

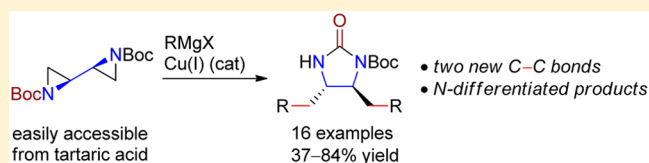
Enantiopure *Trans*-4,5-Disubstituted 2-Imidazolidinones via Copper(I)-Catalyzed Ring Opening of 1,1'-DiBoc-2,2'-Biaziridine with Grignard Reagents

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S Supporting Information

ABSTRACT: The copper-catalyzed ring opening of chiral-pool-derived 1,1'-diBoc-2,2'-biaziridine with Grignard reagents affords enantiopure 2-imidazolidinones in a desymmetrizing, cascade process involving the Boc protecting group. This divergent strategy provides reaction-ready, *N*-differentiated products and allows two C–C bond constructions concurrent to imidazolidinone formation. A variety of alkyl, cyclic, and aryl Grignard reagents are tolerated in reasonable to good yields.



2-Imidazolidinones are important heterocycles represented in bioactive compounds¹ and peptidomimetics,² as well as chiral ligands³ and auxiliaries⁴ in stereoselective synthesis (e.g., 1–4, Figure 1). Additionally, these five-membered cyclic ureas are precursors to other useful compound classes including vicinal diamines,⁵ cyclic guanidines⁶ and imidazolidinethiones.⁷

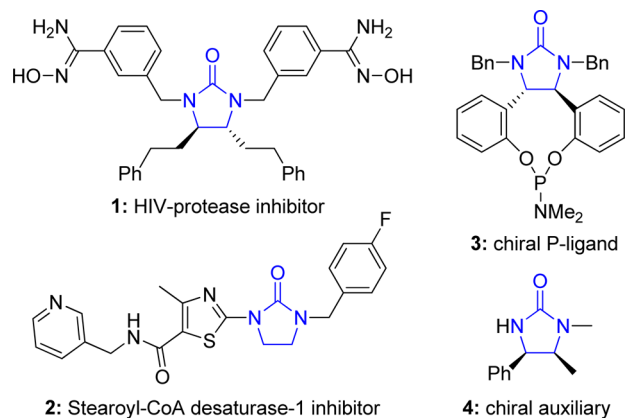


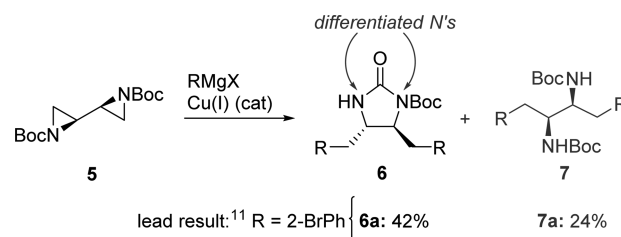
Figure 1. Exemplary 2-imidazolidinones.

Although the traditional route to this heterocycle involves treatment of a vicinal diamine with an electrophilic carbonyl source,⁸ an abundance of alternate methods are now available which avoid the requirement for presynthesized diamines, offering greater product diversity in modular fashion.⁹ Despite these advances, however, there remains comparatively few general methods which allow access to 4- and/or 5-substituted 2-imidazolidinones with control of absolute stereochemistry.¹⁰

Previously in our laboratory, as an intermediary step toward the synthesis of 2,2'-biindoline, we attempted the ring opening of tartaric acid derived biaziridine **5** with a Grignard reagent, affording an imidazolidinone **6a** as the major product arising

from an unforeseen participation of the Boc protecting group (Scheme 1).¹¹ Although **5** is an easily synthesized,¹² bench-

Scheme 1. Proposed Synthesis of 2-Imidazolidinones

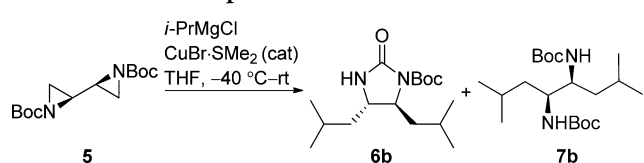


stable solid, its reactivity has remained unexplored beyond this example; thus, we were inspired to further investigate the ring opening of **5** by Grignard reagents. As well as harboring the potential to prepare enantiopure 2-imidazolidinones **6** in a divergent manner, this approach would allow direct access to reaction-ready, *N*-differentiated products, thus presenting downstream opportunities for sequential, asymmetric *N*-functionalization.¹³ Furthermore, this method would constitute a useful addition to the limited existing synthetic strategies to enantioenriched *trans*-4,5-disubstituted imidazolidinones, which are specific to vinyl derivatives¹⁴ or require multistep routes from amino acids¹⁵ or 1,3-dihydro-2-imidazolone.¹⁶

We began this investigation by examining the effect of reaction parameters on the product ratio, in the search for conditions favoring imidazolidinone formation (Table 1). We were not concerned with pursuing a separate optimization of **7** in this study, as we have recently shown that the analogous tosyl-biaziridine cleanly provides vicinal diamines of this type upon ring opening.¹⁷ For convenience, we selected commer-

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Table 1. Reaction Optimization^a

entry	equiv <i>i</i> -PrMgCl	mol % Cu (wrt <i>i</i> -PrMgCl)	[5] ₀ (mol L ⁻¹)	ratio 6b : 7b ^b
1	4.0	15	0.10	25:75
2	4.0	5	0.10	21:79
3	4.0	0	0.10	—
4	4.0	15	0.025	34:66
5	2.4	15	0.025	55:45 ^c
6	2.4	15	0.025	56:44 ^d
7	2.4 ^e	15	0.025	—

^aReactions performed by premixing **5** and CuBr·SMe₂ in THF at -40 °C, adding *i*-PrMgCl and allowing the cooling bath to warm to rt over 16 h. ^bDetermined by ¹H NMR analysis of the crude mixture. ^cIsolated yields of **6b** and **7b** were 48% and 26%, respectively. ^dReaction time was 96 h. ^e*i*-PrMgCl added dropwise over 2 h to the reaction mixture at -20 °C.

cially available *i*-PrMgCl as the model Grignard reagent. Our initial experiment was performed under similar conditions to those reported previously,^{11,17} affording a mixture of the desired heterocycle **6b** and vicinal diamine **7b** in a 25:75 ratio (entry 1). Immediately, we noted a clear dependency of the product ratio on the Grignard reagent, given the reversal in major product from the previous reaction (see Scheme 1).

Undeterred by this result, we examined variations in the quantity of the catalyst: a reduction to 5 mol % gave a similar outcome (Table 1, entry 2), while omitting the copper salt completely resulted in neither product being observed (entry 3). Encouragingly, when the starting concentration of **5** was reduced, the ratio of **6b**:**7b** was increased favorably (entry 4 versus entry 1). Maintaining this concentration and removing the excess Grignard reagent¹⁸ provided a further advantage, enabling **6b** to emerge as the major product in 48% isolated yield (entry 5), along with **7b** obtained in 26% yield, which was easily separated from **6b** by flash chromatography due to its significantly lower polarity on silica gel. Subsequent experiments proved unsuccessful in further optimizing the outcome; increasing the reaction time (prior to NH₄Cl quench) had a negligible effect (entry 6), while performing slow addition of the Grignard reagent at -20 °C returned mostly unreacted **5** (entry 7).¹⁹

Although the yield of **6b** was affected by the persistent formation of **7b**, we remained optimistic that screening a variety of Grignard reagents would provide more favorable results, given the apparent dependency of the product ratio on the Grignard reagent. Therefore, we proceeded to examine the scope of the process under the newly established conditions (Table 2). A range of structurally and electronically diverse Grignard reagents such as cyclic, primary alkyl, and functionalized benzylic and aryl carbanions, including *ortho*-substituted substrates, were found to be accommodated, affording the desired imidazolidinones **6a**–**6p** in modest to good yields (37–84%). With the majority of Grignard reagents examined, the yield of **6** was notably lower than would be expected based on the product ratio, indicating biaziridine decomposition as a competing reaction pathway. The products were purified by

silica gel flash chromatography and were observed to be stable to these conditions.

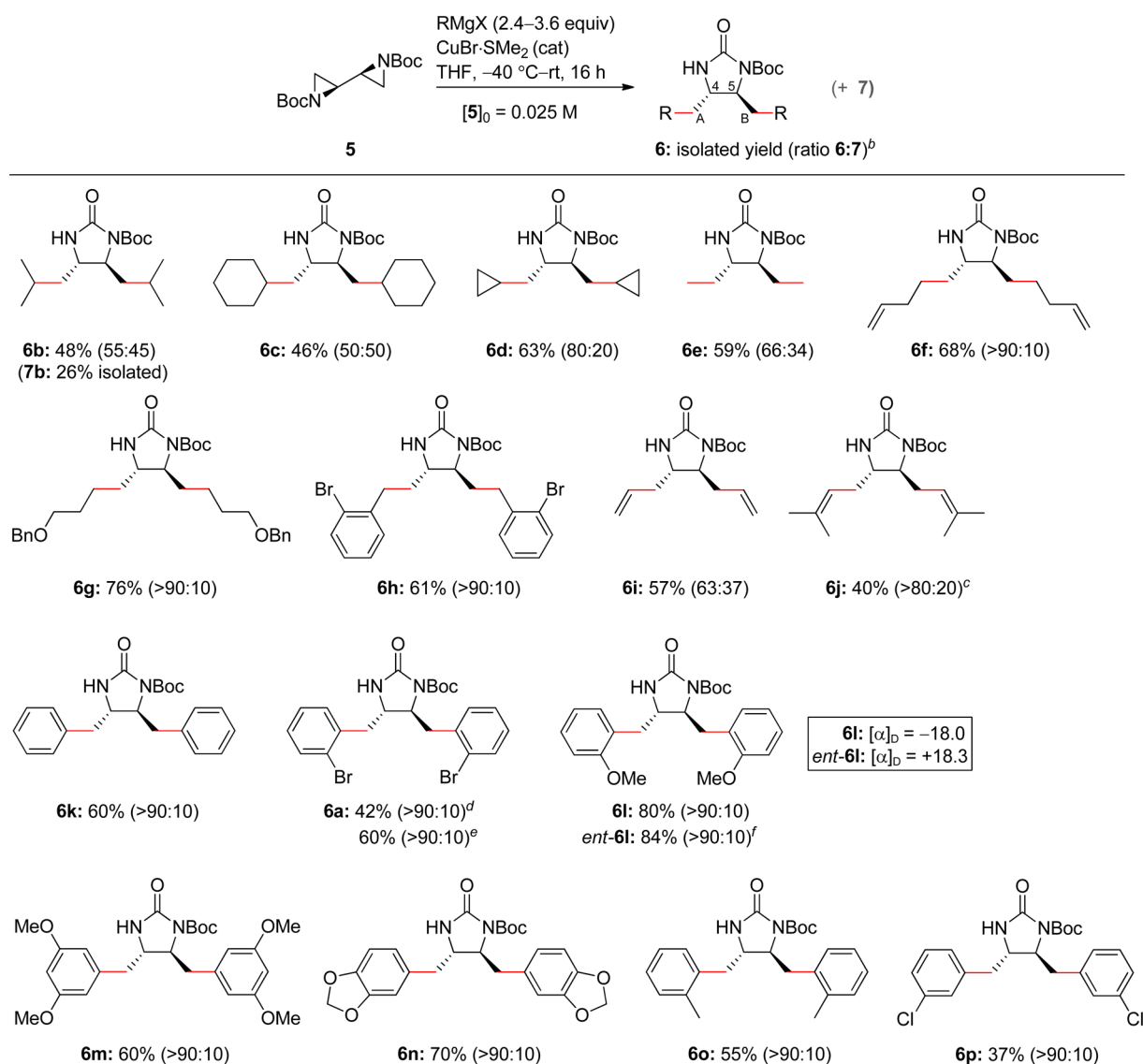
Similarly to the isopropyl test substrate, clean C–C bond formation took place with the cyclohexyl Grignard reagent, but equimolar amounts of **6c** and **7c** were formed, resulting in a 46% yield of **6c** (Table 2). Notably, all other Grignard reagents surveyed provided higher ratios of **6**:**7** than observed with the secondary carbanions (isopropyl and cyclohexyl). Primary alkyl (nonmethyl) and aryl Grignard reagents were particularly good performers in this regard, providing molar ratios of **6**:**7** in excess of 90:10 in all cases. With aryl and vinyl Grignard reagents, up to 3.6 equiv of the carbanion was required for complete consumption of **5**, although not at the expense of the product ratio.

The method was revealed to be somewhat sensitive to inductive effects: the electron-rich 2-methoxyphenyl Grignard reagent furnished **6l** in 80% yield (Table 2), whereas the electron-deficient 3-chloro derivative provided **6p** in a reduced 37% yield. In the latter case, a number of unidentified side products were observed. The 2-bromophenyl Grignard reagent was required in 4-fold excess for complete consumption of **5**, presumably due to nucleophile loss via decomposition to benzyne.²⁰ Under these conditions, **6a** was obtained in 60% yield, with, at most, a trace of **7a** formed, representing a significant improvement to our original lead result (Scheme 1). Unsuccessful substrates under the standard conditions included *tert*-butyl, ethynyl, and 2-thienyl Grignard reagents (products not shown). In these cases, unreacted **5** was the predominant component in the crude mixture after workup.

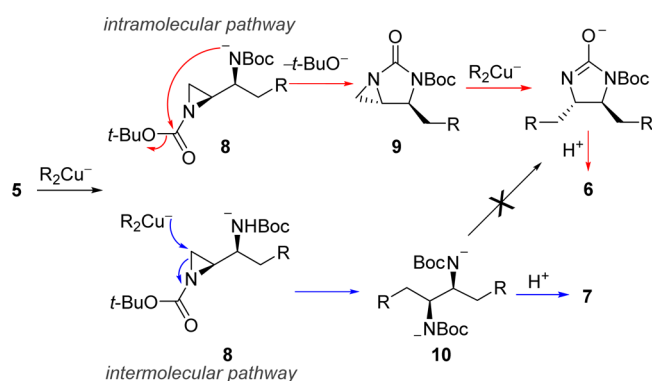
NMR analysis of the products revealed some notable general characteristics. H4 was observed in all cases as an apparent triplet (δ 3.14–3.63 ppm, J = 5.7–7.4 Hz), while H5 routinely resonated further downfield as a doublet (δ 3.73–4.40 ppm, J = 7.8–10.8 Hz). These multiplicities were attributed to vicinal coupling with their adjacent methylene protons (HA and HB), as no correlations between H4 and H5 were observed by gCOSY analysis. The diastereotopic methylene protons at HA, as well as HB, were fully resolved as two distinct doublets of doublets for some compounds derived from aryl Grignard reagents (e.g., **6k**, **6n**). In regards to the ¹³C NMR spectra, several products bearing pendant aryl moieties exhibited up to two doubly degenerate signals (ArC's), likely as a consequence of the pseudo C₂-symmetric nature of the compounds.

As anticipated, all evidence pertaining to the stereochemical purity of the products pointed conclusively to a complete chirality transfer from the biaziridine. The absence of diastereoisomers in the NMR spectra of all crude materials and purified products served as primary evidence against epimerization under the basic ring-opening conditions. In addition, representative ring-opening product *ent*-**6l** was prepared and was found to have a specific rotation equal and opposite to **6l** (Table 2, insert). The optical purities of **6l** and *ent*-**6l** were further confirmed by analytical chiral HPLC.²¹

A divergent reaction mechanism is proposed in Scheme 2 to account for the formation of **6** and side product **7**. Initially, nucleophilic addition of the organocuprate produces common intermediate **8**, which can either be attacked by a second equivalent of the carbanion to give the fully ring-opened diamine **7** (blue arrows, intermolecular pathway) or undergo an intramolecular *N*-acylation^{22,23} to produce bicyclic intermediate **9** (red arrows, intramolecular pathway).²⁴ Subsequent addition of a second equivalent of the organocuprate to **9** ultimately produces imidazolidinone **6**. This mechanistic proposal is

Table 2. Grignard Substrate Scope^a

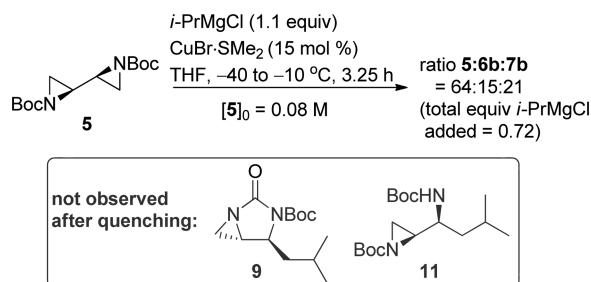
^aReactions performed with 0.14 mmol of **5** and 10–15 mol % CuBr·SMe₂ (wrt RMgX). ^bThe product ratio was determined by ¹H NMR analysis of the crude reaction mixture, and **6** was isolated by flash chromatography. ^cProduct ratio unable to be determined with more precision due to multiple side products. ^d4 equiv of RMgX used; some unreacted **5** was returned. ^e8 equiv of RMgX used. ^fent-**5** used. Red-colored bonds highlight new C–C bond formation.

Scheme 2. Proposed Reaction Mechanism^a

^a(MgX)⁺ counterions are omitted for clarity.

consistent with our earlier data in that the resultant ratio of **6:7** was found to increase with higher dilution and lesser equivalents of the carbanion, conditions which would be expected to favor the intramolecular pathway. Furthermore, the propensity for secondary alkyl and cyclic Grignard reagents to produce greater quantities of **7** can be rationalized by the higher reactivity of their derived organocuprates toward **8**, as the rate of competing cyclization to **9** is presumably independent of the pendant R group. Notably, the possibility of an alternative entry (or additional contribution) to **6** via cyclization of intermediate **10** can be ruled out on the basis that an extended stirring time did not alter the final product ratio, although this mode of ring closure has been reported for the lithium dianion of an aryl *ortho*-dicarbamate.²⁵

In an attempt to characterize the reaction products of monocarbanion addition, we performed an experiment with a limiting amount of *i*-PrMgCl and maintained the temperature below -10 °C (Scheme 3). Interestingly, TLC and NMR

Scheme 3. Reaction of **5** with Limiting *i*-PrMgCl

analyses of the crude mixture did not reveal any new reaction products; only the previously characterized diaddition products **6b** and **7b** were present, in addition to unreacted **5** as the major component. The absence of **11** was not overly surprising, given that there are presumably two modes for the consumption of its anionic precursor **8** (see Scheme 2), but the lack of observation of **9** is more difficult to rationalize. Essentially, if **9** is formed during the ring opening process, its absence in the crude mixture suggests either its instability to the aqueous workup conditions²⁶ or a significantly greater reactivity to ring opening than **5**, thereby being consumed more rapidly by the available carbanion. In line with the latter, a number of related aziridine-fused imidazolidinones²⁷ and oxazolidinones²⁶ have been shown to undergo facile and regioselective nucleophilic ring opening at the terminal methylene position, including by organocuprates.^{26b,c,27b}

In summary, we have developed a new, enantiospecific route to 2-imidazolidinones via the ring opening of Boc-protected 2,2'-biaziridine with Grignard reagents. As demonstrated, this method has the potential to access a diverse range of enantiopure 2-imidazolidinones in a single step from a common, easily prepared chiral-pool precursor. This approach can be considered as a variant of the classical 'vicinal diamine + carbonyl source' imidazolidinone synthesis, whereby in this case the latent diamine is embedded in the biaziridine. Further elaboration of the products prepared herein toward new catalysts and medicinally relevant materials can be readily envisioned, taking advantage of the embedded halogen, alkoxy, and olefin moieties, as well as the numerous methods available for *N*-functionalization of 2-imidazolidinones.²⁸

EXPERIMENTAL SECTION

General Methods and Materials. All reactions were carried out in standard laboratory glassware with magnetic stirring under N₂. Thin layer chromatography (TLC) was performed on aluminum-backed 0.20 mm silica gel plates. Visualization was accomplished with UV light or a solution of phosphomolybdic acid in ethanol. Flash chromatography was performed under positive air pressure using Silica Gel 60 of 230–400 mesh (40–63 μm). Melting points (mp) are uncorrected. Optical Rotations were measured in CH₂Cl₂ with a path length of 1.0 dm (λ = 589 nm). Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded at 300 MHz, or at 500 MHz, as specified. Spectra were acquired in CDCl₃ and are reported relative to tetramethylsilane (¹H: δ = 0.00 ppm) and solvent resonance (¹³C: δ = 77.0 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. High resolution mass spectrometry (HRMS) was performed on a QTOF ESI spectrometer or on a TOF EI spectrometer.

Anhydrous tetrahydrofuran was obtained commercially. (2*S*,2'*S*)-1,1'-Di-(*tert*-butoxycarbonyl)-2,2'-biaziridine **5** and its (*R,R*)-enantiomer (*ent*-**5**) were prepared from *D*- and *L*-tartaric acid, respectively,

according to a published procedure.¹² Notably, **5** is a bench-stable solid that can be stored indefinitely at ambient temperature without decomposition. 2-Bromophenylmagnesium chloride was prepared from 2-bromiodobenzene via I/Mg exchange with *i*-PrMgCl.²⁹ 3-Chlorophenylmagnesium chloride was prepared from 1-bromo-3-chlorobenzene via Br/Mg exchange with *i*-PrMgCl·LiCl.³⁰ Other Grignard reagents were obtained commercially or prepared from freshly acid-washed Mg turnings. All other reagents and solvents were obtained reagent grade from commercial sources and used as received.

General Procedure for the Ring Opening of Biaziridine **5 with Grignard Reagents.** To a suspension of **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10–15 mol % wrt the Grignard reagent) in THF at -40 °C (liquid N₂/MeCN slush bath) was added a Grignard reagent (2.4–3.6 equiv) in THF (total volume of THF = 5.6 mL; individual proportions vary depending on the Grignard concentration). The resulting solution was allowed to warm to rt with stirring over 16 h. The mixture was quenched with saturated NH₄Cl (2 mL), diluted with brine (10 mL), and extracted with EtOAc (20 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was analyzed by ¹H NMR spectroscopy to determine the product ratio, before being subjected to flash chromatography to isolate the desired imidazolidinone.

(4*S*,5*S*)-2,7-Dimethyl-4,5-di(*N*-*tert*-butoxycarbonylamino)octane (**7b**) and (4*S*,5*S*)-4,5-Diisobutyl-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6b**). The title compounds were prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (5.4 mL) and a solution of *i*-PrMgCl (1.8 M in THF, 0.19 mL, 0.34 mmol). Flash chromatography (2.4 g silica, 5% EtOAc/hexanes) gave **7b** (13.5 mg, 26%) as a white solid. Mp 146–147 °C; TLC (15% EtOAc/pet ether) R_F = 0.71; [α]_D²¹ -65.9 (c 2.77, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃, major rotamer only) δ 4.45 (bd, J = 9.1 Hz, 2H), 3.63–3.46 (m, 2H), 1.74–1.61 (m, 2H), 1.43 (s, 18H), 1.36–1.22 (m, 4H), 0.94–0.88 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3, 79.0, 52.9, 42.4, 28.4, 24.9, 23.4, 21.9; IR (neat) ν 3351, 2949, 1685, 1534, 1362, 1291, 1179, 1011 cm⁻¹; HRMS (EI) calcd for C₂₀H₄₀N₂O₄ 372.2988 [M]⁺, found 372.3001. Further elution (5% to 20% EtOAc/hexanes) gave **6b** (20.0 mg, 48%) as a colorless gum. TLC (30% EtOAc/pet ether) R_F = 0.32; [α]_D²¹ -5.4 (c 4.23, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 6.33 (bs, 1H), 3.77 (t, J = 7.2 Hz, 1H), 3.25 (t, J = 7.2 Hz, 1H), 1.53 (s, 9H), 1.74–1.32 (m, 5H), 1.30–1.22 (m, 1H), 0.97–0.91 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 150.4, 82.0, 59.5, 52.1, 45.4, 42.4, 28.1, 24.3, 24.2, 23.9, 23.0, 22.0, 21.5; IR (neat) ν 3289, 2952, 2866, 1787, 1711, 1370, 1336, 1254, 1164, 1131, 1102, 778 cm⁻¹; HRMS (EI) calcd for C₁₆H₃₀N₂O₃ 298.2256 [M]⁺, found 298.2259.

(4*S*,5*S*)-4,5-Di(cyclohexylmethyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6c**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (5.2 mL) and a solution of cyclohexylmagnesium chloride (1.84 M in THF, 0.20 mL, 0.37 mmol). Flash chromatography (2.0 g silica, 20% EtOAc/hexanes) gave **6c** (24.3 mg, 46%) as an amorphous solid. TLC (20% EtOAc/pet ether) R_F = 0.14; [α]_D²⁵ = -2.2 (c 1.20, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 5.93 (s, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.28 (t, J = 7.0 Hz, 1H), 1.86–1.38 (m, 21H), 1.38–1.11 (m, 9H), 1.08–0.87 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 150.4, 82.0, 58.9, 51.5, 43.9, 41.0, 34.4, 34.0, 33.9, 33.5, 33.0, 32.5, 28.2, 26.4, 26.3, 26.10, 26.07; IR (neat) ν 3284, 2921, 2346, 1776, 1744, 1701, 1340, 1250, 1157, 857, 774, 733 cm⁻¹; HRMS (ESI) calcd for C₂₂H₃₈N₂NaO₃ 401.2780 [M + Na]⁺, found 401.2765.

(4*S*,5*S*)-4,5-Di(cyclopropylmethyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6d**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (4.55 mL) and a solution of cyclopropylmagnesium bromide (0.5 M in THF, 0.85 mL, 0.42 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6d** (26.2 mg, 63%) as an amorphous solid. TLC (40% EtOAc/pet ether) R_F = 0.40; [α]_D²⁵ = -6.8 (c 1.20, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.05 (s, 1H), 3.94 (d, J = 9.0 Hz, 1H), 3.49 (t, J = 5.7 Hz, 1H), 1.79–1.70 (m, 2H), 1.61–1.47 (m, 10H), 1.40–1.30 (m, 1H), 0.76–0.64 (m, 2H), 0.58–0.41 (m, 4H), 0.20–0.08 (m, 4H); ¹³C NMR (125 MHz,

CDCl_3) δ 155.6, 150.4, 82.0, 60.6, 54.1, 41.0, 38.0, 28.1, 6.8, 6.3, 5.0, 4.4, 3.9, 3.5; IR (neat) ν 3303, 2987, 2335, 1772, 1701, 1343, 1251, 1162, 1018, 855, 824, 775, 756 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{NaO}_3$ 317.1841 $[\text{M} + \text{Na}]^+$, found 317.1826.

(4*S*,5*S*)-4,5-Diethyl-1-*tert*-butoxycarbonyl-2-imidazolidinone (6e). This was prepared according to the general procedure using **5** (41.5 mg, 0.15 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (14.2 mg, 0.069 mmol) in THF (5.58 mL) and a solution of methylmagnesium chloride (1.8 M in THF, 0.26 mL, 0.46 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6e** (21.0 mg, 59%) as a pale yellow gum. TLC (40% EtOAc/pet ether) R_F = 0.37; $[\alpha]_D^{25}$ = -2.0 (*c* 1.05, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 5.63 (bs, 1H), 3.73 (d, *J* = 8.3 Hz, 1H), 3.14 (t, *J* = 6.0 Hz, 1H), 1.84–1.57 (m, 4H), 1.53 (s, 9H), 0.98–0.88 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 150.5, 82.1, 61.2, 54.6, 29.2, 28.1, 26.4, 9.1, 8.5; IR (neat) ν 2968, 1774, 1738, 1702, 1344, 1253, 1161, 1102, 855, 775, 757 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{NaO}_3$ 265.1528 $[\text{M} + \text{Na}]^+$, found 265.1530.

(4*S*,5*S*)-4,5-Di(4-pentenyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6f). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (4.6 mL) and a solution of but-3-en-1-ylmagnesium bromide (0.44 M in THF, 0.83 mL, 0.37 mmol). Flash chromatography (2.0 g silica, 20% EtOAc/hexanes) gave **6f** (31.6 mg, 68%) as an amorphous solid. TLC (20% EtOAc/pet ether) R_F = 0.10; $[\alpha]_D^{25}$ = -2.6 (*c* 1.60, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.49 (bs, 1H), 5.84–5.71 (m, 2H), 5.08–4.92 (m, 4H), 3.75 (d, *J* = 8.5 Hz, 1H), 3.19 (t, *J* = 6.5 Hz, 1H), 2.13–2.02 (m, 4H), 1.76–1.61 (m, 2H), 1.59–1.31 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 150.5, 137.93, 137.86, 115.2, 115.1, 82.1, 60.4, 53.7, 35.8, 33.4, 33.3, 33.0, 28.1, 24.1, 23.7; IR (neat) ν 3309, 2931, 2358, 1773, 1700, 1340, 1249, 1157, 909, 855, 775, 756, 638 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{30}\text{N}_2\text{NaO}_3$ 345.2154 $[\text{M} + \text{Na}]^+$, found 345.2142.

(4*S*,5*S*)-4,5-Di(4-benzyloxybutyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6g). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (3.9 mL) and a solution of 3-benzyloxypropylmagnesium bromide (0.24 M in THF, 1.53 mL, 0.37 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6g** (54.3 mg, 76%) as an amorphous solid. TLC (40% EtOAc/pet ether) R_F = 0.23; $[\alpha]_D^{25}$ = -3.8 (*c* 2.70, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.24 (m, 10H), 5.65 (bs, 1H), 4.48 (s, 4H), 3.75 (d, *J* = 8.7 Hz, 1H), 3.46 (q, *J* = 5.8 Hz, 4H), 3.16 (t, *J* = 6.7 Hz, 1H), 1.77–1.57 (m, 6H), 1.54–1.31 (m, 16H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 150.4, 138.40, 138.36, 128.31, 128.30, 127.60, 127.56, 127.51, 127.48, 82.1, 72.90, 72.87, 69.8, 69.7, 60.4, 53.6, 36.2, 33.3, 29.5, 29.4, 28.1, 21.6, 21.1; IR (neat) ν 3929, 2858, 2360, 1773, 1696, 1457, 1340, 1249, 1098, 855, 736, 697 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{NaO}_5$ 533.2991 $[\text{M} + \text{Na}]^+$, found 533.3013.

(4*S*,5*S*)-4,5-Di(2-(2-bromophenylethyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6h). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (3.8 mL) and a solution of 2-bromobenzylmagnesium bromide (0.25 M in Et_2O , 1.60 mL, 0.40 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6h** (47.4 mg, 61%) as an amorphous solid. TLC (30% EtOAc/pet ether) R_F = 0.21; $[\alpha]_D^{25}$ = -15.1 (*c* 2.35, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.52 (t, *J* = 8.9 Hz, 2H), 7.29–7.02 (m, 6H), 6.77 (bs, 1H), 3.99–3.93 (m, 1H), 3.44 (t, *J* = 5.7 Hz, 1H), 2.85–2.68 (m, 4H), 2.06–1.96 (m, 2H), 1.94–1.81 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3 , one doubly degenerate ArC) δ 155.7, 150.2, 140.0, 139.9, 132.91, 132.88, 130.4, 130.2, 128.0, 127.9, 127.7, 127.6, 124.2, 82.3, 60.0, 53.0, 36.5, 33.7, 31.7, 31.2, 28.1; IR (neat) ν 3298, 2966, 2360, 1772, 1472, 1340, 1249, 1154, 1022, 854, 749, 659 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{28}(\text{Br})_2\text{N}_2\text{NaO}_3$ 573.0364 $[\text{M} + \text{Na}]^+$, found 573.0386.

(4*S*,5*S*)-4,5-Di(2-propenyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6i). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (14.2 mg, 0.069 mmol) in THF (5.34 mL) and a solution of vinylmagnesium chloride (1.6 M in THF, 0.29 mL, 0.46 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6i** (21.5 mg, 57%) as a pale yellow gum. TLC

(40% EtOAc/pet ether) R_F = 0.36; $[\alpha]_D^{25}$ = -13.4 (*c* 0.74, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 5.84 (bs, 1H), 5.77–5.64 (m, 2H), 5.19–5.11 (m, 4H), 3.87 (d, *J* = 8.4 Hz, 1H), 3.33 (t, *J* = 5.9 Hz, 1H), 2.56–2.48 (m, 1H), 2.46–2.38 (m, 1H), 2.30–2.18 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.3, 150.2, 132.2, 132.1, 119.41, 119.35, 82.4, 59.0, 52.0, 40.3, 37.7, 28.1; IR (neat) ν 2913, 1771, 1704, 1343, 1251, 1158, 1103, 914, 855, 774, 756, 621 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{NaO}_3$ 289.1528 $[\text{M} + \text{Na}]^+$, found 289.1516.

(4*S*,5*S*)-4,5-Di(3-methyl-2-butenyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6j). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (4.55 mL) and a solution of 2-methylprop-1-en-1-ylmagnesium bromide (0.5 M in THF, 0.84 mL, 0.42 mmol). Flash chromatography (2.0 g silica, 20% EtOAc/hexanes) gave **6j** (18.0 mg, 40%) as an amorphous solid. TLC (30% EtOAc/pet ether) R_F = 0.31; $[\alpha]_D^{25}$ = -17.6 (*c* 0.90, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) δ 5.77 (s, 1H), 5.12–4.96 (m, 2H), 3.77 (d, *J* = 7.8 Hz, 1H), 3.18 (t, *J* = 6.4 Hz, 1H), 2.51–2.05 (m, 4H), 1.72 (s, 6H), 1.64 (s, 3H), 1.62 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3 , one doubly degenerate CH_3) δ 155.5, 150.4, 136.2, 136.0, 118.0, 117.7, 82.1, 59.8, 53.0, 34.7, 31.7, 28.1, 25.8, 18.1, 18.0; IR (neat) ν 3287, 2979, 2360, 1769, 1340, 1249, 1157, 853, 774, 756 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{30}\text{N}_2\text{NaO}_3$ 345.2154 $[\text{M} + \text{Na}]^+$, found 345.2147.

(4*S*,5*S*)-4,5-Dibenzyl-1-*tert*-butoxycarbonyl-2-imidazolidinone (6k). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (14.2 mg, 0.069 mmol) in THF (5.30 mL) and a solution of phenylmagnesium chloride (1.4 M in THF, 0.33 mL, 0.46 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6k** (31.2 mg, 60%) as an amorphous solid. TLC (40% EtOAc/PE) R_F = 0.38; $[\alpha]_D^{25}$ = -25.3 (*c* 1.12, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.17 (m, 6H), 7.14 (d, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 2H), 4.87 (bs, 1H), 4.13 (d, *J* = 10.0 Hz, 1H), 3.46 (t, *J* = 6.8 Hz, 1H), 3.26 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.71 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.59 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.2 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.0, 150.1, 136.0, 135.8, 129.2, 128.9, 128.69, 128.65, 126.82, 126.79, 82.5, 60.7, 53.5, 42.0, 39.1, 28.1; IR (neat) ν 1762, 1490, 1340, 1152, 1061, 1022, 847, 748, 701 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{NaO}_3$ 389.1841 $[\text{M} + \text{Na}]^+$, found 389.1827. Note that *ent*-**6k** has been previously synthesized in nine steps from a protected L-aspartic acid derivative, although neither the specific rotation nor ^{13}C NMR data were reported.^{15c}

(4*S*,5*S*)-4,5-Di(2-bromobenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6a). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (3.52 mL) and a solution of 2-bromophenylmagnesium chloride (0.6 M in THF, 1.88 mL, 1.13 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **6a** (44.3 mg, 60%) as a pale yellow gum. Spectral data for **6a** were consistent with those reported previously.¹¹

(4*S*,5*S*)-4,5-Di(2-methoxybenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (6l). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and $\text{CuBr}\cdot\text{SMe}_2$ (10.8 mg, 0.053 mmol) in THF (4.50 mL) and a solution of 2-methoxyphenylmagnesium bromide (0.46 M in THF, 0.92 mL, 0.42 mmol). Flash chromatography (2.0 g silica, 40% EtOAc/hexanes) gave **6l** (48.1 mg, 80%) as a white solid. Mp 136–138 °C; TLC (40% EtOAc/pet ether) R_F = 0.33; $[\alpha]_D^{25}$ = -18.0 (*c* 0.61, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.20–7.10 (m, 2H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.85–6.75 (m, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.26 (bs, 1H), 4.28 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.68 (s, 3H), 3.59 (s, 3H), 3.55 (t, *J* = 7.2 Hz, 1H), 3.21 (dd, *J* = 13.0, 4.3 Hz, 1H), 2.71 (t, *J* = 10.7 Hz, 1H), 2.62 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.55 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.6, 157.3, 155.3, 150.4, 131.4, 130.9, 128.1, 128.0, 124.6, 124.5, 120.4, 120.3, 110.21, 110.18, 81.9, 59.0, 55.0, 54.9, 51.6, 37.1, 34.1, 28.2; IR (neat) ν 2921, 1776, 1492, 1351, 1250, 1153, 1117, 1026, 754 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_5$ 426.2155 $[\text{M}]^{+}$, found 426.2163.

(4*R*,5*R*)-4,5-Di(2-methoxybenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**ent-6l**). This was prepared according to the general procedure using **ent-5** (40.6 mg, 0.14 mmol) and CuBr·SMe₂ (14.2 mg, 0.069 mmol) in THF (4.78 mL) and a solution of 2-methoxyphenylmagnesium bromide (0.46 M in THF, 0.92 mL, 0.42 mmol). Flash chromatography (2.0 g silica, 30% EtOAc/hexanes) gave **ent-6l** (51.3 mg, 84%) as a white solid. Spectral data for **ent-6l** were consistent with those reported above for **6l**. [α]_D²⁵ +18.3 (c 2.08, CH₂Cl₂).

(4*S*,5*S*)-4,5-Di(3,5-dimethoxybenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6m**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (4.4 mL) and a solution of 3,5-dimethoxyphenylmagnesium bromide (0.49 M in THF, 1.0 mL, 0.49 mmol). Flash chromatography (2.0 g silica, 40% EtOAc/hexanes) gave **6m** (40.8 mg, 60%) as an amorphous solid. TLC (50% EtOAc/pet ether) R_F = 0.35; [α]_D²⁵ = -15.0 (c 2.00, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.30 (s, 1H), 6.25 (s, 1H), 6.24 (s, 2H), 6.06 (s, 2H), 5.17 (bs, 1H), 4.08 (d, J = 9.5 Hz, 1H), 3.75 (s, 6H), 3.72 (s, 6H), 3.47 (t, J = 7.2 Hz, 1H), 3.19 (dd, J = 13.2, 3.4 Hz, 1H), 2.62–2.52 (m, 2H), 2.41 (dd, J = 13.3, 6.1 Hz, 1H), 1.58 (s, 9H); ¹³C NMR (125 MHz, CDCl₃, two doubly degenerate ArC's) δ 160.9, 154.7, 150.2, 138.2, 138.1, 107.2, 106.8, 98.8, 82.6, 60.8, 55.2, 55.1, 53.7, 42.6, 39.5, 28.2; IR (neat) ν 1772, 1607, 1595, 1458, 1429, 1340, 1293, 1205, 1148, 1064, 831, 691 cm⁻¹; HRMS (ESI) calcd for C₂₆H₃₄N₂NaO₇ 509.2264 [M + Na]⁺, found 509.2265.

(4*S*,5*S*)-4,5-Di(3,4-methylenedioxybenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6n**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (4.4 mL) and a solution of 3,4-(methylenedioxy)phenylmagnesium bromide (0.42 M in THF, 1.0 mL, 0.42 mmol). Flash chromatography (2.0 g silica, 40% EtOAc/hexanes) gave **6n** (44.5 mg, 70%) as an amorphous solid. TLC (50% EtOAc/pet ether) R_F = 0.36; [α]_D²⁵ = +1.8 (c 0.80, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.66 (d, J = 7.7 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.50–6.45 (m, 2H), 6.38 (d, J = 7.9 Hz, 1H), 6.34 (s, 1H), 5.97–5.89 (m, 4H), 5.78 (bs, 1H), 3.99 (d, J = 9.7 Hz, 1H), 3.40 (t, J = 7.1 Hz, 1H), 3.12 (dd, J = 13.3, 3.3 Hz, 1H), 2.60 (dd, J = 13.5, 6.5 Hz, 1H), 2.52 (dd, J = 13.2, 10.4 Hz, 1H), 2.40 (dd, J = 13.5, 7.5 Hz, 1H), 1.58 (s, 9H); ¹³C NMR (125 MHz, CDCl₃, one doubly degenerate ArC) δ 154.9, 150.2, 147.74, 147.69, 146.4, 129.6, 129.4, 122.3, 122.1, 109.2, 109.0, 108.20, 108.18, 101.01, 100.99, 82.6, 60.6, 53.7, 41.8, 38.8, 28.2; IR (neat) ν 3285, 2331, 1769, 1490, 1341, 1242, 1188, 1037, 928, 854, 813, 773, 735 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₆N₂NaO₇ 477.1638 [M + Na]⁺, found 477.1649.

(4*S*,5*S*)-4,5-Di(2-methylbenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6o**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (4.9 mL) and a solution of *o*-tolylmagnesium chloride (1.0 M in THF, 0.47 mL, 0.47 mmol). Flash chromatography (2.0 g silica, 20% EtOAc/hexanes) gave **6o** (30.7 mg, 55%) as an amorphous solid. TLC (20% EtOAc/pet ether) R_F = 0.10; [α]_D²⁵ = -14.7 (c 1.55, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.16–6.92 (m, 7H), 6.76 (d, J = 7.4 Hz, 1H), 6.28 (bs, 1H), 4.14 (dd, J = 10.8, 4.5 Hz, 1H), 3.46 (t, J = 7.4 Hz, 1H), 3.27 (dd, J = 13.4, 4.5 Hz, 1H), 2.80–2.44 (m, 3H), 2.12 (s, 3H), 1.91 (s, 3H), 1.55 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 150.3, 136.5, 136.1, 134.1, 134.0, 130.52, 130.48, 130.45, 129.6, 126.9, 126.8, 126.0, 125.9, 82.5, 58.3, 51.5, 39.0, 36.6, 28.1, 19.2, 18.9; IR (neat) ν 3298, 2331, 1772, 1700, 1456, 1340, 1243, 1151, 854, 741 cm⁻¹; HRMS (ESI) calcd for C₂₄H₃₀N₂NaO₃ 417.2154 [M + Na]⁺, found 417.2145.

(4*S*,5*S*)-4,5-Di(3-chlorobenzyl)-1-*tert*-butoxycarbonyl-2-imidazolidinone (**6p**). This was prepared according to the general procedure using **5** (40.0 mg, 0.14 mmol) and CuBr·SMe₂ (10.8 mg, 0.053 mmol) in THF (4.6 mL) and a solution of 3-chlorophenylmagnesium chloride (0.64 M in THF, 0.80 mL, 0.51 mmol). Flash chromatography (two iterations were required: 2.0 g silica, 25% EtOAc/hexanes) gave **6p** (22.4 mg, 37%) as a colorless gum. TLC (30% EtOAc/pet ether) R_F = 0.19; [α]_D²⁵ = -8.0 (c 0.38, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.22–7.10 (m, 4H), 7.03 (s, 1H), 6.93 (d, J = 6.9 Hz, 1H), 6.88 (s,

1H), 6.80 (d, J = 7.2 Hz, 1H), 5.69 (bs, 1H), 4.04 (d, J = 8.4 Hz, 1H), 3.42 (t, J = 7.0 Hz, 1H), 3.19 (dd, J = 13.2, 3.6 Hz, 1H), 2.70–2.59 (m, 2H), 2.48 (dd, J = 13.5, 7.0 Hz, 1H), 1.58 (s, 9H); ¹³C NMR (125 MHz, CDCl₃, two doubly degenerate ArC's) δ 154.6, 150.1, 137.8, 137.5, 134.53, 134.51, 129.9, 129.2, 129.0, 127.31, 127.29, 127.1, 82.9, 60.3, 53.5, 41.7, 38.8, 28.2; IR (neat) ν 3302, 2328, 1762, 1574, 1424, 1337, 1198, 1148, 1050, 786, 689 cm⁻¹; HRMS (ESI) calcd for C₂₂H₂₄Cl₂N₂NaO₃ 457.1062 [M + Na]⁺, found 457.1079.

■ ASSOCIATED CONTENT

📄 Supporting Information

NMR spectra and HPLC traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00832.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) (a) DasGupta, S.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Bioorg. Med. Chem.* **2009**, *17*, 3604–3617. (b) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 5457–5460. (c) Park, H.; Min, K.; Kwak, H.-S.; Koo, K. D.; Lim, D.; Seo, S.-W.; Choi, J.-U.; Platt, B.; Choi, D.-Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2900–2904. (d) Li, J. J.; Sutton, J. C.; Nirschl, A.; Zou, Y.; Wang, H.; Sun, C.; Pi, Z.; Johnson, R.; Krystek, S. R., Jr.; Seethala, R.; Golla, R.; Slep, P. G.; Beehler, J. B. C.; Grover, G. J.; Fura, A.; Vyas, V. P.; Li, C. Y.; Gougoutas, J. Z.; Galella, M. A.; Zahler, R.; Ostrowski, J.; Hamann, L. G. *J. Med. Chem.* **2007**, *50*, 3015–3025. (e) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249–4251. (f) De Luca, G. V. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 495–500.
- (2) (a) Doan, N.-D.; Hopewell, R.; Lubell, W. D. *Org. Lett.* **2014**, *16*, 2232–2235. (b) Sun, S.; Zhang, Z.; Kodumuru, V.; Pokrovskaia, N.; Fonarev, J.; Jia, Q.; Leung, P.-Y.; Tran, J.; Ratkay, L. G.; McLaren, D. G.; Radomski, C.; Chowdhury, S.; Fu, J.; Hubbard, B.; Winther, M. D.; Dales, N. A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 520–525.
- (3) (a) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651–655. (b) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223–14230. (c) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488–10489. (d) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916–8918. (e) Zhang, Y. J.; Park, J. H.; Lee, S.-g. *Tetrahedron: Asymmetry* **2004**, *15*, 2209–2212. (f) Lee, S.-g.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 847–849.
- (4) (a) Bixa, T.; Hunter, R.; Andrijevic, A.; Petersen, W.; Su, H.; Dhoro, F. *J. Org. Chem.* **2015**, *80*, 762–769. (b) Duarte, F. J. S.; Bakalova, S. M.; Cabrita, E. J.; Santos, A. G. *J. Org. Chem.* **2011**, *76*, 6997–7004. (c) MacNevin, C. J.; Moore, R. L.; Liotta, D. C. *J. Org. Chem.* **2008**, *73*, 1264–1269. (d) Treweeke, N. R.; Hitchcock, P. B.; Pardoe, D. A.; Caddick, S. *Chem. Commun.* **2005**, 1868–1870. (e) Chun, C. C.; Lee, G.-J.; Kim, J. N.; Kim, T. H. *Tetrahedron: Asymmetry* **2005**, *16*, 2989–2992. (f) Davies, S. G.; Evans, G. B.; Pearce, S. *Tetrahedron* **1994**, *50*, 7521–7534.
- (5) (a) Li, J.; Stewart, I. C.; Grubbs, R. H. *Organometallics* **2010**, *29*, 3765–3768. (b) Fu, R.; Zhao, B.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 7577–7580. (c) Vasanthakumar, G. R.; Bhor, V. M.; Suroliya, A. *Synth. Commun.* **2007**, *37*, 2633–2639. (d) Blaszczyk, R.; Gajda, T. *Tetrahedron Lett.* **2007**, *48*, 5859–5863. (e) Nadir, U. K.; Krishna, R. V.; Singh, A. *Tetrahedron Lett.* **2005**, *46*, 479–482.
- (6) (a) Ishikawa, T. *ARKIVOC* **2006**, vii, 148–168. (b) Isobe, T.; Fukuda, K.; Ishikawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1729–1735.

- (7) Thanigaimalai, P.; Lee, K.-C.; Bang, S.-C.; Lee, J.-H.; Yun, C.-Y.; Roh, E.; Hwang, B.-Y.; Kim, Y.; Jung, S.-H. *Bioorg. Med. Chem.* **2010**, *18*, 1135–1142.
- (8) (a) Badru, R.; Singh, B. *RSC Adv.* **2014**, *4*, 38978–38985. (b) Tamura, M.; Noro, K.; Honda, M.; Nakagawa, Y.; Tomishige, K. *Green Chem.* **2013**, *15*, 1567–1577. (c) Lee, A. V.; Sajitz, M.; Schafer, L. L. *Synthesis* **2009**, 97–104. (d) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1998**, *39*, 9407–9410.
- (9) Selected examples: (a) He, T.; Gao, W.-C.; Wang, W.-K.; Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 1113–1118. (b) Han, S.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 5386–5389. (c) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665–3678. (d) Strambeanu, I. I.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 12032–12037. (e) Shu, W.; Yu, Q.; Jia, G.; Ma, S. *Chem.—Eur. J.* **2011**, *17*, 4720–4723. (f) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365–6368. (g) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076. (h) Katritzky, A. R.; Luo, Z.; Fang, Y.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 2858–2861.
- (10) (a) Fu, S.; Yang, H.; Li, G.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 1018–1021. (b) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9886–9890. (c) Du, H.; Zhao, B.; Yuan, W.; Shi, Y. *Org. Lett.* **2008**, *10*, 4231–4234. (d) Kim, M. S.; Kim, Y.-W.; Hahn, H. S.; Jang, J. W.; Lee, W. K.; Ha, H.-J. *Chem. Commun.* **2005**, 3062–3064. (e) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 1537–1540.
- (11) Wales, S. M.; Willis, A. C.; Keller, P. A. *Chem. Commun.* **2010**, 46, 9226–9228.
- (12) Kanger, T.; Ausmees, K.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2003**, 1055–1057.
- (13) Chemoselective acidolysis of the Boc group in the presence of cyclic ureas is well precedented; for an example, see: Yoo, D.; Kwon, S.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 3762–3766.
- (14) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590–8591. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.
- (15) (a) Hoang, C. T.; Alezra, V.; Guillot, R.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 2521–2524. (b) Zhao, L.; Qiao, L.; Rong, S.-B.; Kozikowski, A. P. *Tetrahedron Lett.* **2000**, *41*, 8711–8715. (c) Seki, M.; Shimizu, T.; Matsumoto, K. *J. Org. Chem.* **2000**, *65*, 1298–1304.
- (16) (a) Abdel-Aziz, A. A.-M.; El Bialy, S. A. A.; Goda, F. E.; Kunieda, T. *Tetrahedron Lett.* **2004**, *45*, 8073–8077. (b) Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353–6355.
- (17) Bailey, S. J.; Wales, S. M.; Willis, A. C.; Keller, P. A. *Org. Lett.* **2014**, *16*, 4344–4347 and references cited therein.
- (18) Using 2.4 equiv of *i*-PrMgCl and 15 mol % of CuBr-SMe₂ (wrt *i*-PrMgCl), 0.36 equiv of the Grignard reagent is presumably “wasted” to unreactive RCu. Therefore, there is a negligible excess of reactive carbanion under these conditions.
- (19) TLC analysis had previously indicated very slow reaction rates at –40 °C. Therefore, the mixing temperature was modified to –20 °C in this case to allow an effect of a slow Grignard addition on the product ratio. This may have led to decomposition of the organocuprate.
- (20) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336. (b) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333–4339.
- (21) See the Supporting Information for full details.
- (22) For a related example of intramolecular *N*-acylation involving an *N*-Boc aziridine, see: Funaki, I.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 9909–9924.
- (23) For a review of the electrophilic reactivity of the Boc group, see: Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724.
- (24) For a recent example of a cascade (mono)aziridine ring-opening/aza anion intramolecular Boc group addition using a fluoride nucleophile to give bicyclic imidazolidinones, see: Nonn, M.; Kiss, L.; Haukka, M.; Fustero, S.; Fülöp, F. *Org. Lett.* **2015**, *17*, 1074–1077.
- (25) Brugier, D.; Outurquin, F.; Paulmier, C. *Tetrahedron* **2000**, *56*, 2985–2993.
- (26) (a) Maciagiewicz, I. M.; Fang, F.; Roberts, D. A.; Zhou, S.; Hines, J. V.; Bergmeier, S. C. *Synthesis* **2012**, *44*, 551–560. (b) Means, J. A.; Katz, S.; Nayek, A.; Anupam, R.; Hines, J. V.; Bergmeier, S. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3600–3604. (c) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852–2859.
- (27) (a) Cheung, L. L. W.; He, Z.; Decker, S. M.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 11798–11802. (b) Agami, C.; Amiot, F.; Couty, F.; Dechoux, L. *Tetrahedron Lett.* **1998**, *39*, 5373–5374. (c) Berges, D. A.; Schmidt, S. J. *J. Org. Chem.* **1984**, *49*, 4555–4557.
- (28) (a) Zhang, J.; Hong, S. H. *Org. Lett.* **2012**, *14*, 4646–4649. (b) Stabile, P.; Lamonica, A.; Ribecai, A.; Castoldi, D.; Guercio, G. *Tetrahedron Lett.* **2010**, *51*, 3232–3235. (c) Li, J.; Sun, Y.; Chen, Z.; Su, W. *Synth. Commun.* **2010**, *40*, 3669–3677. (d) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373. (e) Maki, T.; Ishihara, K.; Yamamoto, H. *Synlett* **2004**, 1355–1358. (f) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014.
- (29) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701–1703.
- (30) Shi, L.; Chu, Y.; Knochel, P.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 2760–2764.