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Modular enantioselective access to β-amino amides by Brønsted acid-catalysed multicomponent reactions

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β-Amino acids are structural motifs widely found in therapeutic natural products, novel biomimetic polymers and peptidomimetics. As a convergent method, the synthesis of stereoenriched β-amino amides through the asymmetric Mannich reaction requires specialized amide substrates or a metal catalyst for enolate formation. By a redesign of the Ugi reaction, a conceptually different solution to prepare chiral β-amino amides was established using ambiphilic ynamides as two-carbon synthons. The modulation of ynamides or oxygen nucleophiles concisely furnished three classes of β-amino amides with generally good efficiency as well as excellent chemo- and stereo-control. The utility is verified in the preparation of over 100 desired products that bear one or two contiguous carbon stereocentres, including those that directly incorporate drug molecules. This advance also provides a synthetic shortcut to other valuable structures. The amino amides could be elaborated into β-amino acids, *anti*-vicinal diamines, γ-amino alcohols and β-lactams or undergo transamidation with amino acids and amine-containing pharmaceuticals.

Work published by Seebach in 1996 showing that peptides composed of β-amino acids could form more stable helical secondary structures than their natural α-counterparts initiated numerous syntheses and structural studies on this class of peptidic oligomers[1]. With an additional methylene group between two functional termini, the self-assembly or distinctive conformations adopted by peptides with β-amino acid residues could modify and improve the properties of materials[2–4]. Special attention has been paid to the β-amino acid building blocks that are also common structural motifs in medicinally important natural products such as Taxol, andrimid and guineamide A (Fig. 1a)[5–8]. The related peptidomimetics could exhibit potent biological activity with enhanced metabolic stability and proteolytic resistance[9,10]. With possible substitution on C2 (β^2-derivative), C3 (β^3-derivative) or both positions ($\beta^{2,3}$-derivative), β-amino acids present an adaptable platform to design chiral building blocks that could span a rather broad range of functional, regio- and stereo-chemical diversity.

While asymmetric Mannich reactions that unite imines and (latent) enolates through redox-neutral carbon–carbon bond formation are well-studied for the synthesis of β-amino carbonyl compounds, catalytic access to the carboxyl derivatives is hindered by the poor enolizability of substrates[11–16]. List's group has recently published work on inventive methods for accessing free β-amino acids[17] and the ester derivatives[18] using their developed imidodiphosphorimidate catalysts. The former involves enantioselective addition of silyl ketene acetals to α-aminomethyl ethers as methylene imine equivalents, whereas the synthesis of esters employs electrophilic silyl nitronates derived from nitroalkanes. The reactivity constraint is even more remarkable as it uses simple amides as pronucleophiles[19–21]. In Yamashita's successful endeavour, chiral enolates of simple amides were generated in situ by association of the potassium enolate with a chiral potassium Box salt[22]. Alternatively, Shibasaki and Kumagai employed tailored 7-azaindoline amides to impart high reactivity

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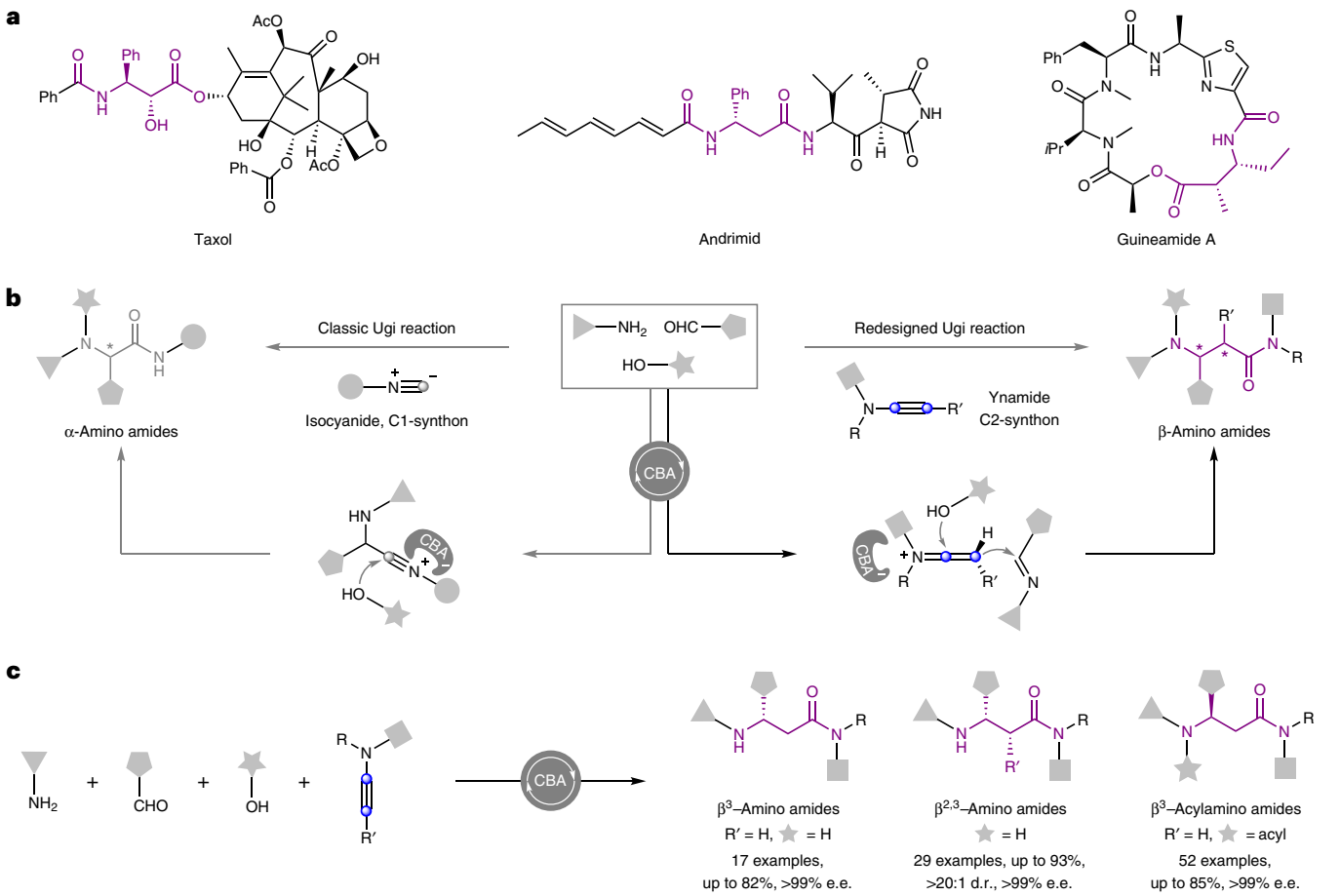

Fig. 1 | Research status of β-amino amides and our design blueprint. **a**, Representative examples of β-amino acid-containing bioactive natural products. **b**, The classic Ugi reaction and our scheme to construct the β-amino amide scaffold. **c**, This work: CBA-catalysed four-component reaction for unified access to β^3- and $\beta^{2,3}$-amino amides and β^3-acylamino amides. Compared to the Ugi reaction, this transformation is a more complex system and multiple competitive reaction sites are present. This entails a more stringent control of selectivity. The amino amide products could undergo versatile synthetic derivatizations to access other important chiral compounds. CBA, chiral Brønsted acid. Star, the substituents of the hydroxyl nucleophile, which could be carboxylic acid or water; triangle, substituent on the amine component; pentagon, substituent of aldehyde; circle, substituent of isocyanide. Rectangle and R, nitrogen substituents on ynamide; R', alkyne substituent. The filled symbol denotes the carbons originated from the alkyne on ynamide substrates.

and stereoselectivity with the combined use of a Lewis-acidic chiral copper catalyst[23–27].

To circumvent this inherent challenge in using a Mannich-type reaction for convergent access to β-amino amides without functional group manipulation, we envisaged that the asymmetric multicomponent reaction (AMCR) would constitute a promising arena for innovative reaction development. In particular, the atom- and step-efficiency of this chemistry would support diversity-oriented synthesis of these chiral motifs with vast therapeutic potential. As one representative MCR, the Ugi four-component reaction (Ugi-4CR) could implement one-pot assembly of α-peptide-like moieties from isocyanides, carboxylic acids, aldehydes and primary amines[28]. The original reaction has seen creative extensions, including the Ugi-3CR published by List that used water as the internal nucleophile in lieu of carboxylic acid[29]. More recently, our team addressed the decades-old stereochemical challenge in Ugi-4CRs to forge chiral α-amino amides using a chiral Brønsted acid (CBA) catalyst (Fig. 1b)[30].

To adapt this venerable reaction for constructing β-amino amides, the identification of a suitable ambiphilic C2-synthon to substitute for the isocyanide as a C1-synthon in the Ugi reaction was necessary to accommodate this skeletal extension in target products. To this end, ynamides with C_α-electrophilicity and C_β-nucleophilicity were envisaged to be a uniquely suitable linchpin that could bring together the imine and nucleophile components (Fig. 1b)[31–33]. The chemical reactivity of ynamides has offered numerous synthetic possibilities especially in cycloaddition, rearrangement and cycloisomerization reactions, but their engagement in catalytic asymmetric transformations has not been investigated as thoroughly[34–37]. Key advances have only emerged recently from the Ye group in which a chiral phosphoric acid (CPA) catalyst was shown to activate the alkyne and control the stereoselectivity for dearomatization of tethered (hetero)arenes[38] and intramolecular hydroalkoxylation/Claisen rearrangement[39] and cyclization reactions[40]. However, the reactivity of ynamides under the auspices of a CBA catalyst in an intermolecular setting has, to the best of our knowledge, not been reported. In our design, a CBA would be likely to activate a ynamide as an electrophilic keteniminium ion and then yield a hydrogen-bond-assisted ion pair to react with an oxygen nucleophile such as water or carboxylic acid. The generated enol amide then adds to the imine activated by the CBA via hydrogen bonding to furnish the β-amino amide. While strategically ideal, the incorporation of ynamides as a reacting component in an asymmetric four-component reaction that entails rigorous control of chemo-, enantio- and diastereo-selectivity could be compounded by their versatile reactivity. Compared to the classic Ugi reaction, unproductive pathways could outnumber the desired reaction due to this reactant switch. Markedly, the hydroacyloxylation of ynamides by the acid

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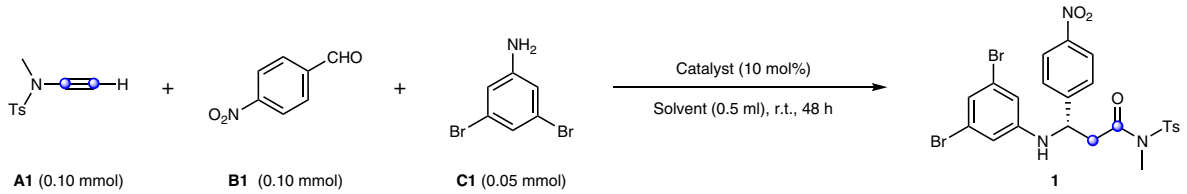
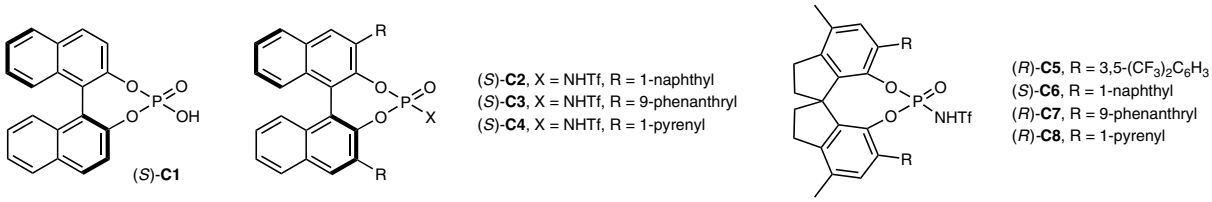
Table 1 | Reaction condition optimization for catalytic asymmetric multicomponent synthesis of β³-amino amides



Entry	Catalyst	Solvent	Yield (%)	e.e. (%)	Entry	Catalyst	Solvent	Yield (%)	e.e. (%)
1	(*S*)-**C1**	CH_2Cl_2	0	–	7	(*S*)-**C4**	MTBE	40	63
2	(*S*)-**C2**	CH_2Cl_2	Trace	26	8	(*R*)-**C5**	MTBE	22	70
3	(*S*)-**C2**	CCl_4	0	–	9	(*S*)-**C6**	MTBE	21	–76
4	(*S*)-**C2**	EtOAc	10	29	10	(*R*)-**C7**	MTBE	33	84
5	(*S*)-**C2**	MTBE	36	27	11	(*R*)-**C8**	MTBE	84 (80)[a]	97
6	(*S*)-**C3**	MTBE	29	64	12	(*R*)-**C8**	MTBE	79[b]	97



Reaction conditions: the reaction of **A1** (0.10 mmol), **B1** (0.10 mmol), **C1** (0.05 mmol) and catalyst (10 mol%) was carried out in solvent (0.5 ml) at r.t. for 48 h. Yield was determined by ^{1}H NMR analysis of the crude mixture with triphenylmethane as the internal standard and e.e. was determined by chiral stationary HPLC. The filled symbol denotes the carbons originated from the alkyne on ynamide substrates. [a]Isolated yield for 0.2 mmol-scale reaction. [b]15 mol% catalyst loading.

catalysts could lead to their deactivation[41]. The orchestration of this MCR sequence could be further disrupted by competitive amination of ynamides by amine[42], hydration under acidic conditions or their susceptibility to undergo metathesis with aldehyde or imine species present in the reaction system[43,44]. These challenges notwithstanding, in this Article the development of such a CBA-catalysed AMCR of amines, aldehydes and ynamides with water or carboxylic acids to forge optically active β-amino amides is realized and described. This method presents an organocatalytic MCR for the streamlined construction of β³- and β²,³-amino amides and β³-acylamino amides in enantioenriched forms (Fig. 1c).

Results and discussion

Reaction optimization

At the outset, the *p*-toluenesulfonyl (Ts)-protected terminal ynamide **A1** was chosen as the model substrate, considering that this group would be a convenient handle for synthetic manipulation. The proof-of-concept experiment was performed with **A1**, 4-nitrobenzaldehyde **B1** and 3,5-dibromoaniline **C1** in dichloromethane (CH_2Cl_2) in the presence of (*S*)-**C1** (10 mol%) at room temperature (r.t.) (Table 1, entry 1). Due to competitive addition of the phosphoric acid catalyst onto the ynamide to form an inactivated enol phosphate, the desired compound was not observed in this reaction system[41]. When the more acidic *N*-triflylphosphoramide derivative (*S*)-**C2** was screened[45], β³-amino amide **1** was formed in trace amount and 26% e.e. (Table 1, entry 2), which gave an initial hint at the feasibility of this reaction design. A solvent switch to methyl *tert*-butyl ether (MTBE) brought meaningful improvement of yield (36%) while 27% e.e. could be achieved for the target **1** (Table 1, entry 5). In investigating various axially chiral *N*-triflylphosphoramides, outstanding enantioinduction was consistently imposed by most *N*-triflylphosphoramides that bear substituents with an extended π system, regardless of the variations of other parameters (Table 1, entries 6–11). In particular, Me-SPINOL (4,4′-dimethyl-1,1-spirobiindane-7,7′-diol)-derived (*R*)-**C8** promoted the model reaction with the best product yield and stereoselectivity control (Table 1, entry 11)[46]. An increased catalyst loading of 15 mol% slightly decreased the product yield and did not further improve the e.e. (Table 1, entry 12). Further optimization of reaction conditions by varying the catalyst loading and temperature did not further enhance the results (for details, see Supplementary Table 1). Therefore, following optimal conditions were used to survey the substrate generality: **A1** (0.2 mmol) was treated with **B1** (0.2 mmol) and **C1** (0.1 mmol) in the presence of catalyst (*R*)-**C8** (10 mol%) in MTBE (1.0 ml) at r.t. for 48 h. Using these conditions, desired product **1** was obtained in 80% isolated yield with 97% e.e. (Table 1, entry 11).

With viable conditions in hand for the transformation of terminal ynamides, the study was advanced with full exploration of substrate compatibility. As shown in Table 2, the CBA-catalysed AMCR was applicable for a range of aromatic aldehydes, aromatic amines and ynamides to afford β³-amino amides with excellent enantiocontrol for most cases (**1**–**17**). First, moderate to good yields (60–82%) were obtained for aromatic aldehydes with electron-withdrawing functionality such as *meta* and/or *para* substituents (**1**–**6**). For the aniline partner, trifluoromethyl (CF_3) and halogen substituents could be diversely installed at the *meta*- and *para*-positions (**7**–**10**). From the performance of mono-substituted substrates, a positive influence of *meta*-substitution on the enantiocontrol could be discerned (**11** versus **12**). Compared to dibromosubstitution (**7**, 72%, 94% e.e.), the product yields for 4-bromoanilines (**13**) and 3-bromoanilines (**14**) decreased substantially to 28 and 30%, respectively. The effect on product e.e. was not as drastic where the 4-bromo analogue could achieve 86% e.e. while 96% e.e. was seen for the 3-bromo derivative. The use of electron-poor substituents at the *meta*- and/or *para*-positions on aldehydes and anilines was found to be important in facilitating the MCR. Benzaldehyde as well as the *o*-trifluoromethyl, *p*-methoxy and *m*-methoxy derivatives gave rise to only minute quantities of products. Similar outcomes were observed in the reactions of unsubstituted, *p*-methoxy, *m*-methoxy and *o*-trifluoromethyl anilines. The reaction details for these unsuccessful substrates can be found in Supplementary Fig. 3. On the other hand,

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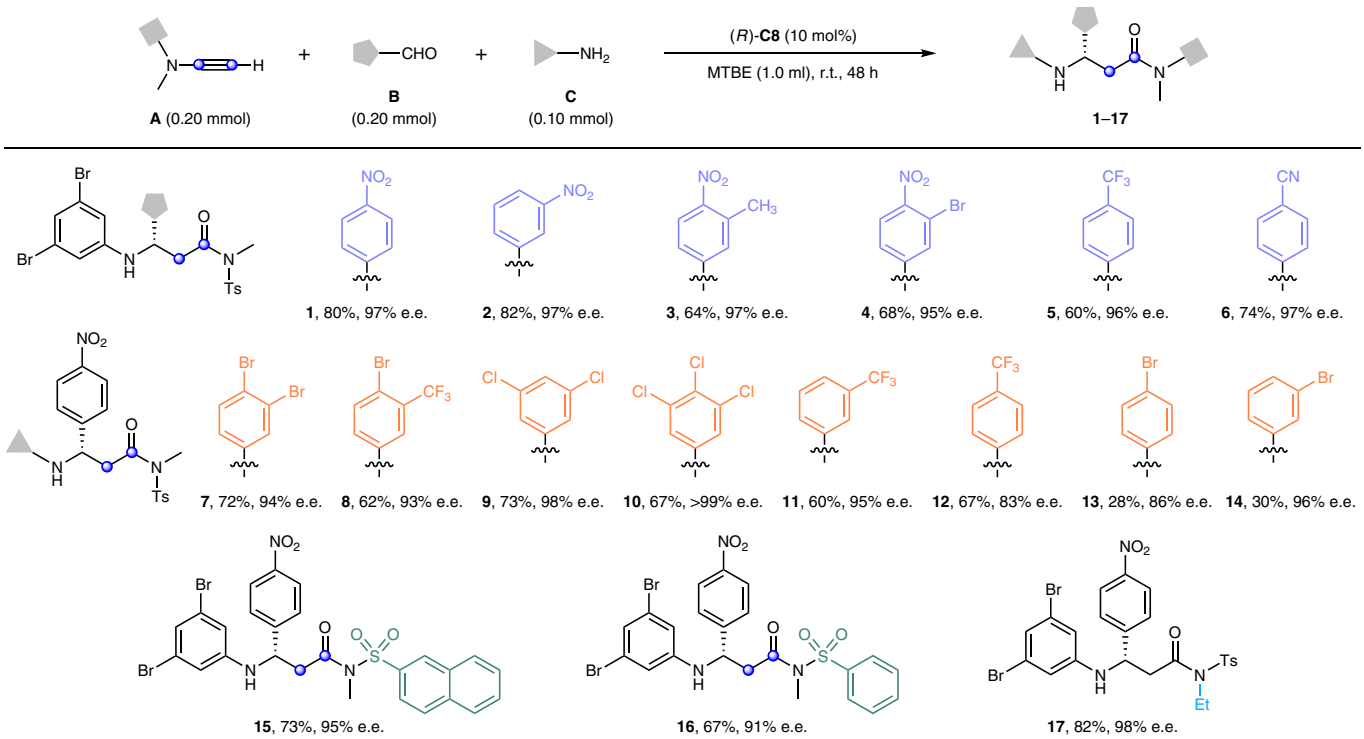
Table 2 | Substrate scope for catalytic asymmetric multicomponent synthesis of β³-amino amides



Reaction conditions: **A** (0.20 mmol), **B** (0.20 mmol), **C** (0.10 mmol) and (*R*)-**C8** (10 mol%) in MTBE (1.0 ml) at r.t. for 48 h. Isolated yield was based on amine and e.e. was determined by chiral stationary HPLC. Rectangle, nitrogen substituent on ynamide; pentagon, substituent on aldehyde; triangle, substituent on amine. The filled symbol denotes the carbons originated from the alkyne on ynamide substrates.

the *N*-tosyl and *N*-methyl groups on the ynamides could also be varied, affording β³-amino amides **15**–**17** in good yields with 91–98% e.e.

Having validated the applicability of terminal ynamides in the envisioned AMCR, the more challenging study to realize enantio- and diastereo-selective MCRs of internal ynamides was undertaken with **A5** as the model substrate. This would give rise to $\beta^{2,3}$-amino amides with two contiguous carbon stereocentres. Favourably, by applying (*R*)-**C8** (15 mol%) and replacing MTBE with an ethyl acetate/diethyl ether (EtOAc/Et_2O) mixture (1/1), $\beta^{2,3}$-amino amide **18** could be obtained in 83% yield with >99% e.e. and >20:1 d.r. (for details, see Supplementary Table 2). Efforts then turned to verify the generality of this set of conditions in the assembly of enantioenriched $\beta^{2,3}$-amino amides (Table 3). Generally, aromatic aldehydes with electron-withdrawing substituents gave the expected $\beta^{2,3}$-amino amides in good yields with complete stereocontrol (**18**–**23**). The aldehyde with an electron-rich methoxy substituent and 2-naphthaldehyde with a more substantial structural variation delivered **24** and **25** in good yields with complete stereocontrol. However, 2-nitrobenzaldehyde could not provide any desired product (for details, see Supplementary Fig. 4). The compatibility of a panel of aromatic amines was next examined. When the *meta*-position was equipped with electron-withdrawing functionalities, anilines could be smoothly incorporated into amino amides **26**–**28** in serviceable yields and excellent enantioselectivities. Although noticeable erosions of stereoselectivities were observed for *para*-brominated aniline (**29**), excellent stereocontrol returned with improved yields when anilines bearing di- or tri-halogen substituents at the *meta*- and *para*-positions were utilized (**30**–**33**). In the presence of the electron-rich thiomethyl group, the aniline furnished **34** in moderate yield (72%) and poorer stereoselectivity (65% e.e., 2.3:1 d.r.). Similar to the aldehyde component, the *ortho*-substitution on aniline imposed a detrimental effect on the reaction. A representative substrate, 2-bromoaniline did not provide any desired product either (for details, see Supplementary Fig. 4). Subsequently, the tolerance of current chemistry towards different ynamides was assessed. A variety of groups that impart differentiated electronic properties could be effectively introduced on the terminal benzene ring (**35**–**38** and **41**–**43**). Ynamides connecting to the 3-thienyl (**39**) or 2-naphthyl (**40**) group were also applicable substrates. Generally, the reactions with 3,4-dibromoaniline as the amine component offered much higher yields but lower stereoselectivities than those with 3,5-dibromoaniline (**35**–**40** versus **41**–**43**). In addition, the estrone-based ynamide with more distinct structural features provided **44** in 93% yield with virtually perfect stereocontrol. We completed the scope survey by examining different protecting groups on ynamides. Expectedly, benzenesulfonyl and *p*-methoxybenzenesulfonyl (**45** and **46**) furnished the desired products in reasonable yields and remarkable stereocontrol. For these MCRs that involve water, the formation of side products accounts for the moderate product yields observed in some cases. The metathesis of a ynamide with an aldehyde would generate an α,β-unsaturated amide and a ynamide could also be hydrated to form an amide. The stereochemistry of products in this series was assigned based on the absolute configurations of **23** and **24** that have been confirmed by X-ray diffraction analysis (CCDC 2175112 and CCDC 2175113).

To further explore the capacity of this AMCR, the possibility of trapping the keteniumium intermediate with a carboxylate ion was hypothesized to produce β³-acylamino amides. To the best of our knowledge, this reaction mode has been elegantly verified in a racemic fashion[47] but not been achieved enantioselectively. The reaction optimization commenced with benzoic acid **D1** as the standard acid component (for details, see Supplementary Table 3). A complex reaction mixture with no target product **47** was observed when the reactants were mixed in CH_2Cl_2 at r.t. for 12 h. Based on Cui's work that constructed β³-acylamino amides via MCR of ynamides[47] and triazenyl alkenes[48], we reasoned that the order of delivery of reactants might influence the reaction outcome. To generate the acyloxyenamide intermediate in

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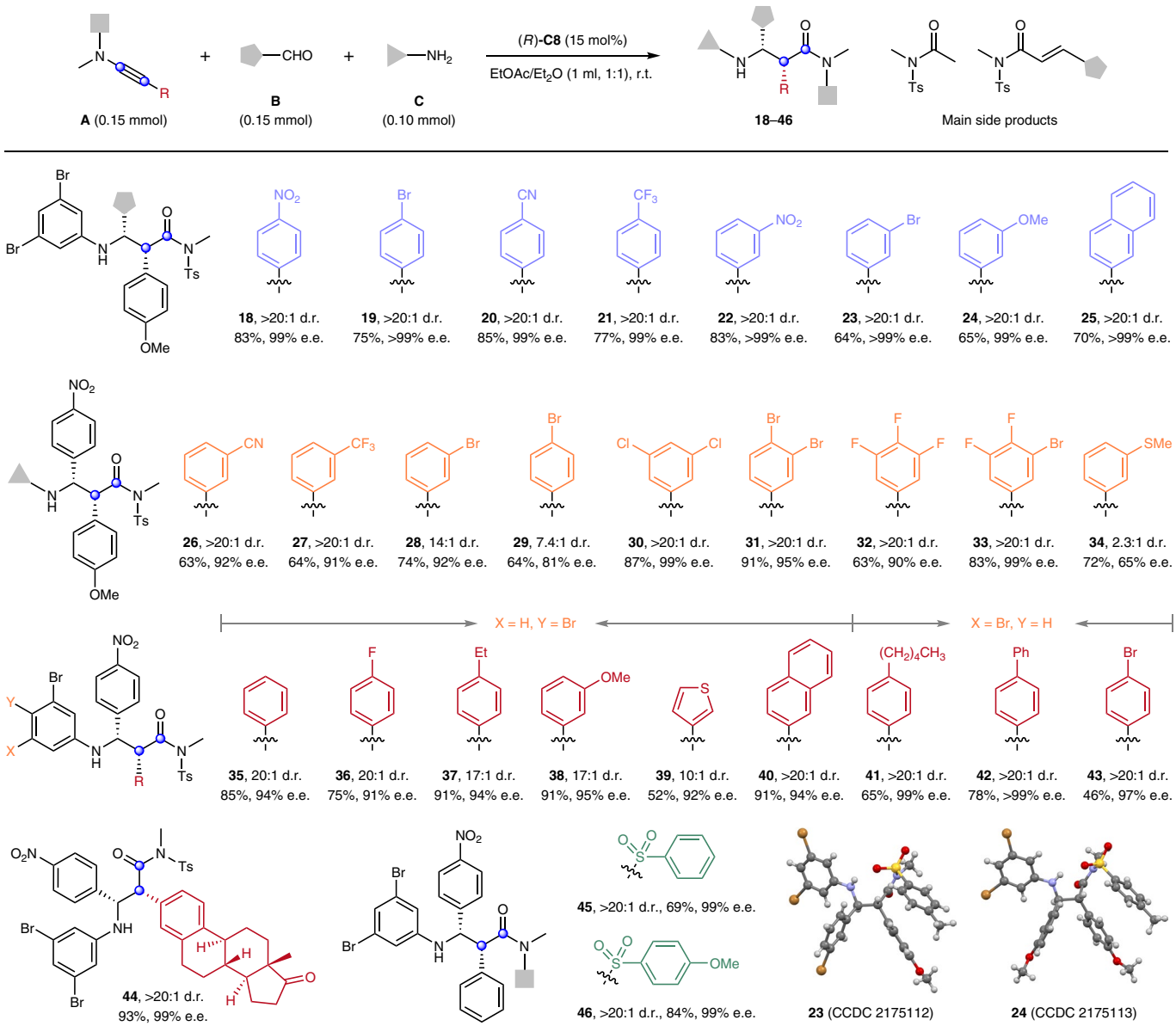
Table 3 | Substrate scope for catalytic asymmetric multicomponent synthesis of β^{2,3}-amino amides



Reaction conditions: **A** (0.15 mmol), **B** (0.15 mmol), **C** (0.10 mmol) and (*R*)-**C8** (15 mol%) in EtOAc/Et_2O (1.0 ml, 1:1) at r.t. for 48 h. Isolated yield was based on amine, d.r. was determined by ^{1}H NMR and e.e. was determined by chiral stationary HPLC. Rectangle, nitrogen substituent on ynamide; pentagon, substituent on aldehyde; triangle, substituent on amine. The filled symbol denotes the carbons originated from the alkyne on ynamide substrates.

readiness for electrophilic interception, **A1** and **D1** were first mixed in CH_2Cl_2 at r.t. before inclusion of **B1**, **C1** and *N*-triflylphosphoramide (*R*)-**C7**. This led to formation of the postulated β^3-acylamino amide product **47** in 35% yield with 96% e.e. (Supplementary Table 3, entry 6). Subsequent optimization by varying the solvent, temperature and catalyst loading led to the optimal conditions as follows: carboxylic acid **D** (0.12 mmol) was reacted with ynamide **A** (0.12 mmol) in CH_2Cl_2 (0.5 ml) for 6 h. Benzaldehyde **B** (0.12 mmol) and aniline **C** (0.1 mmol) were then added and the reaction mixture was stirred for 1 h followed by addition of (*R*)-**C7** (10 mol%) and *n*-hexane (0.5 ml) at −40 °C. The reaction mixture was stirred for another 48 h at this temperature (Supplementary Table 3, entry 16).

With this established working process, the scope and limitation of this reaction were evaluated by systematic examination of different components (Table 4). Interestingly, this reaction was characterized by ample scope with respect to the acid component. Benzoic acids bearing a CF_3, halogen, alkyl or phenyl substituent at the *para*-position furnished the chiral β^3-acylamino amides **47**–**54** in 52–83% yields with >99% e.e. in most cases. The outcome was upheld with *ortho*- and *meta*-substitutions as well as with 2-naphthoic acid (**55**–**57**). The use of aromatic acids was not mandatory: a linear alkyl carboxylic acid was converted into **58** in moderate yield with absolute enantiocontrol and 3-phenylpropiolic acid (**59**) and 2-octynoic acid (**60**) were transformed into the corresponding products with excellent results. The generality of this strategy was reinforced in the direct engagement of anti-Duchenne muscular dystrophy (DMD) drug ataluren and anti-acne drug adapalene in AMCRs with **A1**, **B1** and **C1**. Both drug molecules were enantioselectively incorporated into β^3-acylamino amides (**61** and **62**) with reasonable yields, signifying utility in direct diversification of pharmaceuticals and bioactive molecules. In line with previous observations, it could be gleaned from experimental data of **63**–**75** that higher yields could arise from the electron-poor aldehydes compared

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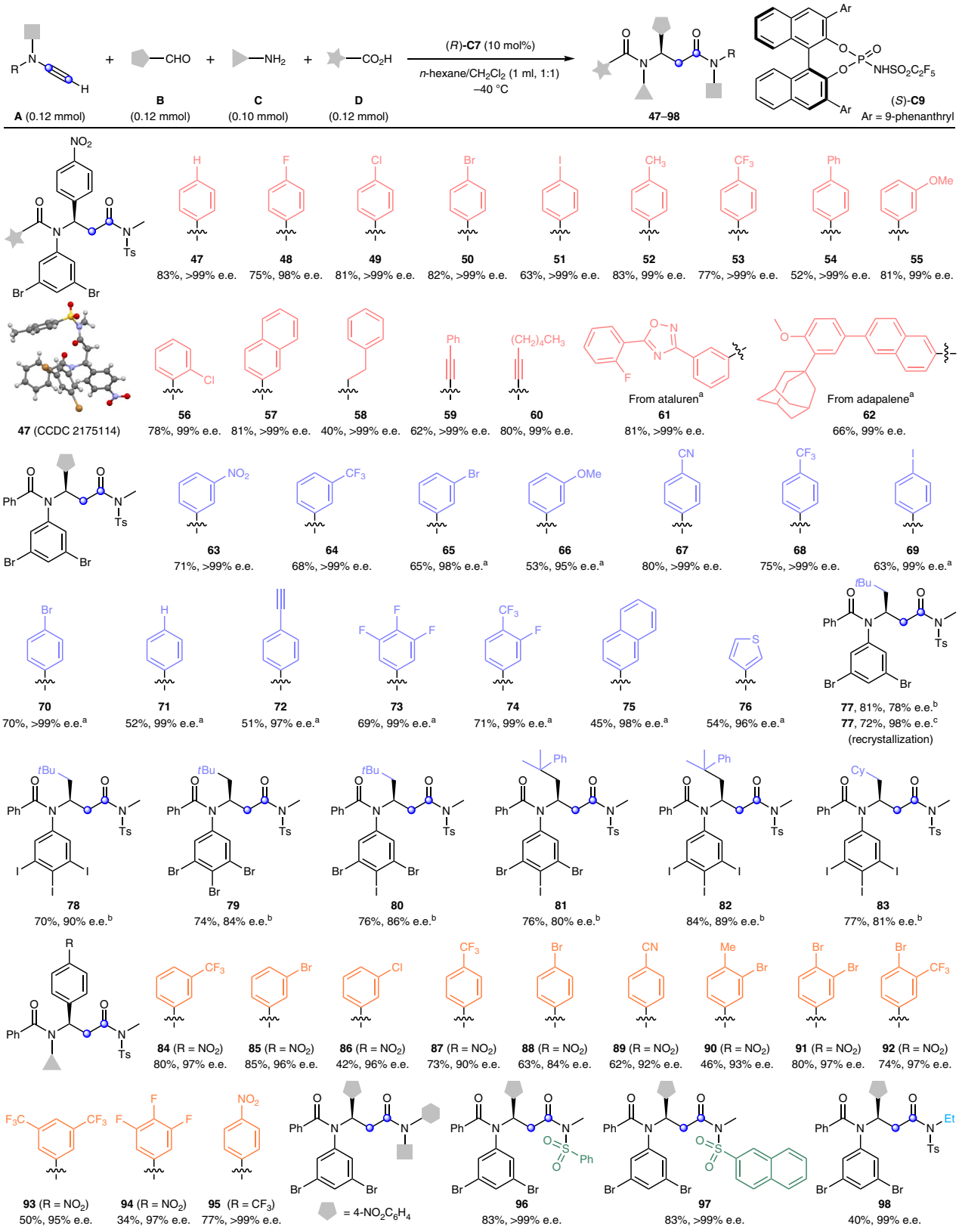
Table 4 | Substrate scope for catalytic asymmetric multicomponent synthesis of β³-acylamino amides



Reaction conditions: **D** (0.12 mmol) was reacted with **A** (0.12 mmol) in CH_2Cl_2 (0.5 ml) at r.t. for 6 h (until the ynamide was completely consumed). Then **B** (0.12 mmol) and **C** (0.10 mmol) were added and the reaction mixture was stirred for 1 h. Then (*R*)-**C7** (10 mol%) and *n*-hexane (0.5 ml) at −40 °C were added and the reaction mixture was stirred for 48 h at this temperature. Isolated yield was based on amine and e.e. was determined by chiral stationary HPLC. Rectangle, nitrogen substituent on ynamide; pentagon, substituent on aldehyde; triangle, substituent on amine; star, substituent on carboxylic acid. The filled symbol denotes the carbon originated from the alkyne on ynamide substrates. [a]−20 °C. [b]**D** (0.12 mmol) was reacted with **A** (0.12 mmol) in CH_2Cl_2/toluene (0.2/0.8 ml) until the ynamide was completely consumed. Then **B** (0.12 mmol), **C** (0.10 mmol) and (*S*)-**C9** (10 mol%) were added at −30 °C and then the reaction mixture was stirred for 48 h at this temperature. [c]Recrystallization with CH_2Cl_2/isopropanol (1/4).

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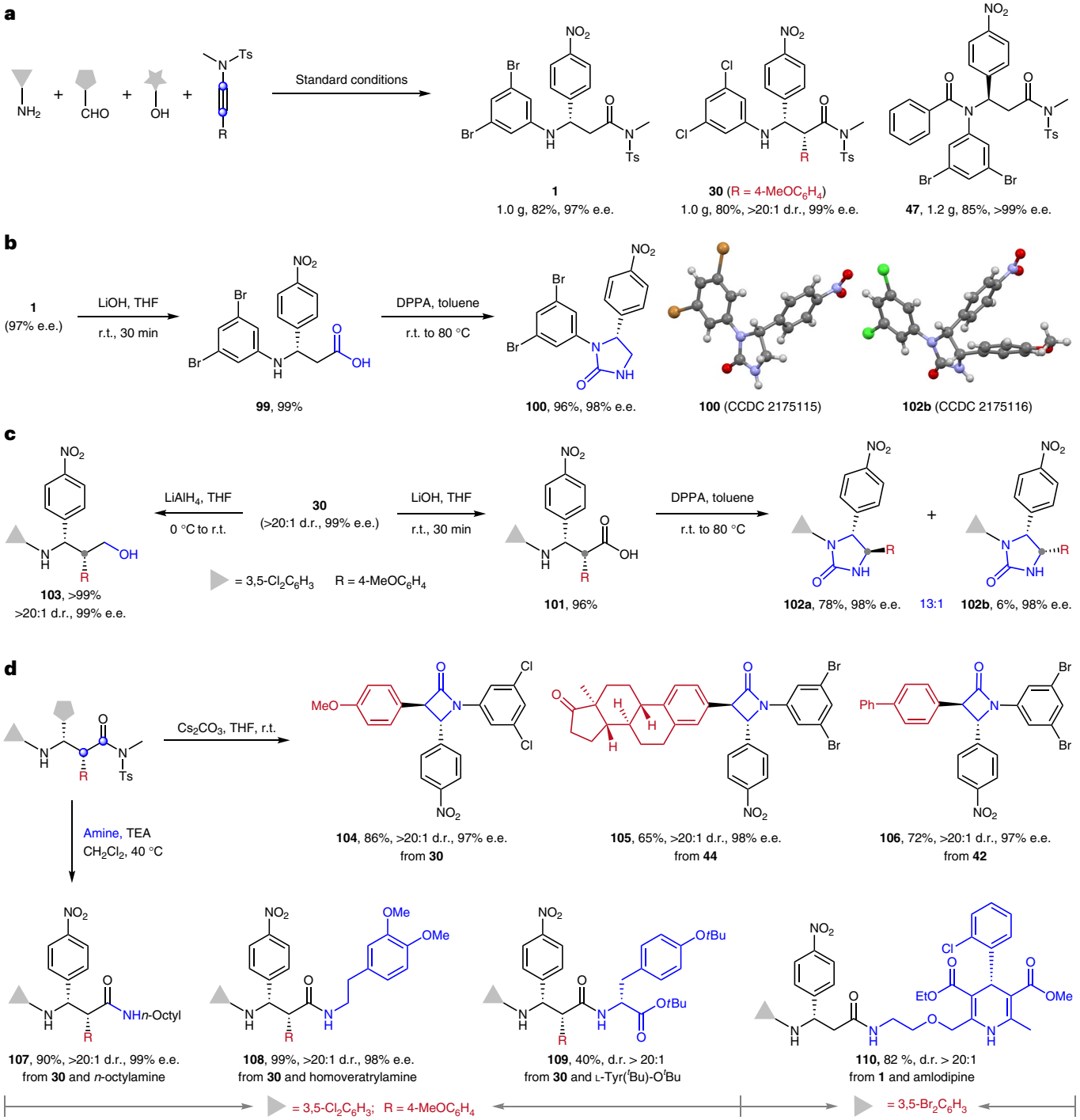

Fig. 2 | Scale-up syntheses, product derivatization, late-stage modification of drugs and synthesis of dipeptide. a, Gram-scale preparation of compounds **1**, **30** and **47**. **b**, Representative amino amide product **1** was shown to undergo hydrolysis to amino acid **99**, which could be subjected to DPPA for intramolecular cyclization towards chiral *anti*-vicinal diamine derivative **100**. **c**, Another model product **30** was subjected to hydrolysis to amino acid **101** or reduction to amino alcohol **103**. In the presence of DPPA, intramolecular cyclization proceeded for β-amino acid **101** to form chiral *anti*-vicinal diamine **102**. **d**, Treatment with caesium carbonate triggers lactamization of several model amino amide products (**30**, **44** and **42**) into β-lactams **104**, **105** and **106**, respectively. In addition, the amide group of the products could be replaced through transamidation of **1** or **30** with alkyl amine (to give **107**), amino acid L-Tyr(^{t}Bu)-O^{t}Bu (to give **109**) and amine drugs such as homoveratrylamine (to give **108**) and amlodipine (to give **110**). These post-synthetic modifications occurred with excellent retention of optical purities. TEA, triethylamine. Triangle, substituent on the amine component; pentagon, substituent on aldehyde; star, substituent on hydroxyl nucleophile, which could be carboxylic acid or water. The filled symbol denotes the carbons originated from the alkyne on ynamide substrates.

to the electron-rich (**66**) or electron-neutral analogues (**71**, **72** and **75**). Thiophene-3-carboxaldehyde also competently provided **76** in a good yield with high enantiopurity. Although imines formed from aliphatic aldehydes showed insufficient reactivity in a previous study[47], the present catalytic system efficiently facilitated the transformation of these aldehydes after slight adjustment of the reaction conditions (for details, see Supplementary Table 4). This result bears significance as aliphatic groups are native substituents of the α-amino acid subunit

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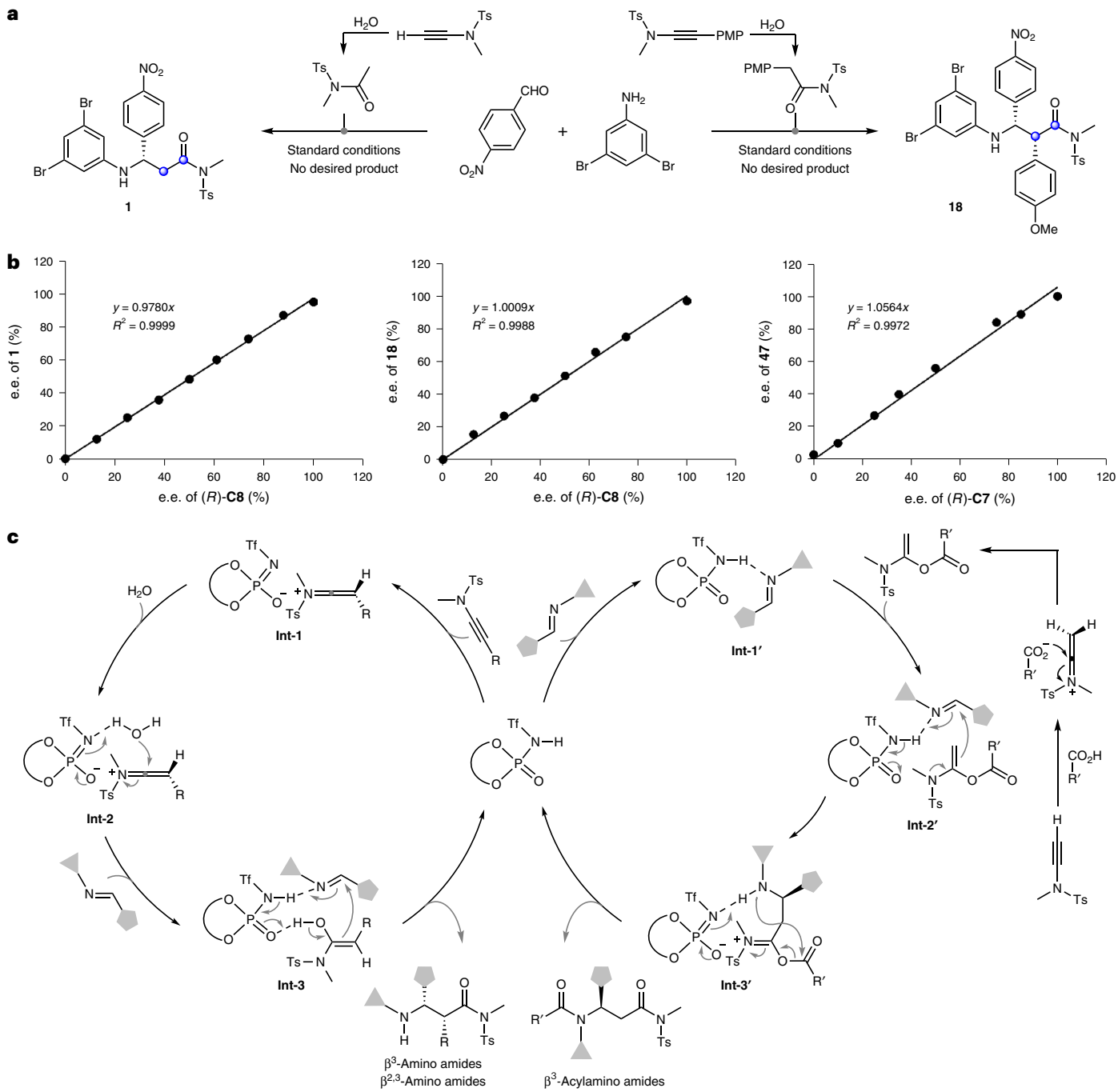

Fig. 3 | Mechanistic studies and proposed mechanism. a, Control experiments. The amides derived from representative terminal and internal ynamides were subjected to standard reaction conditions. The failure to form target products (**1** and **18**) implies that the hydration of ynamides is not involved in product formation. **b**, Nonlinear effect studies. As the e.e. values of product and catalyst are linearly correlated in the formation of amino amides **1**, **18** and **47**, a single chiral catalyst is likely to be involved in the stereodetermining transition state. **c**, Proposed reaction mechanism. In the catalytic cycle on the left, the CBA activates the ynamide substrate in the form of a chiral ion pair that comprises the keteminium ion and CBA anion (**Int-1**). The acid-catalysed addition of water onto the keteminium ion (**Int-2**) yields an enol amide that undergoes *anti*- and stereoselective addition with the imine (generated from condensation of the aldehyde and amine) via a bifunctional activation mode (**Int-3**). This releases the β^3- or $\beta^{2,3}$-amino amide and catalyst for turnover. The catalytic cycle on the right depicts the pathway to form β^3-acylamino amides from terminal ynamides. The initial formation of the ketiminium ion is succeeded by addition of the carboxylic acid to give the acyloxyenamide. The catalyst then activates the imine intermediate for stereoselective addition with the acyloxyenamide (**Int-2′**). A rapid catalyst-mediated Mumm rearrangement (**Int-3′**) furnishes the β^3-acylamino amide product and regenerates the catalyst. Triangle, substituent on the amine component; pentagon, substituent on aldehyde; R, terminal alkyne substituent on ynamides; R', aliphatic or aromatic substituent of carboxylic acid component.

found in biologically relevant compounds, especially for the severe acute respiratory syndrome coronavirus 2 main protease (SARS-CoV-2 M^{pro}) inhibitors[49]. 3,3-Dimethylbutyraldehyde delivered the desired product **77** in 81% yield and moderate enantiopurity. The enantiomeric purity was facilely upgraded to 98% e.e. after one recrystallization with CH_2Cl_2/isopropanol. When tri-substituted anilines were employed, amino amides (**78**–**83**) derived from aliphatic aldehydes could be furnished in good yields with 80–90% e.e. Aldehydes that bear an

α-substituent including 3,3-dimethylbutanal and pivaldehyde did not form any target product, possibly due to steric influence (for details, see Supplementary Fig. 5). We next conducted the focused screening of anilines, verifying the compatibility of derivatives with *meta*- and/or *para*-positions occupied by mono- (**84**–**89** and **95**), di- (**90**–**93**) or tri-substitution (**94**). CF_3, cyano (CN), nitro (NO_2) and halogen functionalities endowed suitable substrate compatibility to achieve excellent enantiocontrol and generally good efficiencies. Compared to the *meta*-bromo-substituted substrate, inferior product yields were achieved for the chloro substituent and when an additional methyl substituent was introduced (**85** versus **86** and **90**). In this method, while the yield dropped substantially when the *N*-methyl group on the ynamide was replaced by *N*-ethyl (**98**, 40% yield), modification of the sulfonyl group (**96** and **97**) was well tolerated. In these reactions that formed β^3-acylamino amides, the hydrolysis of the iminium intermediate before Mumm rearrangement could be observed. The side product was found to be optically active and possessed the same e.e. as the β^3-acylamino amide product. The compatibility of other nucleophiles such as ethanol, benzyl alcohol, 2-nitrophenol, 2-hydroxypyridine and an aromatic sulfonic acid was examined as well (for details, see Supplementary Fig. 6). None of them were found to undergo this MCR. The absolute configuration of **47** was determined by X-ray diffraction analysis and the stereochemistry of other products from this series was assigned by analogy (CCDC 2175114).

To verify the preparative utility of this catalytic AMCR, the gram-scale syntheses of **1** (1.0 g), **30** (1.0 g) and **47** (1.2 g) were performed (Fig. 2a). The good efficiencies and remarkable selectivities paved the way for large-scale production. The synthetic manipulations of β-amino amides provide a shortcut to other appealing compounds (Fig. 2b–d). Hydrolysis of **1** yielded amino acid **99** that could be further diversified to chiral *anti*-vicinal diamine derivative **100** upon treatment with diphenyl azidophosphate (DPPA) in toluene at 80 °C (Fig. 2b). Similarly, amino amide **30** could be hydrolysed to amino acid **101**, followed by conversion into the *anti*-vicinal diamine **102** when subjected to DPPA (Fig. 2c). The chiral diamines are valuable building blocks in the synthesis of medicinal agents, together with chiral ligands as well as the catalysts[50,51]. The enantiopurities were perfectly retained while the absolute configurations of **100** (CCDC 2175115) and the minor product (**102b**, CCDC 2175116) generated alongside **102a** were determined by X-ray diffraction analysis. Amide **30** could be reduced by $LiAlH_4$ to deliver γ-amino alcohol **103** in >99% yield without affecting the stereocentre. In view of the broad representation of the β-lactam ring within a range of drugs and bioactive molecules[52,53], the generation of β-lactam **104** from **30** was realized in 86% yield by using caesium carbonate (Cs_2CO_3) to trigger intramolecular cyclization (Fig. 2d). Likewise, amino amides **44** and **42** provided β-lactams **105** and **106** in moderate yields and excellent enantiopurities. Encouraged by the facile aminolysis of **30** by 1-octylamine (to give **107**), the late-stage modification of drug molecules was pursued by treating β-amino amides **30** and **1** with homoveratrylamine (to give **108**) and amlodipine (to give **110**), respectively. β/α-Dipeptide **109** was also assembled by ready attachment of protected α-amino acid L-Tyr(^{t}Bu)-O^{t}Bu to the obtained β-amino amide **30**. This reactivity might have important implications in designing biomimetic polymers with distinctive folding patterns and biological properties that surpass the natural analogues.

Mechanistic investigations

To elucidate the mechanistic details, we probed the intermediacy of amides that were isolated in reactions involving H_2O as the internal nucleophile. The use of standard reaction conditions did not yield **1** and **18**, suggesting that product formation did not occur via the hydration of ynamides (Fig. 3a). Studies of the nonlinear effect for the three model reactions (**1**, **18** and **47**) were also performed, where a linear relationship between the enantiopurities of product and catalyst was invariably determined. These studies indicated that only one catalyst has participated in the enantiodetermining step[54,55] (Fig. 3b).

Guided by these experimental insights as well as previous reports[47,56–58], a plausible mechanistic pathway for the established AMCR was postulated (Fig. 3c). The reaction proceeds with the ynamide being catalytically activated by the formation of a keteniminium ion (**Int-1**) that associates with the CBA anion as an ion pair. The nucleophilic interception is promoted by the acid catalyst that concurrently orients the H_2O molecule via hydrogen bonding (**Int-2**). The catalyst then organizes the generated enol amide and imine via a bifunctional catalytic mode (**Int-3**). This leads to stereoselective nucleophilic addition that occurs with *anti*-selectivity to yield a $\beta^{2,3}$-amino amide and releases the catalyst for further turnover. On the other hand, the order of addition of reactants influences the pathway of reaction that employs carboxylic acids as external nucleophiles: the union of a carboxylic acid with a ynamide first gives rise to an acyloxyenamide. The imine intermediate could be activated by the CBA as the hydrogen bonded species (**Int-1′**), followed by the stereoselective nucleophilic addition of an acyloxyenamide to form **Int-3′** through **Int-2′** via a mono-activation mode[59]. This is followed by a rapid Mumm rearrangement promoted by the chiral *N*-triflylphosphoramide to release the β^3-acylamino amide and regenerate the catalyst.

Conclusion

Grounded in the use of ynamides as ambiphilic two-carbon synthons, a redesign of the asymmetric Ugi reaction was realized for efficient synthesis of β-amino amides with excellent yields and diastereo- and enantio-selectivities. The utility of this strategy was demonstrated in the preparation of three classes of analogues, covering more than 100 β-amino amides that bear one or two well-defined carbon stereocentre(s). In addition to atom- and step-efficiency, the protocol demonstrates good scalability and could operate on drug molecules in native form. The suitability of amide products to synthesize the related amino acids, amino alcohols, β-lactams and chiral *anti*-vicinal diamines or undergo direct transamidation with amine-containing drugs and amino acids was verified. As a strategic step forward for MCRs, this approach bodes well for adoption in natural product synthesis as well as the development of therapeutic agents and peptidic oligomers.

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/s41557-023-01179-0.

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Methods

Procedure for the enantioselective syntheses of 1–17

To a dry Schlenk tube (10 ml) were added an amine (0.1 mmol), an aldehyde (0.2 mmol), a ynamide (0.2 mmol), (*R*)-**C8** (10 mol%) and MTBE (1.0 ml). Then the mixture was stirred at r.t. for 48 h. The reaction mixture was purified directly by preparative thin-layer chromatography (TLC) (petroleum ether/EtOAc = 5:1) to give the pure product.

Procedure for the enantioselective syntheses of 18–46

To a dry Schlenk tube (10 ml) were added an amine (0.1 mmol), an aldehyde (0.15 mmol), a ynamide (0.15 mmol), (*R*)-**C8** (15 mol%) and EtOAc/Et_2O (0.5 ml/0.5 ml). Then the mixture was stirred at r.t. for 48 h. The reaction mixture was purified directly by preparative TLC (petroleum ether/EtOAc = 5:1) to give the pure product.

Procedure for the enantioselective syntheses of 47–76 and 84–98

To a dry Schlenk tube (10 ml) were added an acid (0.12 mmol), a ynamide (0.12 mmol) and dry CH_2Cl_2 (0.5 ml). The resulting solution was stirred until the ynamide was completely consumed (for carboxylic acids with poor solubility, it was appropriately heated to 60 °C until the ynamide was completely consumed). An amine (0.1 mmol) and an aldehyde (0.12 mmol) were then added and the mixture was stirred for about 1 h followed by addition of (*R*)-**C7** (10 mol%) and *n*-hexane (0.5 ml) at −40 °C. The reaction mixture was stirred for another 48 h at this temperature. The mixture was purified directly by preparative TLC (petroleum ether/CH_2Cl_2 = 1:3) to give the pure product.

Procedure for the enantioselective syntheses of 77–83

To a dry Schlenk tube (10 ml) were added benzoic acid (0.12 mmol), a ynamide (0.12 mmol) and dry CH_2Cl_2/toluene (1.0 ml, v/v = 1:4). The resulting solution was stirred for 6 h at r.t. until the ynamide was completely consumed. An amine (0.1 mmol), an aldehyde (0.12 mmol) and (*S*)-**C9** (10 mol%) were then added at −30 °C. The reaction mixture was stirred for another 48 h at this temperature. The mixture was purified directly by preparative TLC (petroleum ether/CH_2Cl_2 = 1:3) to give the pure product.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2175112 (**23**), CCDC 2175113 (**24**), CCDC 2175114 (**47**), CCDC 2175115 (**100**) and CCDC 2175116 (**102b**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. The data supporting the findings of this work are provided in the Supplementary Information including experimental procedures and characterization of new compounds.

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Author contributions

B.T. and S.-H.X. conceived and directed the project. J.W. designed and performed the experiments. J.Z., S.-H.X. and J.K.C. helped with the collection of some new compounds and data analysis. B.T., J.W., S.-H.X. and J.K.C. wrote the paper with input from J.Z. All authors discussed the results and commented on the paper.

Competing interests

The authors declare no competing interests.

Additional information

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