JOC Article

An Expedient and Practical Method for the Synthesis of a Diverse Series of Cyclopropane α-Amino Acids and Amines

Ryan P. Wurz and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

andre.charette@umontreal.ca

Received October 30, 2003

A practical synthesis for the preparation of a diverse series of cyclopropane α-amino acids is described. Nitrocyclopropane carboxylates can be readily prepared through treatment of α-nitroesters and iodobenzene diacetate or α-nitro-α-diazoesters with a Rh(II) catalyst and an olefin. Reduction of the nitro group using zinc/HCl in *i*-PrOH affords substituted cyclopropane α-amino esters in modest to high yields (54−99%). A "one-pot" procedure involving sequential cyclopropanation and reduction is described. The method can also be applied to the preparation of arylcyclopropyl amines (three examples).

Introduction

Considerable interest has been drawn to cyclopropane α-amino acids (ACCs) in recent years on account of their diverse biological activities as low molecular weight inhibitors or as nonproteogenic components in peptides. Substituted ACCs represent challenging synthetic targets due to their chiral quaternary center and the presence of an often sensitive cyclopropane subunit. There have been many methods developed for their preparation,[1] yet few methods allow facile preparation of a diverse series of derivatives from readily available starting materials. Furthermore, only a few compounds are naturally occurring, making their isolation from these sources inconvenient for large-scale production.

The parent compound 1-amino-1-cyclopropane carboxylic acid (ACC) occurs naturally[2] as the immediate biosynthetic precursor of the plant hormone ethylene,[3] and also displays properties of pharmaceutical interest when incorporated into peptides. A variety of other naturally occurring substituted ACCs exist including coronatine, a novel phytotoxin produced by *Pseudomonas syringae*,[4] and carnosadine, a natural product isolated from the red algae *Grateloupia carmasa* which can be regarded as the cyclopropane analogue of arginine (Figure 1).[5]

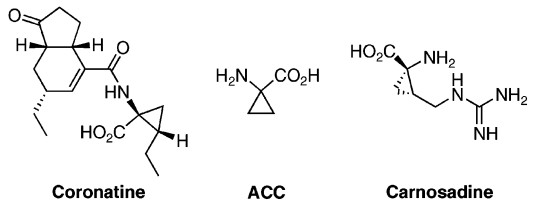


FIGURE 1. Naturally occurring cyclopropane amino acids.

Perhaps, the greatest pharmacological potential of ACCs exists in the field of conformationally constrained peptide mimetics.[6] It has been observed that their incorporation into peptides affects the 3-dimensional conformation, leading to more compact structures. This compression of the peptide results in reduced rates of hydrolysis, resulting in increased bioavailability of the peptide.[7] In principle, replacement of any amino acid by its cyclopropane analogue could potentially lead to desirable modifications to the peptide's conformation.

Synthetic ACCs have also been shown to have important biological activities including *m*-tyrosine cyclopropane amino acid (cyclo-*m*-Tyr), which is a competitive

* To whom correspondence should be addressed. Phone: (514) 343-2432. Fax: (514) 343-5900.

(1) For reviews see: (a) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (c) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (d) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najera, C. *J. Org. Chem.* **2000**, *65*, 3034.

(2) For the first isolation see: (a) Burroughs, F. *Nature* **1957**, *179*, 360. (b) Vähätalo, M. L.; Virtanen, A. I. *Acta Chem. Scand.* **1957**, *11*, 741.

(3) For the mechanism of ethylene biosynthesis see: (a) Zhou, J.; Rocklin, A. M.; Lipscomb, J. D.; Que, L., Jr.; Solomon, E. I. *J. Am. Chem. Soc.* **2002**, *124*, 4602. (b) Pirrung, M. C. *Acc. Chem. Res.* **1999**, *32*, 711.

(4) (a) Ichihara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636. (b) Bender, C. L.; Alarcon-Chaidez, F.; Gross, D. C. *Microbiol. Mol. Biol. Rev.* **1999**, *63*, 266.

(5) (a) Wakamiya, T.; Nakamoto, H.; Shiba, T. *Tetrahedron Lett.* **1984**, *25*, 4411. (b) Wakamiya, T.; Oda, Y.; Fujita, H.; Shiba, T. *Tetrahedron Lett.* **1986**, *27*, 2143.

(6) (a) Jiménez, A. I.; Cativiela, C.; Aubry, A.; Marraud, M. *J. Am. Chem. Soc.* **1998**, *120*, 9452. (b) Gademann, K.; Häne, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534. (c) Bednarek, M. A.; MacNeil, T.; Kalyani, R. N.; Tang, R.; Van der Ploeg, L. H. T.; Weinberg, D. H. *J. Med. Chem.* **2001**, *44*, 3665. (d) Díaz, M.; Jiménez, J. M.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2465. (e) Díaz, M.; Ortuño, R. M.; *Tetrahedron: Asymmetry* **1996**, *7*, 3465.

(7) (a) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 54. (b) Burgess, K.; Ke, C.-Y. *J. Org. Chem.* **1996**, *61*, 8627. (c) Kimura, H.; Stammer, C. H.; Ren-Lin, C.; Stewart, J. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 112. (d) Ogawa, T.; Shimohigashi, Y.; Yoshitomi, H.; Sakamoto, H.; Kodama, H.; Waki, M.; Stammer, C. H. *Pept. Chem.* **1988**, 25. (e) Ogawa, T.; Shimohigashi, Y.; Shiota, M.; Waki, M.; Stammer, C. H.; Ohno, M. *Pept. Chem.* **1989**, 43.

10.1021/jo035596y CCC: $27.50
Published on Web 01/22/2004

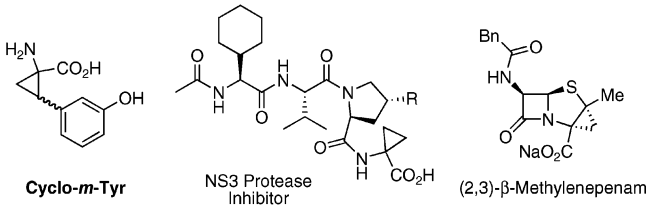


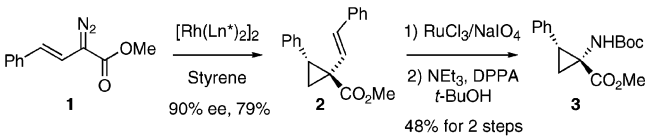
FIGURE 2. Biologically active products containing cyclopropane amino acid subunits.

inhibitor of pig liver L-aromatic amino acid decarboxylase (Dopa decarboxylase, DCC) against D-*m*-tyrosine.[8] Researchers at Boehringer-Ingelheim recently incorporated substituted ACCs into small peptides[9] and macrocycles,[10] resulting in potent NS3 protease inhibitors against hepatitis C. The cyclopropane derivative of penicillin G, (2,3)-*β*-methylenepenam, serves as a probe for the *β*-lactamase mechanism of action and was found to be a *β*-lactamase inhibitor (Figure 2).[11]

Results and Discussion

There are four general strategies for the synthesis of functionalized ACCs including (a) cyclopropanation of functionalized α,*β*-dehydro amino acids,[12] (b) Curtius or Hofmann rearrangements of carboxylic acid containing cyclopropanes,[13] (c) double alkylation of glycine anion equivalents,[14] and (d) cyclopropanation using amino acid equivalents.[15] Using the latter approach as a synthetic strategy, unmasking an amine equivalent could avoid the additional steps required when Curtius or Hofmann rearrangements are employed in the synthetic strategy.

SCHEME 1



1 **2** **3**

Furthermore, these reactions are often tedious and proceed with only modest yields. One of the most expedient and reliable approaches to date involves the method reported by Davies and co-workers which employs a Curtius rearrangement for the incorporation of the quaternary amine (Scheme 1).[13b,c] Cyclopropanation of an alkene with vinyldiazo ester **1** and a chiral rhodium(II) carboxylate catayst proceeds in high yields and enantioselectivities for a variety of alkenes. The quaternary amine is then incorporated in a sequence involving oxidative cleavage of the vinylcyclopropane **2**, followed by a Curtius rearrangement with the resulting carboxylic acid, leading to the protected aminocyclopropane ester **3** in modest yields for the two-step sequence **(**Scheme 1**)**.

In an attempt to reduce the number of required steps for the synthesis of cyclopropane α-amino acids and allow for the synthesis of substituted ACCs with sensitive functionalities, we envisioned a metal-catalyzed cyclopropanation of an α-nitro-α-diazocarbonyl, **4**,[16] affording the nitrocyclopropane carboxylate **5** (Table 1).[16a,17] We recently described an alternative cyclopropanation procedure to avoid the potentially dangerous α-nitro-α-diazocarbonyl substrates. In this method, iodobenzene diacetate was used to directly effect a cyclopropanation reaction between α-nitrocarbonyls **6** and olefins in the presence of a catalyst (Table 1). This cyclopropanation presumably proceeds via an iodonium ylide intermediate formed in situ.[18] In both of these methods, the diazo substrate **4** and the α-nitroester **6** are readily available, along with a wide variety of olefinic substrates. The strategy would then afford the corresponding cyclopropane amino acids through reduction of the nitro group and saponification of the ester.

Cyclopropanation using methods A and B allows access to a diverse series of nitrocyclopropane carboxylates **5**. In most cases, similar chemical yields and diastereoselectivities[19] can be obtained for a variety of substrates using either method A or method B. Electron-rich and -deficient styrene derivatives are well tolerated by both methods (Table 1, entries 1−4). Two noteworthy exceptions include the sterically hindered styrene derivative[20] (Table 1, entry 3) and 4-phenyl-1-butene (Table 1, entry 5) for which method B gave only modest yields (ca. 50%) and completely failed, respectively, even under forcing

(8) Ahmad, S.; Phillips, R. S.; Stammer, C. H. *J. Med. Chem.* **1992**, *35*, 1410.

(9) Poupart, M.-A.; Cameron, D. R.; Chabot, C.; Ghiro, E.; Goudreau, N.; Goulet, S.; Poirier, M.; Tsantrizos, Y. S. *J. Org. Chem.* **2001**, *66*, 4743.

(10) (a) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; 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*, 186−189. (b) Tsantrizos, Y. S.; Bolger, G.; Bonneau, P.; Cameron, D. R.; Goudreau, N.; Kukolj, G.; LaPlante, S. R.; Llinàs-Brunet, M.; Nar, H.; Lamarre, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1355.

(11) (a) Keith, D. D.; Tengi, J.; Rossman, P.; Tobaro, L.; Weigele, M. *Tetrahedron* **1983**, *39*, 2445. (b) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (c) Adlington, R. M.; Baldwin, J. E.; Challis, G. L.; *Tetrahedron Lett.* **1998**, *39*, 8537. (d) Sebffleber, F. C.; Geiger, W. E., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 5020.

(12) (a) Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 3034. (d) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270. (e) Calmes, M.; Daunis, J.; Escale, F. *Tetrahedron: Asymmetry* **1996**, *7*, 395.

(13) For asymmetric syntheses see: (a) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721. (b) Davies, H. M. L.; Cantrell, W. R., Jr. *Tetrahedron Lett.* **1991**, *32*, 6509. (c) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(14) (a) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814.

(15) For racemic syntheses see: (a) Barluenga, J.; Aznar, F.; Gutiérrez, I.; Garcia-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett.* **2002**, *4*, 4273. (b) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965. (c) Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 192.

(16) For preparation of these reagents see: (a) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468. (b) Charette, A. B.; Wurz, R. P.; Ollevier, T. *J. Org. Chem.* **2000**, *65*, 9252. (c) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron Lett.* **1989**, *30*, 4197. (d) Schöllkopf, U.; Toone, P. *Ann. Chem.* **1971**, *753*, 135. (e) Schöllkopf, U.; Markusch, P. *Ann. Chem.* **1971**, *753*, 143. (f) Schöllkopf, U.; Toone, P.; Schaefer, H.; Markusch, P. *Ann. Chem.* **1969**, *722*, 45.

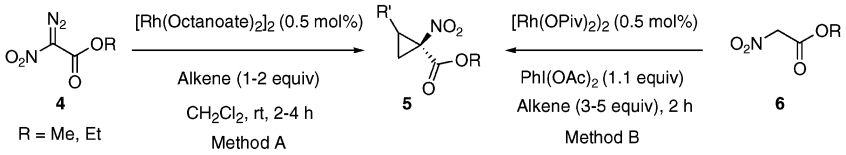
(17) (a) O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1989**, *54*, 3096. (b) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341.

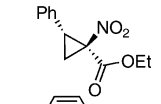
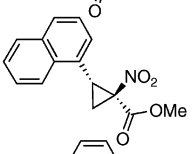
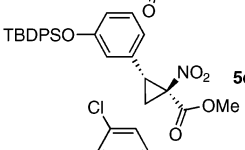
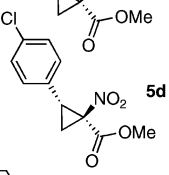
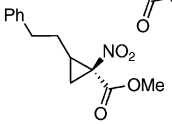
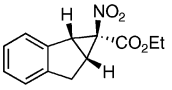
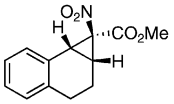
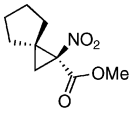
(18) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327.

(19) The diastereoselectivities for the two methods vary less than ±2%.

(20) The steric bulk associated with the TBDPS ether appears to be the only factor influencing the reduced chemical yield when using method B. It should be noted that 4-vinylanisole undergoes efficient cyclopropanations using methods A and B (see ref 18).

TABLE 1. Preparation of Substituted Nitrocyclopropane Carboxylates



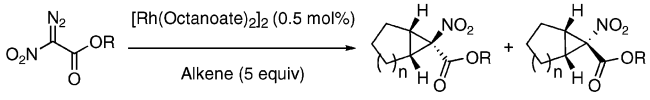
entry	cyclopropane (**5**)		method	*E*:*Z* ratio[a]	yield (%)[b]
1		**5a**	A	93:7	90
			B		84
2		**5b**	A	95:5	86
			B		87[c]
3		**5c**	A	92:8	92
4		**5d**	A	91:9	87
			B		80
5		**5e**	A	53:47	70[c,d]
6		**5f**	A	97:3[e]	79
			B		83
7		**5g**	A	97:3[e]	84
			B		72[f]
8		**5h**	A	N/A	83
			B		73[f]

[a] The major isomer is depicted. [b] Isolated yields after purification by flash chromatography. [c] Reaction allowed to stir overnight. [d] Five equivalents of alkene used. [e] Refers to the exo:endo ratio. [f] Reaction required heating at 40 °C for 3 h.

conditions.[21] However, when α-stabilized electron-rich olefins are used (e.g., the olefin in entry 8 is more α-stabilized than that in entry 5), the in situ procedure can be scaled up with ease, even with reduced catalyst loadings.[22]

A series of cyclic *cis*-olefins were also good substrates for the cyclopropanation reaction with α-nitro-α-diazocarboxylates **4**, with the reaction yields varying as a function of ring size. Cyclopropanation of cyclopentene afforded excellent yields of the corresponding cyclopropane **5i**, with preference for the *exo*-diastereomer (Table 2, entry 1). In contrast, cyclohexene proved to be less reactive under the cyclopropanation conditions and gave disappointing yields of the corresponding cyclopropane

TABLE 2. Preparation of Symmetric Nitrocyclopropane Carboxylates



entry	n	R	cyclopropane **5**	exo:endo ratio	yield[a] (%)
1	1	Bn	**5i**	87:13	81
2	2	Me	**5j**	88:12	55
3	2	Bn	**5k**	86:14	39
4	4	Bn	**5l**	80:20	66
5	4[b]	Bn	**5m**	74:26	71

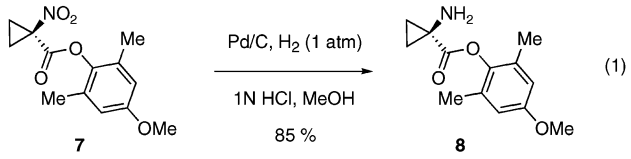
[a] Isolated yields after purification by flash chromatography. [b] Alkene derived from cyclooctadiene.

(21) A variety of additives were tested including toluene, KBr aqueous solutions, molecular sieves, MgO, etc.

(22) Ethyl nitroacetate and styrene undergo a cyclopropanation reaction when treated with $PhI(OAc)_2$ (1.05 equiv) and $[Rh(Octanoate)_2]_2$ (0.04 mol %) on a 3.0 g scale. The reaction was heated at 40 °C for 4.5 h, affording 79% isolated yield of cyclopropane **5a** in a 92:8 *E*:*Z* ratio. For a recent example of reduced catalyst loadings in Rh(II)-catalyzed cyclopropanation reactions see: Davies H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403.

5j or **5k** (Table 2, entries 2 and 3).[23] Cyclooctene- and cyclooctadiene-derived cyclopropanes could also be prepared with acceptable yields (Table 2, entries 4 and 5). Attempts to cyclopropanate these substrates using iodobenzene diacetate derived conditions resulted in only modest yields, between 45% and 50%, of the corresponding cyclopropanes **5i** and **5m** after 24 h at 40 °C in sealed tubes.

With two reliable methods for the preparation of a variety of nitrocyclopropane carboxylates **5** in modest to high yields, we then sought a method for the reduction of the nitro group. Although there exist several reported examples concerning the reduction of nitrocyclopropanes,[24] to the best of our knowledge, only two examples exist for the reduction of nitrocyclopropane carboxylates. The first example was reported by Seebach and Häner[25] involving the parent compound **7** (eq 1), while the second example was recently reported by Kuznetsova and coworkers involving spirohexane amino acids.[26] It is also noteworthy to mention the absence of reports in the literature for the reduction of nitrocyclopropanes containing aromatic groups.

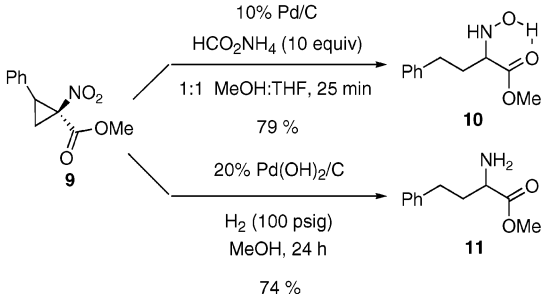


(1)

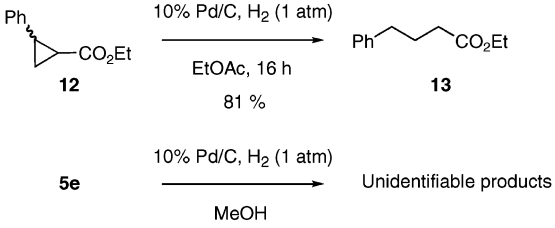
When methyl 2-phenyl-1-nitrocyclopropane carboxylate (**9**) was submitted to the above reaction conditions (Pd/C, H_2, 1 atm), amine **11**, resulting from the hydrogenolysis of the cyclopropane, was isolated in low yields. Ammonium formate was then used as a "H_2" source and led to isolation of hydroxylamine **10** in good yields (Scheme 2). It has been suggested that Pd catalysts are preferable for partial reduction of α-carboxy nitro groups to hydroxyamines probably due to the resulting stabilization imparted by the intramolecular hydrogen bonding.[27] Higher pressures of H_2 with $Pd(OH)_2/C$ led to the hydrogenolysis of the cyclopropane ring, affording amine **11** in 74% isolated yield (Scheme 2). The hydrogenolysis of the cyclopropane ring was found to be regiospecific as only one of the two possible products was observed in the crude reaction mixtures.

We then wondered if hydrogenolysis resulted from the presence of radical species on the nitro group α to the cyclopropane ring during reduction. Alternatively, hydrogenolysis efficiency could be derived from the aromatic substituent in the 2-position. Thus, 2-phenylcyclopropane carboxylate ethyl ester (**12**) was subjected to the above reaction conditions, resulting in high yields of the opened product **13** (Scheme 3). Cyclopropane **5e**, which does not contain an aromatic group directly attached to the cyclopropane ring, was also submitted to the reduction conditions, and only small quantities of the desired amino ester could be recovered (Scheme 3).[28]

SCHEME 2



SCHEME 3



Clearly, the reduction was problematic using Pd catalysts for these cyclopropanes, so a variety of reducing conditions for nitro groups were screened including Raney Ni,[29] Fe/HCl,[24a] and Zn/Ac_2O.[30] All these conditions led to unidentifiable products. The ease of rearrangement of activated (aromatic containing) nitrocyclopropane carboxylates to isoxazoline *N*-oxides[16a] under mildly acidic conditions and their efficient ring opening with a variety of nucleophiles[30,31] further impose the necessity for mild reducing conditions. Lewis acids have also been found to induce rearrangements.[17b]

We then turned to zinc(0) due to its success in reductions involving sterically encumbered α,α-disubstituted nitro carboxylates[27a] and various other tertiary and quaternary nitro groups.[32] A variety of acid sources (NH_4Cl, AcOH, HCl) were screened along with various stoichiometries of acid and zinc. Finally, 20 equiv of zinc (dust) with 10 equiv of aqueous 1 N HCl in methanol

(23) The benzyl ester was used to reduce the volatility of the corresponding cyclopropyl amine upon reduction.

(24) For nitrocyclopropane reduction with Fe/HCl see: (a) Hass, H. B.; Shechter, H. *J. Am. Chem. Soc.* **1953**, *75*, 1382. Pd/C see: (b) Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O.; Yufit, D. S.; Howard, J. A. K.; Meijere de, A. *Synlett* **2000**, 1741. (c) Zindel, J.; Meijere de, A. *Synthesis* **1994**, 190. For Raney nickel see: (d) Yun, Y. K.; Godula, K.; Cao, Y.; Donaldson, W. A. *J. Org. Chem.* **2003**, *68*, 901.

(25) Seebach, D.; Häner, R. *Chimia* **1985**, *39*, 356.

(26) Conditions: 10% Pd/C, NH_4CO_2H (10 equiv), 40 h, rt, EtOH. See: Yashin, N. V.; Averina, E. B.; Gerdov, S. M.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett.* **2003**, *44*, 8241.

(27) (a) Fu, Y.; Hammarström, L. G. J.; Miller, T. J.; Fronczek, F. R.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem.* **2001**, *66*, 7118. (b) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis, Procedures and Commentary*; John Wiley & Sons: New York, 1978; pp 26−39. (c) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; pp 113−125. (d) Boger, D. L.; Lerner, R. A.; Cravatt, B. F. *J. Org. Chem.* **1994**, *59*, 5078.

(28) It is noteworthy to mention that Stammer et al. have reported the cleavage of the benzyl ester of benzyl (*Z*)-2-phenyl-1-amino-1-carboxylate in high yields without hydrogenolysis of the cyclopropane ring. See: King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270.

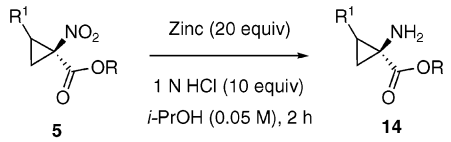
(29) For reduction of nitro groups with Raney nickel see: Norris, T.; Braish, T. F.; Butters, M.; DeVries, K. M.; Hawkins, J. M.; Massett, S. S.; Rose, P. R.; Santafianos, D.; Sklavounos, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1615 (also includes examples of reductions with Zn/methanesulfonic acid and Pt/H_2).

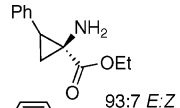
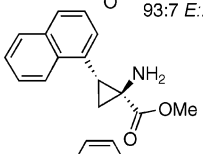
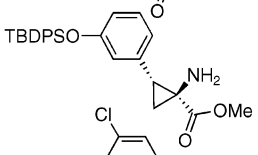
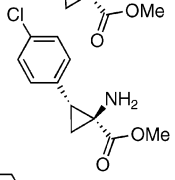
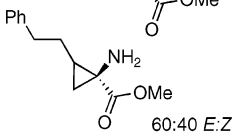
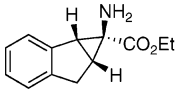
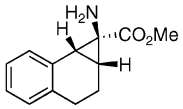
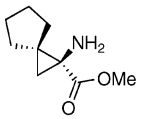
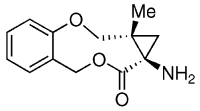
(30) For nitro reductions with Zn/Ac_2O see: Seebach, D. v.; Häner, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507.

(31) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 195.

(32) For Zn/HOAc see: (a) Battersby, A. R.; Baker, M. G.; Broadbent, H. A.; Fookes, C. J. R.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2027. (b) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528.

TABLE 3. Zinc(0) Reduction of Nitrocyclopropane Carboxylates



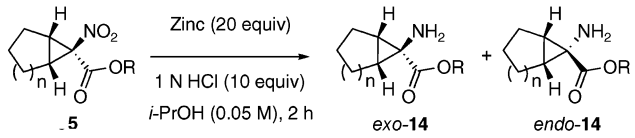
entry	cyclopropane (**14**)	product	yield (%)[a]
1		**14a**	49[b]
2			67[c]
3	93:7 *E*:*Z*		77
4		**14b**	76
5		**14c**	74
6		**14d**	76
7	 60:40 *E*:*Z*	**14e**	93
8		**14f**	79
9		**14g**	86
10		**14h**	54
11		**14n**	70

[a] Isolated yields after purification by flash chromatography. [b] AcOH used as acid. [c] MeOH used as solvent.

(0.05 M) afforded clean reactions with only traces of the hydrogenolysis product. 2-Propanol was found to be a superior solvent, upon further optimization, as it aided in the solubility and led to an increase in yields of 5−10% when compared to methanol. The scope of the reaction was then examined for a variety of structurally diverse nitrocyclopropane carboxylates (Table 3).

Initially, when acetic acid and 2-propanol were used, nitrocyclopropane carboxylate **5a** was reduced, affording ethyl 2-phenyl-1-aminocyclopropane carboxylate (**14a**) in 49% yield (Table 3, entry 1). Upon changing the acid source to HCl, an isolated yield of 67% of **14a** could be obtained in methanol (Table 3, entry 2). This protocol gave acceptable yields for most of the examples tested, except **5c**, which only gave 32% isolated yield of **14c**. This

TABLE 4. Zinc(0) Reduction of Symmetric Nitrocyclopropane Carboxylates



entry	n	R	product **14**	yield[a] (%)
1	1	Bn	**14i**	88
2	2	Me	**14j**	74[b]
3	3	Bn	**14k**	87
4	4	Bn	**14l**	>99
5	4[c]	Bn	**14m**	94

[a] Isolated yields after purification by flash chromatography. [b] Product was found to be volatile. [c] Alkene derived from cyclooctadiene.

result was probably due to the low solubility of the cyclopropane in methanol, resulting in conglomeration of the reactants. Thus, replacement of the methanol with 2-propanol gave more general reduction conditions. Finally, the best results (77%, Table 3, entry 3) were obtained when the zinc dust was added in small portions over 15 min (reaction is exothermic) to the acidic alcohol solution containing the cyclopropane. In contrast, however, slow addition of 1 N HCl to the heterogeneous mixture of cyclopropropane, alcohol, and zinc dust gave increased degradation. Other zinc(0) sources, including zinc powder, were also tested and found to give inferior results.

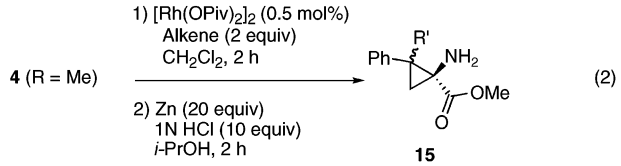
Cyclopropane **5b** underwent smooth reduction, affording the corresponding amino ester **14b** in 76% yield. Cyclopropane **5c**, in 2-propanol, gave acceptable yields of 74% and serves as a precursor to cyclo-*m*-Tyr (Figure 2). *E*- and *Z*-isomers of cyclopropane **5e**, which do not contain an aromatic substituent directly attached to the cyclopropane ring, gave excellent yields (93%) of the corresponding amino ester (Table 3, entry 7). It is noteworthy to mention that the *E*- and *Z*-isomers (of **14e**) could now be easily separated by flash chromatography. Cyclopropane **5f**, derived from indene, and its homologue **5g**, underwent smooth reductions, affording 79% and 86% yields, respectively, of the corresponding amino esters **14f** and **14g**. Surprisingly, the reduction of cyclopropane **5h** under the standard reduction conditions yielded only a modest 54% yield of the pure amino ester **14h** (Table 3, entry 10). Attempts to reduce cyclopropane **5h** under the conditions reported by Kuznetsova and co-workers[26] yielded only traces of the desired amino ester **14h** in addition to hydroxy amines and products resulting from the hydrogenolysis of the cyclopropane. The nitrocyclopropyl lactone prepared by intramolecular cyclopropanation was also reduced successfully to its amine **14n** (70%, Table 3, entry 11).[33]

Zinc(0) reduction of the symmetric cyclopropanes proceeded in excellent yields, affording the corresponding amino esters (Table 4). The minor *endo*-diastereomer can now be easily separated from the major *exo*-diastereomer. Cyclopropane **5j**, derived from cyclohexene, was found to be volatile, affording amino ester **14j** in 74% yield (Table 4, entry 2), whereas the less volatile benzyl ester **14k**

(33) Charette, A. B.; Wurz, R. P. *J. Mol. Catal. A* **2003**, *196*, 83.

afforded 87% yield (Table 4, entry 3). Satisfyingly, reduction of the unsaturated nitrocyclopropane **5m** resulted in the chemospecific reduction of the nitro group in the presence of the alkene, and the corresponding amino ester **14m** was isolated in 94% yield (Table 4, entry 5).

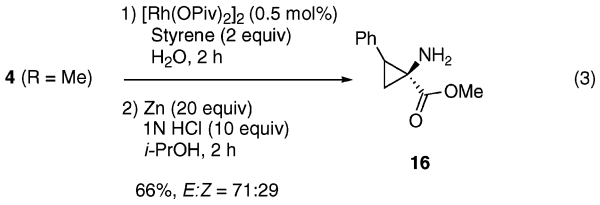
The reduction of more sensitive cyclopropanes such as 2,2-diphenyl-1-nitrocyclopropane carboxylate represents a more challenging example as they readily rearrange to the corresponding *N*-oxides on silica gel if it is not pretreated with triethylamine.[16a,17] To avoid decomposition during purification, the products were prepared using the standard cyclopropanation reaction, the solvent was removed, and then the crude material was subjected directly to the reduction conditions, yielding the cyclopropane amino esters. Modest yields were obtained (62% and 57%, respectively) for the two-step sequence, with the total reaction time amounting to only 4 h (eq 2).



(2)

Alkene = 1,1-diphenyl ethene 57%**15a** (R^1 = Ph)
α-methyl styrene 62% (*E*:*Z* 18:82)**15b** (R^1 = Me)

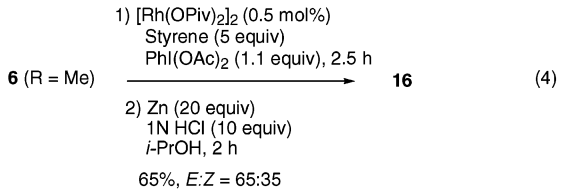
This one-pot cyclopropanation/reduction procedure can also be applied to biphasic, aqueous cyclopropanations.[34] To illustrate this, an aqueous solution of methyl nitrodiazoacetate **4** was added over 30 min to a mixture of styrene (2 equiv) and catalyst, effecting an efficient cyclopropanation reaction. Treatment of the reaction mixture after 2 h with 2-propanol, 1 N HCl, and zinc(0) afforded the corresponding aminocyclopropane carboxylate **16** in 66% yield for two steps (eq 3).[35]



(3)

66%, *E*:*Z* = 71:29

In a similar fashion, the cyclopropanation using iodonium ylides could also be applied (eq 4). This practical method offers the advantage of avoiding the handling of the potentially dangerous diazo compounds and does not require purification of the nitrocyclopropane.



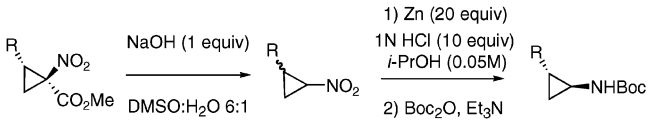
(4)

65%, *E*:*Z* = 65:35

(34) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531.

(35) There is some erosion of the stereochemical integrity (ca. 10−15%) for styrene-derived cyclopropanes during the course of the nitro reduction. The implicated mechanism pertaining to this surprising observation is under closer examination.

TABLE 5. Preparation of Aromatic Substituted *trans*-Aminocyclopropanes



entry	R	decarboxylation yield of **17** (%)	*trans*:*cis* ratio	reduction yield of **18**[a] (%)
1	phenyl (**9**)	91 (**17a**)	81:19	60 (**18a**)
2	1-naphthyl (**5b**)	79 (**17b**)	82:18	61 (**18b**)
3	4-chlorophenyl (**5d**)	96 (**17c**)	83:17	67 (**18c**)

[a] Refers to the isolated yield for two steps on reduction of pure *trans*-isomer only.

Finally, the amino esters can be converted to the corresponding amino acids by saponification of the ester, according to previously reported methods.[12b,26]

There has been much interest in the preparation of cyclopropyl amines as they are found in a number of biologically active products.[36] We also wondered if this reduction could be applied to aromatic substituted nitrocyclopropanes, again noting the absence of reports in the literature concerning reduction of these compounds. There are a variety of methods for the preparation of nitrocyclopropanes[37] including the decarboxylation of nitrocyclopropane carboxylates **5** as reported by O'Bannon and Dailey.[38] Using a slight modification of the procedure reported by O'Bannon and Dailey, the nitrocyclopropane carboxylates **9**, **5b**, and **5d** were treated with NaOH in a mixture of DMSO/H_2O and heated to 80 °C for 2 h, resulting in the saponification and then decarboxylation of the nitrocyclopropane carboxylate. Upon extraction, the corresponding nitrocyclopropanes **17** were afforded in high yields with slight erosion of their stereochemical integrity.[39] These cyclopropanes were found to efficiently yield the corresponding cyclopropyl amines under the standard reduction conditions. The amines were protected as their *tert*-butyl carbamates (Boc) for ease of purification (Table 5).

The reduction of *trans*-1-nitro-2-phenylcyclopropane (**17a**) affords the corresponding amine, which represents

(36) For recent syntheses of biologically active amino cyclopropanes see: (a) Aggarwal, V. K.; de Vincente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785. (b) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331. (c) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980. (d) *Chem. Eng. News* **2003**, May 23, 31.

(37) (a) Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F.; Seebach, D.; Kalinowski, H.-O. *Helv. Chim. Acta* **1982**, *65*, 137. (b) Yu, J.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1992**, *57*, 3757. (c) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267. (d) Asunskis, J.; Shretcher, H. *J. Org. Chem.* **1968**, *33*, 1164. (e) Russel, G. A.; Makosza, M.; Hershberger, J. *J. Org. Chem.* **1979**, *44*, 1195. (f) Arai, S.; Nakayama, K.; Hatano, K.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 9572. (g) Galley, G.; Hüner, J.; Anklam, S.; Jones, P. G.; Pätzel, M. *Tetrahedron Lett.* **1996**, *37*, 6307.

(38) (a) O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1990**, *55*, 353. (b) O'Bannon, P. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 9244. See also: (c) Ivanova, O. A.; Yashin, N. V.; Averina, E. B.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirov, N. S. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 2101.

(39) The *cis*- and *trans*-isomers of the nitrocyclopropanes can be easily separated by column chromatography. Only the pure *trans*-isomers were submitted to the reduction conditions.

an intuitively straightforward, yet novel synthesis of the antidepressant (±)-transcycloamine.[40] Typically, the cyclopropyl amine is prepared via a Curtius rearrangement from the corresponding acid and often results in low isolated yields.[41] Reductions involving nitrocyclopropanes **17b** and **17c** also proceed with similar efficiencies, affording >60% yield for the two-step sequence.

Conclusions

In summary, the above methodology represents a rapid and efficient method for the preparation and reduction of a diverse series of aminocyclopropane carboxylates and aromatic substituent containing aminocyclopropanes. It represents an attractive method to access symmetric and racemic substituted ACCs from commercially available α-nitroesters and -olefins. Modest to high yields of aminocyclopropane carboxylates can be obtained in short reaction times. The asymmetric version of this reaction proceeds with modest enantioselectivities, up to 72% ee, and is still under examination.[33] Furthermore, a variety of methods exist for the resolution of cyclopropane amino acids and can be applied to access the enantiomerically enriched materials.[42]

Experimental Section

See the Supporting Information for general synthetic methods and materials.

Nitrocyclopropane Carboxylates. Cyclopropanes **5a**,[17a] **5d**,[18] **5f**,[16a] **5h**,[18] **5j**,[17a] **5n**,[33] **9**,[16a] and **17a**,[38] have been previously reported. See the Supporting Information for the characterization data (^{1}H and ^{13}C NMR spectra) of new nitro- and aminocyclopropanes.

Caution. *Although we have not experienced any problems in the handling of these compounds (trifluoromethanesulfonyl azide and the α-nitro-α-diazocarbonyl derivatives), extreme care should be taken when they are manipulated due to their explosive nature.*

General Procedure for Rhodium(II) Carboxylate-Catalyzed Cyclopropanations of Alkenes with α-Nitro-α-diazoesters (Tables 1 and 2). Styrene (145 mg, 0.16 mL, 2 equiv) was added to a 10 mL round-bottomed flask containing the required amount of $[Rh(Octanoate)_2]_2$ catalyst (2.7 mg, 3.5×10^{-3} mmol, 0.5 mol %). Ethyl nitrodiazoacetate (111 mg, 0.70 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (0.70 mL, 1.0 M) and added slowly dropwise to the alkene/catalyst solution, allowing for a controlled rate of N_2 evolution (over ca. 15−20 min). CH_2Cl_2 (0.5 mL) was then used to rinse the flask containing the diazo to ensure complete transfer of material. The reaction was allowed to stir for 2−4 h and then concentrated under reduced pressure. The diastereoselectivity of the cyclopropanation was determined by ^{1}H NMR of the crude reaction mixture. Purification by chromatography on silica gel, first eluting with hexanes (to remove excess alkene) and then 5% EtOAc/hexane, afforded **5a** as a clear, colorless oil (148 mg, 90%) in a 93:7 *E*:*Z* ratio. Separation of the diastereomers is possible using a less polar eluent (3% EtOAc/hexane).

General Procedure for the in Situ Rhodium(II) Carboxylate-Catalyzed Cyclopropanations of Alkenes with α-Nitroesters and $PhI(OAc)_2$ (Table 1). Styrene (587 mg, 0.65 mL, 5 equiv) was added to a 25 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (3.4 mg, 5.6×10^{-3} mmol, 0.5 mol %) and ethyl nitroacetate (150 mg, 1.13 mmol, 1 equiv). Iodobenzene diacetate (400 mg, 1.24 mmol, 1.1 equiv) was then added in one portion and the mixture allowed to stir for 2 h open to air. The crude reaction mixture was then chromatographed directly on silica gel, first eluting with hexane (to remove excess alkene) and then with 5% EtOAc/hexane, affording **5a** as a clear, colorless oil (223 mg, 84%) in a 92:8 *E*:*Z* ratio.

General Reduction Procedure (Tables 3 and 4). 2-Phenyl-1-nitrocyclopropane carboxylate ethyl ester (**5a**) (104 mg, 0.44 mmol) was dissolved in 8.8 mL of *i*-PrOH (0.05 M) and treated with 1 N HCl (4.4 mL, 10 equiv). Zinc dust (578 mg, 8.80 mmol, 20 equiv) was then added in small portions over 10−15 min and the solution allowed to stir for 2 h at room temperature. The suspension was quenched by addition of a saturated solution of $NaHCO_3$ (15 mL), stirred for 15 min, and filtered through a small plug of Celite, washing with EtOAc (20 mL). The aqueous phase was further extracted with dichloromethane (2 × 10 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude residue was then chromatographed on silica gel pretreated with 1:5:19 Et_3N/EtOAc/hexane, rinsed with 20% EtOAc/hexane, and eluted with a 20−80% gradient of EtOAc/hexane. The *E*- and *Z*-diastereomers were easily separated and the appropriate fractions combined (ninhydrin used as a developer), affording the corresponding amino esters **14a** (70 mg, 77%).

Data for (*E*)-Ethyl 1-Amino-2-phenyl-1-cyclopropanecarboxylate ((*E*)-14a): pale yellow oil; R_f 0.16 (60% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.27 (m, 5H), 3.68−3.83 (m, 2H), 2.66 (t, J = 8.7 Hz, 1H), 2.20 (s (br), 2H), 1.99 (dd, J = 7.9, 5.0 Hz, 1H), 1.45 (dd, J = 9.5, 5.0 Hz, 1H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.9, 129.4, 128.1, 126.7, 60.8, 43.2, 36.4, 20.0, 13.8; IR (film) 3374 (NH), 1713 (C=O), 1144 cm^{-1}.

Data for (*Z*)-Ethyl 1-Amino-2-phenyl-1-cyclopropanecarboxylate ((*Z*)-14a): pale yellow oil; R_f 0.57 (80% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.35 (m, 2H), 7.23−7.27 (m, 3H), 4.22 (q, J = 7.1 Hz, 2H), 2.82 (t, J = 9.5 Hz, 1H), 1.84 (dd, J = 9.6, 4.9 Hz, 1H), 1.56 (s (br), 2H), 1.44 (dd, J = 7.6, 4.9 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 136.0, 129.4, 128.3, 127.0, 61.5, 41.3, 33.2, 22.1, 14.5; IR (film) 3384 (NH), 1717 (C=O), 1262, 1148, 834 cm^{-1}; LRMS (APCI, Pos) *m*/*z* calcd for $C_{12}H_{15}NO_2$ $[M + H]^+$ 206.3, obsd 206.1.

"One-Pot" Cyclopropanation Reduction Procedure for the Preparation of Sensitive Cyclopropanes 15a and 15b (Eq 2). $[Rh(Octanoate)_2]_2$ (4.5 mg, 0.5 mol %) was added to a 100 mL round-bottomed flask, followed by 1,1-diphenylethene (415 mg, 2.30 mmol, 2 equiv). Methyl nitrodiazoacetate[16a] (167 mg, 1.15 mmol, 1 equiv) was then added slowly dropwise as a solution in CH_2Cl_2 (1.2 mL, 1.0 M) to the catalyst/alkene mixture over 20 min. The solution was allowed to stir at room temperature for 2 h, and then the CH_2Cl_2 was removed under reduced pressure. The crude residue was dissolved in *i*-PrOH (23 mL, 0.05 M) and treated with 1 N HCl (11.5 mL, 10 equiv). Zinc dust (1.50 g, 23.0 mmol, 20 equiv) was added in small portions over 10−15 min, and the resulting suspension was allowed to stir for an additional 2 h. It was quenched by the addition of a saturated solution of $NaHCO_3$ (ca. 15 mL) and allowed to stir for 15 min. The suspension was filtered through a small Celite plug, washing with EtOAc (25 mL). After separation of the organic phase, the aqueous phase was re-extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic

(40) A monoaminooxidase inhibitor (MAOI), tranylcypromine (Parnate, Jatrosom N), which is an oral MAOI-type antidepressant, is used to treat major depression in patients who have not responded to other antidepressant therapies.

(41) (a) Shu, F.-C.; Zhou, Q.-L. *Synth. Commun.* **1999**, *29*, 567. (b) Csuk, R.; Schabel, M. J.; Scholz, Y. v. *Tetrahedron: Asymmetry* **1996**, *7*, 3505. (c) Wang, M.-X.; Feng, G.-Q. *Tetrahedron Lett.* **2000**, *41*, 6501.

(42) (a) Wakamiya, T.; Oda, Y.; Fujita, H.; Shiba, T. *Tetrahedron Lett.* **1986**, *27*, 2143. (b) Shiraishi, K.; Ichihara, A.; Sakamura, S. *Agric. Biol. Chem.* **1977**, *41*, 2497. (c) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. H. *Tetrahedron Lett.* **1985**, *26* 485. (d) Kimura, H.; Stammer, C. H. *J. Org. Chem.* **1983**, *46*, 2440. (e) Kimura, H.; Stammer, C. H.; Shimohigashi, Y.; Ren-Lin, C.; Stewart, J. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 112.

extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel pretreated with 1:5:19 Et_3N/EtOAc/hexane was achieved by eluting with a gradient of 10−40% EtOAc/hexane, affording pure **15a** (174 mg, 57%). The same procedure was repeated for the preparation of **15b**.

One-Pot Cyclopropanation Reduction Procedure for Rhodium(II) Carboxylate-Catalyzed Cyclopropanation of Styrene with Methyl Nitrodiazoacetate in Water (Eq 3). Styrene (158 mg, 0.17 mL, 2 equiv) was added to a 100 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (2.3 mg, 3.8×10^{-3} mmol, 0.5 mol %) and distilled water (0.5 mL). Methyl nitrodiazoacetate[16a] (110 mg, 0.76 mmol, 1 equiv) was dissolved in hot water (4.0 mL, at 40 °C), cooled, and added slowly dropwise to the aqueous catalyst/styrene mixture over 30 min. After being stirred for an additional 2 h, the reaction mixture was diluted with *i*-PrOH (15 mL, 0.05 M) and treated with 1 N HCl (7.6 mL, 10 equiv). Zinc dust (987 mg, 15.1 mmol, 20 equiv) was added to the solution over 10−15 min in small portions, and the resulting suspension was allowed to stir for an additional 2 h. It was quenched by the addition of a saturated solution of $NaHCO_3$ (ca. 15 mL) and stirred for an additional 15 min. The suspension was filtered through a small Celite plug, washing with EtOAc (25 mL). After separation of the organic phase, the aqueous phase was re-extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel pretreated with 1:5:19 Et_3N/EtOAc/hexane and eluting with a gradient of 20−80% EtOAc/hexane afforded pure **16** (96 mg, 66%, 71:29 *E*/*Z*).

One-Pot Cyclopropanation Reduction Procedure for Rhodium(II) Carboxylate-Catalyzed Cyclopropanation of Styrene with Methyl Nitroacetate and $PhI(OAc)_2$ (Eq 4). Styrene (525 mg, 0.58 mL, 5 equiv) was added to a 100 mL round-bottomed flask containing the required amount of $[Rh(OPiv)_2]_2$ catalyst (3.1 mg, 5.0×10^{-3}mmol, 0.5 mol %) and methyl nitroacetate (120 mg, 1.01 mmol, 1 equiv). Iodobenzene diacetate was then added (357 mg, 1.11 mmol, 1.1 equiv) in one portion and the mixture allowed to stir for 2.5 h. The reaction mixture was then concentrated under reduced pressure to remove iodobenzene and excess alkene. The crude residue was suspended in *i*-PrOH (20 mL, 0.05 M) and treated with 1 N HCl (10.1 mL, 10 equiv). Zinc dust (1.32 g, 20.2 mmol, 20 equiv) was then added in small portions over 10−15 min and the solution allowed to stir for 2 h at room temperature. The suspension was quenched by addition of a saturated solution of $NaHCO_3$ (ca. 15 mL), stirred for 15 min, and filtered through a small plug of Celite, washing with EtOAc (25 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 15 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was then chromatographed on silica gel pretreated with 1:5:19 Et_3N/EtOAc/hexane, eluting with a 20−80% gradient of EtOAc/hexane. The *E*- and *Z*-diastereomers were easily separated and the appropriate fractions combined (ninhydrin used as a developer), affording the corresponding amino esters **16** (125 mg, 65%).

Typical Procedure for the Synthesis of Nitrocyclopropanes. Cyclopropane **5d**[18] was treated with DMSO (7.0 mL) and NaOH (62.6 mg, 1.57 mmol, 1 equiv) dissolved in distilled water (2.5 mL). The reaction mixture was heated to 80 °C for 2 h and then quenched with a saturated solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL), washed with distilled water (3 × 25 mL) and brine (1 × 25 mL), and dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure afforded the crude nitrocyclopropane **17c**. It was purified by column chromatography on silica gel using a 4−10% gradient of EtOAc/hexane, allowing separation of the *trans*- and *cis*-diastereomers of **17c** (301 mg, 96%, 83:17 *trans*/*cis*).

Typical Procedure for the Synthesis of Boc-Protected *trans*-Aminocyclopropanes. The standard reduction procedure was followed as described above. The crude residue was dissolved in anhydrous THF and treated with Et_3N (1.0 equiv), while being cooled in an ice bath. Boc_2O (1.1 equiv) was added in one portion, and the solution was allowed to stir in an ice bath for an additional 10 min before it was removed and allowed to stir at room temperature overnight. The reaction mixture was then concentrated and the residue dissolved in EtOAc. The solution was washed with 10% citric acid (2 × 15 mL) and brine (1 × 25 mL) before being dried over $MgSO_4$. Filtration, removal of the solvent under reduced pressure, and purification by column chromatography on silica gel using a 5−15% gradient of EtOAc/hexane afforded the pure Boc-protected cyclopropanes.

Acknowledgment. This work was supported by NSERC (Canada), Merck Frosst, Boehringer Ingelheim (Canada) Ltd., and the Université de Montréal. R.P.W. is grateful to NSERC (PGS B) for a postgraduate fellowship. We also thank Prof. Jean Lessard and his students for helpful discussions.

Supporting Information Available: General experimental procedures and ^1H and ^{13}C NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO035596Y