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Stereoselective Synthesis of Quaternary Center Bearing Azetines and Their β-Amino Acid Derivatives

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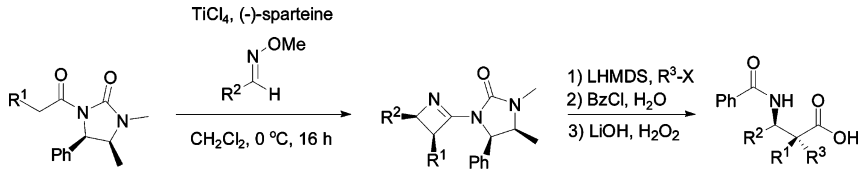

We describe here the use of a stable, four-membered azetine heterocycle for the preparation of highly substituted β-amino acid derivatives. Imidazolidinone chiral auxiliaries were found to eliminate a competitive reaction pathway that had been present under previously reported conditions for azetine synthesis. The ephedrine derived imidazolidin-2-one **21** was allowed to react as its chlorotitanium enolate with *O*-methyl or -benzyl oximes under optimized conditions to gain improved access to azetines at the gram scale. The azetines were further found to undergo alkylation with complete diastereocontrol, affording the creation of a quaternary center. Subsequent ring opening with benzoyl chloride and auxiliary cleavage provided the corresponding $\beta^{2,2,3}$-amino carbonyl derivatives in good yields.

Introduction

The stereoselective synthesis of β-amino acids has attracted increased attention in recent years. Compounds containing such moieties often show potent biological activity and have been found to exhibit such diverse properties as HIV protease inhibition,[1] angiotensin-converting enzyme inhibition,[2] antifungal activity,[3] antibiotic activity (both in peptidic form[4] and as precursors to the β-lactam antibiotics[5]), and cytotoxic activity, as seen in the potent antitumor agents paclitaxel (Taxol)[6] and docetaxel (Taxotere).[7] Also, oligomers of the β-amino acids, the β-peptides, have been shown to form unusually stable secondary structures and may serve as useful tools in facilitating the design of synthetic biopolymers with novel biological and catalytic properties.[8] While several methodologies are available for the creation of monosubstituted β-amino acids, either at the β^2 or β^3 positions (Figure 1),[9] relatively few approaches exist for preparing geminally disubstituted species,[10] as this requires the synthetically challenging formation of a quaternary center.[11]

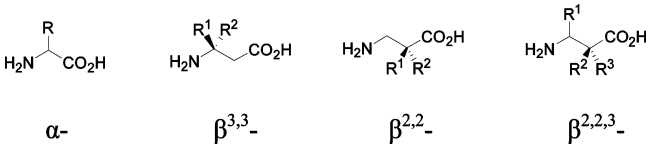

FIGURE 1. Designation of representative amino acids.

Previous work within our laboratory revealed that the reaction of *N*-acyl thiazolidinethione enolates with *O*-alkyl oximes as

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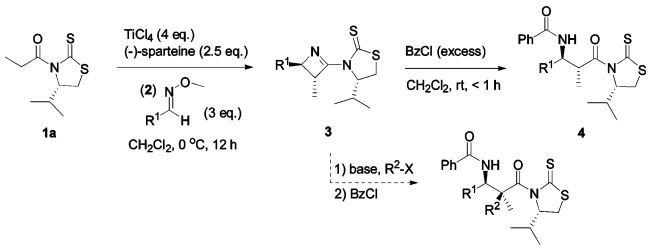
SCHEME 1. Azetine Formation and Hydrolytic Ring Opening to β^2-Amino Carbonyl Derivative



imine equivalents resulted in the formation of a trans-substituted azetine ring (**3**, Scheme 1) that can be subsequently opened with benzoyl chloride to afford the corresponding β-amino carbonyl derivative (**4**).[12] We believed that an azetine such as **3**, with the auxiliary still intact, had further potential to serve as a useful template for stereoselective functionalization of its enolate, thereby creating a quaternary center at what would become the β^2 position of the ring opened, β-amino carbonyl derivative.

Results and Discussion

The methodology as envisioned was limited, however, by low isolable yields at gram scale of the azetine substrates themselves (Table 1). The azetine was recovered along with a pyrimidinone side product in up to a 1:1 ratio (**5**, Figure 2), depending on the type of auxiliary employed. The pyrimidinone is the result of a competitive cyclization pathway thought to involve nucleophilic attack of the transient nitrogen anion to the auxiliary, rather than acyl, carbonyl (Figure 2). Pyrimidinone formation was also observed to be increasingly favored with increasing reaction scale. The origins of this trend are not fully understood, but it is believed that the heterogeneity of the reaction mixture may play an important role. We therefore sought to develop a scaleable method for improved azetine access through an approach aimed toward elimination of the pyrimidinone reaction pathway.

Imidazolidin-2-one based chiral auxiliaries are not as widely used as their oxazolidinone or thiazolidinethione counterparts, but they have nevertheless been shown to exhibit high selectivity over a range of asymmetric synthesis applications.[13] There are also distinct advantages present among the imidazolidinones, including their crystallinity, N bifunctionality,[14] and resistance to nucleophilic ring opening.[15] We believed that an auxiliary such as (*S*)-5-isopropyl-1-propionyl-imidazolidin-2-one (**13**, Scheme 2) could be particularly useful for our desired application in that deprotonation of the free N−H would render the adjacent carbonyl carbon much less electrophilic, thereby strongly disfavoring formation of the pyrimidinone side product.

Preparation of substrate **13** proved to be challenging due to difficulties associated with both diamine synthesis and regioselective acylation. Initial access was afforded through the Michael addition of (*S*)-4-phenyl-oxazolidin-2-one **6** to 3-methyl-1-nitrobutene **7**, followed by reduction, cyclization, and benzylic cleavage to the free imidazolidinone **11**.[16] Di-acylation and finally regioselective de-acylation with potassium *t*-butoxide provided **13** in an overall yield of 21% (six steps). Once in hand, reaction of **13** with benzaldehyde *O*-methyl oxime under our standard azetine forming conditions (4 equiv of $TiCl_4$, (−)-sparteine, CH_2Cl_2, 0 °C, 12 h) with an additional equivalent of base for deprotonation of the free N−H afforded no desired azetine product. Alteration of reaction variables, including the use of lithium amide bases, different solvents, and higher temperatures, did not achieve any measurable improvements.

We next considered the possibility that deprotonation of the free N−H was not necessary to deactivate the auxiliary carbonyl toward nucleophilic attack if in fact the resonance delocalization provided by a substituted nitrogen lone pair, relative to that of sulfur or oxygen, was sufficiently enhanced. An efficient route to such auxiliaries was found in the addition of L-valinol **14** to isocyanates, followed by base promoted cyclization (Scheme 3).[17] This method provided the additional benefit of eliminating the need for regiochemical acylation in the subsequent step. When the phenyl-substituted auxiliary **17a** was allowed to react with benzaldehyde *O*-methyl oxime under standard conditions, no pyrimidinone product was evident in the product mixture. The major products were instead a combination of *cis*- and *trans*-azetines **18a**, separable by conventional chromatography

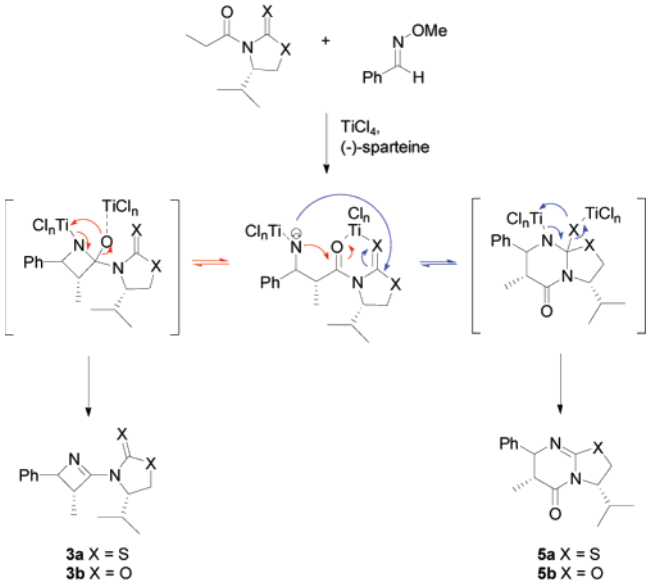


FIGURE 2. Competitive reaction pathways leading to the formation of either azetine (**3**) or pyrimidinone (**5**) products.

TABLE 1. Azetine/Pyrimidinone Product Distribution and Yield Relative to Auxiliary Type

entry	auxiliary: X	oxime **2**: R^1	azetine	**3** substitution	**3** yield %	ratio **3**/**5**[a]
1	**1a**: S	Ph	**3a**	*trans*	20−25	2:1
2	**1b**: O	Ph	**3b**	*cis*	20−25	1:1

[a] Ratios based on isolated product yields obtained at gram scale.

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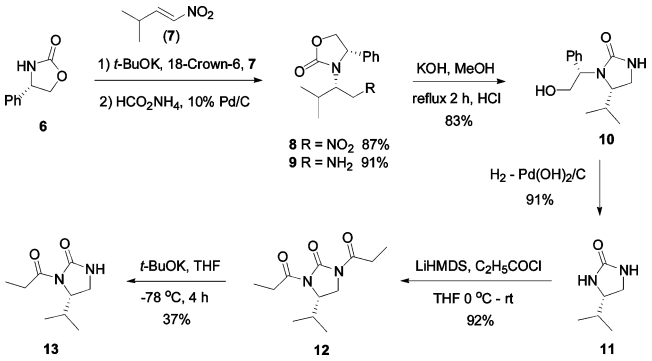
(17) (a) Kim, T. H.; Lee, G.-J. *Tetrahedron Lett.* **2000**, *41*, 1505. (b) Kim, T. H; Lee, G.-J. *J. Org. Chem.* **1999**, *64*, 2941.

SCHEME 2. Synthesis of (*S*)-5-Isopropyl-1-propionyl-imidazolidin-2-one Auxiliary (13)



and recovered in 61% total yield in a 1:1.7 (cis/trans) diastereomeric ratio.

Several differentially substituted imidazolidinones were then prepared to investigate the potential effect of the N substituent on the yield and diastereomeric ratio (Table 2). Urea formation proceeded rapidly in all cases, generating solid products that were recrystallized or simply filtered, washed, and carried on to the next step without additional purification. Cyclization yields were found to be highly substrate dependent and varied from a low of 19% for the *N*-phenyl imidazolidinone **17a** to a high of 90% for the *N*-benzyl **17b**. Only the *N*-phenyl (**17a)** and *N*-*p*-tolyl (**17e**) isocyanate derived auxiliaries were successfully carried forward to generate azetines. Total azetine yields were uniformly improved relative to that obtained from either the thiazolidinethione or the oxazolidinone auxiliaries. However, no significant effects on yield or stereoselectivity due to N substitution were observed among the reactive substrates.

Ephedrine derived imidazolidinone auxiliaries were thought to provide a number of potential benefits, including their ease

SCHEME 3. Isocyanate Route to Imidazolidin-2-one Auxiliaries

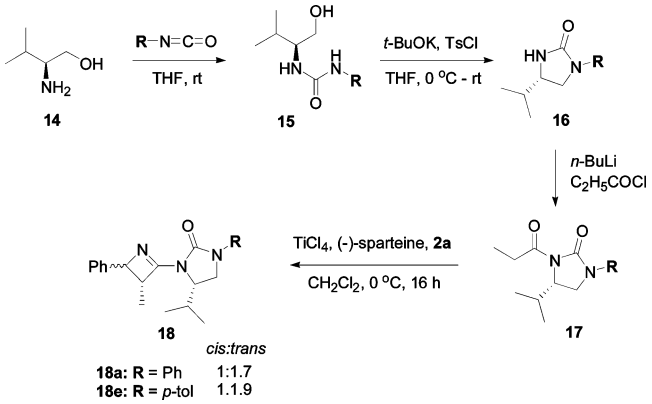
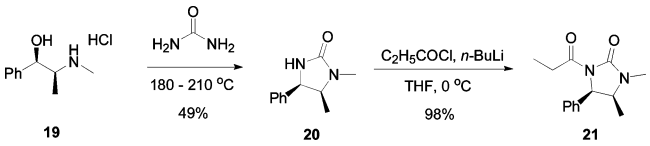


TABLE 2. Azetine Yield and Selectivity Data for Variably Substituted Imidazolidinones

entry	R−N=C=O	product: yield %			**18**: total yield %	cis/trans **18**
1	Ph	**15a**: 79	**16a**: 19	**17a**: 87	**18a**: 61	1:1.7
2	Bn	**15b**: 75	**16b**: 90	**17b**: 51	ni[a]	
3	*t*-Bu	**15c**: 99[b]	**16c**: 38	**17c**: 41	ni	
4	*p*-MeOPh	**15d**: 90	**16d**: 60	**17d**: 40	ni	
5	*p*-Tol	**15e**: 99[b]	**16e**: 23	**17e**: 84	**18e**: 65	1:1.9
6	Et	**15f**: 72	**16f**: 88	**17f**: 46	ni	

[a] ni = not isolated. [b] Product carried forward without recrystallization.

SCHEME 4. Synthesis of Ephedrine Derived Chiral Auxiliary



of preparation, low cost, and the availability of either enantiomer.[18] The fusion cyclization of (1*R*,2*S*)-(−)-ephedrine hydrochloride **19** with urea provided solid (4*R*,5*S*)-1,5-dimethyl-4-phenyl-imidazolidin-2-one **20** that could be crystallized in large quantities and subsequently acylated in high yield (**21**, Scheme 4).[19] Once again, benzaldehyde *O*-methyl oxime was chosen as the test substrate and allowed to react with the acylated auxiliary under standard azetine reaction conditions. Initial experiments at the 1 mmol scale returned a 1.6:1 mixture of *cis*-/*trans*-azetines (**22a**) in 60% total yield. The reaction was subsequently optimized for both yield and diastereoselectivity responses using a randomized 3 factor/2 level design evaluating possible time, temperature, and concentration effects (Figure 3). None of these factors was shown to affect the diastereomeric

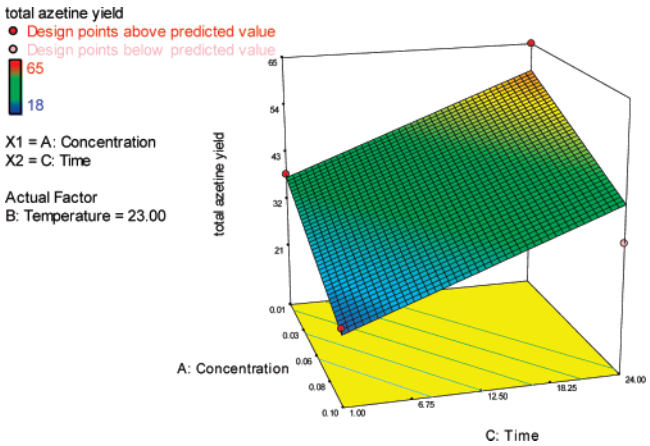


FIGURE 3. Randomized 3 factor/2 level optimization study results: response surface plot for total azetine yield.

ratio, but both time and concentration proved to be significant with respect to overall yield.[20] These results translated to an experimentally manageable concentration of 0.03 M and an increased reaction time of at least 24 h (Scheme 5). The reaction mixtures were also now allowed to warm to ambient temperature after initial oxime addition, thus eliminating the need for prolonged temperature management.

These conditions were applied at the gram scale across a range of both enolizable and non-enolizable oximes to afford azetine products in good yields (Table 3). We were, however, surprised to find a mixture of cis/trans selectivity among the different cases. The auxiliary **21** was hydrogenated to afford the more hindered cyclohexyl derivative, but no appreciable effect on selectivity was found when it was allowed to react under otherwise standard azetine reaction conditions. Neither the choice of *O*-Me or *O*-Bn oxime nor the E/Z ratio of the oxime mixture was shown to have any influence on selectivity. Further optimization aimed at improving diastereoselectivity remains an area of active investigation.

(18) Clark, W. M.; Bender, C. *J. Org. Chem.* **1998**, *63*, 6732.
(19) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.
(20) Model *F* value: 11.71; concentration $p = 0.029$ and time $p = 0.01$.

SCHEME 5. Preparation of *O*-Methyl and *O*-Benzyl Oximes and Their Reaction with 21 under Optimized Conditions

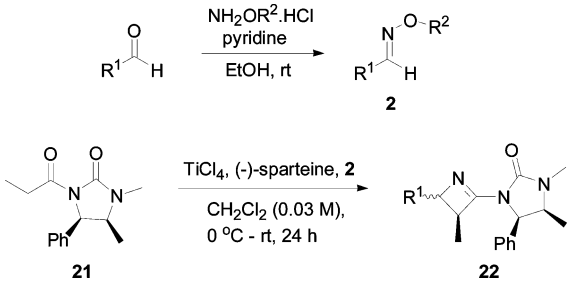
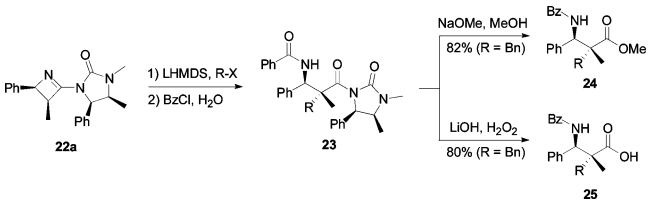


TABLE 3. Gram Scale Additions of Oximes to Ephedrine Derived Auxiliary 21

entry	oxime (R^1, R^2)	yield **2** (%)	product	total yield **22** (%)	dr[a] (*cis:trans*)
1	**2a** (Ph, Me)	84	**22a**	69	1.8:1
2	**2b** (Bn, Me)	62	**22b**	77	1:2.5
3	**2c** (*c*-Hex, Bn)	82	**22c**	72	1:1.8
4	**2d** ( , Bn)	86	**22d**	61	1:1.3
5	**2e** ( , Bn)	86	**22e**	64	1.2:1
6	**2f** ( , Bn)	86	**22f**	62	1:1.6

[a] Diastereomeric ratios determined from ^{1}H NMR spectra for crude reaction mixtures.

SCHEME 6. Azetine Alkylation, Hydrolytic Ring Opening, and Auxiliary Cleavage to Access $\beta^{2,2,3}$-Amino Acid Derivatives



It remained to be seen as to whether the imidazolidinone auxiliary bearing azetines could be successfully functionalized as originally intended. Initial alkylation experiments using cis-substituted azetine **22a** revealed lithium hexamethyldisilazide (4 equiv) to be the optimum base for azetine enolate formation. Reactions were carried out in THF at 0 °C with 1.5−5 equiv of alkyl halide and quenched with aqueous 1 N HCl after 1 h. Although the reactions appeared to be nearing completion as determined by TLC, isolated yields were lower than expected following chromatographic purification. The crude product from the alkylation step was therefore carried on to subsequent hydrolytic ring opening of the azetine without intermediate purification (Scheme 6). Treatment with excess benzoyl chloride, followed by aqueous workup, afforded access to a number of geminally disubstituted $\beta^{2,2,3}$-amino carbonyl derivatives in good yield (Table 4). Analysis of the ^{1}H NMR spectra revealed that all products were formed as a single diastereomer. The absolute configuration at the quaternary center of the addition product **23f** was determined from its X-ray crystal structure. The observed stereochemistry was consistent with attack of the electrophile as directed by the mutually reinforcing orientation of azetine phenyl and auxiliary phenyl groups assumed to exist

TABLE 4. Alkylation of α-Substituted Azetines and Hydrolysis to *β*-Amino Acid Derivatives

entry	R−X	product	**23** yield % (two steps)	diastereomeric ratio
1	benzyl bromide	**23a**	69	>95:5
2	iodoethane	**23b**	63	>95:5
3	iodopropane	**23c**	70	>95:5
4	iodobutane	**23d**	51	>95:5
5	allyl iodide	**23e**	71	>95:5
6	1-iodo-2-methylpropane	**23f**	66	>95:5

within a chelated transition state (Figure 4). The developed alkylation/ring opening conditions were also applied to the trans-substituted azetine **22a**, but the reaction proceeded with only modest yield and selectivity (28%, diastereomeric ratio 2:1 for the benzyl bromide adduct). This result may be attributable to the now mutually opposing phenyl directing groups present within the hypothesized transition state. Removal of the chiral auxiliary was demonstrated for compound **23a**, from which both the methyl ester **24** and the acid **25** were obtained in good yield.

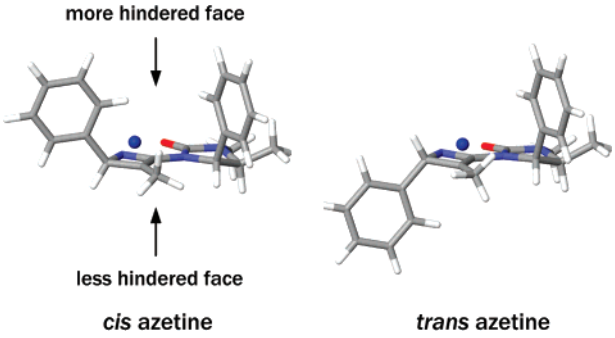


FIGURE 4. Substituent directed approach of electrophile to hypothesized azetine transition state.

In summary, we have found imidazolidin-2-one based chiral auxiliaries to be effective in eliminating the appearance of the pyrimidinone side product as encountered under previously reported conditions for azetine formation. Specific use of the ephedrine derived imidazolidinone auxiliary **21**, in combination with optimized reaction conditions, resulted in improved accessibility to the azetine substrates at gram scale. The further utility of cis-substituted azetine **22a** as a substrate for stereoselective alkylation demonstrates what we believe to be a uniquely practical method for the diastereoselective synthesis of $\beta^{2,2,3}$-amino acid derivatives with a potentially wide ranging scope and application.

Experimental Section

General Procedure for the Preparation of Oximes. Representative example for **2a**: methoxylamine hydrochloride (4.09 g, 48.0 mmol, 1.20 equiv) was suspended in 30 mL of absolute ethanol, and 12.9 mL (160 mmol, 4.00 equiv) of anhydrous pyridine was added quickly dropwise. A 4.06 mL (40.0 mmol) volume of benzaldehyde was added, and the reaction was stirred at room temperature for 4 h. The ethanol was removed to reveal a white solid and clear liquid that was redissolved in dichloromethane and extracted with 5% citric acid. The citric acid washes were combined and extracted with dichloromethane. The organic layers were combined and washed with brine, dried with $MgSO_4$, filtered, and concentrated to give a clear oil. The oil was distilled under vacuum (0.18 mbar, 30−32 °C) to give 4.52 g (84%) of clear oil.

Benzaldehyde *O*-Methyl-oxime (2a). $R_f = 0.60$ (4:1 hexanes/EtOAc); 25:1 mixture of isomers; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 8.04 (s, 1H), 7.55 (d, 2H, $J = 3.6$ Hz), 7.37−7.34 (m, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 148.72, 132.38, 130.00, 128.85, 127.18, 62.17; IR (neat): 2937, 2898, 2817, 1462, 1447, 1211, 1049, 946, 916, 844, 753, 690 cm^{-1}; HRMS-ESI *m/z* 136.0756 ([M + H]$^+$, $C_8H_{10}NO$ requires 136.0757).

(*S*)-4-Isopropyl-1,3-dipropionyl-imidazolidin-2-one (12). 4-Isopropyl-imidazolidinone (1.28 g, 10.0 mmol) was added with 25 mL of anhydrous THF to an oven dried flask under argon, and the solution was chilled in an ice bath. A 25.0 mL (25.0 mmol, 2.50 equiv) volume of 1.0 M lithium hexamethyldisilazide in THF was added quickly dropwise. A 2.17 mL (25.0 mmol, 2.50 equiv) volume of propionyl chloride was added, and the reaction was allowed to gradually equilibrate to room temperature. The solution was quenched after 16 h with saturated aqueous ammonium chloride and transferred to a separatory flask with a water and diethyl ether rinse. The aqueous phase was washed with additional ether. The organic layers were then washed with brine, dried with $MgSO_4$, filtered, and concentrated to give a pale amber oil. The oil was loaded onto a silica column and eluted with 98:2 CH_2Cl_2/MeOH. The main product was collected as a white waxy solid of mass 2.21 g (92%). $R_f = 0.79$ (95:5 CH_2Cl_2/MeOH); $[\alpha]^{23}_D$ +59.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31−4.27 (m, 1 H), 3.74 (dd, 1 H, $J = 12.0$, 2.8 Hz), 3.60 (dd, 1H, $J = 12.0$, 9.2 Hz), 3.02−2.83 (m, 4H), 2.38−2.30 (m, 1H), 1.16 (t, 6H, $J = 7.2$ Hz), 0.92 (d, 3H, $J = 6.8$ Hz), 0.76 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 174.7, 152.5, 54.7, 40.2, 30.2, 29.9, 29.0, 18.2, 14.4, 8.7, 8.6; IR (film): 2964, 1750, 1693, 1362, 1251, 1199, 864, 806 cm^{-1}; HRMS-ESI *m/z* 241.1543 ([M + H]$^+$, $C_{12}H_{21}N_2O_3$ requires 241.1547).

(*S*)-5-Isopropyl-1-propionyl-imidazolidin-2-one (13). Compound **12** (2.90 g, 12.1 mmol) in 30.0 mL of THF (0.40 M) was chilled to −78 °C, and 12.1 mL (12.1 mmol, 1.00 equiv) of 1.00 M potassium *t*-butoxide in THF was added dropwise over the course of 10 min. The reaction was stirred at −78 °C for a total of 4 h. The solution was transferred dropwise by cannula to a second flask containing 50 mL of stirring water at room temperature. The aqueous phase was extracted with ethyl acetate and ether. The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated to give a crude oil of 2.6 g. The oil was prepared as a silica cake, loaded onto a silica column, and eluted with 99:1 CH_2Cl_2/MeOH. Main product containing fractions were combined and submitted to preparative HPLC in 3−10% isopropanol in hexane over 90 min at a 25 mL/min flow rate. Main peak fractions were combined to give a clear oil of mass 0.873 of 90−95% purity as determined by ^{1}H NMR (37% yield). $R_f = 0.30$ (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.39 (dt, 1H, $J = 9.2$, 3.6 Hz), 3.42 (t, 1H, $J = 9.2$ Hz), 3.24−3.21 (m, 1H), 3.00−2.83 (m, 2H), 2.43−2.35 (m, 1H), 1.13 (t, 3H, $J = 7.2$ Hz), 0.88 (d, 3H, $J = 6.8$ Hz), 0.83 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 157.7, 58.4, 37.7, 29.4, 28.9, 18.2, 14.7, 8.99; IR (film): 3309, 2962, 1729, 1683, 1375, 1295, 1247, 807 cm^{-1}; HRMS-ESI *m/z* 185.1285 ([M + H]$^+$, $C_9H_{17}N_2O_2$ requires 185.1285).

General Procedure for Gram Scale Preparation of Azetines. Representative example for **22a**: a solution of 1.00 g (4.06 mmol) of **21** in anhydrous dichloromethane (150 mL, 0.027 M) was chilled to 0 °C under argon. Titanium tetrachloride (1.78 mL, 16.2 mmol, 4.00 equiv) was added, followed after 5 min by dropwise addition of (−)-sparteine (2.33 mL, 10.2 mmol, 2.50 equiv). The solution was stirred for 30 min, and oxime **2a** (1.65 g, 12.2 mmol, 3.00 equiv) was added. The solution was allowed to equilibrate to room temperature and was stirred for 24 h. The reaction mixture was quenched with half saturated aqueous ammonium chloride, and the aqueous phase was extracted with dichloromethane. The organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried with $MgSO_4$, filtered, and concentrated to give a dark amber oil that was loaded neat onto a silica column and eluted with a 1−10% isopropanol in hexanes gradient. The first main peak fractions were combined and concentrated to give 0.602 g of white solid (*cis*-azetine). The second main product was isolated as 0.334 g of white solid (trans isomer). Total yield was 69% with a ratio of 1.8:1 cis/trans products as determined by analysis of the crude ^{1}H NMR spectrum and confirmed in final isolated yields.

(4*R*,5*S*)-1,5-Dimethyl-3-((3*S*,4*S*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-4-phenyl-imidazolidin-2-one (22a). *cis*-Azetine: white solid; $R_f = 0.25$ (95:5 CH_2Cl_2/MeOH); mp 162−165 °C; $[\alpha]^{23}_D$ +214.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 10H), 5.31 (d, 1H, $J = 8.0$ Hz), 4.80 (d, 1H, $J = 4.4$ Hz), 4.08−4.01 (m, 2H), 2.82 (s, 3H), 0.95 (d, 3H, $J = 7.6$ Hz), 0.83 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.4, 140.1, 136.0, 128.8, 128.4, 127.9, 127.5, 127.3, 127.0, 65.5, 58.6, 55.9, 45.0, 28.2, 15.0, 12.8; IR (film): 3030, 2976, 2934, 1718, 1602, 1459, 1397, 1285, 969, 907, 703 cm^{-1}; HRMS-ESI *m/z* 334.1914 ([M + H]$^+$, $C_{21}H_{24}N_3O$ requires 334.1914); Anal. calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; O, 4.80. Found C, 75.36; H, 7.12; N, 12.55; O, 4.86. *trans*-Azetine: white solid; $R_f = 0.33$ (95:5 CH_2Cl_2/MeOH); mp 144−146 °C; $[\alpha]^{23}_D$ +32.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.33 (m, 3H), 7.27−7.24 (m, 2H), 7.15−7.13 (m, 3H), 6.88−6.84 (m, 2H), 5.26 (d, 1H, $J = 8.4$ Hz), 4.31 (d, 1H, $J = 1.6$ Hz), 4.09−4.02 (m, 1H), 3.30 (dq, 1H, $J = 7.2$, 1.6 Hz), 2.84 (s, 3H), 1.61 (d, 3H, $J = 8.4$ Hz), 0.89 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 156.3, 141.7, 136.0, 128.7, 128.3, 128.2, 127.5, 127.0, 125.9, 69.9, 59.0, 55.6, 50.8, 28.2, 16.1, 15.1; IR (film): 2960, 2933, 1721, 1598, 1426, 1397, 1293, 1181, 957, 783, 747, 706 cm^{-1}; HRMS-ESI *m/z* 334.1913 ([M + H]$^+$, $C_{21}H_{24}N_3O$ requires 334.1914); Anal. calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; O, 4.80. Found C, 75.53; H, 6.92; N, 12.58; O, 4.81.

General Procedure for the Alkylation of Azetines. Representative example for **23a**: a solution of 0.133 g (0.400 mmol) of *cis*-azetine **22a** in anhydrous THF (4 mL) was chilled to 0 °C under argon. Lithium hexamethyldisilazide (1.60 mL of 1.0 M solution in THF, 1.60 mmol, 4.00 equiv) was added dropwise. After 45 min, benzyl bromide (0.0714 mL, 0.600 mmol, 1.50 equiv) was added, and the solution was stirred for 30 min. The reaction was quenched with 1 N HCl, and ethyl acetate was added. The organic layer was washed with 1 N HCl. The aqueous layers were combined and extracted with ethyl acetate. The aqueous layer was basified to pH > 9 with 4 N NaOH and extracted with dichloromethane. The organic layers were combined and dried with anhydrous K_2CO_3. The solution was filtered and concentrated to give a brown oil that was carried on to the next step without further purification.

General Procedure for Hydrolytic Ring Opening of Azetines to $\beta^{2,2,3}$-Amino Carbonyl Derivatives. Representative example for **23a**: to a solution of azetine alkylation crude sample in dichloromethane (5 mL) was added 0.0837 mL (0.600 mmol, 1.20 equiv) of triethylamine and 0.232 mL (2.00 mmol, 5.00 equiv) of benzoyl chloride at room temperature. The solution was stirred for 1 h and quenched with half saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layers were washed with aqueous saturated sodium bicarbonate and brine, dried with anhydrous K_2CO_3, filtered, and concentrated. Column chromatography on silica with 10−20% ethyl acetate in hexanes provided the product **23a** as an oil of mass 0.150 g (69% from **22a**).

***N*-[(1*R*,2*R*)-2-Benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenyl-imidazolidin-1-yl)-2-methyl-3-oxo-1-phenyl-propyl]-benzamide (23a).** $R_f = 0.60$ (95:5 CH_2Cl_2/MeOH); $[\alpha]^{23}_D$ +30.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38−6.88 (m, 20H), 6.44 (bs, 1H), 5.07 (d, 1H, $J = 8.4$ Hz), 4.18 (d, 1H, $J = 13.8$ Hz), 3.75−3.70 (m, 1H), 2.82 (s, 3H), 2.36 (d, 1H, $J = 13.2$ Hz), 1.18 (s, 3H), 0.67 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4, 166.2, 155.5, 139.6, 137.9, 136.9, 135.0, 131.2, 130.6, 129.3, 128.5, 128.4, 128.3, 128.1, 127.8, 127.5, 127.3, 127.1, 126.7, 62.5, 57.1, 54.3, 54.1, 39.9, 28.6, 19.9, 15.1; IR (neat): 3439, 3316, 3034,

2984, 1725, 1664, 1513, 1424, 1247, 1073, 911, 703 cm^{-1}; HRMS-ESI *m*/*z* 546.2748 ($[M + H]^+$, $C_{35}H_{36}N_3O_3$ requires 546.2751).

(2*R*,3*R*)-3-Benzoylamino-2-benzyl-2-methyl-3-phenyl-propionic Acid Methyl Ester (24). Compound **23a** (0.050 g, 0.092 mmol) was dissolved in 1.5 mL of anhydrous MeOH and chilled to 0 °C, and sodium methoxide (0.200 mL of 0.5 M in MeOH, 0.10 mmol, 1.10 equiv) was added. The solution was allowed to warm to room temperature and refluxed for 16 h. Water was added, and the methanol was removed by evaporation. The aqueous layer was extracted with dichloromethane, acidified with saturated ammonium chloride, and further extracted with dichloromethane. The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated. Column chromatography on silica and elution with a 0−50% ethyl acetate in hexanes gradient gave compound **24** as 0.029 g (82%) of clear oil. $R_f = 0.53$ (1:1 hexanes/EtOAc); $[\alpha]^{23}_D$ +72.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, 1H, $J = 9.2$ Hz), 7.95−7.92 (m, 2H), 7.54−7.47 (m, 3H), 7.33−7.21 (m, 8H), 7.13−7.10 (m, 2H), 5.17 (d, 1H, $J = 9.2$ Hz), 3.62 (s, 3H), 3.49 (d, 1H, $J = 13.2$ Hz), 2.84 (d, 1H, $J = 13.2$ Hz), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 166.4, 139.5, 136.6, 134.5, 131.8, 130.3, 128.8, 128.6, 128.5, 128.0, 127.9, 127.2, 127.1, 60.6, 52.3, 51.4, 44.5, 19.6; IR (solid): 1728, 1645, 1514, 1485, 1201, 1104, 701 cm^{-1}; HRMS-ESI *m*/*z* 388.1905 ($[M + H]^+$, $C_{25}H_{26}NO_3$ requires 388.1907).

(2*R*,3*R*)-3-Benzoylamino-2-benzyl-2-methyl-3-phenyl-propionic Acid (25). Compound **23a** (0.100 g, 0.183 mmol) was dissolved in 1.5 mL of 4:1 THF/H_2O and chilled to 0 °C. A 0.075 mL volume of 30% aqueous hydrogen peroxide (0.73 mmol, 4.0 equiv) was added dropwise, followed by lithium hydroxide (0.0070 g in 0.5 mL of deionized water, 0.29 mmol, 1.6 equiv). The reaction was allowed to equilibrate to room temperature and was stirred for 16 h. Sodium sulfite (0.7 mmol in 1 mL of deionized water) was added, and the THF was removed by evaporation. The aqueous phase was extracted with dichloromethane. The aqueous phase was then cooled in an ice bath, acidified to pH 1 with 10% HCl, and extracted with ethyl acetate. The ethyl acetate layers were combined, dried with $MgSO_4$, filtered, and concentrated to give 0.055 g (80%) of compound **25** as a clear oil. $R_f = 0.20$ (1:1 hexanes/EtOAc); $[\alpha]^{23}_D$ +73.1 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 11.01 (bs, 1H), 8.47 (d, 1H, $J = 9.2$ Hz), 7.88−7.84 (m, 2H), 7.55−7.16 (m, 13H), 5.26 (d, 1H, $J = 9.2$ Hz), 3.46 (d, 1H, $J = 13.2$ Hz), 2.93 (d, 1H, $J = 13.2$ Hz), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 166.9, 139.1, 136.2, 134.3, 132.0, 130.4, 128.9, 128.7, 128.6, 128.1(2C), 127.3, 127.2, 60.2, 51.2, 44.2, 19.8; IR (solid): 3030, 1626, 1519, 1485, 1203, 908, 698, 585 cm^{-1}; HRMS-ESI *m*/*z* 374.1745 ($[M + H]^+$, $C_{24}H_{24}NO_3$ requires 374.1751).

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Supporting Information Available: Experimental procedures and characterization for all prepared compounds described in this work, as well as ^1H and ^{13}C spectra for all new compounds reported, crystallographic data for *cis*- and *trans*-azetines **18a** and addition product **23f**, and input data and statistical analysis for the optimization study. This material is available free of charge via the Internet at http://pubs.acs.org.

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