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Synthesis of enantiomerically pure vinylcyclopropanes by S_N2' allylic carboxylate displacements

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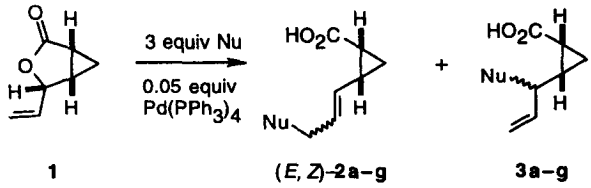
Abstract

Enantiomerically pure vinylcyclopropanes were synthesized from selective palladium-catalyzed and copper-mediated S_N2' nucleophilic reactions of chiral cyclopropyl lactones.

As part of ongoing investigations directed toward inventing methods for the enantioselective synthesis and elaboration of cyclopropanes,[1] we have developed a general approach to enantiomerically pure vinyl cyclopropanes that features the palladium- and copper-mediated S_N2' openings of selected cyclopropyl vinyl lactones. Because vinyl cyclopropanes have recently been exploited as intermediates for the construction of fused [5.3.0] and [5.4.0] bicyclic ring systems,[2] methods for the concise synthesis of enantiomerically pure vinyl cyclopropanes could find application in the synthesis of a variety of natural products.

The cyclopropyl vinyl lactone **1** (>94% ee), which is readily available by asymmetric cyclopropanation of the diazoester of divinyl carbinol,[3] underwent palladium-catalyzed displacement by a variety of nucleophiles to furnish vinyl cyclopropanes (*E,Z*)-**2a–g** together with smaller amounts of the allyl cyclopropanes **3a–g** (Scheme 1 and Table 1). For example, stabilized carbon (entries 1–4), oxygen (entry 5), and nitrogen (entries 6,7) nucleophiles induced the S_N2' opening of the lactone ring. The *E*-isomer was the major S_N2' product,[4] and in those cases wherein a mixture of S_N2' and S_N2 products was formed (entries 3,4,6), the S_N2' product dominated.[5]



1 (*E, Z*)-**2a–g** **3a–g**

Scheme 1.

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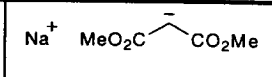
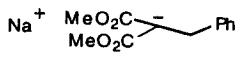
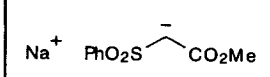
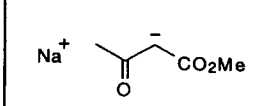
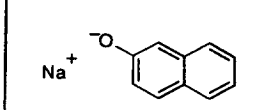
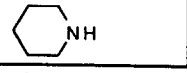
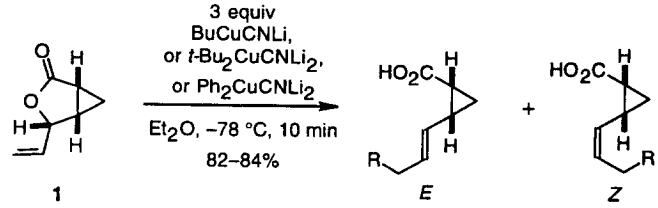
Table 1
Pd(0)-catalyzed reactions of cyclopropyl vinyl lactone **1** with nucleophiles[10]

Entry	nucleophile	conditions	product	yield (%)[a]	2*E*:2*Z*:3
1		rt, 43 h, THF[b]	**2a**	76	100:0:0[c]
2		reflux, 10 min, THF	**2b**	87	95:5:0
3		50 °C, 7 h, THF	**2c**[d]	49	89:0:11
4		rt, 1 h, THF	**2d**[d]	63	86:9:5
5		reflux, 5 min, THF[b,e]	**2e**	78	90:10:0
6	$TMSN_3$	rt, 1 h, CH_2Cl_2[f,g]	**2f**	81	89:9:2
7		reflux, 70 min, CH_2Cl_2[f,h]	**2g**	82	80:20:0

[a]Combined yield of all adducts isolated. [b]With 0.5 equiv PPh_3. [c]Ratios determined from analysis of crude ^1H NMR spectra. [d]1:1 mixture of diastereomers from the stereocenter on the site of attack. [e]1.2 equiv nucleophile. [f]0.1 equiv $Pd(PPh_3)_4$. [g]1.5 equiv nucleophile. [h]Isolated as the methyl ester after treatment with $SOCl_2$ in MeOH.

Although a number of different stabilized enolates were well suited as nucleophilic partners in these reactions, identifying effective nitrogen nucleophiles was somewhat more difficult. For example, a variety of simple amino group equivalents failed to induce lactone opening of **1** via a $Pd(PPh_3)_4$-catalyzed S_N2' reaction; these include $HN(Boc)_2$ in THF/DMF,[6] $TsNH_2$ in THF/DMSO,[7] and potassium phthalimide in THF. Sodium azide in aqueous THF gave a trace amount of the S_N2' azido acid product **2f** after 24 h at 50°C.[8] A modification of this procedure using $TMSN_3$ in anhydrous CH_2Cl_2 gave azido adducts in 81% yield.[9] When secondary amines such as piperidine were employed as nucleophiles, the reaction to form the amino acid product **2g** was found to be highly solvent dependent. For example, use of acetonitrile as solvent did not provide as high a yield as methylene chloride, and there was no observable reaction in refluxing THF.

We also examined the copper-mediated S_N2' reactions of lactone **1** with a number of lower and higher order cyano organocuprates as illustrated in Scheme 2.[11] Primary and tertiary alkyl groups as well as aromatic rings could be transferred to **1** to give the corresponding vinyl cyclopropanes **4a–c** in excellent

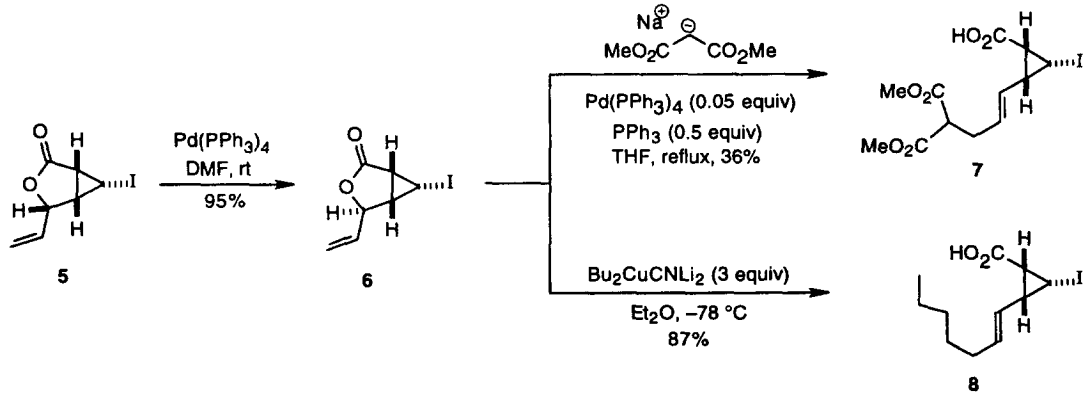


4a: R = Bu *E*:*Z* >20:1
4b: R = *t*-Bu *E*:*Z* = 5:1
4c: R = Ph *E*:*Z* = 4:1

Scheme 2.

yields. As with the Pd-catalyzed reactions, the geometry of the double bond in the products **4a–c** was predominantly *E*, although the reactions with tertiary alkyl and aryl cuprates appeared to be less stereoselective. This preference for the formation of *E* olefins in cuprate reactions on similar substrates has been observed previously.[12]

Owing to an interest in preparing more highly substituted and functionalized vinyl cyclopropanes, we examined the S_N2' reactions of the iodo cyclopropane **6**, which was conveniently prepared by the Pd(0)-catalyzed isomerization of the known lactone **5**[3] (Scheme 3). It is notable that both palladium- and copper-mediated allylic S_N2' carboxylate displacements can be executed on **6** to give compounds such as **7** and **8** without deleterious reaction or reductive cleavage of the cyclopropyl iodide function. This selectivity then allows for subsequent manipulation of the cyclopropyl iodide to introduce a variety of carbon substituents onto the cyclopropane ring, thereby generating a diverse class of highly functionalized compounds bearing a rigid interior core.[13]



Scheme 3.

In summary, we have demonstrated that enantiomerically pure vinyl cyclopropanes can be generated by palladium-catalyzed S_N2' reactions of chiral cyclopropyl vinyl lactones; cyano organocuprates also react with these cyclopropyl vinyl lactones to give the products of S_N2' opening of the lactone moiety. While the Pd-mediated reaction could be performed with stabilized nucleophiles, the cuprate reaction allowed for the complementary formation of vinyl cyclopropanes from unstabilized carbanions. However, unlike the palladium reactions, none of the cuprate reactions afforded isolable amounts of products arising from S_N2 attack. Studies in the application this method to the synthesis of natural and unnatural products will be reported in due course.

Acknowledgements

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10. Representative procedures: Pd-catalyzed synthesis of **2b**. Compound **1** (25 mg, 0.20 mmol) was dissolved in THF (2 mL), and $Pd(PPh_3)_4$ (11 mg, 0.0097 mmol) was added in succession. In a separate flask, NaH (60% dispersion in mineral oil, 24 mg, 0.60 mmol) was added to a solution of benzyl dimethyl malonate (135 mg, 0.61 mmol) in THF (2 mL) with stirring at rt. Each flask was stirred at rt for 10 min. The benzyl dimethyl sodiomalonate solution was then added by syringe to the solution containing **1**, and this mixture was heated to reflux for 10 min. The reaction was quenched by cooling to 0°C, and adding aqueous 1N $NaHSO_4$ (1 mL). CH_2Cl_2 (5 mL) was added, and the layers were separated. The aqueous was extracted with CH_2Cl_2 (2×5 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc:hexane (2:3 to 1:1) to give 60 mg (87%) of **2b** as a clear, colorless oil in a 19:1 ratio of *E*:*Z* isomers by crude ^1H NMR. Cu(I)-mediated synthesis of **4a**. CuCN (54 mg, 0.60 mmol) was suspended in ether (4 mL) under Ar, then cooled to −78°C. To this was added *n*BuLi (2.37 M in hexanes, 250 μL, 0.60 mmol) slowly by syringe. The mixture was then allowed to warm to −40°C, whereupon the grey suspension became a dark red-brown solution of BuCuCNLi. After 30 min, the solution was cooled back to −78°C, and **1** (25 mg, 0.20 mmol) in ether (2 mL) was added over 5 min. This was stirred at −78°C for 10 min, after which the reaction was quenched by addition of aqueous 1N HCl (3 mL), and the mixture was allowed to warm to rt. Caution! Workup releases highly noxious HCN gas and should only be done in a well ventilated hood! The layers were separated, and the aqueous layer was extracted with ether (3×4 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O:pentane (1:1) to give 30 mg (82%) of **4a** as a clear, colorless oil.
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