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Modular α-tertiary amino ester synthesis through cobalt-catalysed asymmetric aza-Barbier reaction

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Unnatural chiral α-tertiary amino acids containing two different carbon-based substituents at the α-carbon centre are widespread in biologically active molecules. This sterically rigid scaffold is becoming a growing research interest in drug discovery. However, a robust protocol for chiral α-tertiary amino acid synthesis remains scarce due to the challenge of stereoselectively constructing sterically encumbered tetrasubstituted stereogenic carbon centres. Herein we report a cobalt-catalysed enantioselective aza-Barbier reaction of ketimines with various unactivated alkyl halides, including alkyl iodides, alkyl bromides and alkyl chlorides, enabling the formation of chiral α-tertiary amino esters with a high level of enantioselectivity and excellent functional group tolerance. Primary, secondary and tertiary organoelectrophiles are all tolerated in this asymmetric reductive addition protocol, which provides a complementary method for the well-exploited enantioselective nucleophilic addition with moisture- and air-sensitive organometallic reagents. Moreover, the three-component transformation of α-ketoester, amine and alkyl halide represents a formal asymmetric deoxygenative alkylamination of the carbonyl group.

Optically active amine is a class with versatile structure motifs that is prevalent in numerous bioactive natural products and pharmaceuticals, and its members are also broadly used as ligands or catalysts to enable chirality induction (Fig. 1a)[1–3]. Among the chiral amine scaffold, 20 proteinogenic amino acids that mostly contain an α-secondary chiral carbon constitute the bases of the origin and evolution of lives on earth. However, the enantio-enriched amino acid derivatives bearing an α-tertiary carbon centre are unable to be accessed by nature. Recent studies have disclosed that the unnatural α-tertiary amino acids could exhibit pronounced helix-inducing potential in peptides, and enhance resistances for chemical and enzymatic degradation[4]. Given the diversity and significance of α-tertiary amino acid derivatives, the development of synthetic methods for this motif has been the focus of substantial effort[5,6]. In sharp contrast to the existence of several robust synthetic methods, including asymmetric reduction of an imine or enamine[7,8], N–H insertion to a carbene precursor[9] and cross-coupling[10] for the α-secondary amino acid synthesis, the facile construction of the highly congested tetrasubstituted carbon centre still largely lags behind due to the requirement of an unnatural chiral α-tertiary amino acid[11–17].

Of the established methods for α-tertiary amino acid derivative synthesis, an organometallic reagent addition towards the ketimine

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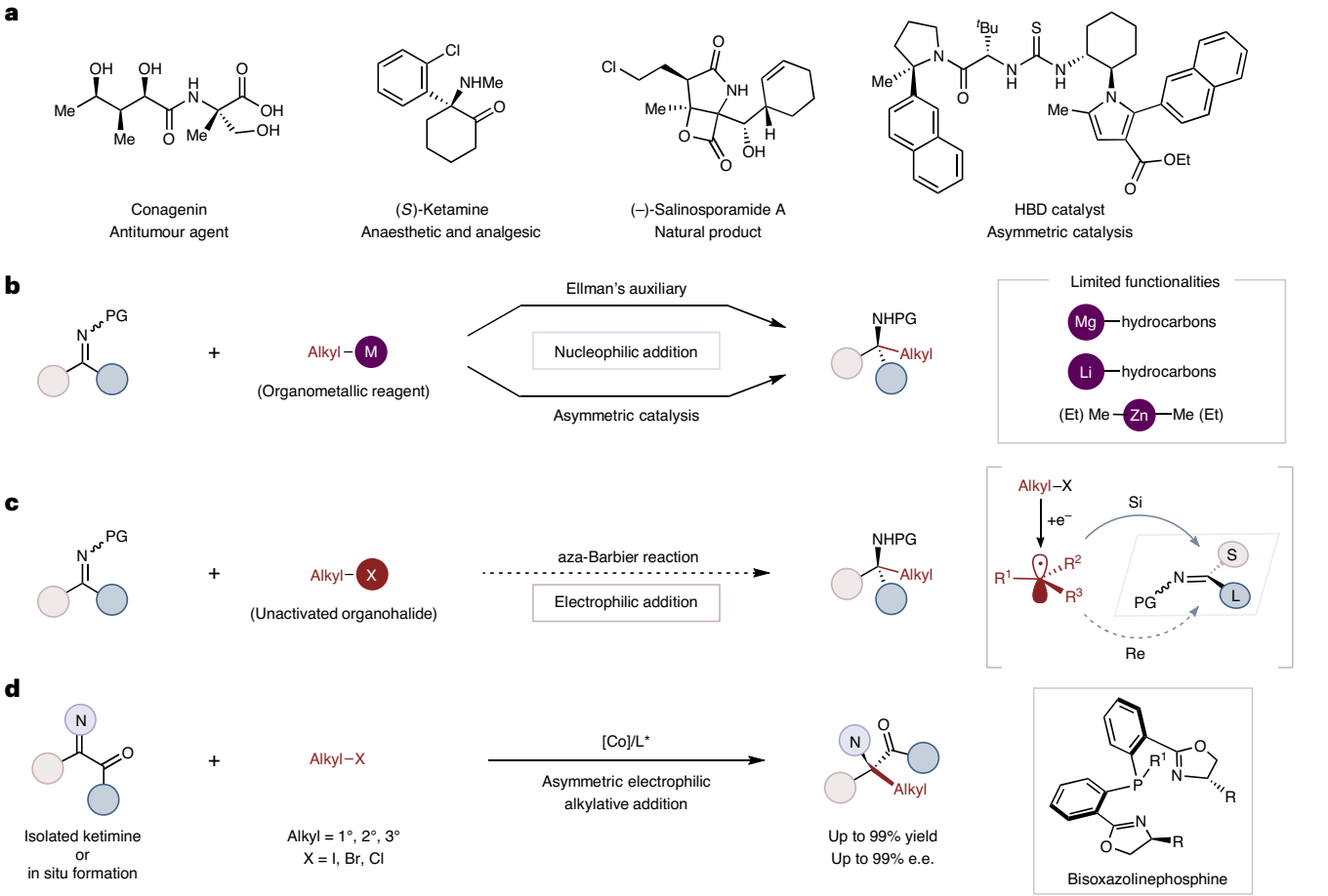

Fig. 1 | Introduction for asymmetric alkylative aza-Barbier reaction. **a**, Representative bioactive molecules and catalyst bearing α-tetrasubstituted chiral amine unit. HBD, hydrogen-bond donor. **b**, The nucleophilic addition of ketimine with organometallic reagent. Reported examples with the use of moisture- and air-sensitive organometallic nucleophiles, including organolithium, the Grignard reagent and dialkylzinc reagents, show limited functional group tolerance. PG, protecting group. M, metal. **c**, Overview of aza-Barbier reaction. Reductive addition of imine with readily available and stable alkyl halides circumvents the use of organometallic reagents. The inherent challenge of this transformation lies in the differentiation of the enantiotopic faces. X, halogen atom; Si, Si face; Re, Re face.; S, small group; L, large group; e^-, electron. **d**, Cobalt-catalysed asymmetric electrophilic addition of ketimine with unactivated alkyl halides (this study). N, protected nitrogen group. L*, chiral ligand.

is perhaps the most exploited transformation (Fig. 1b)[18,19]. The Ellman group seminally developed the nucleophilic addition of chiral auxiliary *N-tert*-butanesulfinyl imines with excellent diastereoisomeric excess[20]. The catalytic asymmetric addition of ketimine with organometallic reagents also represents a well-established method for this scaffold synthesis[21–25]. Nevertheless, these approaches are dominated by the use of moisture- and air-sensitive organometallic reagents. Moreover, the most reliable organometallic nucleophiles, including organolithium, the Grignard reagent and a small number of dialkylzinc reagents, are less functionality-group tolerable, which frequently results in lengthy and cumbersome additional protection–deprotection manipulation in a multistep synthesis. Considering that the organometallic reagents are generally prepared from corresponding alkyl halide precursors that also often require time and resource consumption, there would be a great impetus to achieve the direct asymmetric reductive addition of easily accessible, unactivated alkyl halides to the ketimine, a method that still remains undeveloped.

Harnessing an alkyl halide for electrophilic addition towards the unsaturated carbon–heteroatom bond in the presence of a reductant, namely a Barbier reaction, is a versatile synthetic method for alcohol and amine synthesis[26,27]. Earlier studies mainly rely on the use of a stoichiometric auxiliary with a large excess of alkyl halide[28]. Friestad et al. accomplished copper-mediated enantioselective radical addition of *N*-acyl hydrazones with 1 equivalent chiral bisoxazoline ligand[29]. Recently, transition-metal-catalysed reductive additions to aldimine or aldiminium functional groups have resulted in facile access to α-secondary amine derivatives[30–33]. Particularly, Gaunt and coworkers recently developed an elegant visible light-mediated assembly of the α-ketoester, amine and alkyl iodide, enabling the racemic α-tertiary amino ester synthesis, in which the free alkyl radical undergoes addition to the ketimine intermediate[34,35]. The challenge of the analogous chiral amino acid derivative formation for the aza-Barbier reaction lies in the differentiation of the enantiotopic faces for the free alkyl radical generated in situ from the alkyl halide precursor (Fig. 1c)[36]. Gong and coworkers reported that the use of photoredox bifunctional catalysts enabled the C(sp^3)–H functionalization of hydrocarbons with cyclic *N*-sulfonylimines through the stereoselective coupling of an aminoalkyl radical with an alkyl radical[37]. Recently, Earth-abundant cobalt complexes have been shown to be viable catalysts for the reductive cross-coupling of organoelectrophiles[38–43]. We envisioned that the in situ-formed alkyl radical species might be trapped by the judicious choice of a cobalt catalyst with the assistance of chiral ligand induction to generate the nucleophilic chiral alkyl–Co species. This strategy could offer the possibility of differentiating the enantiotopic face of ketimine, thus accomplishing the construction of a tetrasubstituted stereogenic centre[44]. The rapid combination of alkyl radical species with the cobalt centre is crucial to achieving the high enantioselectivity by obviating the side racemic free-radical addition sequence[35]. Herein we describe

our platform of an enantioselective aza-Barbier reaction for α-tertiary amino ester synthesis by identifying a cobalt-catalysed electrophilic alkylative addition of ketimine with unactivated alkyl halides.

Results and discussion

We selected the ketimine **1a** as the model substrate with primary *n*-heptyl iodide (1.5 equiv.) as the coupling component in the presence of 5 mol% CoI_2 and 6 mol% chiral ligand; 2.0 equiv. Mn as the reductant; and 1.0 equiv. ^{i}PrOH as an additive in MeCN (Table 1). Ligand screening revealed that the desired amino ester **3a** was obtained in 89% isolated yield with 98% e.e. with the use of chiral tridentate bisoxazolinephosphine (NPN) ligand **L27** (refs. 45–47). The alcohol additive should be the same with the substitution on the ester group of the ketimine part. The reaction efficiency dropped with the omission of ^{i}PrOH (68%, 94% e.e.; Supplementary Table 3). We then explored the scope of the asymmetric alkylation of ketimine. First, we investigated the generality of alkyl fragments for this transformation. The protocol worked well with various primary alkyl iodides under standard conditions, providing the corresponding chiral α-tertiary amino ester in good yields and excellent enantioselectivities (**3a**–**3n**). A gram-scale reaction could successfully proceed to give product **3a** while maintaining a high yield and enantioselectivity. Various functional groups such as alkenyl (**3b**); convertible carbonyl groups including ketone (**3c**), ester (**3d**) and acetal groups (**3e**); and amine with an active proton (**3f**) could be tolerated well with this protocol to provide corresponding products in 50–96% yields with 94–99% e.e., illustrating a superior functional group capability over the organometallic reagents. The bulkier cyclohexyl and piperidinyl pendant iodides, along with neopentyl electrophile, could also proceed smoothly, providing the chiral amine products **3g**–**3i** in ideal yields and enantioselectivities. Notably, bioactive fragments such as gemfibrozil (**3j**), indometacin (**3k**), steroid (**3l**), glucoside (**3m**) and uridine (**3n**) were all compatible with the current conditions, furnishing an array of α-tertiary amino esters, which fully demonstrated the potential synthetic utility of this protocol in medicinal chemistry. To our delight, the current protocol was also suitable for diverse sterially hindered secondary alkyl iodides, including both various acyclic and cyclic fragments (**3o**–**3aa**). The size of carbocycles did not compromise the efficiency of the asymmetric aza-Barbier reaction, providing five- to eight-membered carbocyclic adducts (**3p**–**3s**) in 79–96% yields with 97–99% e.e. Various heterocycle-containing iodides, such as *N*-tert-butoxycarbonyl-piperidine (*N*-Boc-piperidine) (**3t**), tetrahydropyran (**3u**), *N*-Boc-azetidine (**3v**) and oxetane (**3w**), as well as electrophiles derived from an aza-bridged ring (**3aa**), were also successfully engaged to deliver plentiful enantio-enriched heterocycle-decorated amines. Intriguingly, our chemistry exhibited great compatibility towards different spirocyclic building blocks (**3x**–**3z**), further demonstrating the underlying application value of this transformation. To demonstrate the generality of this protocol, more easily available alkyl bromide substrates were also investigated (Table 1, ii). It was found that both primary and secondary alkyl bromides were competent electrophiles for this asymmetric aza-Barbier reaction to afford the corresponding products **3a** and **3p** in excellent yields and enantioselectivities with modified conditions. In the case of the bulkiest tertiary coupling partner, this protocol overcame the congested steric hindrance to afford the corresponding adducts, constituted with the synthetically challenging situation of two continuous quaternary centres, with high enantioselectivity and moderate yield with the use of the chiral ligands **L27** and **L28** (**3ab**–**3ad**). The absolute stereochemistry of complex **3d** was determined by X-ray crystallographic analysis. Alkyl chlorides are valuable electrophiles due to their abundance, stability and low toxicity. Nevertheless, unactivated alkyl chlorides are seldom employed in reductive cross-coupling reactions due to their low reactivity compared to the corresponding bromide and iodide analogues. To date, only a handful of racemic cross-electrophile couplings have been reported[48,49]. After extensive investigation of the reaction conditions, it was found that a broad range of alkyl chlorides could successfully be employed under the modified reaction conditions (Table 1, iii). For example, functional groups such as carbonyls (–CO_2Me, –$CONR_2$; **3ag**, **3ah**) and amines (–NHBoc, –NHPh; **3ai**, **3aj**) were very compatible. Primary, secondary and tertiary alkyl chlorides could all furnish the corresponding products at a respectable efficiency and with exceptional enantioselectivity. This reaction represents an asymmetric cross-electrophile transformation involving unactivated alkyl chloride.

Next, further evaluation of the ketimine scope was performed. With respect to α-imino ester substrates (Table 2, i), introducing electron-donating and electron-withdrawing substituents on the *ortho*, *meta* or *para* position of the aromatic ring would barely affect the reaction efficiency (**3am**–**3az**). Ketimines bearing halogens such as F (**3as**), Cl (**3ap**, **3ar**, **3ax**) and Br (**3aq**) atoms were all competent substrates, affording the corresponding products in high yields with commendable e.e. values. Medically useful fenofibrate (**3at**) and sulfadimethoxine (**3au**) analogues were also suitable. Switching phenyl to heterocycle groups such as thienyl and indolyl successfully delivered **3ay** and **3az** in good yields and with high enantioselectivities. In addition, alkyl-substituted ketimines such as primary methyl-substituted (**3ba**, **3bb**), phenylethyl-substituted (**3bc**) and secondary cyclohexyl-substituted (**3bd**) α-imino esters could also successfully participate in this reaction to afford dialkyl α-tertiary amino esters in satisfying yields with excellent enantioselectivities. Notably, switching the phenyl substituent of ketimine to a CF_3 group also successfully delivered the corresponding product **3be**–**3bg** in 59–72% yields with up to 99% e.e. Variations of another aromatic ring on the nitrogen atom generally gave similarly good results (**3bh**–**3bj**); however, methoxyl substitution on the *ortho* position gave a good yield yet lower e.e. (**3bh**), probably due to the competing coordination effect of the methoxyl group during the enantio-determining step. Investigation of other nitrogen-protecting groups revealed that alkyl (**3bk**, **3bl**) as well as removable benzyl (**3bm**, **3bn**) groups were suitable for this transformation, providing the corresponding products with excellent enantioselectivities. Switching the ester fragment to a methyl or ethyl ester that could be prone to hydrolysis did not affect the reaction efficiency (**3bo**–**3bp**).

Enantio-enriched cyclic amines, particularly the α-tetrasubstituted chiral cyclic amino esters, are frequently occurring structural fragments in diverse natural products and pharmaceuticals due to their structural diversity. One of the most powerful strategies for the synthesis of optically active α-quaternary cyclic amino esters is the α-alkylation of chiral oxazol-1-one through an auxiliary strategy[50]. However, this method is restricted to primary alkyl halides and requires chiral substrates, and the requirement of a strong base leads to inferior functional group tolerance. Extensive investigation of the reaction conditions showed that a broad range of alkyl bromides could be used in this Co-catalysed asymmetric aza-Barbier reaction with cyclic imino ester substrates and **L30** as the chiral ligand (Table 2, ii). Through the interaction with simple primary (**3bq**, **3br**), secondary acyclic or (hetero)cyclic (**3bs**–**3bx**) and tertiary (**3by**) alkyl bromides, diverse chiral pyrrolidines bearing a tetrasubstituted stereocentre at the α-position could be furnished with high enantioselectivity. With respect to the cyclic imino esters with a pre-existing chiral centre, the change of configuration of the chiral ligand **L30** would stereodivergently afford the desired product **3bz** with excellent diastereoselectivity. Moreover, six-membered cyclic imino esters also proved to be an effective substrate, providing a chiral piperidine product (**3ca**) in moderate yield with 98% e.e. In addition, this protocol was also amenable to isatinimine substrates with simple primary or secondary alkyl iodides, delivering products **3cb** and **3cc** with remarkable efficiencies (Table 2, iii). The substitution on the aromatic ring substructure had little influence on the reaction efficiency; thus isatinimines with various functional groups were compatible, with high yields and enantioselectivities (**3cd**–**3ck**).

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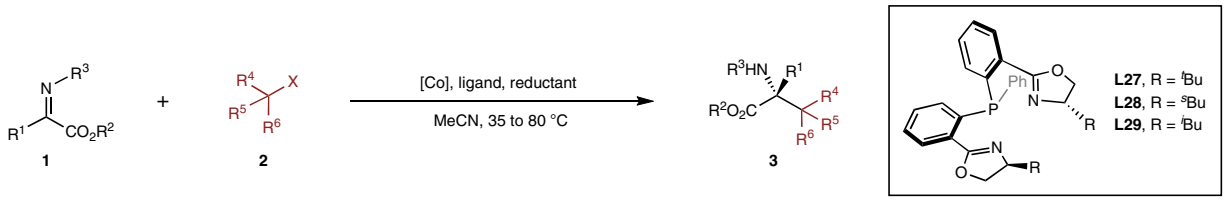
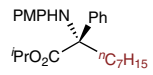
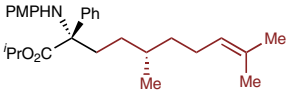
Table 1 | Substrate scope of unactivated alkyl halide



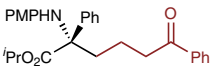
(i) Alkyl iodides[a]



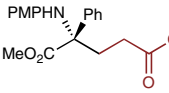
3a, 89%, 98% e.e.
Gram scale, 84%, 98% e.e.



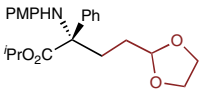
3b, 96%, 99:1 d.r.



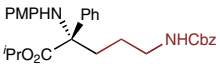
3c, 67%, 99% e.e.



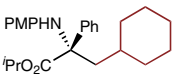
3d, 50%, 97% e.e.



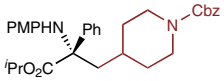
3e, 79%, 94% e.e.



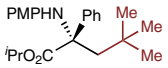
3f, 61%, 99% e.e.



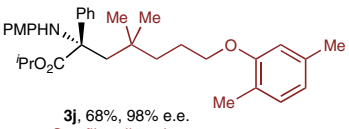
3g, 73%, 99% e.e.



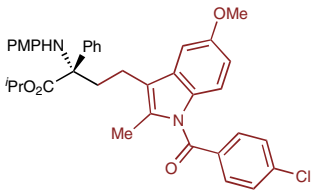
3h, 83%, 98% e.e.



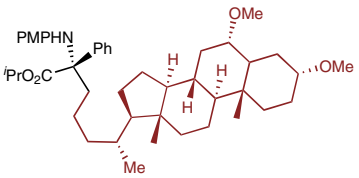
3i, 70%, 98% e.e.



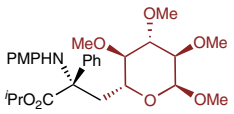
3j, 68%, 98% e.e.
Gemfibrozil analogue



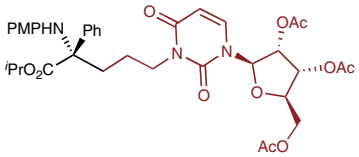
3k, 87%, 97% e.e.
Indometacin analogue



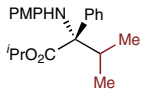
3l, 79%, 98:2 d.r.
Hyodeoxycholic acid analogue



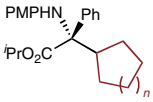
3m, 66%, >99:1 d.r.
α-D-Methylglucoside analogue



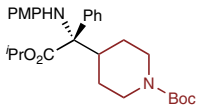
3n, 68%, 98.5:1.5 d.r.
2′,3′,5′-Tri-*O*-acetyluridine analogue



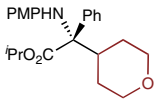
3o, 99%, 99% e.e.



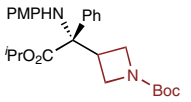
3p, *n* = 1, 96%, 98% e.e.
3q, *n* = 2, 90%, 98% e.e.
3r, *n* = 3, 79%, 99% e.e.
3s, *n* = 4, 85%, 97% e.e.



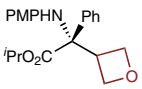
3t, 68%, 96% e.e.



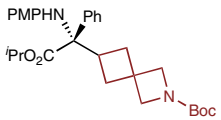
3u, 93%, 97% e.e.



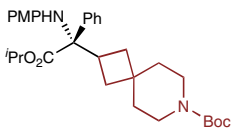
3v, 54%, 89% e.e.



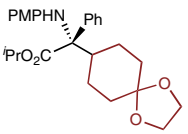
3w, 72%, 95% e.e.



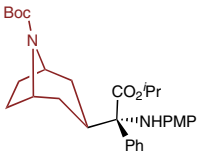
3x, 67%, 95% e.e.



3y, 79%, 97% e.e.

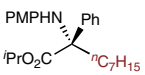


3z, 74%, 98% e.e.

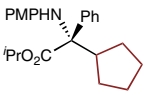


3aa, 64%, 94.5:5.5 d.r.

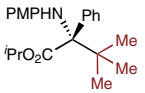
(ii) Alkyl bromides[a]



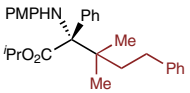
3a, 88%, 97% e.e.[b]



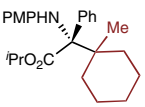
3p, 99%, 98% e.e.[b]



3ab, 61%, 95% e.e.[c]

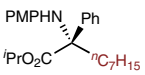


3ac, 55%, 92% e.e.[d]

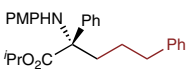


3ad, 26%, 95% e.e.[c]

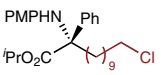
(iii) Alkyl chlorides[a]



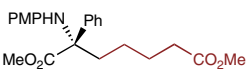
3a, 84%, 99% e.e.



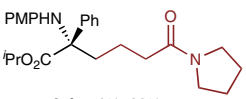
3ae, 76%, 98% e.e.



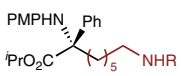
3af, 44%, 97% e.e.



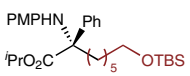
3ag, 68%, 98% e.e.



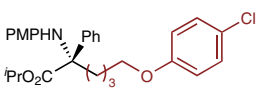
3ah, 56%, 98% e.e.



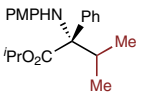
3ai, R = Boc, 42%, 99% e.e.
3aj, R = Ph, 72%, 99% e.e.



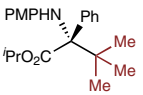
3ak, 63%, 95% e.e.



3al, 50%, 98% e.e.



3o, 40%, 97% e.e.[f]

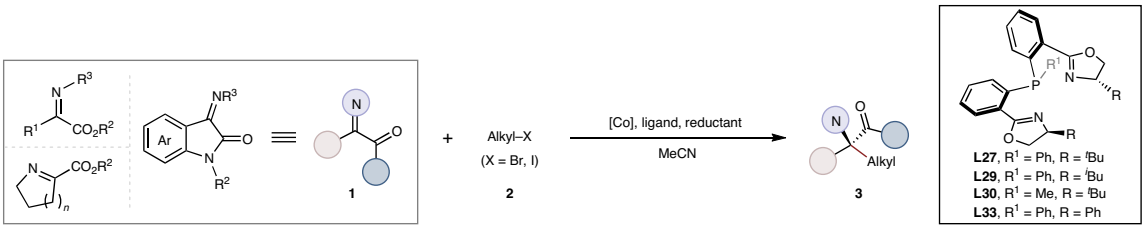


3ab, 77%, 98% e.e.[g]

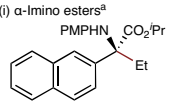
[a]The reactions were run with ketimine **1** (1.0 equiv.), alkyl halide (1.5 equiv.), CoI_2 (5 mol%), **L27** (6 mol%), Mn (2.0 equiv.) and R^2OH (1.0 equiv.) in MeCN (0.2 M) at 35 °C for the required time. Isolated yields were reported and the e.e. was determined by chiral HPLC analysis. [b]2.0 equiv. LiI was added. [c]CoI_2 (10 mol%) and **L28** (12 mol%) were used. [d]CoI_2 (10 mol%) and **L27** (12 mol%) were used. [e]The reactions were run with ketimine **1** (1.0 equiv.), alkyl chloride (3.0 equiv.), $CoBr_2$ (10 mol%), **L29** (12 mol%), In (3.0 equiv.) and NaI (3.5 equiv.) in MeCN (0.4 M) at 80 °C for 48 h. [f]$CoBr_2$ (20 mol%) and **L29** (24 mol%) were used. [g]$CoBr_2$ (20 mol%), **L29** (24 mol%) and MeCN (0.2 M) were used. PMP, *p*-methoxyphenyl.

https://doi.org/10.1038/s41557-023-01378-9

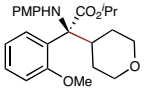
Table 2 | Substrate scope of ketimine



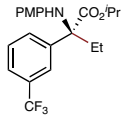
(i) α-Imino esters[a]



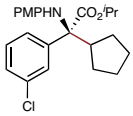
3am, 75%, 98% e.e.



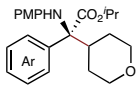
3an, 73%, 96% e.e.



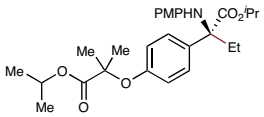
3ao, 67%, 95% e.e.



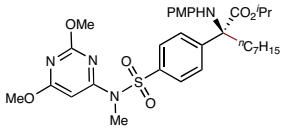
3ap, 86%, 98% e.e.



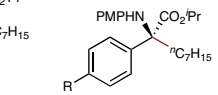
3aq, Ar = 4-Br-C_6H_4, 53%, 93% e.e.
3ar, Ar = 3,4-diCl-C_6H_3, 98%, 90% e.e.
3as, Ar = 3,5-diF-C_6H_3, 87%, 89% e.e.



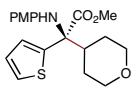
3at, 66%, 97% e.e.
Fenofibrate analogue



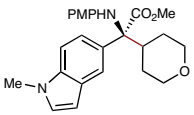
3au, 57%, 94% e.e.
Sulfadimethoxine analogue



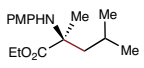
3av, R = OMe, 86%, 99% e.e.
3aw, R = CF_3, 86%, 98% e.e.
3ax, R = Cl, 88%, 93% e.e.



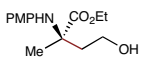
3ay, 61%, 94% e.e.



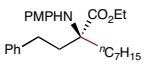
3az, 65%, 97% e.e.



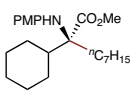
3ba, 71%, 93% e.e.[b]



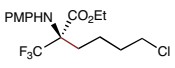
3bb, 84%, 90% e.e.[c]



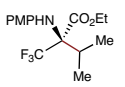
3bc, 45%, 92% e.e.[d]



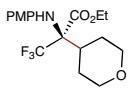
3bd, 63%, 99% e.e.[e]



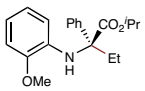
3be, 59%, 97% e.e.[f]



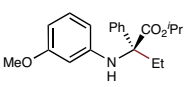
3bf, 72%, 98% e.e.[f]



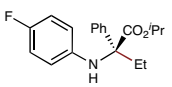
3bg, 60%, 99% e.e.[f]



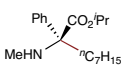
3bh, 74%, 81% e.e.



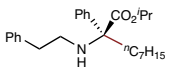
3bi, 62%, 94% e.e.



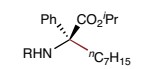
3bj, 68%, 93% e.e.



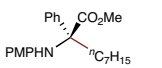
3bk, 83%, 96% e.e.[g]



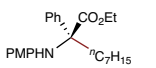
3bl, 70%, 97% e.e.[g]



3bm, R = PMB, 67%, 97% e.e.[g]
3bn, R = Bn, 61%, 97% e.e.[g]

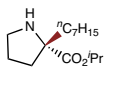


3bo, 74%, 98% e.e.

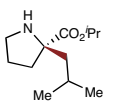


3bp, 75%, 97% e.e.

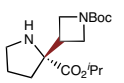
(ii) Cyclic iminoesters[h]



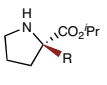
3bq, 72%, 99% e.e.



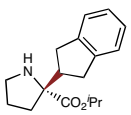
3br, 64%, 99% e.e.



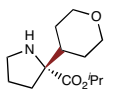
3bs, 61%, 90% e.e.



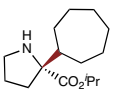
3bt, R = ^{i}Pr, 49%, 99% e.e.
3bu, R = cyclopentyl, 70%, 99% e.e.



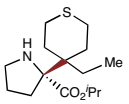
3bv, 75%, 98% e.e.



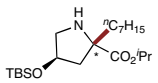
3bw, 71%, 99% e.e.



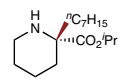
3bx, 75%, 99% e.e.



3by, 63%, 97% e.e.

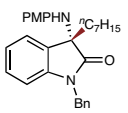


(*S*)-**L30**, (2*S*,4*R*)-**3bz**, 61%, >20:1 d.r.
(*R*)-**L30**, (2*R*,4*R*)-**3bz**, 56%, >20:1 d.r.

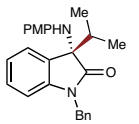


3ca, 55%, 98% e.e.[i]

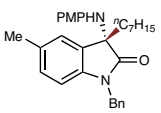
(iii) Isatinimine[j]



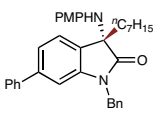
3cb, 96%, 93% e.e.



3cc, 92%, 95% e.e.[k]



3cd, 97%, 90% e.e.



3ce, 87%, 91% e.e.

3cf, 94%, 89% e.e.

3cg, 91%, 90% e.e.

3ch, 68%, 91% e.e.

3ci, 73%, 93% e.e.

3cj, 85%, 86% e.e.

3ck, 84%, 90% e.e.

[a]The reactions were run with ketimine **1** (1.0 equiv.), alkyl iodide (1.5 equiv.), CoI_2 (5 mol%), **L27** (6 mol%), Mn (2.0 equiv.) and R^2OH (1.0 equiv.) in MeCN (0.2 M) at 35 °C for the required time. Isolated yields were reported, and the e.e. was determined by chiral HPLC analysis. [b](*R*)-**L27** was used. [c]*tert*-butyl(2-iodoethoxy)dimethylsilane was used; the reaction was quenched with aqueous HCl (1.0 M, 3.0 equiv.). [d]The alkyl-substituted ketimine was formed in situ, while CoI_2 (10 mol%), **L29** (12 mol%), In (2.0 equiv.) and $^nC_7H_{15}I$ (2.0 equiv.) were used. [e]**L29** (6 mol%) was used. [f]CoI_2 (10 mol%), **L29** (12 mol%), alkyl iodide (2.0 equiv.) and MeCN (0.1 M) were used. [g]The *N*-alkyl ketimine was formed in situ, while CoI_2 (10 mol%), **L29** (12 mol%) and $^nC_7H_{15}I$ (2.0 equiv.) were used. [h]The reactions were run with cyclic imine **1** (1.0 equiv.), alkyl bromide (2.0 equiv.), CoI_2 (5 mol%), **L30** (6 mol%), Mn (2.0 equiv.), TBAI (20 mol%) and ^{i}PrOH (1.0 equiv.) in MeCN (0.3 M) at 30 °C for 24 h. [i]NaI (20 mol%) was used instead of TBAI. [j]The reactions were run with isatinimine **1** (1.0 equiv.), alkyl iodide (1.5 equiv.), CoI_2 (5 mol%), **L29** (6 mol%), Mn (2.0 equiv.) and ^{i}PrOH (1.0 equiv.) in MeCN (0.05 M) at 35 °C for the required time. [k]**L33** (6 mol%) and MeOH (1.0 equiv.) were used. TBAI, tetrabutylammonium iodide.

To further demonstrate the practical synthetic application of this protocol, various transformations were conducted (Fig. 2). The Co-catalysed aza-Barbier reaction of ketimine that was formed in situ by condensation of ketoester and aniline provided the α-amino ester at the same efficiency in both yield and enantiomeric excess with the isolated ketimines by the use of either primary (**3h**), secondary (**3y**,**3z**) or tertiary (**3ab**) alkyl halides as the coupling component (Fig. 2a). These encouraging results could be viewed as a formal asymmetric

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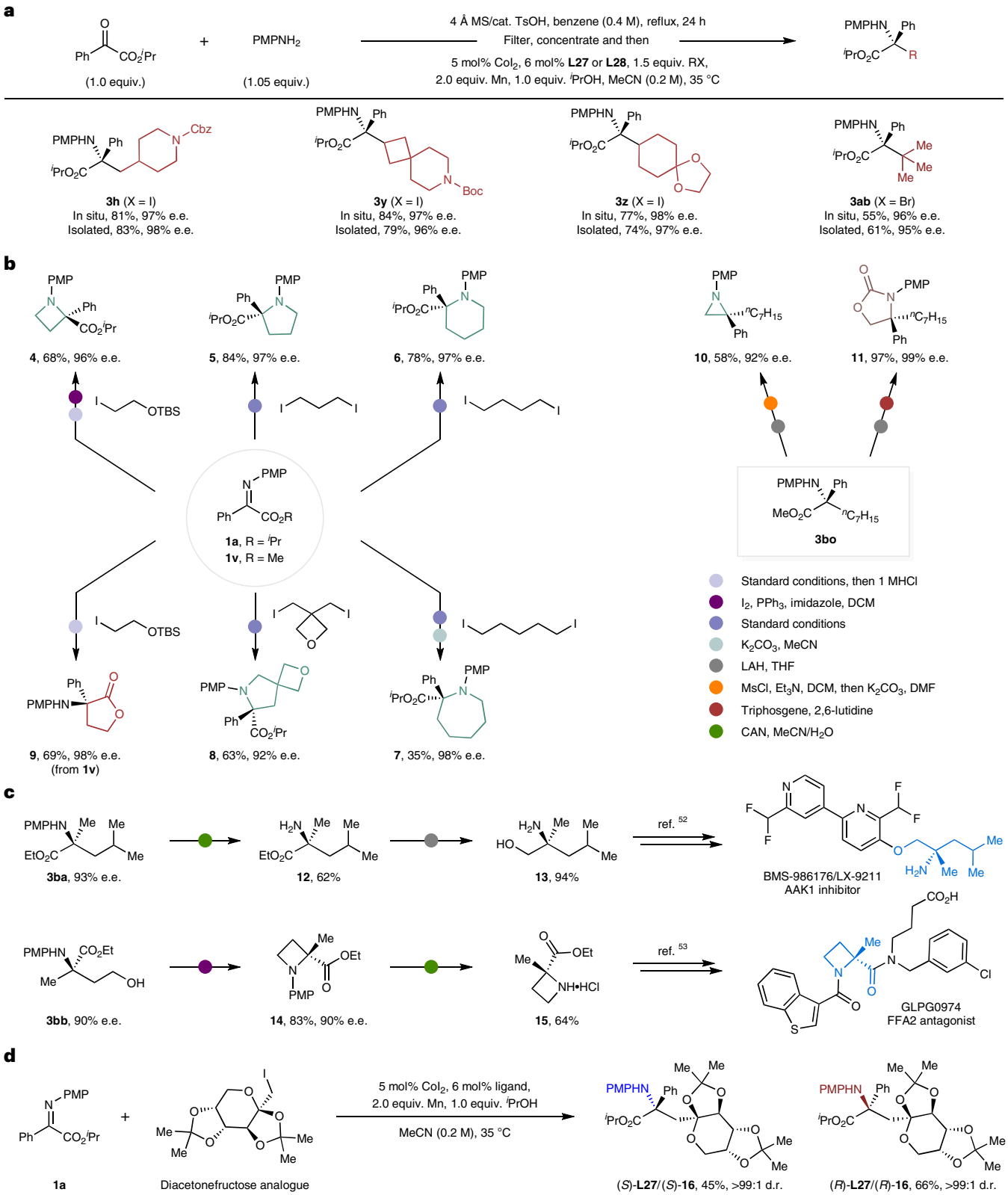

Fig. 2 | Synthetic applications. a, Formal asymmetric deoxygenative alkylamination of ketoesters. Reaction of the ketimine that was formed in situ by condensation of ketoester and aniline under standard conditions provided products with the same efficiency in both yield and enantioselectivity as did the isolated ketimines. MS/cat, molecular sieve/catalytic. **b**, Modular synthesis of chiral heterocycles. Use of different alkyl electrophiles through a tandem aza-Barbier reaction/cyclization sequence enabled the expedient construction of enantio-enriched divergent heterocycles. DCM, dichloromethane; LAH, lithium aluminium hydride; THF, tetrahydrofuran; MsCl, methanesulfonyl chloride; DMF, *N*,*N*-dimethylformamide; CAN, ceric ammonium nitrate. **c**, Formal synthesis of core structure of bioactive molecules by the further transformation of products **3ba** and **3bb**. **d**, Stereodivergent synthesis of **16**.

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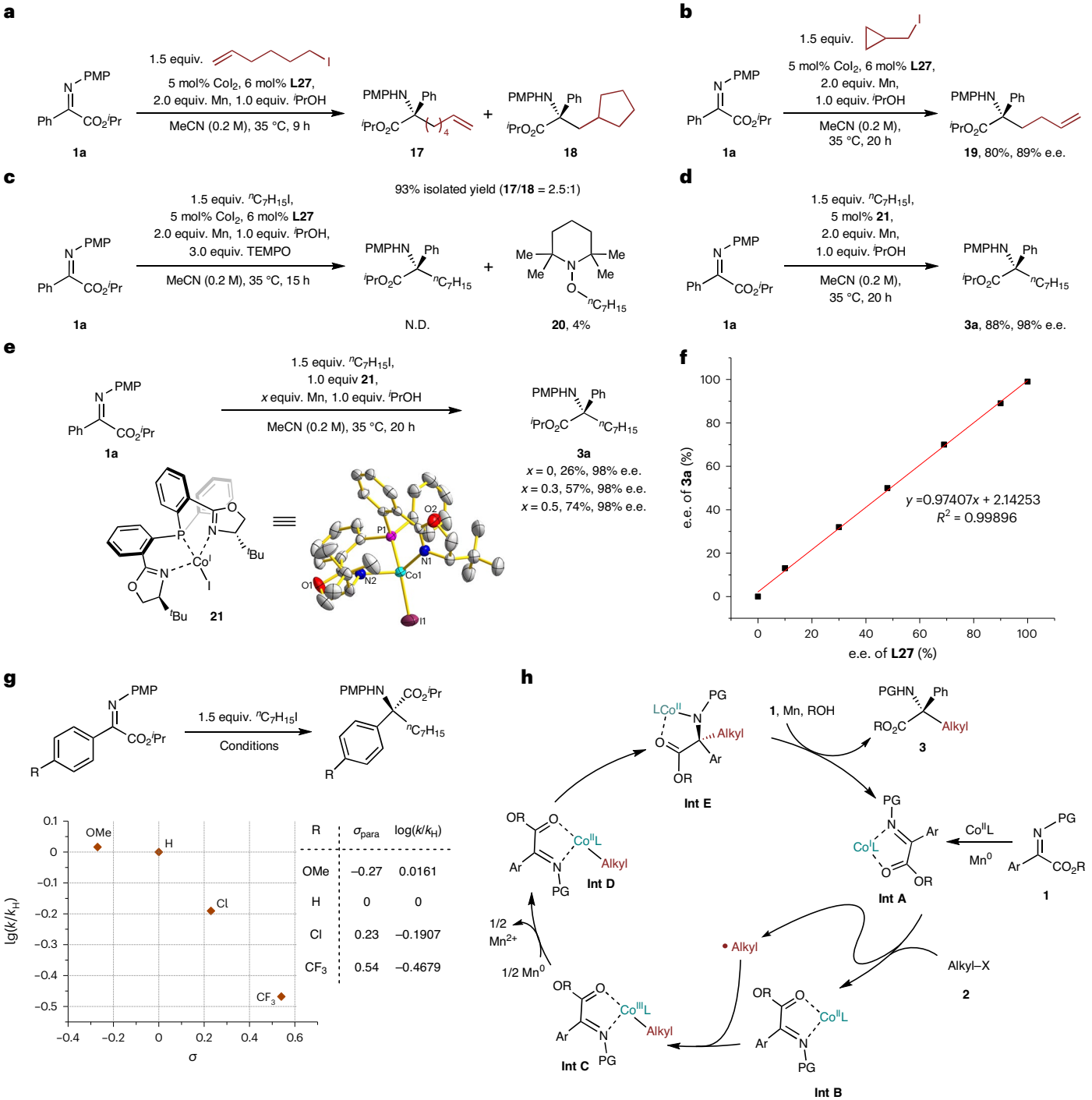

Fig. 3 | Preliminary mechanistic studies. a, Radical cyclization experiment. Use of 6-iodohex-1-ene as the coupling partner provided cyclized product **18**, indicating that the alkyl radical species might be generated during the reaction. **b**, Radical clock experiment. Employment of ketimine **1a** with (iodomethyl) cyclopropane furnished ring-opening product **19**, further implying the existence of alkyl radical species. **c**, Radical trap reaction. The addition of TEMPO completely inhibited the reaction with the formation of TEMPO adduct **20**, suggesting the possibility of a SET process with the generation of alkyl radical species during the reaction. The yield was reported as a gas chromatography yield with dodecane as the internal standard. **d**, Catalytic aza-Barbier reaction with complex **21** gave corresponding product **3a** with a similar result, indicating that Co(I) complex might be an initiator of the reaction. **e**, Stoichiometric reactions with different amounts of Mn. The results indicated that an alkyl–Co(II) species instead of alkyl–Co(III) species may be the reactive species. **f**, A linear relationship experiment revealed that the active cobalt catalyst possibly coordinated with a single ligand. R^2, coefficient of determination. **g**, Hammett plot study. A negative ρ value indicated that the reaction proceeded faster with electron-rich ketimines. k, equilibrium constant with substituent; k_H, reference constant with a hydrogen atom substituent; σ, substituent constant; σ_{para}, para substituent constants. **h**, A plausible mechanism.

deoxygenative difunctionalized alkylamination of the carbonyl group. Given the significance of heterocycles in medicinal chemistry[51], modular synthesis of diverse chiral heterocycles from a single starting material is highly desirable (Fig. 2b). Nitrogen-containing heterocycles such as pyrrolidine (**5**), piperidine (**6**) and azepane (**7**) bearing a quaternary stereocentre at the α-position could be efficiently constructed by subjecting ketimine **1a** respectively with 1,3-, 1,4- and 1,5-diiodides as the coupling component through a tandem alkylative

addition and in situ nucleophilic substitution. Likewise, the use of 3,3-bis(iodomethyl)oxetane as an electrophile allowed direct access to the chiral azaspirocyclic oxetane (**8**). Intriguingly, chiral azetidine (**4**) and γ-lactone (**9**) could be selectively obtained by employing different ketoimine substrates with *tert*-butyl(2-iodoethoxy)dimethylsilane under simple conditions. Transformation of product **3bo** enabled the expedient synthesis of enantio-enriched aziridine (**10**) and oxazolidinone (**11**). Several bioactive molecules could be expediently, formally synthesized by the transformation of chiral amine products (Fig. 2c). Amino ester **12** derived from product **3ba** could be converted into **13**, a key intermediate for the synthesis of adaptor protein-2 associated kinase 1 (AAK1) inhibitor[52]. Additionally, a vital synthon **15** for pharmaceutically interesting free fatty acid receptor-2 (FFA2) antagonist, which was obtained by preparative chiral chromatography[53], could also be constructed efficiently by further two-step transformations of **3bb**. Our protocol shows an advantage on both steps and shows yields over those of previously reported procedures to construct these drug targets starting from commercially available feedstocks (Supplementary Figs. 2 and 3). The sugar-derived alkyl iodide could be engaged in this protocol to selectively furnish diastereoisomers (*S*)-**16** and (*R*)-**16** with >99:1 d.r. based on the configuration of the chiral ligand, indicating that the stereoselectivity of the newly formed tetrasubstituted carbon centre was solely determined by the chiral ligand rather than the substrate with a pre-existing stereocentre (Fig. 2d).

To gain more insight into the reaction mechanism, several preliminary mechanistic studies were performed (Fig. 3). A radical cyclization reaction employing 6-iodohex-1-ene as the coupling partner afforded a mixture of **17** and **18** in 93% yield (Fig. 3a). A radical clock experiment employing ketimine **1a** with (iodomethyl)cyclopropane delivered ring-opening product **19** (Fig. 3b). Moreover, the addition of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) completely shut down the reaction with the concomitant formation of TEMPO adduct **20**, albeit in low yield (Fig. 3c). These results suggested the possibility of a single electron transfer (SET) process with the generation of an alkyl radical species during the reaction[54,55]. An X-ray of low-valent (*S*)-^{t}Bu-NPN^{Ph}-CoI complex **21** suggested the tridentate coordination pattern between the cobalt centre and chiral NPN ligand. The use of the Co(I) complex (**21**) as a catalyst gave corresponding product **3a** with a similar yield and enantioselectivity, which indicated that the Co(I) complex might be an initiator of the reaction (Fig. 3d). To gain a deeper understanding on the oxidation state of the cobalt centre during the reaction, different amounts of Mn reductant were evaluated in stoichiometric reaction with Co(I) complex **21** (Fig. 3e). Although the reaction proceeded without Mn, only 26% yield of the product was observed, indicating that an alkyl–Co(III) species may not be the reactive species. While the comproportionation process between a Co(I) species and an alkyl–Co(III) species might occur during the reaction to give the reactive alkyl–Co(II) intermediate for the following migratory insertion step. Additionally, using 0.3 equiv. or 0.5 equiv. Mn resulted in 57% and 74% yields of **3a**, respectively, further suggesting that an alkyl–Co(II) species might be the reactive Co species in the catalytic cycle. A linear relationship experiment revealed that the active cobalt catalyst possibly coordinated with a single ligand (Fig. 3f). To investigate the susceptibility of this protocol towards the electronic effect of the substituents, a Hammett plot was created. A negative reaction constant (ρ) value indicated that the reaction proceeded faster with electron-rich ketimines (Fig. 3g). Based on the preliminary mechanism studies, we postulated the following tentative mechanism (Fig. 3h). Imine substrate **1** goes through ligand (L) exchange with LCo(II), followed by reduction with Mn to give **int A**, which subsequently undergoes a SET process with alkyl halide **2** to produce **int B** and an alkyl radical. The alkyl radical next combines with the Co(II) of **int B** followed by reduction to give **int D**, which then undergoes the addition process to afford **int E**. It is also possible that the alkyl radical species proceeded through the radical addition towards the chiral cobalt-chelated α-amino ester intermediate to construct the chiral tetrasubstituted carbon centre. Final protonation with alcohol additive would generate product **3** and the Co(II) species, which would be reduced by Mn to regenerate **int A** with imine **1** to finish the catalytic cycle.

Conclusions

This reaction demonstrates that the enantioselective aza-Barbier reaction of ketimines is a versatile and highly efficient strategy for the construction of α-tertiary amino acid derivatives. This cobalt-catalysed asymmetric reductive addition protocol with the leverage of a variety of electrophilic unactivated alkyl halides allows the formation of tetrasubstituted stereogenic carbon centres with a high level of enantioselectivity and exceptional substrate scope. We anticipate that this asymmetric electrophilic Barbier-type addition, by circumventing the use of organometallic reagents, provides the possibility for further exploitation towards more challenging carbon–heteroatom or even carbon–carbon unsaturated bonds, thereby enabling changes to the conventional carbon–carbon formation in organic synthesis.

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/s41557-023-01378-9.

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Methods

General procedure for cobalt-catalysed asymmetric aza-Barbier reaction of α-imino ester with alkyl iodide or alkyl bromide

To a dried 8 ml vial were added ligand (6 mol%), Mn (2.0 equiv.) and imine **1** (1.0 equiv.). The vial was transferred into a glove box. CoI_2 (5 mol%), MeCN (0.2 M), alkyl iodide or alkyl bromide (1.5 equiv.) and R^2OH (1.0 equiv.) were added in sequence. (To avoid transesterification between imine **1** and alcohol, the type of alcohol should be the same as that of the protecting group of the α-imino ester.) The reaction vial was capped and stirred at 35 °C for the required time. After completion, the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed with EtOAc. The resulting filtrate was then concentrated under reduced pressure to give the crude product, which was purified by silica gel flash column chromatography to afford product **3**. The reaction maintained the same efficiency when using standard Schlenk techniques.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 2215368 (**3d**), 2260751 (**3cc**) and 2211548 (**21**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All data supporting the findings of this research are available within the Article and its Supplementary Information.

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Author contributions

X.W. and Y.C. conceived the project. X.W., H.X., C.G., B.L., L.W., C.Z., D.Y., L.H., N.L., T.X. and H.L. performed the experiments under the supervision of J.Q. and Y.C.; X.W. and Y.C. wrote the manuscript with the feedback of all other authors.

Competing interests

The authors declare no competing interests.

Additional information

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