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Ugi multicomponent reactions of optically active aldehydes and chiral aminoindanols: diastereoselective synthesis of bisamides relevant to SARS-CoV-2 Mpro inhibitors

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We have investigated diastereoselective Ugi-multicomponent reactions (Ugi-MCR) relevant to bis-amide scaffolds related to SARS-CoV-2 main protease (Mpro) inhibitors. The studies were mainly focussed on development of diastereoselective tools for generation of Ugi products. Ugi reactions using either chiral aldehyde or chiral amine provided bis-amide derivatives with marginal diastereoselectivity. However, the reaction with a matched combination of (*R*)-isopropylidene glyceraldehyde and (1*S*,2*R*)-aminoindanol derivatives provided good diastereoselectivity, up to a dr of 91 : 9. The stereochemistry of 1,2-aminoindanol plays an important role in diastereoselectivity. The stereochemical outcome of the MCR reaction was rationalized using Felkin transition state models. The Ugi-MCR products generated from these studies did not show any appreciable SARS-CoV-2 Mpro inhibitory activity.

Introduction

The Ugi multicomponent reaction (Ugi-MCR) is a versatile reaction that combines an aldehyde or ketone, a primary amine, an isocyanide, and a carboxylic acid to form products known as α-acylaminoamides or bis-amides.[1,2] The Ugi-MCR sets up multiple carbon–carbon and carbon-heteroatom bonds, conveniently providing molecules with structural complexities and incorporating important functionalities in a one-pot operation.[3–6] Not surprisingly, Ugi reactions are often utilized in the context of drug discovery and medicinal chemistry ventures.[7,8] It is widely employed in the generation of peptidomimetic derivatives for potential pharmaceutical applications and also for the preparation of compound libraries for lead generation using screening.[9,10] The Ugi-MCR reaction has also been extensively utilized in a variety of fields including in the total syntheses of bioactive natural products.[11–13] It was utilized in achieving the total synthesis of Ecteinascidin 743 (**1**, Fig. 1), a potent antitumor agent isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[14,15] The Ugi-MCR was also used in synthesizing pseudoridimycin (**2**), an antimicrobial agent with potent activity against both Gram-positive and Gram-negative bacteria, including drug-resistant strains.[16,17] The reaction was also employed in the synthesis of

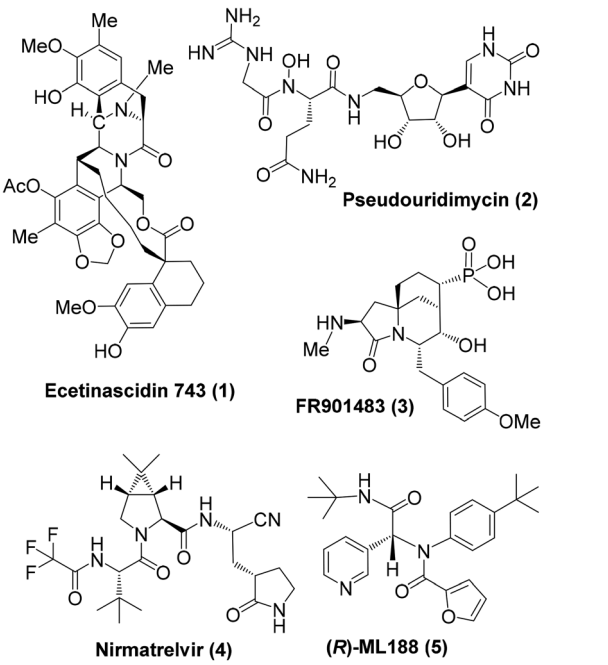

Fig. 1 Various products obtained from utilizing an Ugi-multicomponent reaction protocol.

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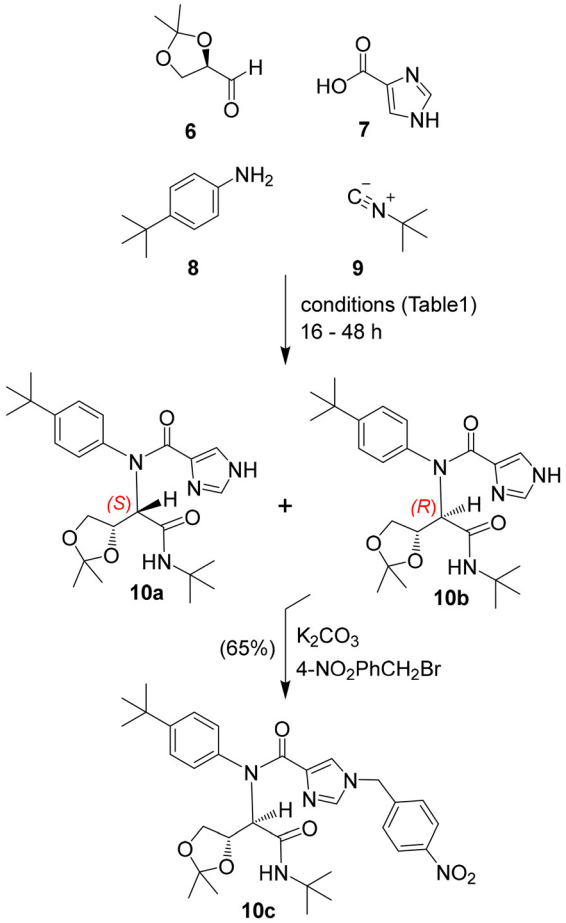
(−)-FR901483 (**3**), a potent immunosuppressive agent extracted from the fermentation broth of *Clasdobotryum* sp.[18,19] Besides the applications in natural product syntheses, the Ugi reactions have been extensively utilized in drug discovery and medicinal chemistry.[20–22] Variations of the Ugi reaction have also been used to provide alternative and more scalable routes to medicinally significant compounds.[23,24] One such example includes nirmatrelvir (**4**), the SARS-CoV-2 Mpro inhibitor drug recently developed and approved for the treatment of SARS-CoV-2 infection.[25,26] Interestingly, it is shown that it can be accessed in a highly diastereoselective manner *via* a three component Ugi strategy utilizing a cyclic imine precursor.[27]

The Ugi-MCR reaction has been utilized in accessing bisamide derivatives for the development of both noncovalent and covalent SARS-CoV-2 Mpro inhibitors.[28] Mesecar and coworkers first reported the bis-amide structural platform ML-188 (**5**) as a non-covalent inhibitor of the SARS-CoV-1 Mpro (IC_{50} value 1.5 μM). They have shown that this class of compounds bind to the SARS-CoV-1 Mpro active site.[28] Subsequently, bisamide scaffolds have been explored to develop potent SARS-CoV-2 Mpro inhibitors in recent years. Song and coworkers reported the Ugi-MCR approach to synthesize various epoxide-containing covalent inhibitors, describing additional mechanistic insights of this enzyme pocket.[29,30] Despite efforts in synthesizing SARS-CoV-2 Mpro inhibitors utilizing the Ugi-MCR reaction, there has yet to be practical methods for synthesizing these particular compounds using asymmetric synthetic methodologies.[31,32] In general, diastereoselective Ugi-MCR reactions using optically active starting materials are seldom explored.[33,34] Chiral aminoindanols are widely used in various asymmetric methodologies due to their constrained architecture as well as ready availability.[35,36] However, to the best of our knowledge, their application in diastereoselective Ugi reactions has not been explored. Herein, we report on the diastereoselective syntheses of bisamide derivatives employing the Ugi-MCR reaction using optically active aminoindanols paired with optically active aldehydes. Our studies particularly focused on examining diastereoselectivity associated with chiral amine and aldehyde pairs as well as generation of α-acylaminoamides with (*R*)-configuration.

Results and discussion

Our initial optimization efforts involved the use of (*R*)-isopropylidene glyceraldehyde **6** as the only optically active starting material, which can be readily synthesized from D-mannitol in 2-steps.[37,38] The rationale behind the selection of this aldehyde is the fact that the inherent α-chirality on this aldehyde has been shown to direct a variety of asymmetric reactions.[39,40] As shown in Scheme 1, we examined the Ugi-MCR reaction with this aldehyde in combination with equimolar amounts of 1*H*-imidazole-5-carboxylic acid **7**, *t*-butyl aniline **8**, and *t*-butyl isocyanide **9** in methanol at 23 °C to provide MCR product **10ab** as a diastereomeric mixture



Scheme 1 Ugi-MCR reaction with (*R*)-isopropylidene glyceraldehyde.

(44 : 56) in 33% yield. The ratio of the diastereomer was determined by ^{1}H-NMR analysis of the crude mixture after workup. The reaction was then optimized under various conditions, and the results are shown in Table 1. The reaction at 0 °C for 48 h provided a lower yield of diastereomers **10ab** (entry 2) with no appreciable increase in diastereoselectivity. Running the reaction at 40 °C for 45 h (entry 3) resulted in no overall

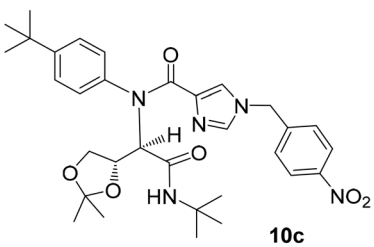
Table 1 Diastereoselectivity associated with Ugi-MCR reaction of (*R*)-isopropylidene glyceraldehyde

Entry	Solvent[a]	Temp. (°C)	Time (h)	Yield[b] (%)	dr (**10a** : **10b**)[c]
1	MeOH	23	36	33	44 : 56
2	MeOH	0	48	17	42 : 58
3	MeOH	40	45	34	44 : 56
4	MeCN	0–23	24	9	35 : 65
5	DCM	0–23	24	NR	N/A
6	Toluene	0–23	24	NR	N/A
7[d]	MeOH	0–23	16	67	43 : 57
8[d]	TFE[e]	0–23	16	39	58 : 42

[a] All reactions are performed in 0.2 M MeOH relative to aldehyde. [b] Isolated yield of both isomers after column chromatography. [c] The dr was determined by ^{1}H-NMR of crude product after workup. [d] Reaction utilized two equivalents of aldehyde. [e] TFE = 1,1,1-trifluoroethanol.

improvement over the reaction at 23 °C. Solvent screening showed that methanol is the ideal solvent for the reaction, as shown by its higher yields across the board compared to other solvents (entries 3 and 7). We examined the reaction using 2 equiv. aldehyde and 1 equiv. all other reagents which resulted in an increase of reaction yield to 67%, however the diastereoselectivity remained unchanged (entry 7). The reason for the use of 2 equiv. of aldehyde is due to the tendency of isopropylidene glyceraldehyde **6** to polymerize over time.[41] We also examined this optimized reaction in 1,1,1-trifluoro ethanol as the solvent. This condition provided lower yield of products, interestingly however it improved diastereoselectivity in favor of the isomer **10a** (entry 8). The diastereomers can be separated by column chromatography. To confirm the stereochemical identity, the dominant diastereomer **10b** from entry 1 was converted to its nitrobenzyl derivative **10c** in 65% yield by treatment of **10b** with K_2CO_3 and 4-nitrobenzylbromide in CH_3CN at 60 °C for 1.5 h. The X-ray structural analysis of **10c** showed that the α-stereocenter has (*R*)-configuration.[42,43] The ORTEP picture is shown in Fig. 2.

We then screened a variety of readily available cyclic and acyclic aldehydes containing an α-chiral center to see if the α-chiral center in different steric and electronic environments can influence the ratio of diastereomers. The results are shown in Scheme 2. Ugi-MCR was performed with 1 equiv. of aldehyde and equimolar amounts of amine, carboxylic acid, and isonitrile in dry methanol (0.2 M solution relative to aldehyde) from 0 °C to 23 °C for 24 h. The diastereoselectivity was determined by using ^{1}H-NMR of crude mixture after workup, or by



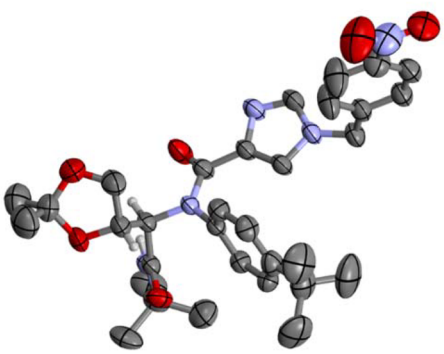
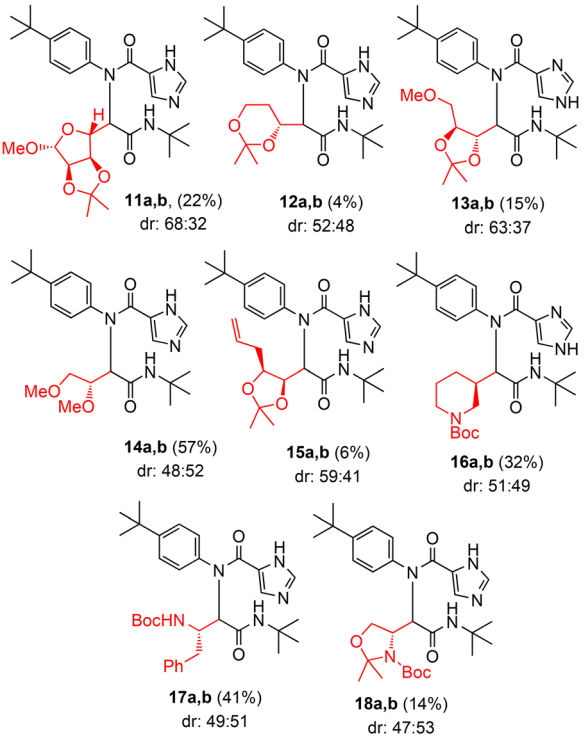


Fig. 2 The ORTEP diagram of compound **10c**. Carbon = black, oxygen = red, and hydrogen = white.

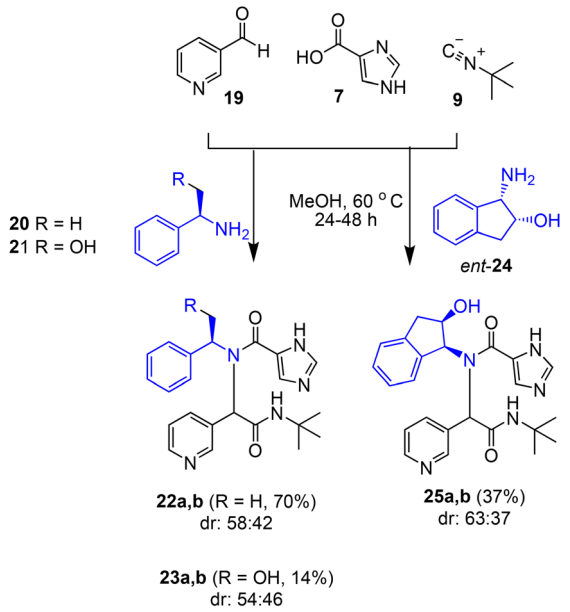


Scheme 2 Various Ugi-MCR products aldehydes containing an α-chiral center.

HPLC analysis for chromatographically inseparable mixtures. As can be seen, the diastereoselectivity of the reaction products **11–18** never breached far beyond 2 : 1, regardless of the structural complexity of the aldehyde. The yields of the Ugi-MCR products were particularly low for some hindered aldehydes. The modest yield for the Ugi adducts is possibly due to the bulky nature of the amine and aldehyde substrates.[44] For compound **14**, 2 equiv. of aldehyde was used. In general, the α-chiral center of these aldehydes did not show much influence on the diastereoselectivity.

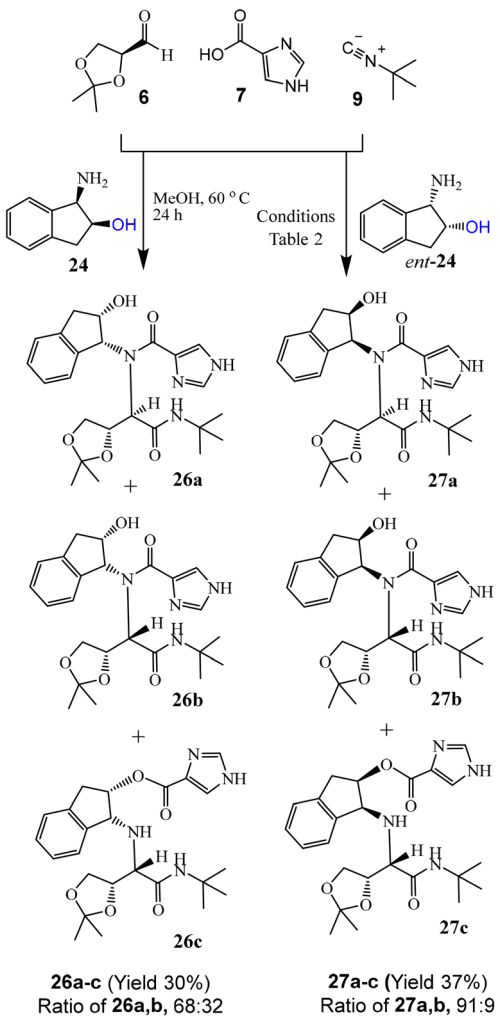
We briefly explored the diastereoselectivity associated with reactions with pyridine-3-carbaldehyde **19** and chiral acyclic amines **20** and **21** in combination with carboxylic acid **7** and isocyanide **9** as shown in Scheme 3. Ugi-MCR products **22** and **23** were obtained in 70% and 14% yields, respectively. However, diastereomeric ratios were moderate. We then investigated commercially available chiral cyclic aminoindanols. Reaction of (1*S*,2*R*)-1-amino-2-indanol *ent*-**24** at 70 °C for 24 h resulted in product **25** as a 63 : 37 mixture of diastereomers in 37% yield. The reaction was slow at 23 °C and it was necessary to heat up the reaction to 60 °C to improve product yield. This is particularly the case with less reactive aromatic aldehydes. However, the higher temperature predictably eroded the diastereoselectivity of the reaction.

We then explored the diastereoselectivity associated with reactions with (*R*)-isopropylidene glyceraldehyde **6** in combination with commercially available optically active *cis*-amino indanol derivatives. As shown in Scheme 4, reaction of 2 equiv.



Scheme 3 Ugi-MCR reaction with chiral acyclic and cyclic amines.

aldehyde **6**, 1 equiv. (1*R*,2*S*)-1-amino-2-indanol **24**, 1 equiv. imidazole carboxylic acid **7**, and 2 equiv. isocyanide **9** in MeOH at 0 °C to 40 °C for 24 h resulted in MCR products **26ab** as a mixture of diastereomers. In addition to distereomers **26ab**, ester derivative **26c** also formed in this reaction and provided 30% combined yield. The dominant diastereomer **26a** was separated by chromatography, however diastereomer **26b** and ester **26c** were isolated as an inseparable mixture. The combined yield of **26a–c** was 30%. HPLC analysis of crude reaction mixture showed the ratio of diastereomers **26a** and **26b** was marginal (68 : 32). The ratio of products **26a–c** was 62 : 28 : 10. Reaction of the enantiomeric (1*S*,2*R*)-1-amino-2-indanol *ent*-**24** under similar conditions also resulted in diastereomeric MCR products **27ab** as well as ester derivative **27c** in a combined isolated yield of 37%. The ratio of diastereomers **27a** and **27b** was determined to be 91 : 9 by HPLC analysis of the crude mixture. The ratio of products **27a–c** was 83 : 8 : 9. Diastereomer **27a** was separated by silica gel chromatography using 5% MeOH in CH_2Cl_2 as the eluent. Compounds **27b** and **27c** could not be separated by chromatography. However, compound **27c** was separated by HPLC using a TOSOH Bioscience CM-2SW column using a 10%-90% MeCN/H_2O gradient. The stereochemical identity of the major diastereomer **27a** and ester derivative **27c** was determined by single crystal X-ray analysis.[41,45,46] The ORTEP drawing is shown in Fig. 3. The Ugi-MCR reaction with (1*S*,2*R*)-1-amino-2-indanol created a new α-stereo center which was shown to have (*R*)-configuration for the dominant diatereomer **27a**. However, the ester derivative **27c** possessed (*S*)-configuration. It was previously shown that (*R*)-configuration is the biologically active configuration for SARS-CoV-2 Mpro inhibitors using this scaffold.[27,28]



Scheme 4 Ugi-MCR reaction with chiral aminoindanols.

In an effort to improve yield and diastereoselectivity we further surveyed other reaction conditions as shown in Table 2. Reaction of 2 equiv. aldehyde **6** in combination with 1 equiv. amount of amine, acid and isocyanide at 0 °C to 23 °C for 24 h resulted in MCR with similar diastereomeric ratio, however the isolated yield depleted to 17% (entry 1). Modifying the reaction by increasing the amount of isocyanide to 1.5 equiv. under similar conditions led to a slight improvement of yield and diastereomeric ratio (entry 2). Further reactions with 2 equiv. and 3 equiv. of isocyanide did not improve ratio (entries 3 and 4). We also examined reactions with 2 equiv. isocyanide at 0 °C to 50 °C for 24 h and separately at 0 °C to 60 °C for 24 h. In both cases, product yields were unchanged and the ratio of diastereoselectivity was decreased (entries 6 and 7).

The above results show the importance of stereochemistry of chiral aminoindanols. To assess the origin of diastereoselectivity, we examined the effect of the hydroxyl functionality and the stereochemistry of the aminoindanols. The results are shown in Scheme 5. Reaction of optically active 1-(*R*)-aminoin-

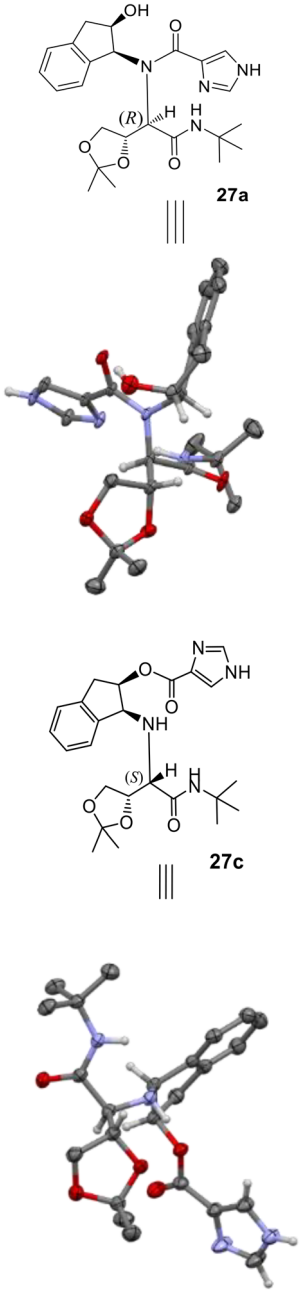


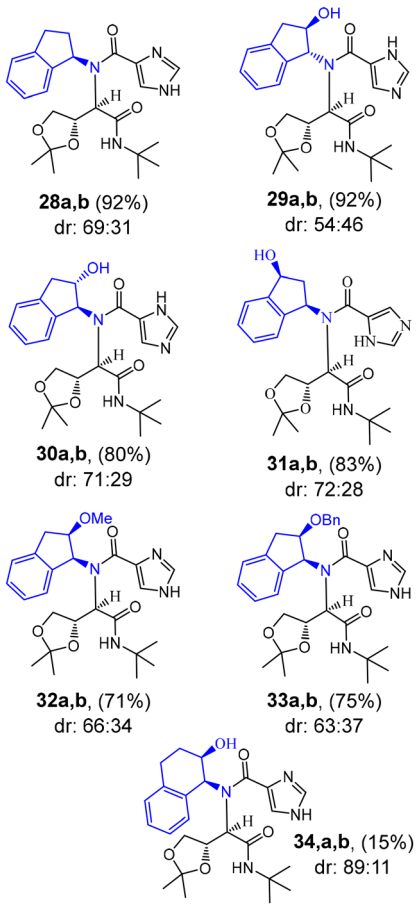
Fig. 3 The ORTEP diagram of compound **27a** and **27c**. Carbon = black, oxygen = red, and hydrogen = white.

dane using reaction condition described in entry 5, Table 2, resulted in MCR product **28a,b** in 92% yield. HPLC analysis of the crude products showed that the product contains as a (69 : 31) mixture of diastereomers. This result indicates the importance of alcohol functionality in (1*S*,2*R*)-1-amino-3-indanol *ent*-**24**. Reaction with enantiomerically pure *trans*-aminoindanols resulted in significant improvement of yields. However, diastereoselectivity in products **29a,b** and **30a,b** was reduced. Reaction of (1*S*,3*R*)-1-amino-3-indanol did not improve diastereoselectivity for the MCR product **31a,b**. Interestingly, the yield of these MCR products was significantly

Table 2 Results of studies utilizing (1*S*,2*R*)-aminoindanol **24** with aldehyde **6**

Entry	Isocyanide (equiv.)	Temp. (°C)	Yield[a,b] (%)	dr[c] (**a** : **b**)
1	1	0 °C to 23 °C	17	89 : 11
2	1.5	0 °C to 23 °C	25	90 : 10
3	2	0 °C to 23 °C	23	88 : 12
4	3	0 °C to 23 °C	30	87 : 13
5	2	0 °C to 40 °C	37	91 : 9
6	2	0 °C to 50 °C	27	85 : 15
7	2	0 °C to 60 °C	28	80 : 20

[a] All reactions are done in 0.2 M MeOH relative to aldehyde. Aldehyde (2 equiv.), acid (1 equiv.), amine (1 equiv.) were used at specified temperature for 24 h. [b] Isolated yield after chromatography. [c] The dr obtained *via* HPLC analysis of mixture after chromatography.

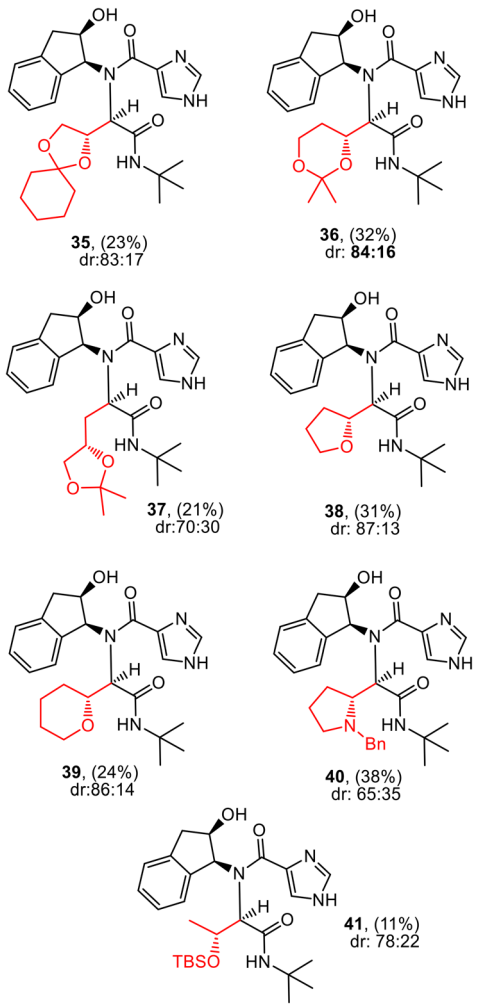


Scheme 5 Ugi-MCR with various chiral cyclic aminoindanols.

better than the sterically hindered *cis*-1,2-aminoindanols. Ugi-MCR reactions with 2-methyl ether and benzyl ether also resulted in very good yield of MCR products **32a,b** and **33a,b** with reduction of diastereoselectivity. We also have investigated the effect of ring size using 1-(*S*)-amino-2(*R*)-hydroxy-tetrahydronaphthalene. The Ugi-MCR reaction resulted in products **34a,b** in 17% yield, comparable to the reaction with *cis*-aminoindanol derivatives.

We further carried out reactions with (1*S*,2*R*) aminoindanol *ent*-**24** in combination with various other aldehydes that have the same (*R*)-configuration as aldehyde **6**. The results are shown in Scheme 6. As can be seen, reaction with a bulkier (*R*)-cyclohexylidene glyceraldehyde[47] provided MCR products **35a,b** in 23% yield and a diastereomeric ratio of 83 : 17. The reaction of (*R*)-2,2-dimethyl-1,3-dioxane-carbaldehyde[48] furnished products **36a,b** with good diasteroselectivity. HPLC analysis of compound mixture showed the presence of a very small amount unidentified, possibly an ester byproduct as seen previously. Reaction of (*R*)-2(2,2-dimethly-1,3-dioxolan-4yl) acetaldehyde[49] resulted in products **37a,b** in 21% yield and 2-carbaldehyde[50] exhibited MCR products **38a,b** with good diastereoselectivity (dr 87 : 13). The corresponding reaction with (*R*)-tetrahydropyran carbaldehyde[51] gave products **39a,b** with similar diastereoselectivity and yield compared to tetrahydrofuranyl derivatives **38a,b**. HPLC analysis of compound **39** showed the presence of a very small amount ester byproduct. Further reaction with (*R*)-1-benzylprrolidine-carbaldehyde[52] provided MCR product **40a,b** in 38% yield and showed lower diastereomeric ratio (65 : 35) compared to reactions with tetrahydrofuran and tetrahydropyran derivatives in **38a,b** and **39a, b**. We also examined reaction of (*R*)-silyloxypropanal[53] which resulted in major diastereomer **41a,b** with a dr of 78 : 22, however the isolated yield was only 11%. The major diastereomer maintained (*R*) stereochemistry at the α-amino stereocenter, which was confirmed by X-ray crystallography. The ORTEP picture of the major diastereomer **41a** is shown in Fig. 4.[40,54] As can be seen, the newly created α-amino stereocenter possesses (*R*)-configuration which was shown previously as the required stereochemistry for SARS-CoV-1 Mpro inhibitory activity.[27,28] Our current studies are directed towards the development of a diastereoselective Ugi-MCR reaction for the generation of biologically active SARS-CoV-2 Mpro inhibitors in a stereo predictable fashion. Due to structural similarities of many Ugi-MCR products with (*R*)-ML188 (**5**), we have evaluated all products in our SARS-CoV-2 Mpro inhibitory assays. However, none of these current derivatives show any appreciable SARS-CoV-2 Mpro inhibitory activity. The assay protocols and the results of SARS-CoV-2 Mpro inhibitory activity of these compounds are shown in the SI.

The stereochemical outcome and the reason for higher diastereoselectivity can be rationalized using models in Scheme 7. Our results show that the α-stereo center on the aldehyde and the structure and chirality on the amine play important roles in Ugi-MCR product diastereoselectivity. The degree of diastereoselection by using a chiral aldehyde or by a chiral amine alone did not result in high diastereoselectivity. However, matched combination of stereochemistry of the aldehyde and the amine resulted in Ugi-MCR products with significant diastereoselectivity. This is shown in the formation of the Ugi-MCR products between (*R*)-isopropylidene glyceraldehyde



Scheme 6 Ugi-MCR reaction various aldehydes and aminoindanols.

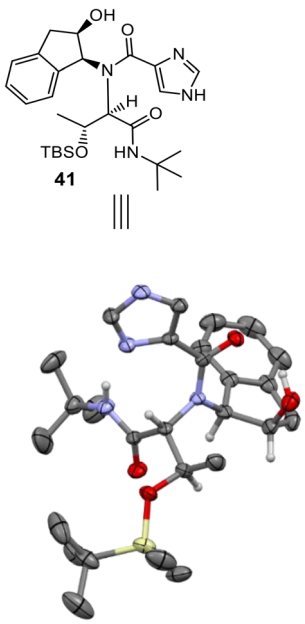
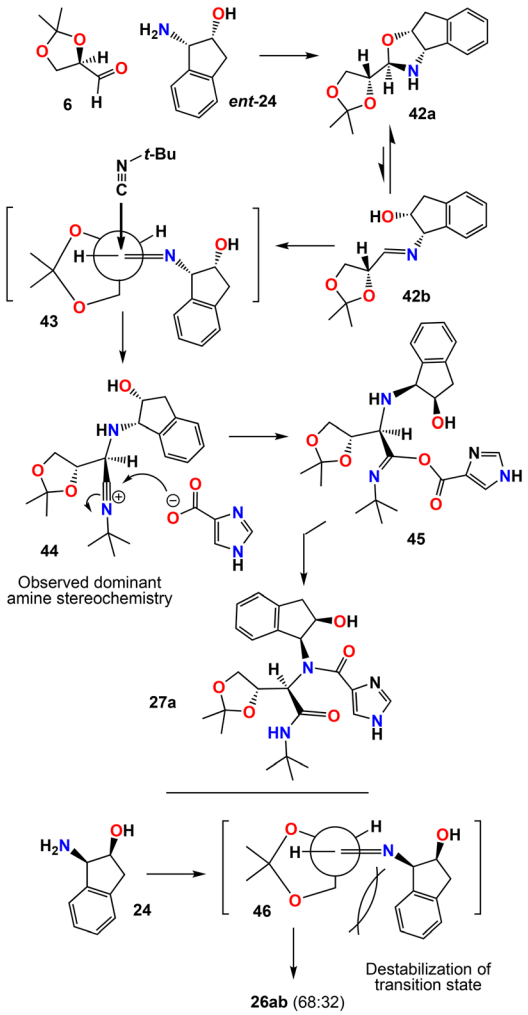


Fig. 4 The ORTEP picture of diastereomer **41**. Carbon = black, oxygen = red, and hydrogen = white.



Scheme 7 Stereochemical models for the origin of diastereoselectivity for the Ugi-MCR reactions.

6 and (1*S*,2*R*) aminoindanol *ent*-**24**. Reaction of aldehyde **6** and *ent*-**24** showed a diastereomeric ratio of 91 : 9 in comparison to reaction between aldehyde **6** and enantiomeric **24** which provided marginal diastereoselectivity. Reactions between aldehyde **6** and amine *ent*-**24** would lead to oxazolidine and imine intermediates **42a** and **42b**, respectively. Presumably, the majority of the imine would exist as stable oxazolidine derivative **42a**. Due to matched stereochemistry of aldehyde **6** and amine *ent*-**24**, the steric clashes are minimum for both intermediates. Presumably, subsequent reaction with isonitrile will proceed through the minor imine intermediate **42b**. We postulate that the attack by the *t*-BuNC nucleophile proceeds through the Felkin transition state intermediate **43** where steric clashes are minimized due to complementary stereochemistry of the aldehyde and amine side chains.[55,56] Subsequent reaction of imidazole carboxylate as shown in **44** leads to imine-ester intermediate **45**. Subsequent Mumm rearrangement provides the major diastereomer **27a**.[57,58] However, the reaction of aldehyde **6** and amine **24** leads to the corresponding diastereomeric Felkin transition state **46** which is destabilized due to steric interactions between the bulky aminoindanol scaffold and the dioxolane ring of the aldehyde. This may explain the lack of diastereoselectivity for the formation of products **26ab** (dr, 68 : 32). The formation of ester derivative **27c** may result from the minor diastereomeric intermediate like **45**. Presumably, the proximity of the hydroxyl group and its favorable stereochemistry allow a competing intramolecular attack by the free hydroxyl group on the imine-ester intermediate prior to Mumm rearrangement,[57,58] resulting in the formation of ester derivative **27c**.

Conclusion

The Ugi reaction plays an important role in generating bis-amide derivatives for versatile applications in medicinal chemistry and drug discovery. Despite many advances in Ugi-multicomponent reactions in terms of efficiency and development of practical protocols, stereoselective generation of Ugi-MCR products is an area that is underdeveloped. We have investigated asymmetric Ugi-MCR reactions in an effort to generate bis-amide derivatives in a stereo predictable fashion. In our studies, we have demonstrated that the α-stereo center on the aldehyde or the chirality of the amine component on their own is not adequate to synthesize bis-amide derivatives diastereoselectively. However, an appropriate matched combination of chiral aldehyde and chiral amine can synergize reactions providing Ugi-MCR products with high diastereoselectivity. In particular, we showed that a combination of (*R*)-isopropylidene glyceraldehyde and (1*S*,2*R*)-aminoindanol provided diastereoselectivity up to a dr of 91 : 9. The corresponding reaction with the (1*R*,2*S*)-aminoindanol enantiomer was less selective (dr: 68 : 32). While the yields were modest, the stereochemistry as well as the presence of alcohol functionality appear to play an important role in diastereoselection. We have proposed stereochemical models where the MCR may have progressed through a Felkin-type transition state that provided these diastereoselective Ugi-MCR products. All current Ugi-MCR products were evaluated in SARS-CoV-2 Mpro inhibitory assays. However, none of the current derivatives showed any appreciable SARS-CoV-2 Mpro activity. The current studies may serve to further the development of practical methods for highly diastereoselective Ugi-MCR reaction products in a stereopredictable manner. Further application of this chemistry in the development of novel SARS-CoV-2 Mpro inhibitors is in progress.

Experimental section

General methods

All reagents were purchased commercially and used without further purification unless specified. Unless otherwise stated, all reactions were carried out under an Argon atmosphere. Tetrahydrofuran was dried over sodium metal and distilled

before use. Anhydrous dichloromethane was prepared by distillation over calcium hydride. Anhydrous methanol was prepared by drying over 3A molecular sieves. TLC analysis was carried out using 60 A, 250 μm thick F-254 glass-backed plates. Flash column chromatography was done using 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra was obtained on either a Bruker AV-III-400-HD or NEO-500. Chemical shifts are reported in ppm, *J*-values in Hz, and all peaks are referenced to the residual deuterated solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet). Optical rotations were obtained using an automatic digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]\lambda$ *T* °C (*c* = 0.1(mg mL^{-1}), solvent). High-resolution mass spectrometry (HRMS) spectra were recorded under positive electron spray ionization (ESI+) at Agilent 6550 Q-TOF LC/MS instrument at the Purdue University Analytical Mass Spectrometry Facility.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((*R*,*S*)-2-(*tert*-butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-1*H*-imidazole-4-carboxamide (10ab).** To a stirred solution of (*R*)-isopropylidene glyceraldehyde **6**,[37,38] (200 mg, 1.54 mmol, 2 equiv.) in anhydrous methanol (0.2 M) and chilled to 0 °C, 1 equiv. (0.12 mL, 0.77 mmol) of 4-*t*-butyl aniline **8**, 1 equiv. (86 mg, 0.77 mmol) of 1-*H*-imidazole-5-carboxylic acid **8**, and 1 equiv. (0.087 mL, 0.77 mmol) of *t*-butyl-isocyanide **9**, in that order, are added to the reaction vessel. The reaction is warmed to 23 °C and stirred for 24 h. The reaction is concentrated *in vacuo*, partitioned between dichloromethane and saturated sodium bicarbonate solution, and the organic layer was separated. The aqueous layer was then extracted 3× dichloromethane, and the organic layers were combined and washed with 2× saturated sodium bicarbonate and 1× brine, dried over Na_2SO_4, filtered, concentrated, and loaded onto silica gel chromatography (5% MeOH/DCM) to provide products **10ab** (233 mg, 67%, 43 : 57 dr) as an amorphous solid. An analytical sample of pure diastereomers **10a** and **10b** was prepared after chromatographic separation.

***10a** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.27. $[\alpha]_D^{23}$ −173.7 (*c* 0.27, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.43–7.13 (m, 0H), 6.53 (s, 1H), 5.45 (s, 1H), 5.23 (d, *J* = 9.4 Hz, 1H), 4.26 (dt, *J* = 9.3, 6.0 Hz, 1H), 4.05 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.72 (dd, *J* = 9.0, 5.7 Hz, 1H), 1.43 (s, 3H), 1.37–1.35 (m, 18H), 1.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 161.7, 153.7, 136.5, 135.0, 131.8, 130.0, 126.8, 125.8, 109.4, 77.4, 77.2, 76.9, 72.3, 67.6, 63.0, 51.6, 35.0, 31.5, 28.8, 27.1, 25.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{37}N_4O_4$ 457.2814. Found 457.2799.

***10b** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.21 $[\alpha]_D^{23}$ +24.5 (*c* 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1H), 5.47 (s, 1H), 4.79 (q, *J* = 6.2 Hz, 1H), 4.63–4.47 (m, 1H), 4.12 (dd, *J* = 8.6, 5.9 Hz, 1H), 3.99 (dd, *J* = 8.6, 5.5 Hz, 1H), 1.44 (s, 3H), 1.36–1.30 (m, 19H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 161.6, 153.1, 138.3, 136.8, 128.9, 127.0, 110.6, 77.4, 77.2, 76.9, 74.2, 68.0, 66.3, 51.5, 35.0, 31.5, 28.9, 27.1, 25.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{37}N_4O_4$ 457.2814. Found 457.2801.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((*R*)-2-(*tert*-butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-1-(4-nitrobenzyl)-1*H*-imidazole-4-carboxamide (10c).** To an oven dried 25 mL roundbottom flask, adduct **10b** (323 mg, 0.71 mmol) was added, which was dissolved in 15 mL of dry acetonitrile and chilled to 0 °C. Potassium carbonate (293 mg, 2.12 mmol) and 4-nitrobenzyl bromide (183 mg, 0.85 mmol) were added, and the reaction was heated to 60 °C and stirred for 1.5 hours. The reaction mixture was filtered through Celite whilst hot, with the filter cake being washed 3× dichloromethane. The filtrate was concentrated to an oily residue, of which was purified by silica gel chromatography (5% MeOH/DCM), which yielded product **10c** in 65% isolated yield as an off white amorphous solid. R_f (5% MeOH/DCM) = 0.31. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 2H), 7.39 (s, 1H), 7.31–7.24 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.11–7.08 (m, 1H), 6.85 (sz, 1H), 5.00 (s, 2H), 4.85–4.50 (m, 1H), 4.05 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.96 (dd, *J* = 8.5, 5.3 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 9H), 1.33 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 164.0, 151.5, 148.0, 142.5, 136.9, 128.6, 127.8, 126.2, 124.4, 110.3, 77.4, 77.2, 76.9, 75.4, 74.1, 67.7, 51.4, 50.1, 34.7, 31.4, 28.9, 27.0, 25.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{41}N_5O_6$: 592.3135. Found 592.3132.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((*S*,*R*)2-(*tert*-butylamino)-1-((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-oxoethyl)-1*H*-imidazole-5-carboxamide (11ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. of (3a*R*,4*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (200 mg, 0.99 mmol) as the reagent, flash chromatography (5% MeOH/CH_2Cl_2) yielded title compound **11ab** (112 mg, 22%, dr 68 : 32). An analytical sample of pure diastereomers **11a** and **11b** was prepared after chromatographic separation.

***11a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.3. $[\alpha]_D^{23}$ +178.6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.30 (m, 5H), 6.59 (s, 1H), 5.47 (s, 1H), 5.40 (d, *J* = 11.6 Hz, 1H), 5.01 (s, 1H), 4.69–4.61 (m, 2H), 4.34 (dd, *J* = 11.6, 0.9 Hz, 1H), 3.27 (s, 3H), 1.42 (s, 3H), 1.37 (s, 9H), 1.36 (s, 8H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 161.9, 153.6, 136.4, 134.1, 131.3, 126.8, 125.8, 112.5, 109.4, 84.9, 82.8, 82.7, 77.3, 77.0, 76.8, 60.9, 55.1, 51.4, 34.9, 31.4, 28.8, 26.4, 24.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{41}N_4O_6$ 529.3026. Found 529.3016.

***11b** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.27. $[\alpha]_D^{23}$ −84.0 (*c* 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.36–7.26 (m, 2H), 6.52 (s, 1H), 5.39 (s, 1H), 5.20–5.15 (m, 1H), 5.03 (s, 1H), 4.88 (d, *J* = 6.0 Hz, 1H), 4.70–4.62 (m, 2H), 3.40 (s, 3H), 1.46 (s, 3H), 1.36 (s, 9H), 1.34 (s, 9H), 1.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 161.2, 153.7, 136.5, 129.9, 127.0, 113.1, 110.3, 85.2, 84.2, 82.1, 77.4, 77.2, 76.9, 56.0, 51.7, 35.1, 31.5, 28.8, 26.7, 25.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{41}N_4O_6$ 457.2814. Found 529.3013.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((*S*,*R*)2-(*tert*-butylamino)-1-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-oxoethyl)-1*H*-imidazole-5-carboxamide (12ab).** Following the general procedure for the synthesis

of **10ab**, using 1 equiv. (52 mg, 0.36 mmol) of (*R*)-2,2-dimethyl-1,3-dioxane-4-carbaldehyde,[59] flash chromatography (5% MeOH/DCM) yielded title compound **12ab** (35 mg, 21%, dr 52 : 48) as an off-white amorphous solid. Analytical samples of pure diastereomers **11a** and **11b** were prepared after chromatographic separation.

***12a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.39. $[\alpha]_D^{23}$ −59.2 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.65 (s, 1H), 5.42 (s, 1H), 4.93 (d, *J* = 9.4 Hz, 1H), 4.05 (t, *J* = 9.9 Hz, 1H), 3.91–3.73 (m, 2H), 1.70–1.52 (m, 2H), 1.35 (d, *J* = 1.7 Hz, 18H), 1.25 (s, 3H), 1.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 161.8, 153.3, 136.5, 135.4, 132.1, 130.5, 126.1, 98.7, 77.4, 77.2, 76.9, 65.4, 59.5, 51.5, 35.0, 31.5, 30.1, 28.7, 28.2, 18.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{39}N_4O_4$ 471.2971. Found 471.2956.

***12b** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.35. $[\alpha]_D^{23}$ +21.0 (*c* 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.29 (m, 4H), 7.09 (s, 1H), 5.54 (s, 1H), 4.96 (s, 1H), 4.13 (d, *J* = 6.8 Hz, 1H), 4.03 (t, *J* = 11.8 Hz, 1H), 3.90 (dd, *J* = 11.7, 5.1 Hz, 1H), 1.86 (d, *J* = 7.8 Hz, 1H), 1.75 (d, *J* = 12.7 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 9H), 1.29 (s, 9H), 1.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 152.7, 140.0, 136.5, 128.8, 126.7, 98.9, 77.3, 77.0, 76.8, 69.6, 59.8, 51.1, 34.8, 31.4, 30.0, 29.7, 28.8, 28.6, 19.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{39}N_4O_4$ 471.2971. Found 471.2959

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((*S*,*R*)2-(*tert*-butylamino)-1-((4*S*,5*S*)-5-(methoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-1*H*-imidazole-4-carboxamide (13ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. (4*R*,5*S*)-5-(methoxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (190 mg, 1.14 mmol), flash chromatography (5% EtOH/EtOAc) yielded title compound **13ab** (86 mg, 15%, dr 63 : 37) as a white amorphous solid. Analytical samples of pure diastereomers **13a** and **13b** were prepared after chromatographic separation.

***13a** (major isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.34. $[\alpha]_D^{23}$ −141.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.52–7.42 (m, 4H), 6.60 (s, 1H), 5.40 (s, 1H), 5.27 (d, *J* = 9.4 Hz, 1H), 4.20–4.11 (m, 1H), 4.11–4.03 (m, 1H), 3.59 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.48–3.36 (m, 1H), 3.34 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.38–1.33 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 161.6, 153.6, 136.5, 135.0, 131.5, 130.1, 126.8, 125.9, 110.3, 79.2, 77.4, 77.2, 76.9, 74.2, 73.8, 59.4, 51.7, 35.0, 31.5, 28.8, 28.7, 27.8, 27.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{41}N_4O_5$ 501. Found 501.3058.

***13b** (minor isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.32. $[\alpha]_D^{23}$ +19.0 (*c* 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.61–7.30 (m, 4H), 6.94 (s, 1H), 5.53 (s, 1H), 4.80 (t, *J* = 7.7 Hz, 1H), 4.41–4.27 (m, 2H), 3.63–3.48 (m, 2H), 3.33 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.35 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 161.5, 153.1, 139.5, 136.7, 131.7, 129.0, 127.0, 126.0, 110.3, 79.4, 77.4, 77.2, 76.9, 76.0, 73.6, 68.2, 59.7, 51.5, 35.0, 31.5, 28.8, 27.4, 27.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{41}N_4O_5$ 501.3077. Found 501.3058.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-((2*R*,2*S*,3*S*)-1-(*tert*-butylamino)-3,4-dimethoxy-1-oxobutan-2-yl)-1*H*-imidazole-5-carboxamide (14ab).** Following the general procedure for the synthesis of **10ab**, using 2 equiv. of (*R*)-2,3-dimethoxypropanal,[60] (135 mg, 1.14 mmol), flash chromatography (8% MeOH/DCM) yielded title compound **14** as an inseparable pair of diastereomers as an off-white amorphous solid (145 mg, 57%, 52 : 48). R_f (5% MeOH/DCM) = 0.22. The dr was determined from the mixture after column chromatography by HPLC (TOSOH BioScience CM-2SW 10–90% MeCN/H_2O over 90 min). Retention times: 93.2 min, 100.2 min. Spectra of the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 12.0, 8.4 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.74 (s, 1H), 5.49 (s, 1H), 4.56 (d, *J* = 8.3 Hz, 1H), 4.26 (d, *J* = 8.2 Hz, 1H), 3.73 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.57 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 1.34 (s, 10H), 1.31 (s, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 167.0, 161.6, 152.8, 136.7, 136.5, 130.3, 129.2, 126.6, 79.2, 77.4, 77.2, 76.9, 76.4, 71.1, 59.5, 59.5, 51.2, 34.9, 31.5, 28.9. LRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{37}N_4O_4$ 445.3. Found 445.3.

***N*-((*S*,*R*)-1-((4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-(*tert*-butyl)phenyl)-1*H*-imidazole-5-carboxamide (15ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. (320 mg, 1.88 mmol), of (4*S*,5*S*)-5-allyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde,[61] flash chromatography (5% MeOH/DCM) yielded title compound **15ab** (54 mg, 6%, dr 59 : 41) as a yellow amorphous solid. Analytical samples of pure diastereomers **15a** and **15b** were prepared after chromatographic separation.

***15a** (major isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.44. $[\alpha]_D^{23}$ +131 (*c* 0.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–6.93 (m, 5H), 6.66 (s, 1H), 5.86 (ddt, *J* = 13.6, 10.1, 6.8 Hz, 1H), 5.47–5.37 (m, 2H), 5.16–5.06 (m, 2H), 4.38–4.22 (m, 1H), 4.17 (dd, *J* = 10.5, 5.5 Hz, 1H), 2.30 (q, *J* = 9.6 Hz, 1H), 2.19 (m, 1H), 1.46 (s, 3H), 1.37 (s, 9H), 1.35 (s, 9H), 1.22 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 161.7, 153.8, 136.6, 134.9, 134.2, 132.1, 127.0, 125.8, 117.3, 108.2, 77.4, 77.2, 76.9, 73.3, 58.8, 51.5, 35.5, 35.0, 31.5, 29.8, 28.7, 28.4, 25.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{41}N_4O_4$ 497.3128. Found 497.3110.

***15b** (minor isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.36. $[\alpha]_D^{23}$ −39 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.41–7.02 (m, 3H), 6.72 (s, 1H), 5.92–5.80 (m, 1H), 5.40 (s, 1H), 5.21 (d, *J* = 9.5 Hz, 1H), 5.14–5.06 (m, 2H), 4.36 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.13 (ddd, *J* = 10.8, 5.5, 3.1 Hz, 1H), 2.44–2.27 (m, 2H), 1.49 (s, 3H), 1.36 (s, 9H), 1.33 (s, 9H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 161.6, 153.5, 136.7, 136.2, 134.5, 129.6, 126.9, 117.7, 108.8, 77.5, 75.2, 59.8, 51.6, 35.0, 34.8, 31.5, 28.8, 28.4, 26.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{41}N_4O_4$ 497.3128. Found 497.3112.

***tert*-Butyl(3*R*)-3-((*S*,*R*)-1-(*N*-(4-(*tert*-butyl)phenyl)-1*H*-imidazole-4-carbox-amido)-2-(*tert*-butylamino)-2-oxoethyl)piperidine-1-carboxylate (16ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. (79 mg, 0.37 mmol) of *tert*-butyl (*R*)-3-formylpiperidine-1-carboxylate,[62] flash chromatography

(5% MeOH/DCM) yielded title compound as an inseparable mixture of diastereomers as an off-white amorphous solid (64 mg, 32%, dr 51 : 49). R_f (5% MeOH/DCM) = 0.41. The dr was determined after column chromatography by HPLC similar to **14ab**. Retention times: 96.3 min, 99.3 min: spectra of dominant diastereomer: ^{1}H NMR (400 MHz, DMSO) δ 7.69–7.07 (m, 8H), 4.97 (d, J = 10.7 Hz, 1H), 3.79 (m, 2H), 2.84–2.57 (m, 3H), 1.89 (m, 2H), 1.63 (m, 2H), 1.32 (s, 9H), 1.25 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 167.6, 161.7, 155.0, 153.2, 136.5, 129.5, 128.8, 126.9, 126.8, 79.7, 77.4, 77.2, 76.9, 53.6, 51.5, 51.5, 35.0, 34.7, 31.5, 29.8, 28.8, 28.6, 27.8, 24.2. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{46}N_5O_4$ 540.4. Found 540.3.

***tert*-Butyl((2*S*,3*R*,3*S*)-3-(*N*-(4-(*tert*-butyl)phenyl)-1*H*-imidazole-5-carbox-amido)-4-(*tert*-butylamino)-4-oxo-1-phenylbutan-2-yl)carbamate (17ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. (267 mg, 1.07 mmol) of *tert*-butyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate,[63] flash chromatography (5% MeOH/DCM) yielded title compound **17**, which was isolated as a chromatographically inseparable mixture of diastereomers as an off-white amorphous solid (129 mg, 41%, dr 51 : 49). R_f (5% MeOH/DCM) = 0.43. The dr was determined from the mixture after column chromatography by HPLC similar to **14**. Retention times: 87.3 min, 89.8 min. Following spectra is reported where both diastereomers are normalized to one compound: ^{1}H NMR (500 MHz, DMSO) δ 7.99–5.96 (m, 13H), 5.32–4.08 (m, 2H), 3.05–2.55 (m, 2H), 1.33 (s, 8H), 1.21 (s, 8H), 1.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 168.0, 166.9, 161.6, 157.0, 155.6, 153.3, 137.7, 137.1, 136.2, 130.3, 129.4, 128.6, 126.7, 79.2, 77.4, 77.2, 76.9, 61.4, 51.7, 50.9, 39.9, 35.0, 31.5, 28.5, 28.5. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{33}H_{46}N_5O_4$ 576.4. Found 576.3.

***tert*-Butyl(4*S*)-4-((*S*,*R*)-1-(*N*-(4-(*tert*-butyl)phenyl)-1*H*-imidazole-5-carboxamido)-2-(*tert*-butylamino)-2-oxoethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (18ab).** Following the general procedure for the synthesis of **10ab**, using 1 equiv. (198 mg, 0.87 mmol) of *tert*-butyl (*R*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate,[64] flash chromatography (5% MeOH/DCM) yielded title compound **18** (68 mg, 14%, dr 53 : 47) as an off-white amorphous solid. Analytical samples of pure diastereomers **18a** and **18b** were prepared after chromatographic separation.

***18a** (major isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.48. $[\alpha]_D^{23}$ −16.0 (c 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.43 (s, 4H), 6.39 (s, 1H), 5.61 (s, 1H), 4.85 (d, J = 5.6 Hz, 1H), 4.67 (s, 1H), 4.02 (dd, J = 9.9, 1.8 Hz, 1H), 3.76–3.68 (m, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.40 (s, 9H), 1.34 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 161.2, 153.3, 153.0, 138.4, 136.5, 131.8, 129.4, 126.8, 126.2, 94.5, 81.0, 77.4, 77.4, 77.2, 76.9, 66.7, 65.4, 57.8, 51.8, 35.0, 31.5, 28.7, 28.4, 27.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{46}N_5O_5$ 556.3499. Found 556.3480.

***18b** (minor isomer).* Off-white amorphous solid. R_f (5% MeOH/DCM) = 0.43. $[\alpha]_D^{23}$ −24.2 (c 0.173, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.35–7.31 (m, 3H), 5.51 (s, 1H), 5.01–4.79 (m, 1H), 4.72–4.49 (m, 1H), 4.13 (d, J = 9.5 Hz, 1H), 3.90 (dd, J = 9.5, 5.2 Hz, 1H), 1.53 (s, 3H), 1.45 (sj, 9H), 1.39 (s, 3H), 1.35 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 167.3, 161.4, 153.7, 153.1, 136.9, 129.6, 128.9, 128.6, 127.0, 94.7, 81.3, 77.4, 77.2, 76.9, 66.1, 57.2, 51.6, 35.0, 31.5, 29.8, 28.8, 28.7, 28.6, 28.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{46}N_5O_5$ 556.3499. Found 556.3488.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-((*R*)-1-phenyl-ethyl)-1*H*-imidazole-5-carboxamide (22ab).** To a stirred solution of 1 equiv. (200 mg, 1.87 mmol) of 3-pyridinecarboxaldehyde **19** in anhydrous methanol (0.2 M) at 0 °C, 1.5 equiv. (0.360 mL, 2.81 mmol) of commercially available (*R*)-1-phenylethylamine **20**, 1.5 equiv. (315 mg, 2.81 mmol) of 1-*H*-imidazole-5-carboxylic acid **7**, and 1.5 equiv. (0.318 mL, 2.81 mmol) of *t*-Bu-isocyanide **9**, in that order, were added to the solution. The reaction was heated to 70 °C and stirred for 24 hours. Afterwards, the reaction was cooled to 23 °C before being concentrated *in vacuo* and dry loaded directly onto silica gel chromatography (10% MeOH/DCM), which yielded title compound **22ab** (167 mg, 45%, dr 58 : 42) as a white amorphous solid. The dr was determined by HPLC of crude material after concentration using a YMC ODS-A C18 column ran at 20% MeCN/H_2O (w/0.1% TFA v/v). Analytical samples of pure diastereomers **22a** and **22b** were prepared after chromatographic separation.

***22a** (major isomer).* White amorphous solid. R_f (5% MeOH (NH_3)/DCM) = 0.25. $[\alpha]_D^{23}$ +225.2 (c 0.46, $CHCl_3$). Retention time: 9.2 min. ^{1}H NMR (500 MHz, DMSO) δ 8.26 (dd, J = 4.7, 1.6 Hz, 1H), 8.20–7.17 (m, 10H), 7.13 (dd, J = 8.0, 4.7 Hz, 1H), 4.90–4.34 (m, 1H), 1.66 (d, J = 7.0 Hz, 3H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 169.0, 164.1, 147.7, 136.5, 135.3, 132.7, 128.2, 122.6, 61.8, 55.1, 54.9, 50.4, 40.0, 39.9, 39.9, 39.8, 39.7, 39.6, 39.5, 39.4, 39.2, 39.0, 28.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_2$ 406.2243. Found 406.2243.

***22b** (minor isomer).* White amorphous solid. R_f (5% MeOH (NH_3)/DCM) = 0.13. $[\alpha]_D^{23}$ +38.0 (c 0.49, $CHCl_3$). Retention time: 17.9 min. ^{1}H NMR (500 MHz, DMSO) δ 8.56–8.50 (m, 1H), 8.44 (d, J = 4.8 Hz, 1H), 7.87 (s, 1H), 7.76 (s, 2H), 7.48 (d, J = 7.5 Hz, 3H), 7.38–7.32 (m, 4H), 5.27–4.56 (m, 1H), 1.60–1.53 (m, 3H), 1.07 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 167.3, 163.8, 149.5, 147.9, 136.4, 135.9, 135.4, 133.2, 128.5, 127.6, 123.2, 122.8, 60.7, 55.2, 50.0, 39.6, 39.5, 28.1, 17.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_2$ 406.2243. Found 406.2247.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-((*S*)-2-hydroxy-1-phenylethyl)-1*H*-imidazole-5-carboxamide (23).** Following the general procedure for the synthesis of **22ab**, using commercially available (*S*)-1-phenyl-glycinol **21** (386 mg, 2.81 mmol), flash chromatography (10% MeOH (NH_3)/DCM) yielded title compound **23ab** (110 mg, 14%, dr 54 : 46) as a white amorphous solid. Dr was obtained similar to procedure for **22ab**. Trace amounts of ester byproduct are detected by HPLC. An analytical sample of pure diastereomer **23a** was prepared after chromatographic separation.

***23a** (major isomer).* White amorphous solid. R_f (10% MeOH (NH_3)/DCM) = 0.41. Retention time: 15.4 min. $[\alpha]_D^{23}$ +2.6 (c 0.5, $CHCl_3$). Note: NMR of this compound shows rotamerization. ^{1}H NMR (500 MHz, DMSO) δ 8.51–8.42 (m, 2H), 7.83 (s, 1H),

7.78 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.46–7.28 (m, 10H), 4.93–4.86 (m, 1H), 4.27 (dd, J = 11.3, 4.6 Hz, 1H), 4.22–4.15 (m, 1H), 4.04–3.94 (m, 2H), 3.63–3.50 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 170.5, 160.7, 148.4, 148.2, 140.8, 136.0, 134.2, 128.9, 128.5, 128.2, 128.1, 127.7, 126.9, 123.3, 64.6, 60.7, 59.9, 50.3, 40.0, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 28.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_3$ 422.2192. Found 422.2189.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-5-carboxamide (25ab).** Following the general procedure for the synthesis of **22ab**, using commercially available (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol *ent*-**24** (419 mg, 2.81 mmol), flash chromatography (10% MeOH/DCM) yielded title compound **25ab** (301 mg, 37%, dr 63 : 37) as a white amorphous solid. Dr was determined by crude ^{1}H-NMR. An analytical sample of the pure dominant diastereomer **25a** was prepared after chromatographic separation.

***25a** (major isomer).* Amber amorphous solid. R_f (5% MeOH/DCM) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69–8.65 (m, 1H), 8.55 (d, J = 1.7 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.39–7.35 (m, 1H), 7.31 (dd, J = 7.9, 4.9 Hz, 1H), 7.25–7.22 (m, 2H), 6.59 (s, 1H), 5.71 (q, J = 2.7 Hz, 1H), 4.54 (s, 1H), 4.28 (d, J = 5.4 Hz, 1H), 3.25 (qd, J = 17.1, 4.5 Hz, 2H), 1.30 (s, 9H), 1.27–1.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 149.3, 148.8, 141.9, 139.3, 135.4, 135.3, 129.7, 128.4, 127.8, 127.2, 126.4, 125.7, 125.2, 124.1, 123.9, 75.5, 64.1, 62.6, 51.4, 36.9, 28.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{28}N_5O_3$ 434.2192. Found 434.2178.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-5-carboxamide (26ab).** To a stirred solution of 2 equiv. (275 mg, 2.11 mmol) of aldehyde **6** in anhydrous methanol (0.2 M) at 0 °C, 1 equiv. (158 mg, 1.06 mmol) of commercially available (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **24**, 1 equiv. (158 mg, 1.06 mmol) 1-*H*-imidazole-5-carboxylic acid **8**, and 2 equiv. (0.24 mL, 2.11 mmol) *t*-Bu-isocyanide **9**, in that order, were added to the reaction vessel. The mixture was warmed to 40 °C and stirred for 24 h. The reaction was cooled to 23 °C before being concentrated to yield a yellow residue. This residue was dry loaded and purified by silica gel chromatography (5% MeOH/DCM), which yielded title compound **26ab** and **26c** (142 mg, 30%, 68 : 32) as a white amorphous solid. HPLC analysis of crude mixture using a TOSOH BioScience CM-2SW column with a gradient of 10–90% MeCN/H_2O over 90 min, flow rate 0.5 mL min^{-1} determined the dr of **26ab**. Ratio of **26abc** based on crude HPLC is 62 : 28 : 10. An analytical sample of **26a** was prepared after chromatographic separation, whilst **26b** and ester byproduct **26c** were chromatographically inseparable.

***26a** (major isomer).* Retention time: 39.9 min. R_f (5% MeOH/DCM) = 0.45. $[\alpha]_D^{23}$ −145.9 (c 0.49, $CHCl_3$) ^{1}H NMR (500 MHz, DMSO) δ 10.06 (s, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.77 (s, 1H), 7.25 (d, J = 7.1 Hz, 2H), 7.13 (dt, J = 19.8, 7.3 Hz, 2H), 6.91 (d, J = 7.3 Hz, 1H), 5.88 (d, J = 6.6 Hz, 1H), 5.21 (d, J = 9.7 Hz, 1H), 4.98 (d, J = 5.1 Hz, 1H), 4.69 (ddd, J = 10.0, 6.2, 3.9 Hz, 1H), 4.60 (m, 1H), 4.09 (dd, J = 9.1, 6.3 Hz, 1H), 3.54 (dd, J = 9.1, 3.9 Hz, 1H), 3.05 (dd, J = 16.1, 4.8 Hz, 1H), 2.88 (d, J = 16.1 Hz, 1H), 1.32 (s, 9H), 1.26 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.2, 166.3, 139.2, 138.9, 135.6, 135.3, 126.9, 125.8, 125.5, 123.9, 122.3, 108.9, 75.9, 73.5, 66.6, 65.4, 64.1, 50.4, 41.5, 40.0, 39.9, 39.9, 39.7, 39.5, 39.4, 39.2, 39.0, 28.2, 26.6, 25.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.2451. Found 457.2440.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-5-carboxamide (27ab).** Following the general procedure for the synthesis of **26ab**, using 1 equiv. (101 mg, 0.68 mmol) of commercially available (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol *ent*-**24**, flash chromatography (5% MeOH/DCM) yielded title compound **27abc** (114 mg, 37%, dr 91 : 9) as a white amorphous solid. Dr of **27ab** was determined from the crude mixture following the same procedure for **26ab**. Ester derivative **27c** was separated by HPLC. An analytical sample of pure diastereomer **27a** was prepared after chromatographic separation. Data for **27b** is reported based on the mixture of **27bc**.

***27a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.33. $[\alpha]_D^{23}$ +57.8 (c 0.49, $CHCl_3$). Retention time: 29.7 min. ^{1}H NMR (500 MHz, DMSO) δ 9.80 (s, 1H), 8.04 (s, 1H), 7.79 (s, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.11 (dt, J = 22.6, 7.4 Hz, 2H), 6.86 (d, J = 7.4 Hz, 1H), 5.38 (d, J = 9.2 Hz, 1H), 5.30 (d, J = 9.8 Hz, 1H), 5.09 (d, J = 5.9 Hz, 1H), 4.80 (ddd, J = 9.9, 6.0, 4.0 Hz, 1H), 4.46 (dt, J = 10.7, 5.6 Hz, 1H), 4.09 (dd, J = 9.2, 6.0 Hz, 1H), 3.72 (dd, J = 9.3, 3.9 Hz, 1H), 3.13 (dd, J = 16.6, 5.6 Hz, 1H), 2.92 (d, J = 16.5 Hz, 1H), 1.36 (s, 10H), 1.26 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 167.7, 165.9, 139.0, 135.8, 134.9, 127.0, 126.0, 125.3, 124.7, 122.4, 108.9, 75.0, 73.2, 65.6, 64.7, 61.9, 50.3, 41.7, 28.4, 26.9, 25.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.2451. Found 457.2432.

***27b** (minor isomer).* Retention time 52.7 min. NMR peaks based on mixture of **27bc**: ^{1}H NMR (500 MHz, DMSO) δ 7.86 (d, J = 23.6 Hz, 1H), 7.60 (d, J = 14.6 Hz, 1H), 7.35–7.26 (m, 3H), 7.22–7.09 (m, 2H), 4.85–4.69 (m, 1H), 4.55 (d, J = 28.3 Hz, 2H), 4.03–3.94 (m, 1H), 3.26–3.14 (m, 2H), 3.14–3.04 (m, 2H), 2.84 (dd, J = 15.8, 9.5 Hz, 1H), 1.34 (s, 3H), 1.27 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 168.1, 141.5, 136.7, 132.0, 129.5, 129.2, 126.8, 126.5, 124.8, 123.6, 106.7, 73.4, 69.5, 63.9, 63.2, 50.1, 37.5, 34.2, 28.4, 28.2, 26.2. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.3 Found 457.2.

*Compound **27c**.* White amorphous solid. $[\alpha]_D^{23}$ −76.3 (c 0.2, $CHCl_3$) Retention time: 55.2 min. ^{1}H NMR (500 MHz, DMSO) δ 7.76–7.70 (m, 2H), 7.56 (s, 1H), 7.46–7.40 (m, 1H), 7.25 (m, 4H), 5.66–5.60 (m, 1H), 4.19 (s, 1H), 4.09 (d, J = 6.7 Hz, 1H), 3.84 (dd, J = 8.5, 6.3 Hz, 1H), 3.79–3.72 (m, 1H), 3.26–3.12 (m, 3H), 3.05–2.89 (m, 1H), 2.64 (m, 1H), 1.22 (s, 9H), 1.09 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 169.7, 142.8, 139.6, 127.7, 126.7, 124.9, 123.9, 108.4, 76.3, 74.0, 65.9, 64.0, 63.0, 49.8, 36.9, 28.3, 25.7, 25.1. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.3 Found 457.2.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((*R*)-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-**

4-carboxamide (28ab). Following the general procedure for the synthesis of **26ab**, using 1 equiv. (103 mg, 0.77 mmol) of commercially available (1*R*)-aminoindane, flash chromatography (5% MeOH/DCM) yielded title compound **28ab** (310 mg, 92%, dr 69 : 31), which was isolated as a chromatographically inseparable mixture of diastereomers as a white amorphous solid. R_f (5% MeOH/DCM) = 0.4. Retention times: 32.2 min, 46.4 min. Spectra values that follow are of the major diastereomer **28a**. ^{1}H NMR (500 MHz, DMSO) δ 9.50 (s, 1H), 7.93 (s, 1H), 7.59 (s, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.12–7.05 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 5.26 (d, J = 9.7 Hz, 1H), 5.05 (t, J = 8.4 Hz, 1H), 4.78 (ddd, J = 10.1, 6.2, 4.1 Hz, 1H), 4.05 (dd, J = 8.6, 6.2 Hz, 1H), 3.54 (dd, J = 8.8, 4.2 Hz, 1H), 3.06–2.98 (m, 1H), 2.87–2.77 (m, 2H), 2.41 (ddd, J = 17.7, 10.0, 5.9 Hz, 1H), 2.33–2.25 (m, 1H), 1.40 (s, 9H), 1.25 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.3, 162.7, 142.6, 142.2, 136.2, 135.0, 126.4, 125.5, 124.2, 122.8, 122.1, 109.0, 73.1, 65.4, 61.5, 60.7, 50.2, 40.1, 40.0, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 30.3, 29.8, 28.5, 26.8, 25.0. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_4$ 441.3. Found 441.2.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxo-ethyl)-*N*-((1*R*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imid-azole-5-carboxamide (29ab).** Following the general procedure for the synthesis of **26ab**, using 1 equiv. (103 mg, 0.69 mmol) of commercially available (1*R*,2*R*)-aminoindanol, flash chromatography (5% MeOH/DCM) yielded title compound **29ab** (287 mg, 92%, dr 54 : 46) as a white amorphous solid. Dr determined by HPLC of crude similar to **26ab**. Analytical samples of pure diasteromers **29a** and **29b** were prepared after chromatographic separation.

***29a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.22. $[\alpha]_D^{23}$ +19.0 (c 0.50, $CHCl_3$). Retention time: 47.1 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.49 (s, 1H), 7.37–7.15 (m, 4H), 6.85 (s, 1H), 6.28 (s, 1H), 5.17 (q, J = 6.5 Hz, 1H), 4.53 (q, J = 6.7 Hz, 1H), 4.10 (dd, J = 8.9, 6.2 Hz, 1H), 3.99 (dd, J = 8.8, 6.0 Hz, 1H), 3.47 (d, J = 7.5 Hz, 1H), 3.20 (dd, J = 15.7, 7.2 Hz, 1H), 2.85 (dd, J = 15.7, 7.1 Hz, 1H), 1.41–1.37 (m, 2H), 1.34 (s, 14H), 1.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 166.3, 141.2, 138.0, 135.5, 128.8, 127.5, 125.7, 125.6, 110.5, 76.6, 76.4, 71.9, 67.6, 62.6, 51.7, 37.3, 28.8, 27.0, 25.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.2451. Found 457.2432.

***29b** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.32. $[\alpha]_D^{23}$ −276.8 (c 0.50, $CHCl_3$). Retention time: 29.0 min ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.78 (s, 1H), 9.78 (s, 1H), 7.34 (s, 1H), 7.29–7.24 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.56 (s, 1H), 5.53 (q, J = 7.8 Hz, 1H), 5.31 (d, J = 10.1 Hz, 1H), 5.08 (d, J = 6.5 Hz, 1H), 4.99 (ddd, J = 9.8, 6.5, 3.0 Hz, 1H), 4.22 (dd, J = 9.4, 6.4 Hz, 1H), 4.01 (s, 1H), 3.78 (dd, J = 9.4, 2.9 Hz, 1H), 3.42 (dd, J = 16.0, 8.3 Hz, 1H), 2.95 (dd, J = 16.0, 8.1 Hz, 1H), 1.41 (s, 9H), 1.35 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 165.5, 140.8, 140.0, 136.6, 135.1, 127.2, 126.4, 125.2, 122.2, 122.2, 110.4, 76.6, 73.8, 70.1, 67.5, 63.2, 51.3, 38.3, 28.8, 27.0, 25.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.2451. Found 457.2435.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*S*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-5-carboxamide (30ab).** Following the general procedure for the synthesis of **26ab**, using 1 equiv. (103 mg, 0.69 mmol) of commercially available (1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol, flash chromatography (5% MeOH/DCM) yielded title compound **30ab** (253 mg, 80%, dr 71 : 29) as an inseparable mixture of diastereomers as a white amorphous solid. Dr obtained after silica gel chromatography by HPLC, similar to that of **26ab**. R_f (5% MeOH/DCM) = 0.20. Retention times: 24.0 min, 42.7 min. Spectra of dominant diastereomer **30a**: ^{1}H NMR (400 MHz, DMSO) δ 9.43 (s, 1H), 7.94 (s, 1H), 7.63–7.58 (m, 1H), 7.13–6.98 (m, 3H), 6.91 (d, J = 7.4 Hz, 1H), 5.36 (d, J = 9.8 Hz, 1H), 5.23 (d, J = 7.0 Hz, 1H), 4.89 (p, J = 6.8 Hz, 1H), 4.85–4.73 (m, 2H), 4.05 (dd, J = 8.9, 5.9 Hz, 1H), 3.59 (dd, J = 8.9, 3.6 Hz, 1H), 3.30–3.24 (m, 1H), 2.69 (dd, J = 16.0, 6.3 Hz, 1H), 1.39 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.3, 163.1, 140.8, 139.9, 136.2, 135.0, 126.7, 125.8, 124.2, 122.9, 122.2, 108.7, 75.4, 73.8, 68.8, 65.9, 60.9, 50.2, 40.3, 28.5, 27.0, 25.3. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.3. Found 457.2.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*R*,3*S*)-3-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-5-carboxamide (31ab).** Following the general procedure for the synthesis of **26ab**, using 1 equiv. (61 mg, 0.41 mmol) of known reagent (1*S*,3*R*)-3-amino-2,3-dihydro-1*H*-inden-1-ol,[65] flash chromatography (5% MeOH/DCM) yielded title compound **31ab** (155 mg, 83%, dr 72 : 28) as an chromatographically inseparable mixture of diastereomers as a white amorphous solid. R_f (5% MeOH/DCM) = 0.40. Retention times: 26.3 min, 40.9 min. Spectral values shown is that of the major diastereomer **31a**: ^{1}H NMR (400 MHz, DMSO) δ 9.53 (s, 1H), 7.95 (s, 1H), 7.62 (s, 1H), 7.32 (d, J = 7.1 Hz, 1H), 7.14 (dt, J = 20.4, 7.4 Hz, 3H), 6.95 (d, J = 7.3 Hz, 1H), 5.39 (d, J = 6.9 Hz, 1H), 5.25 (d, J = 9.7 Hz, 1H), 4.98–4.90 (m, 1H), 4.79 (t, J = 8.1 Hz, 2H), 4.08 (tt, J = 14.5, 7.5 Hz, 1H), 3.53 (dd, J = 8.8, 4.0 Hz, 1H), 2.67–2.55 (m, 1H), 2.48–2.38 (m, 1H), 1.38 (s, 9H), 1.25 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.2, 163.0, 144.5, 141.4, 136.1, 135.1, 126.9, 126.6, 123.9, 122.9, 121.8, 109.1, 73.1, 71.6, 65.3, 61.5, 57.0, 50.2, 41.2, 28.5, 26.8, 25.1. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_5$ 457.3. Found 457.2.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*S*,2*R*)-2-methoxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (32ab).** Following the general procedure of the synthesis of **26ab**, using 1 equiv. (100 mg, 0.61 mmol) of known reagent (1*S*,2*R*)-2-methoxy-indan-1-ylamine,[66] flash chromatography (5% MeOH/DCM) yielded title compound **32ab** (204 mg, 71%, dr 66 : 34) as a white amorphous solid. Dr determined by HPLC of crude similar to **26ab**. Analytical samples of pure diastereomers **32a** and **32b** were prepared after chromatographic separation.

***32a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.45. $[\alpha]_D^{23}$ +208.8 (c 0.50, $CHCl_3$). Retention time: 52.6 min. ^{1}H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 7.86 (s, 1H), 7.58 (s, 1H), 7.15–7.08 (m, 2H), 7.08–7.02 (m, 2H), 5.42 (d,

J = 9.9 Hz, 1H), 5.27 (d, J = 9.0 Hz, 1H), 4.53 (dd, J = 7.8, 5.6 Hz, 1H), 4.20 (q, J = 7.5 Hz, 1H), 3.87 (dd, J = 9.4, 5.7 Hz, 1H), 3.75 (d, J = 9.4 Hz, 1H), 3.19 (qd, J = 14.8, 7.5 Hz, 2H), 1.42 (s, 9H), 1.24 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 169.0, 162.1, 141.8, 140.0, 136.5, 134.6, 127.2, 126.1, 124.1, 123.4, 122.9, 108.4, 79.0, 74.1, 66.1, 61.1, 59.5, 56.9, 50.0, 40.1, 40.0, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 38.0, 28.6, 27.4, 25.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2590.

***32b** (minor isomer).* White amorphous solid. Exists as 2 equal rotamers at 25 °C, signals merge at 125 °C in DMSO-d_6. ^{1}H NMR. R_f (5% MeOH/DCM) = 0.4. $[\alpha]_D^{23}$ −69.8 (c 0.50, $CHCl_3$). Retention time: 60.4 min. ^{1}H NMR (400 MHz, DMSO, 125 °C) δ 7.69 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.22 (s, 3H), 4.72 (q, J = 7.2 Hz, 1H), 4.21–4.15 (m, 1H), 4.06–4.02 (m, 1H), 3.49–3.03 (m, 6H), 2.97–2.88 (m, 2H), 1.32 (s, 9H), 1.23 (s, 2H), 1.09 (s, 3H). ^{13}C NMR (126 MHz, DMSO, 25 °C) δ 168.64, 167.69, 164.63, 164.34, 140.82, 140.70, 140.64, 138.34, 137.19, 137.14, 134.99, 134.40, 128.68, 127.94, 126.79, 126.74, 125.95, 125.03, 124.86, 124.02, 123.57, 121.88, 108.61, 107.26, 81.93, 79.19, 73.90, 73.18, 68.21, 66.97, 64.18, 63.57, 61.97, 60.24, 57.32, 56.80, 50.10, 49.84, 38.23, 35.61, 28.40, 28.28, 26.05, 25.97, 25.38, 24.60. Please note that ^{13}C at 25 °C shows a mixture of rotamers. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2594.

***N*-((1*S*,2*R*)-2-(Benzyloxy)-2,3-dihydro-1*H*-inden-1-yl)-*N*-((*S*,*R*)-2-(*tert*-butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-1*H*-imidazole-4-carboxamide (33ab).** Following the general procedure of the synthesis of **26ab**, using 1 equiv. (100 mg, 0.42 mmol) of known reagent (1*S*,2*R*)-2-(benzyloxy)-2,3-dihydro-1*H*-inden-1-amine,[66] flash chromatography (5% MeOH/DCM) yielded title compound **33ab** (170 mg, 75%, dr 63 : 37) as a chromatographically inseparable mixture of diastereomers as a white amorphous solid. Dr determined based on crude residue by HPLC similar to **26ab**. R_f (5% MeOH/DCM) = 0.41. Retention times: 51.2 min, 61.3 min. Spectral values are that of the major diastereomer. ^{1}H NMR (500 MHz, DMSO) δ 9.25 (s, 1H), 7.86 (s, 1H), 7.59 (s, 1H), 7.41–7.00 (m, 10H), 5.39 (d, J = 9.8 Hz, 1H), 5.29 (d, J = 8.9 Hz, 1H), 4.69–4.58 (m, 1H), 4.56–4.38 (m, 4H), 3.57–3.47 (m, 1H), 3.22–3.03 (m, 2H), 1.41 (s, 9H), 1.18 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 169.1, 162.3, 141.7, 140.0, 138.5, 137.8, 136.6, 134.6, 128.1, 127.7, 127.5, 127.4, 126.3, 126.0, 124.1, 123.4, 122.5, 108.2, 77.0, 73.8, 70.5, 66.1, 61.0, 59.7, 50.0, 39.8, 38.3, 28.6, 27.8, 27.2. LRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{39}N_4O_5$ 547.3. Found 547.3.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)-*N*-((1*S*,2*R*)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-imidazole-4-carboxamide (34ab).** Following the general procedure of the synthesis of **26ab**, using 1 equiv. (229 mg, 1.41 mmol) of known reagent (1*S*,2*R*)-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol,[67] flash chromatography (5% MeOH/DCM) yielded title compound **34ab** (43 mg, 15%, dr 89 : 11) as a white amorphous solid. Dr determined by HPLC of crude similar to **26ab**. The minor diastereomer coelutes with a chromatographically inseparable impurity.

***34a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.39. $[\alpha]_D^{23}$ +163.8 (c 0.50, $CHCl_3$). Retention time: 25.2 min. ^{1}H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.24–6.90 (m, 5H), 6.14 (d, J = 3.2 Hz, 1H), 5.42 (d, J = 9.9 Hz, 1H), 5.00 (d, J = 3.5 Hz, 1H), 4.74 (ddd, J = 9.7, 5.9, 2.8 Hz, 1H), 4.15–3.99 (m, 2H), 3.72 (dd, J = 9.0, 2.9 Hz, 1H), 3.06 (td, J = 15.0, 5.4 Hz, 1H), 2.57 (dd, J = 16.6, 5.0 Hz, 1H), 1.95 (s, 1H), 1.84 (tq, J = 13.2, 5.8 Hz, 1H), 1.34 (s, 9H), 1.24 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 166.9, 166.5, 136.7, 135.9, 134.8, 133.2, 128.6, 126.1, 125.5, 125.2, 125.2, 109.1, 73.4, 68.0, 65.2, 61.7, 60.8, 50.3, 29.6, 28.4, 27.1, 25.1, 23.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2594.

***N*-((*S*,*R*)2-(*tert*-Butylamino)-2-oxo-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)ethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (35ab).** Following the general procedure of the synthesis of **26ab**, using 2 equiv. (107 mg, 0.63 mmol) of known reagent (*R*)-2,3-cyclohexylideneglyceraldehyde,[47] flash chromatography (5% MeOH/DCM) yielded title compound **35ab** (36 mg, 23%, dr 83 : 17) as a white amorphous solid. Dr was determined *via* HPLC of crude similar to **26ab**. An analytical sample of pure diastereomer **35a** was prepared after chromatographic separation.

***35a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.48. $[\alpha]_D^{23}$ +120.2 (c 0.47, $CHCl_3$). Retention time: 36.0 min. ^{1}H NMR (500 MHz, DMSO) δ 9.70 (s, 1H), 8.03 (s, 1H), 7.77 (s, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.11 (dt, J = 23.6, 7.5 Hz, 2H), 6.86 (d, J = 7.4 Hz, 1H), 5.33 (dd, J = 9.8, 6.5 Hz, 2H), 5.12 (t, J = 4.8 Hz, 1H), 4.79 (ddd, J = 9.9, 5.9, 3.6 Hz, 1H), 4.49–4.39 (m, 1H), 4.06 (dd, J = 9.1, 5.9 Hz, 1H), 3.74 (dd, J = 9.7, 3.4 Hz, 1H), 3.13 (dd, J = 16.7, 5.8 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 1.53–1.39 (m, 10H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 167.8, 165.8, 139.1, 135.7, 134.9, 126.9, 126.0, 125.2, 124.7, 122.4, 109.3, 74.8, 73.0, 65.3, 64.5, 61.8, 50.2, 41.7, 40.0, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 36.5, 34.3, 28.4, 28.3, 24.5, 23.6, 23.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{37}N_4O_5$ 497.2764. Found 497.2745.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-1-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-oxoethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (36ab).** Following the general procedure for the synthesis of **26ab**, using known reagent (*R*)-2,2-dimethyl-1,3-dioxane-4-carbaldehyde,[48] flash chromatography (5% MeOH/DCM) yielded title compound **36ab** (62 mg, 32%, dr 84 : 16) as a white amorphous solid. Dr obtained by HPLC of crude similar to **26ab**. Ratio of **36abc** is 67 : 12 : 21. An analytical isomer of major isomer **36a** was prepared after chromatographic separation. Minor diastereomer **36b** was not isolated.

***36a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.47. Retention time: 34.6 min. ^{1}H NMR (500 MHz, DMSO) δ 9.61 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 7.78 (d, J = 3.7 Hz, 1H), 7.29–7.20 (m, 2H), 7.12 (dt, J = 22.2, 7.3 Hz, 2H), 6.86 (d, J = 7.4 Hz, 1H), 5.87 (d, J = 8.7 Hz, 1H), 5.16–5.09 (m, 2H), 4.64–4.52 (m, 2H), 4.05–3.96 (m, 1H), 3.76–3.70 (m, 1H), 3.27–3.09 (m, 2H), 2.90 (d, J = 16.6 Hz, 1H), 2.05–1.98 (m, 1H), 1.33 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (126 MHz,

DMSO) δ 167.1, 166.7, 139.0, 138.6, 135.9, 134.8, 126.9, 125.9, 125.4, 124.6, 122.4, 97.9, 75.4, 66.5, 65.4, 64.4, 58.7, 50.2, 41.6, 40.0, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 29.7, 28.3, 27.4, 19.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2586.

***N*-((*S*,*R*)-1-(*tert*-Butylamino)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxopropan-2-yl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (37ab).** Following the general procedure for the synthesis of **26abc**, using 2 equiv. (110 mg, 0.76 mmol) of known reagent (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde,[49] flash chromatography (5% MeOH/DCM) yielded title compound **37ab** (38 mg, 21%, dr 70 : 30) as a white amorphous solid. Dr determined by HPLC of crude similar to **26ab**. Analytical samples of pure diasteromers **27a** and **27b** were prepared after chromatographic separation.

***37a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.42. $[\alpha]_D^{23}$ +129.8 (*c* 0.45, $CHCl_3$). Retention time: 30.6 min. ^{1}H NMR (500 MHz, DMSO) δ 10.08 (s, 1H), 8.04 (s, 1H), 7.75 (s, 1H), 7.23 (d, *J* = 7.1 Hz, 1H), 7.12 (dt, *J* = 20.1, 7.2 Hz, 2H), 6.91 (t, *J* = 7.1 Hz, 1H), 5.50 (d, *J* = 9.1 Hz, 1H), 5.38 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.88 (d, *J* = 6.0 Hz, 1H), 4.58–4.50 (m, 1H), 4.04 (p, *J* = 6.0 Hz, 1H), 3.81 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.48 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.16 (dd, *J* = 16.6, 5.6 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.32 (ddd, *J* = 13.9, 9.1, 5.3 Hz, 1H), 1.90 (ddd, *J* = 13.1, 7.6, 5.3 Hz, 1H), 1.36 (s, 9H), 1.18 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.5, 166.0, 139.3, 139.1, 135.6, 135.2, 126.9, 125.9, 125.2, 123.9, 122.5, 108.0, 75.6, 72.5, 68.3, 64.8, 57.7, 50.3, 41.8, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 33.9, 28.3, 26.8, 25.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2586.

***37b** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.32. $[\alpha]_D^{23}$ −65.6 (*c* 0.31, $CHCl_3$). Retention time: 50.2 min. ^{1}H NMR (500 MHz, DMSO) δ 8.43 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.43–7.30 (m, 3H), 7.30–7.21 (m, 2H), 5.90 (d, *J* = 7.0 Hz, 1H), 4.53–4.46 (m, 1H), 3.77–3.72 (m, 1H), 3.20 (dd, *J* = 16.1, 8.0 Hz, 2H), 2.95–2.72 (m, 3H), 2.08 (t, *J* = 7.9 Hz, 1H), 1.28–1.22 (m, 2H), 1.18 (s, 9H), 1.14 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 169.2, 141.7, 138.0, 136.5, 135.1, 129.4, 127.4, 127.2, 125.6, 121.4, 107.2, 73.7, 72.2, 66.9, 63.6, 56.8, 49.8, 38.2, 35.3, 28.4, 26.8, 25.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{35}N_4O_5$ 471.2608. Found 471.2610.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-2-oxo-1-((*R*)-tetrahydrofuran-2-yl)ethyl)-*N*-(*S*,*R*)-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (38ab).** Following the general procedure for the synthesis of **26ab**, using 2 equiv. (35 mg, 0.35 mmol) of known reagent (*R*)-tetrahydrofuran-2-carbaldehyde,[50] flash chromatography (5% MeOH/DCM) yielded title compound **38ab** (23 mg, 31%, dr 87 : 13) as a white amorphous solid. Dr determined *via* HPLC of crude similar to **26ab**. An analytical sample of pure diastereomer **38a** was prepared after chromatographic separation.

***38a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.24. $[\alpha]_D^{23}$ +174.8 (*c* 0.46, $CHCl_3$). Retention time: 31.0 min. ^{1}H NMR (500 MHz, DMSO) δ 9.72 (s, 1H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.79 (d, *J* = 1.2 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 5.75 (s, 1H), 5.14–5.08 (m, 2H), 4.57–4.45 (m, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 3.09 (dd, *J* = 16.6, 5.0 Hz, 1H), 2.89 (d, *J* = 16.5 Hz, 1H), 2.22–2.12 (m, 1H), 1.80 (dt, *J* = 12.2, 7.2 Hz, 1H), 1.62 (tq, *J* = 12.3, 6.6 Hz, 1H), 1.54–1.42 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 167.9, 166.2, 139.0, 138.7, 135.8, 134.9, 126.9, 125.9, 125.4, 124.6, 122.3, 76.0, 75.7, 67.6, 65.3, 63.5, 54.9, 50.2, 41.6, 28.4, 25.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{31}N_4O_4$ 427.2345. Found 427.2334.

***N*-((*S*,*R*)-2-(*tert*-Butylamino)-2-oxo-1-((*R*)-tetrahydro-2*H*-pyran-2-yl)ethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (39abc).** Following the general procedure for the synthesis of **26ab**, using 2 equiv. (106 mg, 0.93 mmol) of known reagent (*R*)-tetrahydro-2*H*-pyran-2-carbaldehyde,[51] flash chromatography (5% MeOH/DCM) yielded title compound **39ab** (50 mg, 24%, dr 86 : 14) as a white amorphous solid. Ratio of **39ab** determined *via* HPLC of crude similar to **26ab**. Ratio of **39abc** is 78 : 13 : 9. Analytical sample of **39a** was prepared after chromaotgraphic separation.

***39a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.46. $[\alpha]_D^{23}$ +138.4 (*c* 0.51, $CHCl_3$). Retention time: 30.3 min. ^{1}H NMR (500 MHz, MeOD) δ 9.99 (s, 1H), 7.90 (s, 1H), 7.74–7.70 (m, 1H), 7.30–7.21 (m, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.37 (d, *J* = 9.8 Hz, 1H), 5.30 (d, *J* = 5.3 Hz, 1H), 4.54 (t, *J* = 5.1 Hz, 1H), 4.01 (t, *J* = 10.2 Hz, 1H), 3.90 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.52 (td, *J* = 10.8, 3.1 Hz, 1H), 3.16 (dd, *J* = 16.5, 4.7 Hz, 1H), 3.03 (d, *J* = 16.6 Hz, 1H), 2.24 (d, *J* = 13.3 Hz, 1H), 1.86 (d, *J* = 13.4 Hz, 1H), 1.67–1.56 (m, 2H), 1.56–1.47 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 167.6, 166.5, 138.9, 138.5, 135.8, 134.8, 126.9, 125.9, 125.5, 124.6, 122.3, 75.8, 74.4, 67.7, 65.4, 64.1, 50.2, 41.5, 39.9, 39.7, 39.5, 39.4, 39.2, 39.0, 28.4, 27.6, 25.6, 22.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_4$ 441.2502. Found 441.2489.

***N*-((*S*,*R*)-1-(*R*)-1-Benzylpyrrolidin-2-yl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (40ab).** Following the general procedure for the synthesis of **26ab**, using 2 equiv. (248 mg, 1.31 mmol) of known reagent ((*R*)-1-benzylpyrrolidine-2-carbaldehyde,[52] flash chromatography (5% ($MeOH(NH_3)$)/DCM) yielded title compound **40ab** (128 mg, 38%, dr 65 : 35) as a white amorphous solid. Dr determined *via* HPLC of crude similar to **26ab**, but for solvent system, 0.1% (v/v) TFA in MilliQ H_2O replaced that of solely MilliQ H_2O for the polar mobile phase component. Analytical samples of pure diasteromers **40a** and **40b** were prepared after chromatographic separation.

***40a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.48. $[\alpha]_D^{23}$ +198.8 (*c* 0.45, $CHCl_3$). Retention time: 10.5 min ^{1}H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 1.2 Hz, 1H), 7.40–7.05 (m, 9H), 6.86 (d, *J* = 7.3 Hz, 1H), 5.88 (d, *J* = 8.5 Hz, 1H), 5.24 (d, *J* = 5.3 Hz, 1H), 5.18 (d, *J* = 10.1 Hz, 1H), 4.53 (dt, *J* = 9.5, 5.1 Hz, 1H), 4.38 (d, *J* = 12.8 Hz, 1H), 3.76–3.67 (m, 1H), 3.42 (d, *J* = 12.8 Hz, 1H), 3.12 (dd, *J* = 16.5, 4.9 Hz, 1H), 2.90 (d, *J* = 16.5 Hz, 1H), 2.60–2.55 (m, 1H), 2.23 (td, *J* = 9.8, 6.0 Hz, 1H), 1.99–1.85 (m, 1H), 1.82–1.73 (m, 1H), 1.68–1.56 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 169.2, 166.3, 140.8, 139.3, 138.6, 135.8, 135.1, 128.3, 127.9, 126.8, 126.4, 125.8, 125.4, 124.6,

122.2, 76.0, 65.2, 64.3, 62.7, 60.8, 54.2, 50.3, 41.6, 39.9, 39.7, 39.5, 39.4, 39.2, 39.0, 28.4, 27.2, 24.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{38}N_5O_3$ 516.2975. Found 516.2951.

***40b** (minor isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.43. $[\alpha]_D^{23}$ +3.6 (*c* 0.50, $CHCl_3$). Retention time: 12.1 min. ^{1}H NMR (400 MHz, DMSO) δ 7.88–6.95 (m, 13H), 5.60–5.52 (m, 1H), 4.25 (m, 1H), 3.88 (d, J = 13.4 Hz, 1H), 3.25 (dd, J = 16.4, 5.9 Hz, 0H), 3.20–3.09 (m, 2H), 3.05 (m, 2H), 2.56 (ddd, J = 9.6, 7.1, 2.8 Hz, 1H), 2.03 (q, J = 8.6 Hz, 1H), 1.92–1.78 (m, 1H), 1.66–1.53 (m, 1H), 1.47 (m, 1H), 1.41–1.31 (m, 1H), 1.28–1.20 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 172.0, 162.1, 143.0, 139.7, 139.3, 136.9, 131.9, 128.1, 128.1, 127.8, 126.7, 126.7, 124.9, 124.2, 123.4, 74.7, 64.8, 63.3, 62.0, 58.5, 53.7, 49.3, 36.2, 28.4, 28.0, 22.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{38}N_5O_3$ 516.2975. Found 516.2977.

***N*-((2*R*,2*S*,3*R*)-1-(*tert*-Butylamino)-3-((*tert*-butyldimethylsilyl)oxy)-1-oxobutan-2-yl)-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazole-4-carboxamide (41ab).** Following the general procedure for the synthesis of **26ab**, using 2 equiv. (310 mg, 1.65 mmol) of known reagent (2*R*)-2-(*tert*-butyldimethylsilyloxy)propanal,[53] flash chromatography (5% MeOH/DCM) yielded title compound **41ab** (45 mg, 11%, dr 78 : 22) as a white amorphous solid. Dr determined by HPLC of crude similar to **26ab**. An analytical sample of pure diastereomer **41a** was prepared after chromatographic separation.

***41a** (major isomer).* White amorphous solid. R_f (5% MeOH/DCM) = 0.36. $[\alpha]_D^{23}$ +200.0 (*c* 0.46, $CHCl_3$). Retention time: 35.0 min. ^{1}H NMR (400 MHz, DMSO) δ 9.76 (s, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.82 (d, J = 7.3 Hz, 1H), 5.95 (d, J = 8.6 Hz, 1H), 5.18 (d, J = 5.3 Hz, 1H), 5.03 (d, J = 9.4 Hz, 1H), 4.51–4.40 (m, 2H), 3.12 (dd, J = 16.5, 4.8 Hz, 1H), 2.90 (d, J = 16.6 Hz, 1H), 1.34 (s, 9H), 1.27–1.22 (m, 1H), 1.20 (d, J = 6.0 Hz, 3H), 0.81 (s, 9H), 0.09 (s, 3H), 0.07–0.04 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.0, 166.5, 139.0, 138.5, 135.8, 135.0, 126.9, 125.9, 125.4, 124.7, 122.2, 75.7, 66.5, 66.4, 65.4, 50.2, 41.6, 39.9, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 28.5, 25.7, 20.1, 17.6, −4.5, −5.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{43}N_4O_4Si$ 515.3054. Found 515.3041.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: full characterisation data for all new compounds and crystallographic data collection and refinement statistics. See DOI: https://doi.org/10.1039/d5ob01897h.

CCDC 2474023–2474025 and 2501300 (**27a**, **27c**, **38** and **10c**) contain the supplementary crystallographic data for this paper.[43,45,46,54]

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