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TECHNICAL NOTE

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A Practical Asymmetric Synthesis of Isopropyl (1*R*,2*S*)-Dehydrocoronamate

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Supporting Information

ABSTRACT: A novel asymmetric synthesis of isopropyl (1*R*,2*S*)-dehydrocoronamate is described from (*S*)-1,2,4-butanetriol as the starting material in 28% overall yield. Highlights of this synthetic route include selective cyclopropanation between chiral cyclic sulfate **5** and diisopropyl malonate (**8c**), formation of vinylcyclopropane **3c** via elimination of halide **4c**, selective monohydrolysis of diisopropyl ester **3c**, and Curtius rearrangement of acid **10** to form isopropyl (1*R*,2*S*)-dehydrocoronamate TsOH salt **13** in >99% ee. With the involvement of only three isolations, this chromatography-free process provides a rapid and practical access to (1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid derivatives.

The chiral vinylcyclopropane amino acid ((1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid, **1**) is an important building block for synthesizing a class of heptatitis C virus NS3 protease inhibitors, most notably represented by BILN 2061 (Figure 1).[1] Its synthesis has drawn much attention, and several synthetic approaches have been reported.[2] Beaulieu and co-workers[2a] described an efficient synthesis of racemic 1-amino-2-vinylcyclopropane-1-carboxylic acid methyl ester via dialkylation of a glycine Schiff base using *trans*-1,4-dibromo-2-butene as the electrophile. By combining an enzymatic resolution protocol, a practical synthesis of methyl (1*R*,2*S*)-dehydrocoronamate was developed which was successfully demonstrated at multikilogram scales. On the other hand, little success has been reported on asymmetric synthesis of chiral amino acid **1**, which is in sharp contrast to many asymmetric synthetic methods of saturated chiral cyclopropane amino acids.[3] One method was reported by Fox and colleagues[4] utilizing a palladium-catalyzed asymmetric allylic alkylation reaction. However, the route was less promising for a large scale synthesis due to the formation of a major side product during the closure of the cyclopropane ring. Salaün and co-workers[5] also reported the syntheses of vinylcyclopropane aminonitriles via a palladium-catalyzed tandem alkylation, and only poor enantioselectivities were observed when chiral ligands were employed. With a chiral phase transfer catalyst, a stereoselective cyclopropanation between (*E*)-*N*-phenylmethyleneglycine ethyl ester and *trans*-1,4-dibromo-2-butene was also reported.[6] However, the isolation of the cyclopropanation product and the upgrade of its chiral purity required a preparative supercritical fluid chromatography. Despite these efforts, an efficient asymmetric synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid derivatives remains a challenge. Herein we wish to report a practical and asymmetric synthesis of an isopropyl (1*R*,2*S*)-dehydrocoronamate TsOH salt (**13**) from a readily available chiral starting material (*S*)-1,2,4-butanetriol (**6**).

Our synthetic strategy toward the chiral vinylcyclopropane amino ester **2** is illustrated in Scheme 1. We believe that **2** could be synthesized by a reported method[3,7] from a chiral vinylcyclopropane

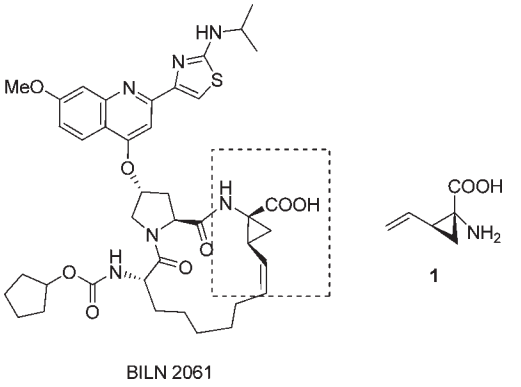

Figure 1. BILN 2061 and (1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid (**1**).

dicarboxylic ester **3** through a regioselective hydrolysis followed by a Curtius rearrangement (Scheme 1). Thus, the key challenge is to develop a practical and economical synthesis of chiral vinylcyclopropane dicarboxylic ester **3**. Although several asymmetric methods[8,9] toward the synthesis of **3** were reported including the use of an asymmetric tandem allylic alkylation[9a] or chiral auxiliaries,[7a] most of those methods showed limitations for scale-up due to severe racemization, a lengthy synthetic route, or employment of expensive reagents. Herein we disclose a novel asymmetric synthetic approach toward **3** from an inexpensive and readily accessible chiral material (*S*)-1,2,4-butanetriol (**6**) by a sequence of cyclic sulfate formation, cyclopropanation, and elimination.

A one-pot synthesis of chiral cyclic sulfate **5** was developed from (*S*)-1,2,4-butanetriol (**6**) as the starting material on modification of

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a reported procedure[10] (Scheme 2). Thus, chiral triol **6** was reacted with $SOCl_2$ in dichloroethane at reflux for 4 h to form quantitatively a chloro-substituted cyclic sulfite **7**, which was then exposed to $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot xH_2O$ to form **5** in 83% isolated yield and >97% ee. The distilled chiral cyclic sulfate **5** is stable and can be stored in a refrigerator for months without noticeable decomposition or racemization.

With chiral cyclic sulfate **5** in hand, we then studied the cyclopropanation between **5** and dimethyl malonate (**8a**). Interestingly, in addition to the desired product **4a**, a cyclopentane side-product **9a**[11] was also formed under the conditions of NaH/DME (Scheme 3). Apparently, there was a competitive intramolecular cyclization through pathway b during the course of the reaction. We envisioned that the solvent and base could have a significant impact on the selectivity of ring closures. Since both dimethyl malonate (**8a**) and the cyclopropanation product **4a** are very susceptible to *trans*-esterification or hydrolysis under various basic conditions, we chose bulkier esters such as di-*tert*-butyl malonate (**8b**) and diisopropyl malonate (**8c**) as the starting material to study the base and solvent effect. As shown in Table 1, the selectivity of the cyclization products was closely related to the solvent and the base employed. Although weak bases such as K_2CO_3 and Cs_2CO_3 did not promote the desired reaction (entries 1−2), stronger bases such as NaH, KO*t*Bu, and LiO*t*Bu led to the formation of cyclization products at rt (entries 3−9). Among the various bases screened, LiO*t*Bu provided the best selectivity of the cyclopropanation product **4b** over the cyclopentane side-product **9b** (entries 5, 7, and 9). A significant solvent effect was observed. Toluene was found to be beneficial for the formation of **4b**. Thus, with toluene as the solvent and LiO*t*Bu as the base, the cyclopropane di-*tert*-butyl product **4b** was obtained in 80% isolated yield (entry 9). Under similar conditions, the cyclopropane diisopropyl ester **4c** was obtained in 75% isolated yield (entry 10).

Next, the key elimination of the chlorocyclopropane diester **4** to form a vinylcyclopropane diester **3** was studied with various bases.[12] Since the selective monohydrolysis of a diisopropyl ester is more

Scheme 1. Synthetic strategy of (1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid ester 2

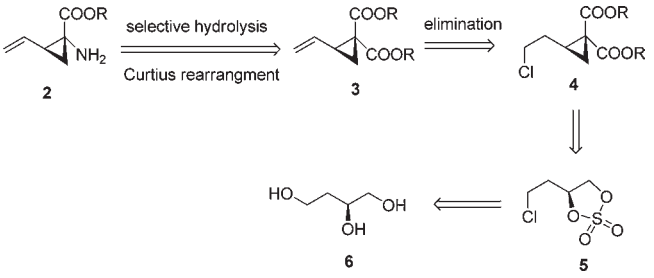
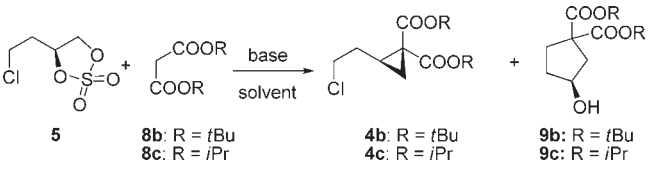


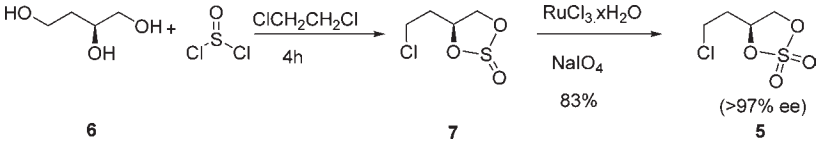
Table 1. Base and solvent effects in cyclopropanation



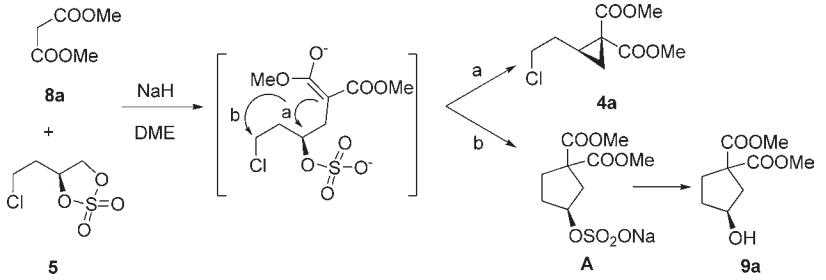
entry[a]	solvent	base	ratio of **4b**:**9b** or **4c**:**9c**	yield of **4b** or **4c** (%)
1[b]	DMF	K_2CO_3	--	0
2[b]	DMF	Cs_2CO_3	--	0
3	DME	NaH	1:3	20
4	DME	KO*t*Bu	1:2	20
5	DME	LiO*t*Bu	1:1	30
6	THF	KO*t*Bu	1:1	36
7	THF	LiO*t*Bu	1:1	50
8	toluene	KO*t*Bu	4:1	50
9	toluene	LiO*t*Bu	10:1	80
10[c]	toluene	LiO*t*Bu	10:1	75

[a] The reactions were carried out at rt in the presence of 2.2 equiv of base with di-*tert*-butyl malonate (**8b**) as the starting material for 12 h unless otherwise specified; ratios of **4b** vs **9b** or **4c** vs **9c** were determined by HPLC on a C-18 reversed-phase column; isolated yields. [b] The reactions were carried out at 100 °C for 12 h. [c] The reaction was carried out with diisopropyl malonate (**8c**) as the starting material.

Scheme 2. Synthesis of chiral cyclic sulfate 5



Scheme 3. Competitive ring closures during cyclopropanation



dx.doi.org/10.1021/op200038y |*Org. Process Res. Dev.* 2011, 15, 1207–1211

Scheme 4. Formation of vinylcyclopropane 3c via elimination

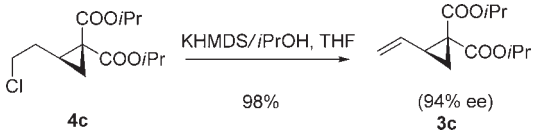
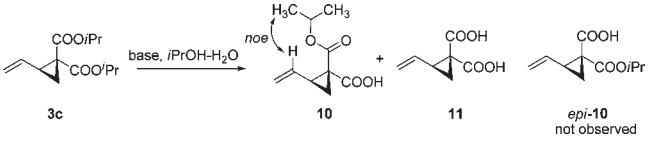


Table 2. Selective hydrolysis of diester 3c with various bases



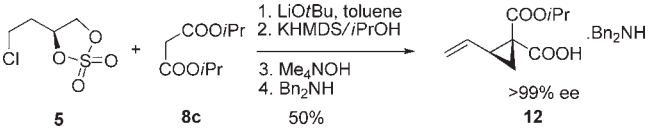
entry	base (equiv)	T (°C)	10:11:3c[a]	10:11[b]
1	LiOH (1.05)	40	62:10:28	10:1
2	LiOH (1.05)	50	55:8:36	6:1
3	NaOH (1.2)	40	77:19:4	17:1
4	KOH (1.2)	40	83:8:9	27:1
5	Me_4NOH (1.2)	40	90:5:5	35:1

[a] The ratios of **10**:**11**:**3c** were determined after 6−12 h by HPLC on a C-18 reversed-phase column. [b] The ratios of **10**:**11** were determined after 1 h.

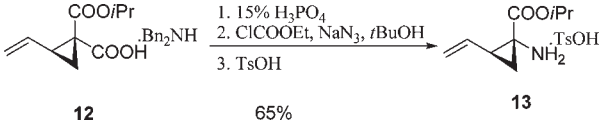
controllable than that of a di-*tert*-butyl ester[13,7b] for the following step, we focused on the elimination of the diisopropyl **4c** to form the vinylcyclopropane diisopropyl ester **3c** (Scheme 4). It was found that strong sterically hindered potassium bases such as KO*t*Bu or KHMDS were necessary for this transformation, while organic bases such as DBU or 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base) were ineffective, providing no trace amount of elimination product. Unfortunately, partial racemization of the vinylcyclopropane product was observed when KHMDS was employed as the base, providing **3c** in ~70% ee. Less racemization (92% ee) was achieved when a weaker base KO*t*Bu was used. In order to avoid the partial *trans*-esterification observed with KO*t*Bu as the base, we sought to employ KO*i*Pr as the base for elimination. Gratifyingly, we found that the *in situ* formed KO*i*Pr from KHMDS/*i*PrOH in THF led to the formation of **3c** in almost quantitative yield with only limited racemization (94% ee). We were optimistic to enhance its optical purity in the following steps by crystallizations.

With vinylcyclopropane diisopropyl ester **3c** in hand, we turned our attention to its selective monohydrolysis with various bases (Table 2). It is important to note that the less sterically hindered ester which is *trans* to the vinyl group in compound **3c** was preferentially hydrolyzed to provide the monoacid **10.**[14] Indeed, no formation of *epi*-**10** was observed during the reaction course. A dramatic base effect on the selectivity of the monohydrolysis product **10** over the double-hydrolysis product **11** was observed, and bulkier bases provided higher selectivities. While only moderate selectivity was observed with LiOH as base (entries 1 and 2), significant improvement was observed when KOH was employed (entry 4). The use of Me_4NOH as the base was very effective, and the desired monoacid **10** was formed in 90% yield after the reaction mixture was stirred at 40 °C for 6 h with H_2O/isopropanol as the solvent (entry 5). In order to isolate the pure monoacid **10** from

Scheme 5. A one-pot synthesis of monoacid salt 12



Scheme 6. A one-pot synthesis of isopropyl (1*R*,2*S*)-dehydrocoronamate TsOH salt (13)



diester **3c** and diacid **11** without chromatographic separation, we sought to isolate a salt of **10** by reacting with an organic base. The dibenzylamine salt **12** was found to be highly crystalline and easy to isolate. More gratifyingly, the optical purity of **12** could be increased from 94% ee to >99% ee by a simple recrystallization from *i*PrOH−water. To our delight, no isolation is necessary at the stage of cyclopropanation, elimination, and selective hydrolysis. We successfully isolated salt **12** in >99% ee from cyclic sulfate **5** in one pot in 50% overall yield (Scheme 5).

The final transformation of monoacid **12** to amino ester **2** via Curtius rearrangement was straightforward. A salt-break of **12** was successfully accomplished with 15% (w/w) H_3PO_4 solution as the reagent. Use of HCl or H_2SO_4 as the acid failed to provide good phase separation. The resulting acid **10** underwent Curtius rearrangement by reacting sequentially with ethyl chloroformate, NaN_3, and *tert*-butanol to form smoothly the Boc-protected amino ester, which was further treated with TsOH in isopropanol to deprotect its Boc group and form the TsOH salt **13**. As a white crystalline solid, compound **13** is easy to handle for its further synthetic applications. A one-pot sequence of salt-break, Curtius rearrangement, Boc deprotection, and salt formation was developed, and the desired product **13** was isolated in 65% overall yield and in >99% ee (Scheme 6). The stereochemistry of **13** was further confirmed by converting to its corresponding methyl ester with treatment of MeONa/MeOH, which was consistent on every aspect with the reported data.[2]

In summary, a novel and efficient synthesis of isopropyl (1*R*,2*S*)-dehydrocoronamate has been developed from (*S*)-1,2,4-butanetriol as the starting materials in a 28% overall yield. As no column chromatographic separation is needed, this process is amenable for scale-up activities. It is noteworthy that this is the first asymmetric synthetic process of chiral vinylcyclopropane amino acid derivatives, which features a sequence of cyclopropanation between chiral cyclic sulfate **5** and diisopropyl malonate (**8c**), olefination via elimination of halide **4c**, selective monohydrolysis of diisopropyl ester **3c**, and final Curtius rearrangement to form amino ester salt **13**. A number of challenging development issues were addressed, including the careful selection of diisopropyl malonate, the base and solvent choice for cyclopropanation, choice of base for elimination, base identification for selective monohydrolysis, and salt formation of the monoacid **15**. With only three isolations involved, the new synthetic method provides a rapid and economical access to isopropyl (1*R*,2*S*)-dehydrocoronamate, which would facilitate its further applications in both synthetic organic chemistry and medicinal chemistry.

EXPERIMENTAL SECTION

(*S*)-4-(2-Chloro-ethyl)-[1,3,2]dioxathiolane 2,2-Dioxide (5). To a 3-L three-necked flask equipped with a condenser and an additional funnel were charged (*S*)-1,2,4-butanetriol (100 g, 0.94 mol) and dichloroethane (600 mL). To the mixture at rt was added thionyl chloride (336.3 g, 2.827 mol, 3 equiv) over 30 min. The resulting mixture was stirred at reflux for 4 h and then concentrated under a reduced pressure. The residue was further treated with MeCN (300 mL), dichloromethane (300 mL), and water (400 mL) to form a biphasic solution. To the mixture at 10 °C was added $RuCl_3 \cdot xH_2O$ (2.4 g) followed by the addition of $NaIO_4$ (282.1 g, 1.32 mol, 1.4 equiv) in portions over 30 min while controlling the reaction temperature below 25 °C. After the addition, the mixture was further stirred at rt for 1 h and then quenched by the addition of MTBE (500 mL) and water (500 mL). The organic phase was separated, filtered though a pad of Celite; washed sequentially with water (500 mL), 10% Na_2SO_3 solution (500 mL), and brine (300 mL); and then concentrated and distilled under vacuum (130−135 °C/6 mmHg) to provide the desired pure product **6** as a colorless oil (145 g, 83%, >97% ee). **5**: $[\alpha]^{20}_D = -60.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.21 (m, 1H), 4.81 (m, 1H), 4.41 (m, 1H), 3.69 (m, 2H), 2.43 (m, 1H), 2.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.9, 72.4, 39.2, 34.9. EI-MS: *m*/*z* 186 $[M + H]^+$; HRMS calcd for $C_4H_8ClO_4S + CH_3OH$ 219.0088, found 219.0111.

(1*S*,2*S*)-2-Vinyl-cyclopropane-1,1-dicarboxylic Acid Isopropyl Ester Dibenzylamine Salt (12). To a solution of (*S*)-4-(2-chloro-ethyl)-[1,3,2]dioxathiolane 2,2-dioxide (**5**, 21.8 g, 117 mmol, 1.1 equiv) and diisopropyl malonate (**4c**, 20.0 g, 106 mmol, 1.0 equiv) in toluene (350 mL) at −10 °C was added lithium *tert*-butoxide (18.7 g, 234 mmol, 2.2 equiv). The mixture was stirred at −10 °C for 20 min, then allowed to warm to rt over 30 min, and further stirred at rt for 12 h. To the mixture was added a 2 N NaOH solution (200 mL), and the resulting mixture was stirred at rt for 10 min. The organic phase was separated, washed sequentially with water (200 mL) and brine (200 mL), and concentrated to give the crude cyclopropane product **4c** as a colorless oil, which was further treated with THF (40 mL) to form a solution. To a solution of KHMDS in THF (0.9 M, 236 mL, 212.5 mmol, 2.0 equiv) at rt was charged isopropanol (12.8 g, 212.5 mmol, 2.0 equiv) over 5 min. The resulting slurry was stirred at rt for 10 min. To the mixture at rt was then charged the aforementioned THF solution of **4c** over 10 min. The resulting solution was then warmed to 40 °C and stirred at this temperature for 4 h. Upon complete elimination monitored by HPLC, the mixture was cooled to 0 °C and quenched by the addition of a 1 N HCl solution (200 mL). To the mixture was added MTBE (300 mL), and the organic phase was separated, washed with water (200 mL) and brine (200 mL), and concentrated to a minimum volume to provide the crude vinylcyclopropane product **3c** as a light yellow oil. To the residue were added isopropanol (120 mL) and water (24 mL) to form a clean solution. Tetramethylammonium hydroxide pentahydrate (20.5 g, 112 mmol, 1.1 equiv) was added in one portion, and the mixture was heated to 40 °C and stirred at this temperature for 6 h. At ∼95% conversion by HPLC, the mixture was quenched by the addition of a 2 N HCl solution (200 mL) and heptane (200 mL), then concentrated under a reduced pressure to remove most of the organic phase, and further treated with heptane (200 mL). After passing through a pad of Celite, the organic phase was separated and concentrated to an ∼200 mL total volume. To the mixture was added dibenzylamine (20.9 g, 106.3 mmol, 1.0 equiv), and the resulting slurry was further stirred at 0 °C for 30 min and then filtered. The white solid was recrystallized from water−isopropanol to provide (1*S*,2*S*)-2-vinyl-cyclopropane-1,1-dicarboxylic acid isopropyl ester dibenzylamine salt (**12**) as a white crystalline solid (21.0 g, 50%, >99% ee). **12**: $[\alpha]^{20}_D = -19.8$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.44 (m, 10H), 5.39 (m, 1H), 5.19 (m, 1H), 4.99 (m, 2H), 4.16 (s, 4H), 2.39 (dd, *J* = 15.6, 8.6 Hz, 1H), 1.37 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 176.1, 171.3, 136.7, 133.6, 131.0, 130.3, 130.2, 69.6, 52.0, 39.7, 31.0, 22.2, 21.0, 19.6; ESI-MS: *m*/*z* 199 $[M - Bn_2NH + H]^+$, 198 $[Bn_2NH + H]^+$; HRMS calcd for $C_{24}H_{30}NO_4$ 396.2169, found 396.2212.

Isopropyl (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylate *p*-Toluenesulfonic Acid Salt (13).[15]. To a suspension of (1*S*,2*S*)-2-vinyl-cyclopropane-1,1-dicarboxylic acid isopropyl ester dibenzylamine salt (**12**, 18 g, 45.5 mmol, 1 equiv) in MTBE (200 mL) was added a 15% H_3PO_4 solution (w/w, 200 mL), and the resulting mixture was stirred at rt for 10 min. The organic phase was separated, washed with 5% NaCl (100 mL), and concentrated to a minimum amount of volume (∼20 mL). To the residue was added acetone (100 mL) and triethylamine (5.1 g, 50.1 mmol, 1.1 equiv), followed by ethyl chloroformate (5.4 g, 50 0.1 mol, 1.1 equiv) at −5 °C over 5 min. The resulting mixture was stirred at −5 to 0 °C for 10 min. Upon the complete formation of the mixed anhydride, sodium azide (5.9 g, 91.0 mmol, 2 equiv) in water (60 mL) was added at −5 to 0 °C over 5 min. The mixture was further stirred at −5 to 0 °C for 10 min. Toluene (200 mL) and water (200 mL) were added. The toluene layer was separated, washed with water (100 mL) and brine (100 mL), and concentrated to an ∼50 mL total volume. To a refluxed mixture of toluene (80 mL) and *tert*-butanol (80 mL) was added the aforementioned toluene solution over 20 min. Gas was generated instantaneously during the addition. The mixture was further stirred at reflux (∼85 °C) for 3 h, then concentrated to a minimum amount of volume, and retreated with 2-propanol (20 mL). $TsOH \cdot H_2O$ (9.52 g, 50.1 mol, 1.1 equiv) was added to the solution, and the mixture was stirred at 50 °C for 12 h before cooled to rt. To the solution was added isopropyl acetate (100 mL), and the mixture was then concentrated to a minimum amount of volume (∼20 mL). The residue was further treated with isopropyl acetate (100 mL), stirred at 0 °C for 10 min, and then filtered. The cake was washed with isopropyl acetate (25 mL × 2) and dried at rt under a reduced pressure to give isopropyl (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylate *p*-toluenesulfonic acid salt (**13**) as a white crystalline solid (10.1 g, 29.6 mmol, 65%). **13**: $[\alpha]^{20}_D = +27.4$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 5.59 (m, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.96 (m, 1H), 5.54 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.35 (s, 3H), 1.91 (dd, *J* = 10.0, 6.4 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 140.5, 131.8, 128.9, 126.0, 119.2, 70.8, 30.4, 21.6, 19.2; ESI-MS: *m*/*z* 170 $[M - TsOH + H]^+$; HRMS calcd for $C_9H_{16}NO_2$ 170.1175, found 170.1195.

ASSOCIATED CONTENT

Supporting Information. Analysis of the enantiomeric purities of **12** and **13**; NMR spectra of compound **5**, **3c**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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