.5 equiv. piperidine in *o*-DCB (0.05 M) at 25 °C for 24 h. [b]Reaction performed with 15 mol% (*R*,*R*)-**FeBIP** for 40 h. [c]5 equiv. BocNHOMs and 7 equiv. piperidine were used instead. [d]CH_2Cl_2 as the solvent instead of *o*-DCB. [e]4 equiv. BocNHOMs and 6 equiv. piperidine were used instead. [f]Isolated after conversion to the methyl ester. [g](*S*,*S*)-**FeBIP** as the catalyst instead of (*R*,*R*)-**FeBIP**. [h]Reaction performed with racemic carboxylic acids.

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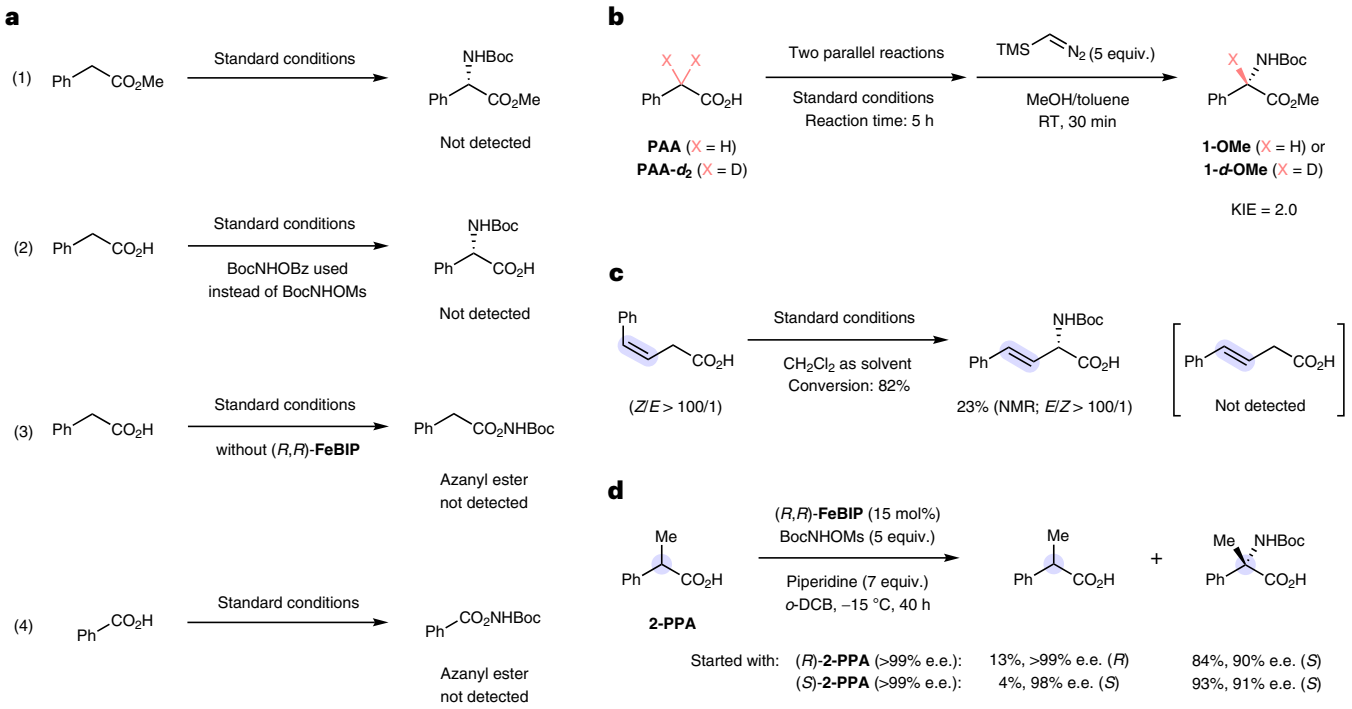

Fig. 2 | Mechanistic investigations. a, Control experiments. Standard conditions: 8 mol% (*R*,*R*)-**FeBIP**, 2 equiv. BocNHOMs, 4 equiv. piperidine in *o*-DCB (0.1 M) at −15 °C for 20 h. **b**, (*R*,*R*)-**FeBIP** catalysed α-amination of carboxylic acids **PAA** and **PAA-*d*$_2$** showed a kinetic isotope effect (KIE) value of $k_H/k_D = 2.0$. **c**, Under the standard reaction condition, the alkene isomerization of (*Z*)-4-phenylbut-3-enoic acid was observed. **d**, The α-amination of enantiopure 2-phenylpropanoic acid (**2-PPA**) proceeded in a stereoconvergent fashion. TMS, trimethylsilyl; RT, room temperature.

e.e. (**29**–**34**). (Note that this is an enantioconvergent reaction since it starts from racemic carboxylic acids.) The methyl group could be replaced with other alkyl groups such as ethyl, *n*-propyl, isopropyl and cyclohexyl to provide the respective α,α-disubstituted α-amino acids in 59–85% yield and with 93–94% e.e. (**35**–**38**). Substituting the phenyl moiety with a thiophene provided amino acid **39** in 45% yield and with 88% e.e. However, the α,α-disubstituted amino acids bearing two aliphatic substituents, such as **40** and **41**, were obtained in more modest yields and with unsatisfactory e.e. values.

Finally, we sought to apply the new one-step α-amination of carboxylic acids to the late-stage functionalization of pharmaceutically relevant molecules. We found that isoxepac (**42**), diclofenac (**43**), indomethacin (**44**), *tert*-butyldimethylsilyl-protected lithocholic acid (**45**), D-desthiobiotin (**46**), racemic ibuprofen (**47**), racemic ketoprofen (**48**) and racemic naproxen (**49**) all underwent stereocontrolled intermolecular amination in 37–88% yield and with up to 91% e.e. These successful examples further underscore the utility of our one-step amino acid synthesis protocol as it enables the expedient conversion of carboxylic acid-containing drugs, drug analogues and natural products to their respective non-racemic α-amino acids.

Mechanistic investigations

Having established the broad scope and utility of our iron-catalysed α-amination reaction, we turned our attention to mechanistic considerations. Formation of transition metal nitrenes from *N*-protected carbamates has been well investigated by several research groups[30–33] and was used as the starting point for our new intermolecular α-C–H amination of carboxylic acids. Several control experiments were conducted to interrogate the intermediates involved in this reaction (Fig. 2a). Under the standard conditions, methyl phenylacetate failed to afford any α-amination product, which was in a stark contrast with the productive PAA substrate, supporting the notion that the carboxylic acid functional group is important for the mechanism. Moreover,

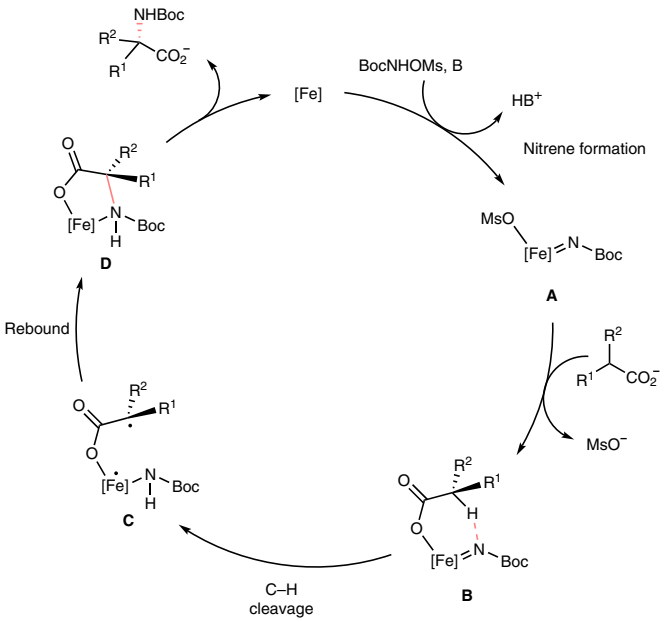

Fig. 3 | Proposed catalytic cycle. Simplified mechanism for the catalytic asymmetric one-step α-amino acid synthesis. B, base.

when *N*-benzoate carbamate was utilized as the aminating reagent, no α-amino acid product was detected (Table 1, entry 1), despite the fact that *N*-benzoate carbamate has proven very effective for metal nitrene formation[42]. However, the base-induced conversion of *N*-benzoate carbamate to a metal nitrene releases benzoate, which will compete with the carboxylate substrate for metal binding. Control experiments also rule out that the reaction occurs through the in situ generation

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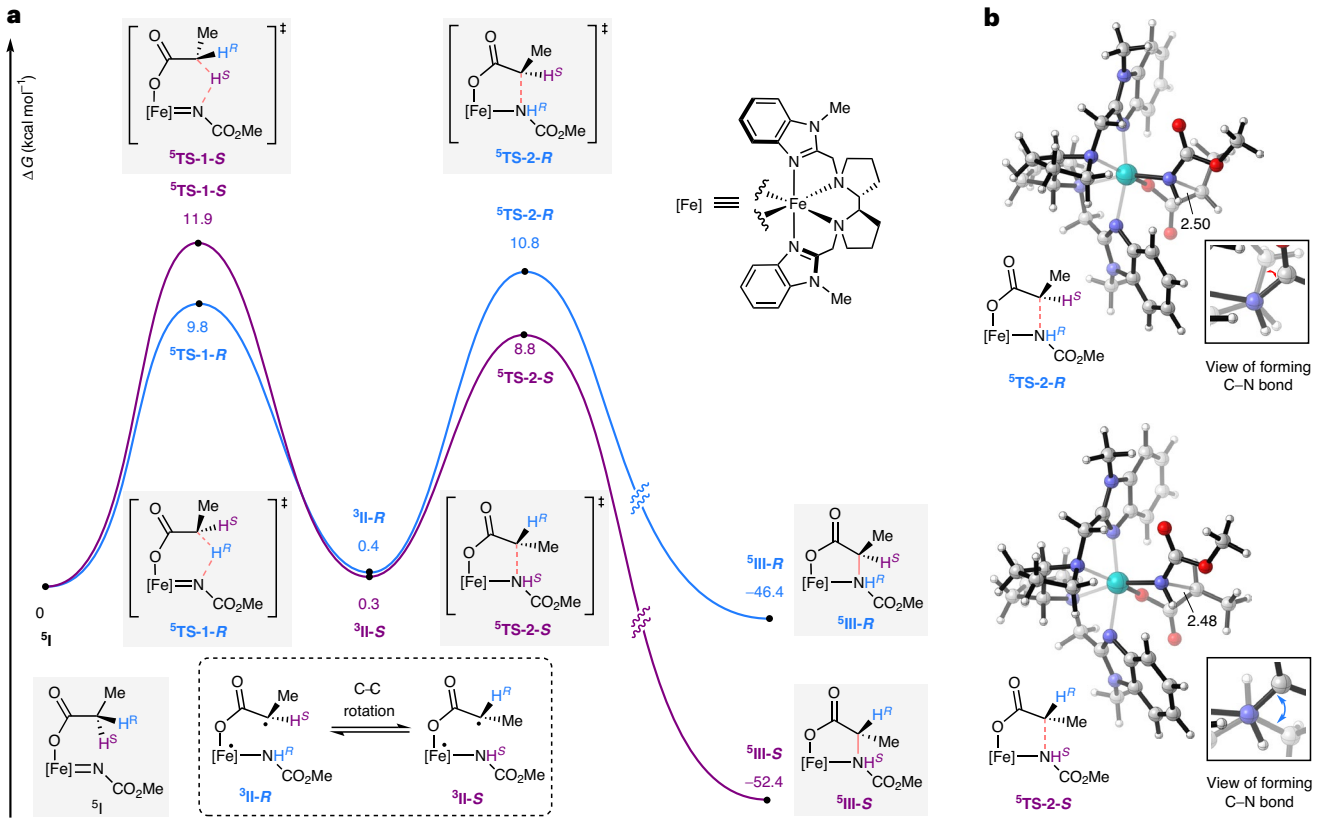

Fig. 4 | Density functional theory calculations regarding the mechanism of stereocontrol. a, Calculated free energy diagram at the B3LYP-D3/def2-TZVPP, SMD(CH_2Cl_2)//B3LYP-D3/def2-SVP level of theory. Note that only the most stable spin state of each species (denoted by superscript) is shown. **b**, Three-dimensional structures of calculated radical rebound transition states **TS-2**. Interatomic distances are in Å.

of azanyl ester under standard conditions, which distinguishes this reaction mechanistically from our previous intramolecular 1,3-nitrene migratory insertion[25]. By comparing the reaction rate constants of non-deuterated **PAA** (k_H) versus deuterated PAA (**PAA-d_2**) (k_D) of two parallel reactions, a kinetic isotope effect of $k_H/k_D = 2.0$ was obtained, indicating that cleavage of the C–H occurs during the rate-determining step (Fig. 2b). When (*Z*)-4-phenylbut-3-enoic acid was subjected to standard reaction conditions, complete *Z*/*E*-isomerization of the C=C bond occurred to provide the corresponding (*E*)-α-amino acid in 23% NMR spectroscopy yield with an *E*/*Z* ratio of >100/1 (Fig. 2c). This implies a radical mechanism proceeding through the formation of an allylic radical intermediate. Furthermore, reactions starting from enantiopure (*R*)- or (*S*)-2-phenylpropanoic acid (**2-PPA**) confirmed that the iron-catalysed α-amination of α,α-disubstituted carboxylic acids proceeds in a stereoconvergent fashion. In both cases, *S*-configurated α-amino acid was predominantly formed and the reisolated intact carboxylic acid after reaction did not show any significant racemization (Fig. 2d). These results suggest that an irreversible stereoablative process occurred in the coordination sphere before the C–N bond formation. Moreover, Hammett studies also revealed that the intermediate formed during the rate-determining step has a strong radical character (see the Supplementary Information section 'Hammett plots' for details).

Based on these experiments, a proposed simplified catalytic cycle for our developed intermolecular C(sp^3)–H amination of carboxylic acids is shown in Fig. 3. Base-induced reaction of the iron catalyst with the amination reagent leads to the formation of the iron nitrene[43] intermediate **A**. Coordination of the deprotonated carboxylic acid substrate to intermediate **B** sets the stage for an intramolecular 1,5-hydrogen atom transfer (HAT) to afford the diradical intermediate **C**, which has a sufficiently long lifetime to adopt a preferred conformation through bond rotation. The subsequent C–N bond formation via radical rebound constitutes the stereodetermining step in the catalytic cycle, thereby affording the intermediate **D**. Release of the deprotonated product concludes the catalytic cycle.

We also perfomed density functional theory calculations to further reveal the mechanism of stereocontrol in the reaction. Propionic acid and a nitrene intermediate containing a methyl carbamate protection group were used as the model system for the computations. Our calculated free energy diagram for the C(sp^3)–H abstraction and subsequent radical rebound steps is shown in Fig. 4a. The quintet spin state was found to be the most stable for **I**, the resting-state iron complex immediately before C(sp^3)–H abstraction (the triplet state and open-shell singlet states were calculated to be ~6 and ~8 kcal mol^{-1} higher in free energy, respectively; the free energy barrier for the N–O cleavage step to generate the iron nitrene intermediate was calculated to be low at 7.9 kcal mol^{-1}; see the Supplementary Information section 'Calculated free energy diagram' for details). Complex **I** undergoes 1,5-HAT via the quintet transition state **TS-1** with a free energy barrier of 9.8 kcal mol^{-1}, while an alternative outer-sphere HAT mechanism was calculated to have a higher free energy barrier of 13.3 kcal mol^{-1} (see the Supplementary Information section 'Calculated free energy diagram' for details). The resulting diradical **II** was calculated to be lowest in energy in its triplet state. While radical rebound (recombination) is often fast or barrierless for C–H functionalizations catalysed by iron-containing enzymes such as P450 (ref. [44]), the C–N bond-forming radical rebound step in our reaction had an unusually high barrier of 8.5 kcal mol^{-1} through the quintet transition state **TS-2**. This result suggested that the diradical intermediate **II** was relatively long lived, which might lead to stereoablation via bond rotation (such stereoablative bond rotation

may involve rotation of the more flexible Fe–O coordinative bond) and render the subsequent radical rebound step enantiodetermining[45]. Our calculations also showed that the 1,5-HAT step favoured the abstraction of the pro-*R* hydrogen by 2.1 kcal mol^{-1} (^{5}**TS-1-*R*** versus ^{5}**TS-1-*S***), which would yield the *R* product enantiomer instead of the experimentally observed *S* enantiomer if it were stereodetermining. In contrast, stereoablation of **II** through facile conformational change[45] and subsequent stereodetermining radical rebound would be in agreement with the preferential formation of the *S* product. Our experimental examples of enantioconvergent C(sp^3)–H amination of racemic α-branched carboxylic acids also indicate that the radical rebound step, not the C(sp^3)–H abstraction, controls the stereochemical outcome. Examination of the radical rebound transition states (Fig. 4b) revealed that the lower free energy of ^{5}**TS-2-*S*** compared with ^{5}**TS-2-*R*** can be at least partially attributed to a more favourable conformation about the forming C–N bond, where the carbon substituents are staggered rather than near-eclipsed.

Conclusions

We developed an expedited catalytic asymmetric synthesis of α-amino acids by intermolecular α-C(sp^3)–H amination of carboxylic acids. Our protocol employs abundant and readily available carboxylic acids as starting materials and converts them in a single step into highly valuable non-racemic *N*-protected α-amino acids suitable for direct use in peptide synthesis and for other synthetic applications. This method utilizes the convenient Boc-protecting group and sustainable iron catalysis without the need for more toxic or less abundant transition metals. This approach also merges nitrene-mediated C(sp^3)–H functionalization with directed C(sp^3)–H functionalization without the requirement for an intermediate cyclometalation. Upon deprotonation, the carboxylic acid substrate coordinates to the iron centre and serves as the directing group, which allows regioselective nitrene-mediated C(sp^3)–H abstraction and ensures high stereocontrol for the subsequent C–N bond formation step. Mechanistic evidence supports a radical mechanism in which the radical rebound step, rather than the initial C(sp^3)–H abstraction, is responsible for stereodiscrimination. Thus, in addition to providing a general method for the expedited synthesis of a wide range of chiral α-monosubstituted and α,α-disubstituted amino acids, including examples of late-stage amination of carboxylic acid-containing pharmaceuticals and natural products, this study is also prototypical for the development of intermolecular asymmetric C–H aminations through directed C(sp^3)–H nitrene insertion. Finally, it is noteworthy that this study discloses enantioselective intermolecular nitrene-mediated C(sp^3)–H aminations catalysed by a synthetic chiral iron complex.

Methods

General procedure for the iron-catalysed α-amination of carboxylic acids

To a dry Schlenk tube was added the carboxylic acid (1 equiv.), BocNHOMs (2–5 equiv.) and (*R*,*R*)-**FeBIP** (8–15 mol%). The tube was evacuated and backfilled with N_2 five times. The indicated solvent (0.1 M) and piperidine (4–7 equiv.) were added via syringe and the tube was sealed. The reaction mixture was further degassed via freeze–pump–thaw once. Then, the reaction mixture was stirred at −15 °C for the indicated time. After completion, the reaction mixture was diluted with Et_2O and washed with aqueous $NaHSO_4$ (1 M). The aqueous layer was extracted with Et_2O. The combined organic layer was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under decreased pressure and the residue was purified by column chromatography on silica gel using a mixture of EtOAc and hexane (with 0.2% acetic acid as the additive) to obtain the non-racemic α-amino acids **1**–**49**.

Data availability

All of the data are available within the main text or Supplementary Information.

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Author contributions

C.-X.Y., S.C. and E.M. wrote the manuscript. C.-X.Y. and E.M. conceived of the project. C.-X.Y. and E.M. devised the synthetic experiments. C.-X.Y. performed the synthetic experiments. D.R.D. and S.C. devised and performed the density functional theory calculations. S.C. and E.M. supervised the project.

Competing interests

C.-X.Y. and E.M. are named inventors on a European patent application filed by the University of Marburg on the expedited synthesis of α-amino acids (EP22193497.9). The remaining authors declare no competing interests.

Additional information

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