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Diastereoselective palladium(0)-catalyzed azidation of 1-alkenylcyclopropyl esters: asymmetric synthesis of (−)-(1*R*,2*S*)-norcoronamic acid

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Abstract

Palladium(0)-catalyzed azidation of (1*R*,2*S*)-1-(1-alkenyl)2-methylcyclopropyl esters **10a**,**b** proceeds with complete retention of configuration to provide, after reduction of the azide and oxidative cleavage of the allylic double bond, the (1*R*,2*S*)-norcoronamic acid **22** (>99% e.e.).

Due to the physiological importance of 1-aminocyclopropanecarboxylic acids (2,3-methanoamino acids) considerable effort has been, and currently still is, devoted towards their total synthesis,[1] and their incorporation into peptidic chains which provide conformationally constrained peptidomimetics with enhanced biological activities.[2] Moreover, incorporation of 2,3-methanoamino acids increases the bioavailability of peptides by reducing their hydrolysis rate (proteolytic degradation).[3] Substituted 1-aminocyclopropanecarboxylic acids also provide enzyme inhibitors, biological probes for mechanistic studies and allow the design of new drugs.[1,2] The different methodologies recently reported for their asymmetric synthesis were mainly based on the cyclopropanation of chiral alkenes or on the enantioselective cyclopropanation performed in the presence of chiral auxiliaries by means of the hazardous diazomethane or Et_2Zn/CH_2I_2 reagents.[4] However, we have previously reported that the base-induced diastereoselective cyclization of 2-(*N*-benzylideneamino)-4-chlorobutyronitriles (d.e. 60–78%)[5] and the palladium(0)-catalyzed substitution on (4*S*)-1-chloropent-2-ene-4-ol (readily available from ethyl (2*S*) lactate) with the anion of *N*-(diphenylmethyleneamino)acetonitrile, followed by a diastereo-selective S_N' cyclization under Mitsunobu conditions (DEAD, PMe_3) (d.e. 88%),[6] provided chiral non-racemic (1*S*,2*S*)-2,3-methanoamino acids (ACCs) with 84–88% enantiomeric excesses.

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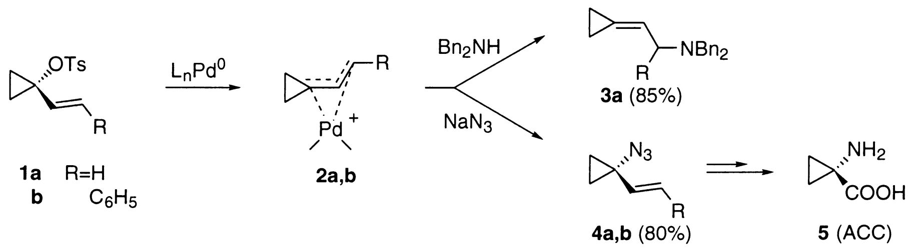
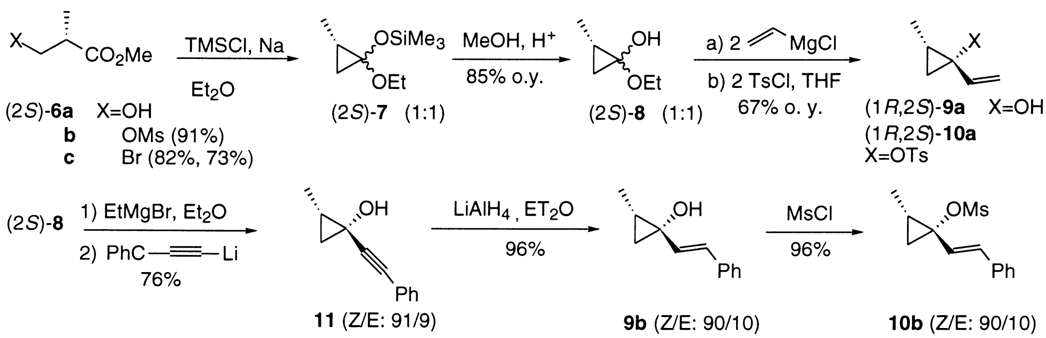
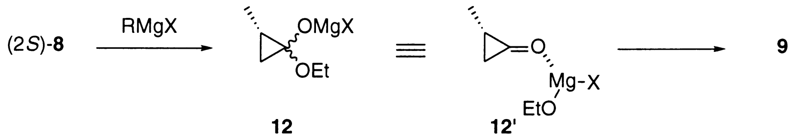


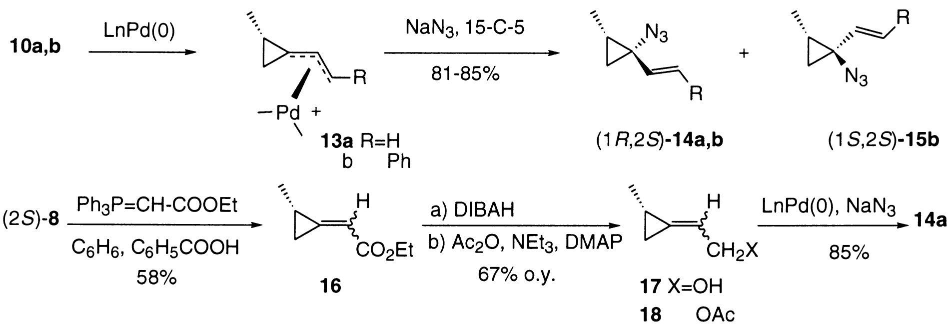
We now report that the palladium(0)-catalyzed azidation of non-racemic 1-(1-alkenyl)cyclopropyl esters can diastereoselectively lead to precursors of (1*R*,2*S*)-ACCs. While the palladium(0)-catalyzed amination with, for example, dibenzylamine of 1-ethenylcyclopropyl tosylate **1a**, which is readily available from cyclopropanone hemiacetal,[7] led exclusively to *N*,*N*-dibenzylcyclopropylideneethylamine **3a** in 85% yield, the palladium(0)-catalyzed azidation of **1a**,**b**, on the other hand, with sodium azide in the presence of 15-crown-5 ether (10%) was reported to provide in 80% yield, the 1-(1-alkenyl)cyclopropyl azides **4a**,**b**, exclusively, suitable precursors of 2,3-methanoalanine **5**.[8] This regioselectivity was shown to result from the non-symmetric charge distribution in the π-1,1-dimethyleneallylpalladium complex **2a** which led to substitution either at the primary allylic end by *soft* nucleophiles (e. g. stabilized carbanions) or on the cyclopropyl ring by *hard* nucleophiles (hydride donors, organometallics, etc., and also by azide).[7]



Commercially available methyl (2*S*) 3-hydroxy-2-methylproponiate **6a** (>99% e.e.)[9] was reacted with mesyl chloride in the presence of NEt_3 to produce the mesylate (2*S*)-**6b** (91%) which was then treated with lithium bromide in NMP to give the bromide (2*S*)-**6c** (82%); alternatively, reaction of (2*S*)-**6a** with carbon tetrabromide/PPh_3 in CH_2Cl_2 led directly to the bromide (2*S*)-**6c**, $[\alpha]_D^{20}=-18$ (c 1, $CHCl_3$), in 73% yield. Cyclization of (2*S*)-**6c** by treatment with sodium in diethyl ether in the presence of chlorotrimethylsilane (Et_2O at reflux) gave a 1:1 diastereomeric mixture of 1-ethoxy-2-methyl-1-trimethylsiloxycyclopropanes (2*S*)-**7**, which on acid-catalyzed methanolysis (MeOH, ClSiMe) led to the hemiacetals (2*S*)-**8** in 85% overall yield from (2*S*)-**6c**.[10] Upon treatment with two equivalents of vinylmagnesium chloride of the 1:1 mixture of (2*S*)-**8**, followed by the addition of two equivalents of tosyl chloride in THF, the (1*R*,2*S*) 2-methyl-1-tosyloxycyclopropane **10a** was obtained directly in 67% overall yield, as a single diastereomer, as revealed by its ^1H and ^{13}C NMR spectra. Likewise, successive addition of one equivalent of ethylmagnesium bromide and of one equivalent of lithium phenylacetylide to (2*S*)-**8** gave in 76% yield a 91:9 diastereomeric mixture of 2-methyl-1-(phenylethynyl)cyclopropanols (**11**), which on lithium aluminum hydride reduction led in 96% yield to the 2-methyl-1-styrylcyclopropanols **9b**. While tosylation of **9b** failed, mesylation was achieved under classical conditions ($MeSO_2Cl$, NEt_3, Et_2O) to produce a 90:10 diastereomeric mixture of the expected mesylates **10b** in 96% yield.

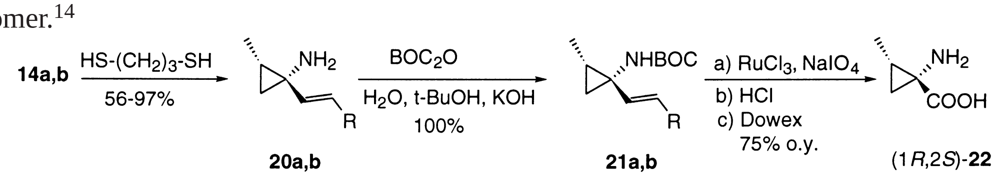


Treatment of the cyclopropanone hemiacetal with one equivalent of Grignard reagent (i.e. methyl-, ethyl- or vinylmagnesium halides) has been shown to produce a magnesium salt which, contrary to the hemiacetal itself, is able to react with organolithium reagents as well as with a second Grignard reagent, to produce 1-alkyl(alkenyl)cyclopropanols in high yields.[11] The diastereoselectivity observed here for the nucleophilic substitutions (2*S*)-**8**→(1*R*,2*S*)-**9a**,**b** strongly suggests that the intermediate magnesium 1-ethoxycyclopropanolate **12** behaves more as the cyclopropanone **12′**, which is probably stabilized by ligation with MgXOEt. In any event, this reaction provides 2-methyl-1-alkenylcyclopropanols like **9a**,**b**, diastereoselectively; non-racemic 1-alkenylcyclopropanols such as **9a**,**b** have also been prepared from the dimethyl (2*S*)-2-methylsuccinate, via sodium-induced acyloin cyclization followed by a diastereoselective C_4→C_3 ring contraction, with total preservation of the chirality of the stereocenter.[12]



Palladium(0)-catalyzed reaction ($Pd(dba)_2$, $2PPh_3$) of the tosylate (1*R*,2*S*)-**10a** and of the 90:10 diastereomeric mixture of mesylates **10b** with sodium azide in the presence of 10% 15-crown-5 ether, gave either the single azide (1*R*,2*S*)-**14a** (R=H) or a 96:4 diastereomeric mixture of azides (1*R*,2*S*)-**14b** and (1*S*,2*S*)-**15b** (R=C_6H_5), respectively, in 81–85% yields. COSY and NOESY experiments on the two-dimensional NMR spectra of the azide **14a** have confirmed the assigned configuration.

Alternatively, reaction of the hemiacetal **8** with ethoxycarbonylmethylenetriphenylphosphorane in benzene in the presence of a catalytic amount of benzoic acid, gave in 58% yield a 2:1 diastereomeric mixture of ethyl 2-(2-methylcyclopropylidene)ethyl acetate **16**[13] which was reduced to the allylic alcohol **17** with DIBAH (CH_2Cl_2, −78°C) and then esterified with acetic anhydride in the presence of DMAP and NEt_3 to give the allylic acetate **18** in 67% overall yield.[8,14] Subsequent palladium(0)-catalyzed azidation of **18**, through the intermediate complex **13a**, provided in 85% yield the same azide **14a** as a single diastereomer.[14]



Reduction of the azides **14a**,**b** with 1,3-propanedithiol in MeOH containing NEt_3,[15] gave the corresponding primary amines **20a**,**b** in 56 and 97% yield, respectively. The lower isolated yield of **20a** most probably was due to its volatility, therefore the total synthesis of the non-racemic (1*R*,2*S*)-norcoronamic acid **22** was performed with the 2-methyl-1-styrylcyclopropylamine **20b**, initially as a 96:4 diastereomeric mixture, as revealed by the ^{1}H NMR spectrum of the crude reduction product, but in fact obtained as a single diastereomer after flash chromatography, $[\alpha]_D^{20}$=+94 (c 1.15, $CHCl_3$).

Subsequent treatment of **20b** with di-*t*-butyldicarbonate in water, containing KOH and *t*-BuOH, provided **21b** in quantitative yield. Finally, oxidative degradation of the styryl group in **21b** by ruthenium tetroxide ($RuCl_3/NaIO_4$),[16] *N*-deprotection by treatment with HCl and ion-exchange chromatography (Dowex 50WX 18) led to the (1*R*,2*S*)-norcoronamic acid **22**,[17] the enantiomeric purity (>99%) of which was determined by deuterium NMR in a cholesteric lyotropic liquid crystal of the deuterated methyl ester of the *N*-(diphenylmethylene)amino acid **22**, following a recently reported accurate method.[18]

It is known that the palladium(0)-catalyzed azidation of allyl esters occurs with *overall retention* of configuration,[19] however, the substitution of the palladium moiety in the chiral complexes **13a**,**b** with the required *inversion* of configuration should lead as previously reported to (cyclopropylideneethyl)amine derivatives (*soft* nucleophile behaviour),[7] while substitution of complexes **13a**,**b** with *retention* of configuration should lead to azides of type (1*S*,2*S*)**-15b** as major products (*hard* nucleophile behaviour).[7,12] Therefore the exclusive formation of azides (1*R*,2*S*)**-14a**,**b** must result via primarily formed (cyclopropylideneethyl) azides and subsequent palladium(0)-induced isomerization[19] which is stereocontrolled by the palladium moiety coordinated to the double bond.

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