Organic Process Research & Development **2010,** *14,* 692–700

Enantioselective Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Ethyl Ester (Vinyl-ACCA-OEt) by Asymmetric Phase-Transfer Catalyzed Cyclopropanation of (*E*)-*N*-Phenylmethyleneglycine Ethyl Ester

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Abstract:

A concise asymmetric synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester, a key intermediate in the preparation of many hepatitis C virus inhibitors, is described. Stereoselective cyclopropanation of (*E*)-*N*-phenylmethyleneglycine ethyl ester was effected by treatment with *trans*-1,4-dibromo-2-butene in the presence of a catalytic amount of a chiral phase-transfer catalyst. Microscale high-throughput experimentation techniques were successfully used to identify a cinchonidine-derived catalyst that provided (1*R*,2*S*)-1-(*E*)-*N*-phenylmethyleneamino-2-vinylcyclopropanecarboxylic acid ethyl ester in up to 84% ee. This was translated to a lab scale process to attain 78% yield and 77.4% ee. Chiral purity upgrade and isolation of the ester was accomplished via preparatory supercritical fluid chromatography followed by crystallization of the ester as its tosylate salt. The improved synthesis described herein represents a potentially more economical preparation of this valuable intermediate.

Introduction

Interest in the development of novel treatments for the hepatitis C virus (HCV) has led to the identification of multiple antiviral targets for HCV.[1] In particular, several potent HCV NS3/4a protease inhibitors have recently been reported.[2] The macrocyclic BILN 2061 (**1**, Figure 1) was the first small-molecule peptidomimetic demonstrated to show antiviral activity in patients infected with HCV genotype 1.[3] One common structural motif present in these inhibitors is derived from (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA) (**2**). This key synthetic intermediate is typically appended at the P1 position of HCV inhibitors such as **3**.[2b] The terminal vinyl-ACCA group can also be fused via ring-closing metathesis[4] (RCM) to form a P1−P3 macrocyclic constraint as found in **1**. We required a cost-effective synthesis of ACCA derivative **4** (vinyl-ACCA-OEt) to minimize the overall cost related to the synthesis of a NS3/4a protease inhibitor in development. Several preparations of various ACCA derivatives have been reported,[5] however, few synthetic routes have been developed for large-scale implementation.

The synthesis of vinyl-ACCA-OMe (**9**) via enzymatic resolution was recently reported by Boehringer-Ingelheim[5a] to be amenable to multikilogram scale (Scheme 1). While this process was fairly cost-effective, a further reduction in manufacturing cost was desired for our purposes. Two other potential alternative preparations of vinyl-ACCA derivatives were recently described. Fox and co-workers[5b] reported on the catalytic asymmetric synthesis of **4** which utilized asymmetric Pd-catalyzed allylic alkylation of 3,4-epoxy-1-butene with glycine equivalents derived from the benzophenone imine of either glycine ethyl ester or 2-aminoacetonitrile. The desired (1*R*,2*S*)-

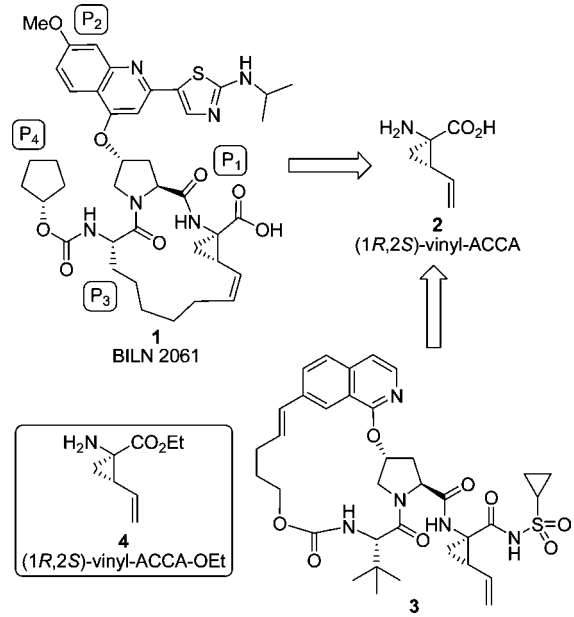
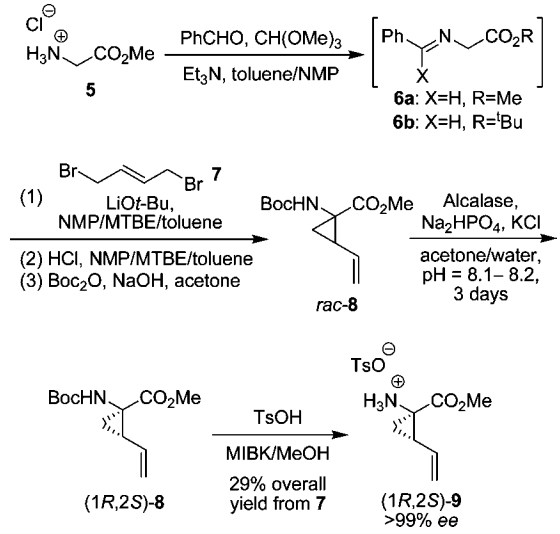


Figure 1. **Structures of HCV NS3/4A protease inhibitors.**

Scheme 1. **Boehringer-Ingelheim enzymatic resolution approach**



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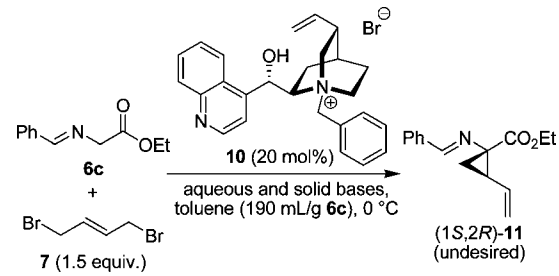
(1) Gordon, C. P.; Keller, P. A. *J. Med. Chem.* **2005**, *48*, 1.

Published on Web 04/07/2010
10.1021/op100070d

1-amino-2-vinylcyclopropane-1-carboxylic acid ethyl ester (**4**) was obtained in 8% overall yield and 88% ee. The Charette group[5c] also demonstrated that Cu(I)-catalyzed asymmetric cyclopropanation of methyl nitroacetate-derived phenyliodonium ylides with 1,3-butadiene provided the corresponding 1-nitro-2-vinyl-cyclopropyl carboxylate in good yield (84%) and enantioselectivity (90% ee), albeit with moderate diastereoselectivity (82:18 dr). While both of these routes provided high selectivity for each of the key enantio-differentiating steps, the cost and commercial availability of the raw materials associated with each of these catalytic steps eliminated them from consideration. Re-evaluation of the other reported syntheses of ACCA derivatives[5] provided few potential alternatives for us to consider. A more detailed analysis of potential cost improvements to the existing enzymatic resolution approach seemed warranted based on the limited number of alternatives available.

The use of inexpensive glycine equivalent **6a** in the resolution approach (Scheme 1), coupled with use of an inexpensive enzyme for the resolution of *racemic*-**8**, set a cost objective that was difficult to improve upon. Any alternative process would almost certainly need to include a stereoselective reaction. One attractive possibility would involve an asymmetric variant of the dialkylation reaction between a glycine equivalent and *trans*-1,4-dibromo-2-butene (**7**). Indeed, such an approach employing asymmetric phase-transfer catalysis (PTC) was previously investigated by the Boehringer-Ingelheim team; however, their initial attempts met with poor results.[6] At first glance, this type of approach appeared limited because a more costly imine-protected *tert*-butyl glycinate derivative (e.g., **6b**) would likely be required in order to achieve the most useful enantioselectivities based on O'Donnell's pioneering investigations with *cinchona* alkaloid-based catalysts[7a] and Maruoka's investigations with *N*-spiro C_2-symmetric chiral quaternary ammonium bromide catalysts.[7b] However, recent success in the asymmetric phase-transfer catalyzed mono- and dialkylation of the cheaper methyl and ethyl glycinate derivatives offered a potential area for further investigation.[8]

Scheme 2. **Phase-transfer catalysis screening conditions using catalyst 10**



We now report the development of a concise asymmetric synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester (**4**) featuring a diastereo- and enantioselective dialkylation reaction under PTC conditions as the key step.

Results and Discussion

Initial evaluation of the phase-transfer catalyzed reaction between **6c** and **7** (Scheme 2) in the presence of 20 mol % *N*-benzylcinchoninium bromide (**10**) under standard PTC conditions (toluene/50% aqueous KOH, 0 °C) showed rapid conversion (<1 h) of **6c**. Unfortunately, multiple species unrelated to the cyclopropanation adduct were formed. Exposing authentic racemic cyclopropanation product (*rac*-**11**) to the same conditions also resulted in rapid decomposition. It was assumed that ester hydrolysis was rapidly occurring under these conditions so we evaluated a variety of inexpensive aqueous and solid inorganic bases (NaOH, KOH, K_2CO_3, and K_3PO_4) under phase-transfer conditions to try to identify clean dialkylation conditions. In general, carbonate and phosphate bases provided little conversion of **6c** to the cyclopropanation product (1*S*,2*R*)-**11** even at 20 °C. Powdered KOH, however, provided 60% conversion of **6c** to (1*S*,2*R*)-**11** while powdered NaOH cleanly provided complete conversion of **6c** at −5 °C (16 h), though the enantioselectivity was only 30% ee. The cinchonine-derived catalysts, in general, provided the undesired (1*S*,2*R*)-*trans*-enantiomer **11**.

While the Maruoka-type phase-transfer catalysts were also considered for asymmetric cyclopropanation, our limited investigations with them proved inferior to the *cinchona* alkaloid-

(2) (a) McCauley, J. A.; Rudd, M. T.; Nguyen, K. T.; McIntyre, C. J.; Romano, J. J.; Bush, K. J.; Varga, S. L.; Ross, C. W.; Carroll, S. S.; DiMuzio, J.; Stahlhut, M. W.; Olsen, D. B.; Lyle, T. A.; Vacca, J. P.; Liverton, N. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9104. (b) Liverton, N. J.; Holloway, K. M.; McCauley, J. A.; Rudd, M. T.; Butcher, J. W.; Carroll, S. S.; DiMuzio, J.; Fandozzi, C.; Gilbert, K. F.; Mao, S.-S.; McIntyre, C. J.; Nguyen, K. T.; Romano, J. J.; Stahlhut, M.; Wan, B.-L.; Olsen, D. B.; Vacca, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4607. (c) Vendeville, S.; Nilsson, M.; Kock, H.; Lin, T.; Antonov, D.; Classon, B.; Ayesa, S.; Ivanov, V.; Johansson, P.; Kahnberg, P.; Eneroth, A.; Wikstrom, K.; Vrang, L.; Edlund, M.; Lindström, S.; Vreken, W.; McGowan, D.; Tahri, A.; Hua, L.; Lenz, O.; Delouvroy, F.; Dooren, M.; Kindermans, N.; Surleraux, D.; Wigerinck, P.; Rosenquist, A.; Samuelsson, B.; Simmen, K.; Raboisson, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1689. (d) Lamarre, D.; Anderson, P. C.; Bailey, M. D.; Beaulieu, P. L.; Bolger, G.; Bonneau, P.; Bös, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St-George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature* **2003**, *426*, 186. (e) McCauley, J. A.; Rudd, M. T.; McIntyre, C. J.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Gilbert, K. F.; Bush, K. J.; Holloway, M. K.; Wan, B.-L.; Carroll, S. S.; DiMuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S.-S.; Stahlhut, M.; Fandozzi, C.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *J. Med. Chem.* **2010**, *53*, 2443.

(3) Hinrichsen, H.; Benhamou, Y.; Wedemeyer, H.; Reiser, M.; Sentjens, R. E.; Calleja, J. L.; Forns, X.; Erhardt, A.; Cröenlein, J.; Chaves, R.; Yong, C.-L.; Nehmiz, G.; Steinmann, G. G. *Gastroenterology* **2004**, *127*, 1347.

(4) (a) Farina, V.; Zeng, X.; Wei, X.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Senanayake, C. H. *Catal. Today* **2009**, *140*, 74. (b) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303.

(5) (a) Beaulieu, P. L.; Gillard, J.; Bailey, M. D.; Boucher, C.; Duceppe, J. S.; Simoneau, B.; Wang, X.-J.; Zhang, L.; Grozinger, K.; Houpis, I.; Farina, V.; Heimroth, H.; Krueger, T.; Schnaubelt, J. *J. Org. Chem.* **2005**, *70*, 5869. (b) Fox, M. E.; Lennon, I. C.; Farina, V. *Tetrahedron Lett.* **2007**, *48*, 945. (c) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (d) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (e) Jiménez, J. M.; Rifé, J.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 537. (f) Cativiela, C.; Díaz-de-Villegas, M. D.; Jiménez, A. I. *Tetrahedron: Asymmetry* **1995**, *6*, 177. (g) Fliche, C.; Braun, J.; Le Goffic, F. *Synth. Commun.* **1994**, *24*, 2873.

(6) See ref 5a. No experimental details or results were provided.

(7) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

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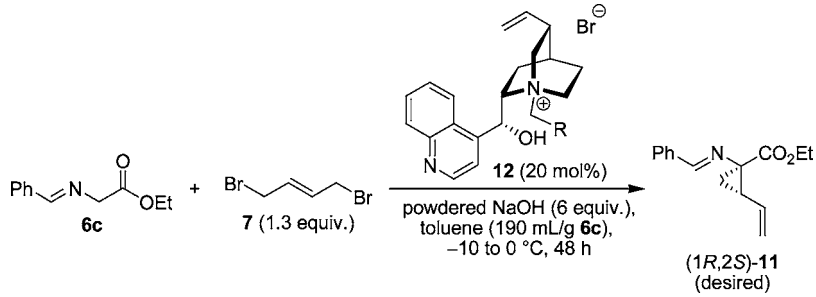
Table 1. **Screening results summary for asymmetric phase-transfer catalyzed dialkylation of 6c**



Entry	Catalyst Structure	% ee (% conversion)	Entry	Catalyst Structure	% ee (% conversion)	Entry	Catalyst Structure	% ee (% conversion)
1	R = **12a**	2 (66)	6	**12f**	79 (77)	11	**12k**	8 (58)
2	**12b**	-5 (80)	7	**12g**	84 (76)			
3	**12c**	36 (79)	8	**12h**	13 (82)	12	**12l**	82 (80)
4	**12d**	24 (81)	9	**12i**	47 (86)			
5	**12e**	72 (87)	10	**12j**	71 (87)	13	**13**	11 (20)

based catalysts.[9] We subsequently demonstrated that the use of the pseudo-enantiomeric cinchonidine-derived catalysts (e.g., **12**, Table 1) led to the formation of the desired (1*R*,2*S*)-*trans*-product **11**, some in useful enantioselectivities. In order to thoroughly investigate the effect of the *cinchona* alkaloid-derived catalyst structure, over 100 cinchonidine-derived catalysts were prepared from a diverse set of commercially available benzyl bromide derivatives. This collection of catalysts was evaluated for asymmetric cyclopropanation[10] and also served as a valuable resource for screening other PTC reactions. These catalysts were efficiently screened against various glycine equivalents using microscale high-throughput experimentation techniques previously described by Merck.[11] All phase-transfer screening experiments were conducted at total reaction volumes of 80−100 μL using only 0.5 μmol phase-transfer catalyst.[12]

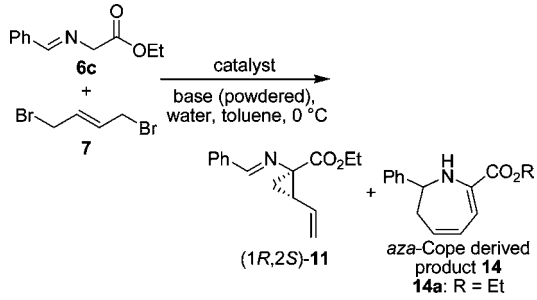
Screening of the reaction between glycine equivalent **6c** and **7** using powdered NaOH in toluene[13] at 0 to −10 °C showed that the enantioselectivity was strongly influenced by both the steric and electronic nature of the substituents present at the *ortho*- and *meta*-positions of catalyst **12**. While *N*-benzylcinchonidinium bromide (**12a**) provided almost no selectivity (entry 1), the incorporation of a trifluoromethyl group at the *meta*-position of the catalyst provided (1*R*,2*S*)-**11** in 36% ee (compare entries 2−4). The enantioselectivity was doubled to >70% ee if another electron-withdrawing group was also incorporated at the *ortho*-position such as for catalysts **12e**−**g**. The bis(trifluoromethyl) catalyst **12g** provided (1*R*,2*S*)- **11** in 84% ee at 76% conversion of **6c** (entry 7). The importance of the 2,5-substitution pattern for high selectivity was reflected in the substantial decrease in enantioselectivity when the positioning of the trifluoromethyl groups was changed (entries 8 and 9). This dramatic change suggested there was a significant steric element involved in how the catalyst and substrate enolate interacted during the enantiodifferentiating step of the final alkylation.

All possible fluorine-substituted variations of *N*-(fluoro-substituted) benzylcinchonidinium bromide phase-transfer catalysts represented by **12** (18 in all) were also evaluated under the same conditions described in Table 1.[14] The *N*-(2′,3′,4′,5′-tetrafluoro)benzylcinchonidinium bromide catalyst (**12j**) provided the highest selectivity (71% ee) amongst this series (Table 1, entry 10). As another indication of the sensitivity of the enantioselectivity of this reaction to catalyst structure, the pentafluoro analogue **12k**, however, provided only 8% ee (entry 11). Capping the hydroxyl group of the catalyst resulted in a

(9) For a review see: Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. Maruoka's catalyst, (11b*S*)-(+)-4,4-dibutyl-4,5-dihydro-2,6-bis(3,4,5-trifluorophenyl)-3*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepinium bromide, provided (1*R*,2*S*)-**11**, albeit in poor selectivity (17% ee) at 9% conversion of **6c** using the conditions described in Table 1.

(10) Only those phase-transfer catalysts most relevant to the discussion of the reported results were included here in the interest of brevity.

Table 2. **Optimization experiments for asymmetric cyclopropanation of 6c with 7[a]**



entry	catalyst (mol %)	base	water (mol %)	% ee (1*R*,2*S*)−**11** (% conversion of **6c**)[b]
1[c]	**12f** (20)	NaOH	−	79 (77)
2	**12f** (5)	NaOH	−	53 (13)
3	**12f** (5)	NaOH	400	72 (99)
4[c]	**12l** (20)	NaOH	−	82 (80)
5	**12l** (5)	NaOH	−	63 (35)
6	**12l** (5)	NaOH	400	60 (98)
7[c]	**12g** (20)	NaOH	−	84 (76)
8	**12g** (5)	NaOH	−	76 (43)
9	**12g** (5)	NaOH	400	79 (99)
10	**12g** (5)	85% KOH	−	79 (55)
11	**12g** (5)	$CsOH\cdot H_2O$	−	61 (96)
12	**12g** (5)	$RbOH\cdot H_2O$	−	52 (98)
13	**12g** (3)	NaOH	500	79 (99)
14	**12g** (1)	NaOH	500	80 (98)
15[d]	**12g** (3)	NaOH[e]	250	77.4 (99)[f,g]

[a] Reactions were run on 100 mg **6c** with 1.3 equiv of **7**, 25 mL toluene/g **6c**, 600 mol % base, 40−48 h at 0 °C unless otherwise stated. [b] %ee and conversion of **6c** were monitored by SFC at 254 nm. [c] Reaction was run at 190 mL toluene/g **6c** using Table 1 conditions. [d] Reaction conducted on 11-g scale of **6c**. [e] 3.0 equiv of pin-milled NaOH used. [f] The yield of **11** was 78% by ^{1}H NMR analysis. [g] The ratio of *trans*-product **11** to *aza*-Cope product **14a** was 15:1 by ^{1}H NMR analysis of the crude reaction mixture.

dramatic decrease in selectivity (11% ee) and conversion (20%) as observed for catalyst **13** (compare entries 12 and 13). This result suggests that the free hydroxyl group of the catalyst plays a critical role in facial recognition of the substrate enolate.

Identification of the top performing catalysts **12f**, **12g**, and **12l** from screening-scale experiments provided a good starting point for development of a scalable, asymmetric, cyclopropanation process. Phase-transfer reactions performed with these catalysts on a larger scale (Table 2) under more concentrated conditions (25 mL of toluene/g **6c**) and at a more reasonable catalyst loading (5 mol % **12**) resulted in a drop in both enantioselectivity for (1*R*,2*S*)-**11** and conversion of **6c** (compare entries 1, 4, and 7 with entries 2, 5, and 8, respectively). Addition of 400 mol % water accelerated the rate of the reactions;[15] however, enantioselectivities were still noticeably lower than seen in screening experiments (entries 3, 6, and 9). Catalyst **12g**, however, still provided the desired trans-product (1*R*,2*S*)-**11** in good selectivity (79% ee). Replacement of NaOH in the phase-transfer reaction with bases such as KOH, $CsOH\cdot H_2O$, or $RbOH\cdot H_2O$ failed to increase the observed enantioselectivity for the dialkylation (entries 10−12).[16]

Further optimization of the phase-transfer conditions demonstrated that the loading of catalyst **12g** could be lowered to 1 mol % if a slightly increased amount of water was added (entry 14).[17] The use of increased amounts of water at lower catalyst loadings led to more hydrolysis-related byproduct in subsequent lab-scale experiments (data not shown). Ultimately, it was found that the correct balance of catalyst loading and water provided a good reaction rate and yield for the dialkylation. The final optimized conditions provided (1*R*,2*S*)-**11** in up to 78% assay yield (77.4% ee) if the amount of NaOH charged was decreased to 3.0 equiv and the amount of water was decreased to 250 mol % (entry 15). Use of pin-milled NaOH with a mean particle-size of ∼30 μm resulted in 99% conversion of **6c** within 24 h at 0 °C. Much longer reaction times (>45 h) and lower yields (<70%) occurred when commercial powdered NaOH was utilized instead.[18] The lower yield was presumably due to the competing hydrolysis pathway. The *aza*-Cope derived byproduct **14a**, arising from the undesired *cis*-cyclopropanation product,[19] was also observed in all phase-transfer catalyzed reactions. A level of ∼6% of **14a** occurred under the final optimized conditions described above.[20] None of the *cis*-cyclopropanation product was ever observed by ^{1}H NMR, so diastereoselectivity for the phase-transfer catalyzed process was estimated to be 94:6 dr if **14a** may be assumed to be an indicator for the *cis*-cyclopropanation product.[21]

A series of other glycine equivalents were also evaluated[22] under the final optimized asymmetric phase-transfer conditions (Table 3) to determine if modification of either the nitrogen protecting group or the ester group could improve the observed

(11) For examples of applying this technique to reaction screening and parallel synthesis, see: (a) Pei, T.; Tellers, D. M.; Streckfuss, E. C.; Chen, C.; Davies, I. W. *Tetrahedron* **2009**, *65*, 3285. (b) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (c) Tellers, D. M.; McWilliams, J. C.; Humphrey, G.; Journet, M.; DiMichele, L.; Hinksmon, J.; McKeown, A. E.; Rosner, T.; Sun, Y.; Tillyer, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 17063. (d) Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 550. (e) Shultz, C. S.; Dreher, S. D.; Ikemoto, N.; Williams, J. M.; Grabowski, E. J. J.; Krska, S. W.; Sun, Y.; Dormer, P. G.; DiMichele, L. *Org. Lett.* **2005**, *7*, 3405. (f) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, *6*, 3147.

(12) See the Experimental Section for details.

(13) Other solvents (e.g. *o*-xylene, *m*-xylene, *p*-xylene, MTBE, CH_2Cl_2) were also evaluated, but none provided significantly superior performance to that of toluene.

(14) For a complete table of experimental results for the *N*-(fluoro-substituted)benzylcinchonidinium catalysts see Table 1 in the Supporting Information. For a detailed study on the electronic effects of *N*-(fluoro-substituted)benzylcinchonidinium catalysts see: Jew, S.; Yoo, M.-S.; Jeong, B.-S.; Park, Y.; Park, P. *Org. Lett.* **2002**, *4*, 4245.

(15) For a review on the role of water in phase-transfer catalyzed processes see: Albanese, D.; Landini, D.; Maia, A.; Penso, M. *Ind. Eng. Chem. Res.* **2001**, *40*, 2396.

(16) Use of other bases (LiOH, $Ca(OH)_2$, and $Mg(OH)_2$ as nanoparticles) resulted in no conversion of **6c**.

(17) A portion of catalyst **12g** (∼40%) could be recovered unchanged from the PTC reaction and recycled with no observed drop in selectivity. The catalyst could be recovered by filtration of the PTC reaction and washing the recovered solids with MTBE.

(18) The powdered NaOH purchased from Sigma-Aldrich had a mean particle-size of ∼70 μm.

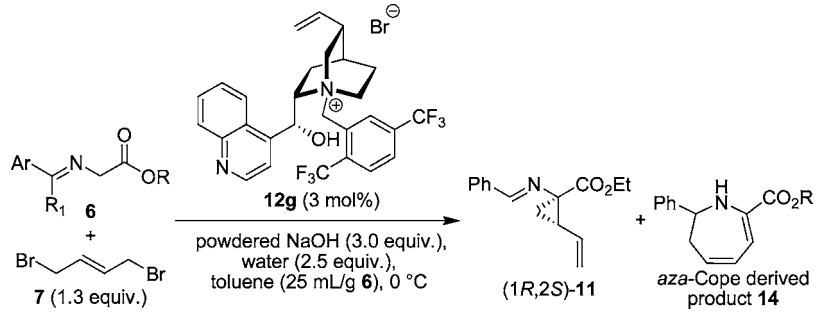
(19) The *cis*-cyclopropanation product is presumed to spontaneously undergo *aza*-Cope rearrangement and then a [1,3]-hydride shift to provide **14**. See ref 5a for a discussion regarding the formation of **14**.

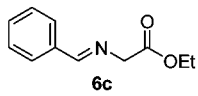
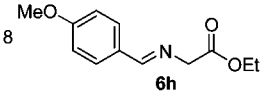
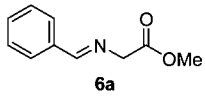
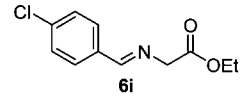
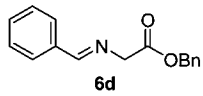
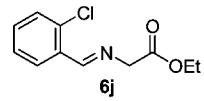
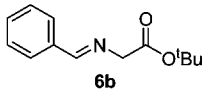
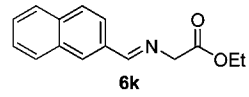
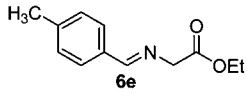
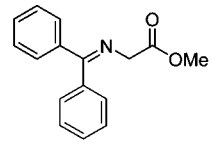
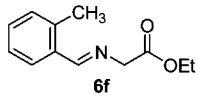
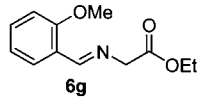
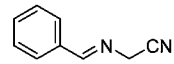
(20) The *aza*-Cope by-product **14** and the intermediate mono-alkylated product of **6c** and **7** were not resolved by our chiral SFC methods. These were readily evaluated by ^{1}H NMR analysis of crude reaction mixtures.

(21) Another major by-product observed to form but not fully characterized was a dimeric species containing two glycine units and one butene unit. This species was not resolved from **14a** under the HPLC conditions utilized for monitoring the lab-scale reaction. The combined amount of **14a** and this species was 14 area % under the HPLC conditions described in the Experimental Section.

(22) For a review of phase-transfer catalysis with achiral Schiff base esters see: O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.

Table 3. **Results for asymmetric phase-transfer catalyzed alkylation of 6a−6l and 15**



Entry	Glycine Equivalent	Results	Entry	Glycine Equivalent	Results
1	 **6c**	77% ee, >99% conv., 20 h 6% **14a**, 78% yield (1*R*,2*S*)-**11**	8	 **6h**	78% ee (61% conv., 47 h) reaction not clean
2	 **6a**	78% ee, >98% conv., 20 h 5% **14**	9	 **6i**	75% ee using Table 3 conditions, 78% ee (30% conv.) using Table 1 conditions
3	 **6d**	ester hydrolysis observed	10	 **6j**	76% ee (22% conv.) using Table 1 conditions
4	 **6b**	58% ee	11	 **6k**	73% ee (60% conv.) using Table 1 conditions
5	 **6e**	78% ee, >98% conv., 20 h 5% **14**	12	 **6l**	only mono-alkylation observed
6	 **6f**	78% ee, >98% conv., 20 h 11% **14**			
7	 **6g**	78% ee, 80% conv., 47 h	13	 **15**	35% ee, >98% conv., 20 h using Table 1 conditions

dialkylation enantioselectivity. The methyl glycinate **6a** provided similar selectivity for the desired *trans*-product (entry 2) while the benzyl glycinate **6d** was observed to readily undergo ester hydrolysis (entry 3). The *tert*-butyl glycinate **6b**, surprisingly, gave substantially lower selectivity (58% ee, entry 4). Evaluation of several aldimine-protected ethyl glycinate derivatives also failed to provide results that improved upon the best enantioselectivity obtained with **6c** (Table 3, entry 1).[23] Aldimines **6e**−**6h** all provided **11** in 78% ee under the optimized conditions. Evaluation of aldimines **6i**−**6k** under the original asymmetric phase-transfer screening conditions (reported in Table 1) with our chiral phase-transfer catalyst library failed to provide any catalyst superior to **12g**.[24] Only monoalkylation of benzophenone imine derivative **6l** occurred even after warming to 20 °C. Asymmetric cyclopropanation of the aldimine-protected α-aminoacetonitrile **15** provided the cyclopropanation product with 35% ee.[25] Overall, glycine equivalent **6c** provided the best balance of both raw material cost and enantioselectivity for the asymmetric cyclopropanation. Both chiral purity upgrade and isolation of (1*R*,2*S*)-vinyl-ACCA-OEt (**4**) were all that remained for demonstration of the new process.

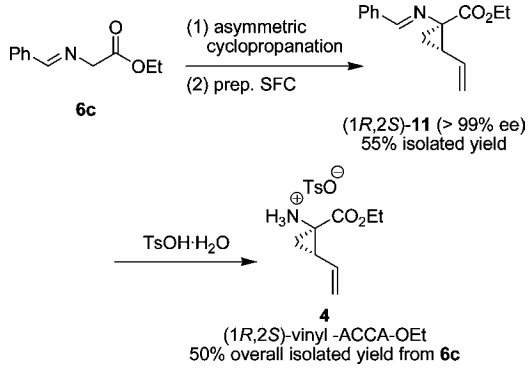
Chiral purity upgrade and isolation of the cyclopropanation product (1*R*,2*S*)-**11** from the phase-transfer reaction was readily accomplished by preparatory supercritical fluid chromatography (SFC) on Chiralcel OJ-H chiral phase (Scheme 3). Chiral SFC separation provided (1*R*,2*S*)-**11** in 55% yield from **6c** with a chiral purity of >99% ee. Deprotection of (1*R*,2*S*)-**11** was accomplished by treatment of the purified material with $TsOH \cdot H_2O$ in 2-propanol. The tosylate salt **4** was isolated by crystallization from the reaction mixture in 91% yield from (1*R*,2*S*)-**11** with a chiral purity of >99% ee and an overall isolated yield of 50% from **6c**.

(23) Glycinate derivatives **6a**, **6b**, and **6d**−**6l** were prepared only for screening purposes and characterized by ^{1}H NMR.

(24) The *trans*-cyclopropanation products **11** and *aza*-Cope derived by-products **14** prepared from glycinate derivatives **6a**−**6l** were identified only by ^{1}H NMR characterization of the crude reaction mixtures. These intermediates were not isolated due to poor stability during purification. Enantioselectivities for **11** were determined by SFC analysis of the crude reaction mixture.

(25) Absolute configuration of the product was not determined.

Scheme 3. **Process for the preparation of (1*R*,2*S*)-vinyl-ACCA-OEt (4)**



Conclusion

A concise asymmetric cyclopropanation of (*E*)-*N*-phenylmethyleneglycine ethyl ester (**6c**) with *trans*-1,4-dibromo-2-butene (**7**) to provide (1*R*,2*S*)-1-(*E*)-*N*-phenylmethyleneamino-2-vinylcyclopropanecarboxylic acid ethyl ester (**11**) under solid−liquid phase-transfer conditions has been developed. Application of high-throughput experimentation techniques was found to be a very useful tool for the rapid screening of a large number of phase-transfer catalysts. A series of cinchonidinium-derived phase-transfer catalysts provided the desired cyclopropanation product (1*R*,2*S*)-**11** in up to 84% ee when using powdered NaOH as a base in toluene at 0 °C. Critical to the successful completion of the reaction under more concentrated conditions was the inclusion of water to accelerate the reaction rate. Various glycine equivalents were evaluated, of which **6c** provided the best balance of both raw material cost and enantioselectivity for the key asymmetric cyclopropanation step. Preparatory SFC chromatography provided a suitable means of upgrading the chiral purity of (1*R*,2*S*)-**11** to >99%. The (1*R*,2*S*)-vinyl-ACCA-OEt (**4**) was isolated as the tosylate salt by acid treatment of (1*R*,2*S*)-**11** to cleave the aldimine. With further optimization of the process described herein, we would expect this asymmetric phase-transfer catalyzed approach to provide a cost-efficient synthesis of **4** superior to those previously reported. We anticipate that classical resolution or an efficient chromatographic separation for the chiral purity upgrade of **4** would provide a viable manufacturing route to this high-value pharmaceutical intermediate. Work on further improving this process is currently ongoing.

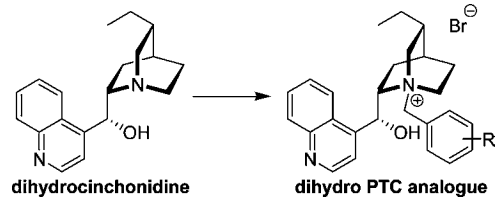
Experimental Section

Material and Methods. Pin-milling of NaOH was carried out using a Hosokawa Mikro LPM. LiOH, $CsOH \cdot H_2O$, and $RbOH \cdot H_2O$ were purchased from Aldrich and ground in a mortar under a nitrogen atmosphere inside a glovebox prior to use. Phase-transfer catalysts **12a**, **12l**, and **13** are commercially available. All other cinchonidine-derived phase-transfer catalysts were prepared using previously reported procedures. All cinchonidine-derived catalysts discussed here have been previously prepared except for catalysts **12b**, **12e**−**12h**, and **12p**. All *N*-arylmethyleneglycine ester derivatives used for screening purposes were prepared using a previously reported procedure.[5a] All high-throughput experimentation and optimization experiments were carried out under a nitrogen atmosphere inside a glovebox unless otherwise noted. The stirring mechanism used for all microscale experimentation was a heated/cooled tumble stirring[26] module obtained from Symyx Technologies. Analytical and Preparative SFC was conducted on a Berger Instruments, Inc. Analytical, and Multigram II instrument, respectively. Melting points were obtained on a Büchi B-545 Melting Point instrument and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and data are reported as $[\alpha]^{20}_D$ (concentration in g/100 mL, solvent). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and DPX-500 NMR spectrometers. Chemical shifts are reported in ppm relative to the residual deuterated solvent. Reactions were monitored by TLC or reverse-phase HPLC on a Hewlett-Packard 1100 series instrument. High-resolution mass spectra were recorded on a Micromass QTOF Ultima API US mass spectrometer by electrospray ionization.

General Procedure for the Preparation of Phase-Transfer Catalysts. A 100 mL three-necked round-bottomed flask equipped with a magnetic stir bar, condenser, thermocouple, and nitrogen inlet was charged with cinchonidine (1 equiv), benzyl bromide (1.2 equiv), and toluene or 2-propanol (17 mL/g of cinchonidine) at RT. The stirred slurry was heated to 105 °C (toluene) or 85 °C (2-propanol) and maintained at that temperature until complete consumption of the cinchonidine starting material (generally requires <3 h, monitored by HPLC). The slurry was then cooled to RT and filtered, washing with fresh solvent (3×). The resulting crude product cake was dried at 35 °C under vacuum with a nitrogen sweep for 24 h. The catalyst product was ground in a mortar and pestle, and then used without further purification in the PTC step.

HPLC conditions: Zorbax Eclipse Plus C18 column, 4.6 mm × 50 mm, 1.8 μm pore size; column temperature 25 °C; flow rate 1.5 mL/min; linear gradient 10:90 MeCN/0.1% aq H_3PO_4 to 95:5 in 5 min, then hold at 95:5 for 1 min, then to 10:90 in 0.1 min, then hold at 10:90 for 1.9 min; UV detection at 210 nm.

Commercial sources of cinchonidine typically contain a small amount of the dihydrocinchonidine analogue, which is not rejected during the catalyst preparation step. The levels of the corresponding dihydro-PTC analogue present in the catalyst batches reported here averaged 6−8%.



***N*-(2-Trifluoromethyl)benzylcinchonidinium Bromide (12b).** Prepared according to the general procedure from cinchonidine (2.87 g, 9.75 mmol) and (2-trifluoromethyl)benzyl bromide (2.8 g, 11.71 mmol) in toluene. Isolated the title compound (4.57 g, 88%) as an off-white powder and as a toluene solvate. Mp 158−159 °C dec; HPLC retention time 3.69 min; $[\alpha]^{20}_D$ −151.0° (*c* 1.12, MeOH); ^1H NMR (400 MHz,

(26) Unlike the typical rotary magnetic stirrer, the tumble stirrer causes a magnetic stir bar to tumble vertically end-over-end inside the microvial instead of spinning the stir bar about the horizontal plane.

dmso-d_6) δ 8.99 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.10 (dd, J = 8.5, 1.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 7.5, 7.5 Hz, 1H), 7.86−7.82 (m, 3H), 7.73 (dd, J = 7.5, 1.5 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 6.57 (s, 1H), 5.67 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.52 (d, J = 13.5 Hz, 1H), 5.42 (d, J = 13.5 Hz, 1H), 5.24 (d, J = 17.5 Hz, 1H), 4.92 (d, J = 10.5 Hz, 1H), 4.38 (br s, 1H), 4.13 (dd, J = 8.5, 8.5 Hz, 1H), 4.03 (d, J = 12.0 Hz), 3.45 (dd, J = 12.0, 12.0 Hz, 1H), 3.15 (ddd, J = 11.0, 11.0, 3.5 Hz, 1H), 2.71 (s, 1H), 2.13−2.04 (m, 2H), 1.99 (br s, 1H), 1.81 (br s, 1H), 1.23−1.17 (m, 1H); ^{13}C NMR (100 MHz, dmso-d_6) δ 150.1, 147.6, 145.1, 137.9, 137.1, 132.7, 131.2, 130.2 (q, J_{C-F} = 29.0 Hz), 129.8, 129.4, 127.8 (q, J_{C-F} = 5.5 Hz), 127.1, 125.6, 124.2, 124.1 (q, J_{C-F} = 255.0 Hz), 123.7, 122.7, 119.9, 116.4, 67.9, 64.7, 59.7, 58.8, 51.2, 37.2, 25.4, 24.3, 21.2; HRMS calcd for $C_{27}H_{28}F_3N_2O^+$ [M^+] 453.2148, found 453.2149.

***N*-(2-Fluoro-5-trifluoromethyl)benzylcinchonidinium Bromide (12e).** Prepared according to the general procedure from cinchonidine (2.5 g, 8.49 mmol) and (2-fluoro-5-trifluoromethyl)benzyl bromide (2.62 g, 10.19 mmol) in toluene. Isolated the title compound (4.51 g, 96%) as a white powder. Mp 234−235 °C dec; HPLC retention time 3.86 min; $[\alpha]^{20}_D$ −141.9° (*c* 1.12, MeOH); ^{1}H NMR (500 MHz, dmso-d_6) δ 8.98 (d, J = 4.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.09−8.07 (m, 1H), 7.84 (dd, J = 8.0, 8.0 Hz, 1H), 7.81 (d, J = 4.5 Hz, 1H), 7.77−7.71 (m, 2H), 6.82 (d, J = 4.0 Hz, 1H), 6.57 (s, 1H), 5.68 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.37 (d, J = 13.0 Hz, 1H), 5.23 (d, J = 13.0 Hz, 1H), 5.21 (d, J = 17.5 Hz, 1H), 4.95 (d, J = 10.5 Hz, 1H), 4.36 (br s, 1H), 4.05 (dd, J = 8.5, 8.5 Hz, 1H), 3.94 (d, J = 12.0 Hz, 1H), 3.47 (dd, J = 11.5, 11.5 Hz, 1H), 3.26 (dd, J = 11.0, 4.0 Hz, 1H), 2.68 (s, 1H), 2.15−2.06 (m, 2H), 2.00 (s, 1H), 1.83−1.79 (m, 1H), 1.29−1.25 (m, 1H); ^{13}C NMR (100 MHz, dmso-d_6) δ 163.9 (d, J_{C-F} = 255.0 Hz), 150.1, 147.6, 145.1, 137.9, 133.3−133.2 (m, 1C), 130.6−130.4 (m, 1C), 129.8, 129.4, 127.2, 125.8 (dq, J_{C-F} = 33.0, 3.5 Hz), 124.2, 123.7, 123.6 (q, J_{C-F} = 272.5 Hz), 120.0, 117.8 (d, J_{C-F} = 24.0 Hz), 116.9 (d, J_{C-F} = 15.5 Hz), 116.4, 67.7, 64.2, 59.1, 55.6, 51.0, 37.1, 25.6, 24.3, 21.0; HRMS calcd for $C_{27}H_{27}F_4N_2O^+$ [M^+] 471.2054, found 471.2061.

***N*-(2-Chloro-5-trifluoromethyl)benzylcinchonidinium Bromide (12f).** Prepared according to the general procedure from cinchonidine (2.5 g, 8.49 mmol) and (2-chloro-5-trifluoromethyl)benzyl bromide (2.79 g, 10.19 mmol) in toluene. Isolated the title compound (4.73 g, 98%) as a white powder. Mp 233.5−234 °C dec; HPLC retention time 3.96 min; $[\alpha]^{20}_D$ −176.9° (*c* 1.05, MeOH); ^{1}H NMR (500 MHz, dmso-d_6) δ 8.99 (d, J = 4.5 Hz, 1H), 8.51 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 8.5, 1.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.86−7.81 (m, 2H), 7.75 (dd, J = 8.5, 8.5 Hz, 1H), 6.88 (d, J = 3.5 Hz, 1H), 6.59 (s, 1H), 5.67 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.47 (d, J = 13.0 Hz, 1H), 5.30 (d, J = 13.0 Hz, 1H), 5.23 (d, J = 17.0 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 4.48 (br s, 1H), 4.06−4.03 (m, 2H), 3.49 (dd, J = 11.5, 11.5 Hz, 1H), 3.24 (ddd, J = 11.0, 11.0, 3.5 Hz, 1H), 2.68 (s, 1H), 2.14−2.05 (m, 2H), 2.01 (s, 1H), 1.79 (br s, 1H), 1.24−1.19 (m, 1H); ^{13}C NMR (100 MHz, dmso-d_6) δ 150.1, 147.6, 145.1, 140.9, 138.0, 133.1 (q, J_{C-F} = 3.5 Hz), 131.8, 129.8, 129.4, 128.9 (q, J_{C-F} = 3.5 Hz), 128.2 (q, J_{C-F} = 32.5 Hz), 127.6, 127.2, 124.2, 123.6, 123.5 (q, J_{C-F} = 272.5 Hz), 119.9, 116.4, 67.7, 64.5, 59.1, 58.9, 51.2, 37.1, 25.4, 24.4, 21.1; HRMS calcd for $C_{27}H_{27}{}^{35}ClF_3N_2O^+$ [M^+] 487.1759, found 487.1758.

***N*-[(2,5-Bis)trifluoromethyl]benzylcinchonidinium bromide (12g).** Prepared according to the general procedure from cinchonidine (2.155 g, 7.32 mmol) and [(2,5-bis)trifluoromethyl]benzyl bromide (2.7 g, 8.79 mmol) in toluene. The title compound was isolated (3.897 g, 89%) as a white powder. Mp 215 °C dec; HPLC retention time 4.15 min; $[\alpha]^{20}_D$ −152.8° (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, dmso-d_6) δ 8.99 (d, J = 4.5 Hz, 1H), 8.65 (s, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.26−8.22 (m, 2H), 8.10 (d, J = 8.5 Hz, 1H), 7.86−7.81 (m, 2H), 7.74 (dd, J = 8.5, 1.0 Hz, 1H), 6.89 (d, J = 3.5 Hz, 1H), 6.57 (s, 1H), 5.66 (ddd, J = 17.5, 10.5, 6.0 Hz, 1H), 5.55 (abq, J = 15.0 Hz, 2H), 5.26 (d, J = 17.5 Hz, 1H), 4.93 (d, J = 10.5 Hz, 1H), 4.40 (br s, 1H), 4.16−4.10 (m, 2H), 3.52 (dd, J = 11.0, 11.0 Hz, 1H), 3.23−3.18 (m, 1H), 2.68 (s, 1H), 2.14−2.01 (m, 3H), 1.84−1.72 (br m, 1H), 1.23−1.14 (br m, 1H); ^{13}C NMR (100 MHz, dmso-d_6) δ 150.2, 147.6, 145.0, 137.9, 134.1 (q, J_{C-F} = 30.0 Hz), 133.7 (q, J_{C-F} = 3.0 Hz), 132.6 (q, J_{C-F} = 33.5 Hz), 129.8, 129.6 (q, J_{C-F} = 5.5 Hz), 129.5, 128.2 (q, J_{C-F} = 3.5 Hz), 127.4, 127.2, 124.2, 123.6, 123.4 (q, J_{C-F} = 275.0 Hz), 123.2 (q, J_{C-F} =273.5 Hz), 119.9, 116.5, 68.0, 64.8, 59.2, 58.2, 51.2, 37.3, 25.4, 24.4, 21.3; HRMS calcd for $C_{28}H_{27}F_6N_2O^+$ [M^+] 521.2022, found 521.2027.

***N*-[(2,4-Bis)trifluoromethyl]benzylcinchonidinium Bromide (12h).** A 100 mL three-necked round-bottomed flask equipped with a magnetic stir bar, condenser, thermocouple, and nitrogen inlet was charged with cinchonidine (1.914 g, 6.5 mmol), [(2,4-bis)trifluoromethyl]benzyl bromide (2.42 g, 7.82 mmol, 1.2 equiv), and 2-propanol (32.5 mL) at RT. The stirred slurry was heated to 85 °C and maintained at that temperature for 19 h. The resulting dark-red solution was cooled to RT and aged for a further 7 h. The solution was then concentrated to a small volume (∼5 mL), and then 1:1 toluene/MTBE (100 mL) was added with stirring. The resulting slurry was aged at RT for 3 h then filtered, washing with MTBE (3×). The product cake was dried at 35 °C under vacuum with a nitrogen sweep for 24 h, to give the title compound (3.569 g, 73%) as a tan powder and as a toluene solvate. Mp 153−155 °C dec; HPLC retention time 4.22 min; $[\alpha]^{20}_D$ −113.5° (*c* 1.08, MeOH); ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.97 (d, J = 4.5 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.52−8.47 (m, 1H), 8.24 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.12−8.10 (m, 1H), 8.01 (d, J = 4.5 Hz, 1H), 7.86−7.81 (m, 2H), 6.68 (s, 1H), 5.74−5.67 (m, 3H), 5.29 (d, J = 17.5 Hz, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.64−4.59 (m, 1H), 4.26 (dd, J = 9.0, 9.0 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.73−3.62 (m, 1H), 3.31−3.26 (m, 2H), 2.80 (br s, 1H), 2.26−2.08 (m, 3H), 1.92−1.86 (m, 1H), 1.33−1.29 (m, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 151.0, 148.5, 147.8, 139.7, 138.6, 134.2 (q, J_{C-F} = 33.5 Hz), 133.9 (q, J_{C-F} = 30.5 Hz), 131.5, 131.4, 130.8−130.6 (m, 1C), 130.1, 129.3, 126.3−126.2 (m, 1C), 126.1, 125.0 (q, J_{C-F} = 274.5 Hz), 124.7, 124.6 (q, J_{C-F} = 272.5 Hz), 121.4, 117.8, 70.2, 66.9, 62.6, 60.1, 53.8,

39.3, 27.5, 26.1, 23.0; HRMS calcd for $C_{28}H_{27}F_6N_2O^+$ [M^+] 521.2022, found 521.2028.

***N*-(2,3,5-Trifluoro)benzylcinchonidinium Bromide (12p).** Prepared according to the general procedure from cinchonidine (1.943 g, 6.6 mmol) and (2,3,5-trifluoro)benzyl bromide (1.8 g, 8.0 mmol) in 2-propanol. Isolated the title compound (2.813 g, 64%) as a peach powder. Mp 182−183 °C dec; HPLC retention time 3.49 min; $[\alpha]^{20}_D$ −137.0° (*c* 1.08, MeOH); ^{1}H NMR (500 MHz, dmso-d_6) δ 8.99 (d, J = 4.5 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.90−7.83 (m, 2H), 7.80 (d, J = 4.5 Hz, 1H), 7.77−7.73 (m, 2H), 6.80 (d, J = 3.5 Hz, 1H), 6.52 (s, 1H), 5.68 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.28 (d, J = 12.5 Hz, 1H), 5.20 (d, J = 17.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 4.96 (d, J = 10.5 Hz, 1H), 4.29 (br s, 1H), 4.02 (dd, J = 8.5, 8.5 Hz, 1H), 3.84 (d, J = 11.5 Hz, 1H), 3.52 (dd, J = 12.0, 12.0 Hz, 1H), 3.32−3.28 (m, 1H), 2.66 (s, 1H), 2.17−2.07 (m, 2H), 2.01 (s, 1H), 1.80 (s, 1H), 1.27 (dd, J = 11.0, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, dmso-d_6) δ 156.9 (ddd, J_{C-F} = 244.0, 11.0, 2.5 Hz), 150.1, 150.0 (ddd, $^1J_{C-F}$ = 249.0, 14.5, 14.5 Hz), 147.5, 146.9 (ddd, J_{C-F} = 247.0, 13.5, 4.0 Hz), 145.1, 137.9, 129.8, 129.4, 127.2, 124.2, 123.6, 120.0, 118.5 (dd, J_{C-F} = 13.0, 10.5 Hz), 117.1 (dd, J_{C-F} = 25.0, 2.5 Hz), 116.4, 108.6 (dd, J_{C-F} = 28.0, 21.5 Hz), 67.8, 64.3, 59.4, 55.5, 51.1, 37.1, 25.5, 24.4, 20.9; HRMS calcd for $C_{26}H_{26}F_3N_2O^+$ [M^+] 439.1992, found 439.1992.

High-Throughput Experimentation Studies for the Dialkylation of Imine 6 Using Sodium Hydroxide and Phase-Transfer Catalysis (Table 1). *General Protocol.* The catalysts were arrayed in microvials, and the phase-transfer reactions were run in parallel using a 96-well plate format to maximize screening efficiency. In a typical experiment, the glycine equivalent (2.5 μmol) and excess alkylating reagent were dispensed as solutions in reaction solvent to an 800 μL microvial predosed with the phase-transfer catalyst (0.5 μmol). Excess base (6 equiv) was then added, and the resulting mixture was agitated at 450 rpm[27] to effect the PTC reaction. Screening experiments were efficiently conducted at total reaction volumes of 80−100 μL and substrate concentrations of about 0.03 M.

Representative Procedure. A chilled (0 °C) solution of **6c** (0.48 mg, 2.5 μmol, 1.0 equiv) in 40 μL toluene was added to the phase-transfer catalyst (0.54 μmol, 0.2 equiv) contained in a 0.65 mm diameter × 30 mm height glass vial containing a 1.98 mm diameter × 4.80 mm length super-tumble stir dowel. The resulting mixture was agitated at 400 rpm on a tumble stirrer for 45 min. A chilled (0 °C) solution of *trans*-1,4-dibromo-2-butene (**7**) (0.68 mg, 3.2 μmol, 1.3 equiv) in 20 μL toluene was then added to the reaction vial followed by 25 μL of a chilled (0 °C) suspension of powdered NaOH (0.6 mg, 15 μmol, 6 equiv) in toluene. The reaction vial was sealed with a Teflon-lined cover and the resulting mixture agitated at 450 rpm on a tumble stirrer at −10 to 0 °C for 40−48 h. The reaction was diluted with 600 μL of chilled (0 °C) toluene, and the solids were allowed to settle prior to chiral analysis by supercritical fluid chromatography (SFC).

(27) Stir rates of >400 rpm were necessary to obtain reproducible results. For systematic studies investigating stir rate effects on phase-transfer catalyzed reactions see: Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; VCH: Weinheim, 1993.

Analytical SFC conditions for reaction monitoring: Chiracel OJ-H column; 250 mm × 4.6 mm; column temperature 35 °C; flow rate 2.0 mL/min; pressure 200 bar; isocratic 4% 2-propanol (containing 25 mM isobutylamine) in CO_2; UV detection at 254 nm. Retention times: 3.53 min (desired enantiomer (1*R*,2*S*)-**11**), 4.17 min (undesired enantiomer (1*S*,2*R*)-**11**), 4.90 min (starting imine **6c**), 5.84 min (*aza*-Cope **14a** + monoalkylated product of **6c** and **7**).

General Procedure: Optimization Studies for the Dialkylation of Imine 6c Using Hydroxide Bases, Water as Additive, with Phase-Transfer Catalyst 12 (Table 3). The following procedure using NaOH is representative. A chilled (0 °C) solution of imine **6c** (100 mg, 0.523 mmol) in 0.65 mLof toluene was added to a chilled (0 °C) suspension of **12g** (9.4 mg, 15.6 μmol, 0.03 equiv) in 1.2 mL of toluene in an 8 mL glass vial containing a Teflon-coated stir bar (1/2 in. × 1/8 in.). The resulting mixture was agitated at 700 rpm on a tumble stirrer for 0.5 h. A chilled (0 °C) solution of *trans*-1,4-dibromo-2-butene (137 mg, 0.64 mmol, 1.22 equiv) in 0.65 mL of toluene was then added followed by addition of powdered NaOH (125 mg, 3.12 mmol, 6.0 equiv) and water (47 μL, 2.6 mmol). The resulting mixture was agitated at 700 rpm on a tumble stirrer at +1 to −3 °C for 24−48 h. Reaction analysis was carried out as described above.

Preparative Scale Synthesis of (1*R*,2*S*)-1-(*E*)-*N*-Phenylmethylene-amino-2-vinylcyclopropanecarboxylic Acid Ethyl Ester (1*R*,2*S*)-11. Toluene (280 mL) cooled to −1 °C (internal temperature) was treated with imine **6c** (11.28 g; 59 mmol, 1.0 equiv), the flask was rinsed down with 20 mL of toluene, and *N*-[(2,5-bis)trifluoromethyl]benzyl cinchonidinium bromide (1.064 g, 1.77 mmol, 0.03 equiv) was charged. This slurry was aged for 5 min, then 1,4-dibromo-2-butene (16.74 g, 77 mmol, 1.3 equiv) was charged as a solid, and the slurry was further aged for 10 min. Sodium hydroxide (pin-milled, 7.30 g, 177 mol, 3.0 equiv) was added in portions at <0 °C. The resulting suspension was aged for another 10 min at 0 °C, then water (2.66 mL, 147 mmol, 2.5 equiv) was added over 8 min at <0 °C. The reaction was agitated at 500 rpm at 0 °C for 22 h to reach >98% conversion (monitored by HPLC). The reaction mixture was filtered through solka-floc, rinsing with ice-cold MTBE (100 mL) (if it was desired to recycle the catalyst, the mixture was instead filtered through filter paper, rinsing with ice-cold MTBE). The filtrate was then concentrated by rotary evaporation under vacuum, maintaining the water bath at <30 °C, to give crude (1*R*,2*S*)-**11** (22.38 g, 50 wt % as determined by ^{1}H NMR analysis against 1,3,5-trimethoxybenzene internal standard, 78% assay yield, 77.4% ee). The crude product mixture was purified by preparative SFC to give the title compound (8.49 g, 93 wt %, >99% ee, 55% overall yield from **6c**) as a colorless oil. $[\alpha]^{20}_D$ −102.3° (*c* 10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.77−7.75 (m, 2H), 7.44−4.40 (m, 3H), 5.79 (ddd, J = 17.0, 10.5, 8.5 Hz, 1H), 5.30−5.26 (m, 1H), 5.13 (dd, J = 10.5, 1.5 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 2.31−2.26 (m, 1H), 2.01 (dd, J = 8.0, 5.5 Hz, 1H), 1.71 (dd, J = 9.5, 8.0 Hz, 1H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 160.3, 136.1, 134.1, 130.9, 128.6, 128.2, 117.3, 61.2, 54.1, 36.0, 21.7, 14.3; HRMS: product fragmented under the ionization conditions with cleav-

age of the aldimine C═N bond to generate the free amine - calcd for $C_8H_{14}NO_2$ $[MH]^+$ 156.1019, found 156.1027.

Analytical SFC conditions for reaction monitoring: Chiralcel OJ-H column, 250 mm × 4.6 mm; column temperature 35 °C; flow rate 2.0 mL/min; pressure 200 bar; isocratic 4% 1:1 2-propanol (containing 25 mM isobutylamine)/*n*-heptane in CO_2; UV detection at 254 nm. Retention times: 3.89 min (desired enantiomer (1*R*,2*S*)-**11**), 4.79 min (undesired enantiomer (1*S*,2*R*)-**11**).

Analytical HPLC conditions for reaction monitoring: Xterra RP18 column, 4.6 mm × 250 mm; column temperature 25 °C; flow rate 1.5 mL/min; linear gradient 40:60 MeCN/10 mM aq sodium tetraborate dicarbonate + 5% acetonitrile (pH 9) to 85:15 in 8 min, then hold at 85:15 for 3 min; UV detection at 254 nm. Retention times: 5.45 min (imine **6c**), 7.84 min (toluene), 8.74 min (dialkylation product **11**), 10.0 min (*aza*-Cope product **14a** and dimeric products).

Preparative SFC conditions: Chiralcel OJ-H column, 25 mm × 3 cm; column temperature 35 °C; flow rate 70.0 mL/min; pressure 100 bar; isocratic 5% 2-propanol in CO_2; UV detection at 290 nm. Retention times: 3.7−4.4 min (desired enantiomer (1*R*,2*S*)-**11**), 4.6−5.4 min (undesired enantiomer (1*S*,2*R*)-**11**).

(1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Ethyl Ester Tosylate Salt (4). A solution of dialkylation product (1*R*,2*S*)-**11** (2.0 g, 93 wt %, 7.64 mmol, 1.0 equiv) in 2-propanol (6 mL) was treated with $TsOH \cdot H_2O$ (1.89 g, 9.94 mmol, 1.3 equiv) in one portion. The mixture was stirred for 10 min, and then the solvent was switched to isopropyl acetate by rotary evaporation, and the mixture was concentrated to a target volume of 4 mL. *n*-Heptane (8 mL) was then added over 5 min, and the resulting slurry was aged 1 h. The slurry was filtered, and the cake was washed with 2:1 *n*-heptane/isopropyl acetate (1 × 4 mL) then *n*-heptane (1 × 4 mL), then dried under vacuum for 4 h to give the title compound (2.28 g, 91%) as a white powder. Mp 136−138 °C, $[\alpha]^{20}_D$ +30.7° (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 3H), 7.74 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.60 (ddd, J = 17.0, 10.5, 8.5 Hz, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 4.15−4.03 (m, 2H), 2.58−2.53 (m, 1H), 2.36 (s, 3H), 1.93 (dd, J = 10.0, 6.5 Hz, 1H), 1.53 (dd, J = 8.0, 6.5 Hz, 1H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 141.3, 140.5, 131.7, 128.9, 125.9, 119.2, 62.3, 40.1, 30.4, 21.3, 19.4, 13.9; HRMS calcd for $C_8H_{14}NO_2$ $[MH]^+$ 156.1019, found. 156.1020.

Acknowledgment

We thank Zainab Pirzada, Wes Shafer, Tanja Brkovic, and Margret Figus for assistance in developing all chiral assays. We thank Lisa DiMichele for assistance in NMR characterization. We also thank Albert Wieczorek for all pin-milling operations and Laura Artino for all particle size measurements.

Supporting Information Available

Complete results table for the *N*-(fluoro-substituted)benzylcinchonidinium catalyst screening, ^{1}H and ^{13}C NMR spectra for catalysts **12b**, **12e**−**12h**, and **12p**, dialkylation product (1*R*,2*S*)-**11**, and tosylate salt **4**, chiral SFC spectra for dialkylation product (1*R*,2*S*)-**11**, and particle size distribution comparison between powdered and pin-milled NaOH. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 12, 2010.

OP100070D