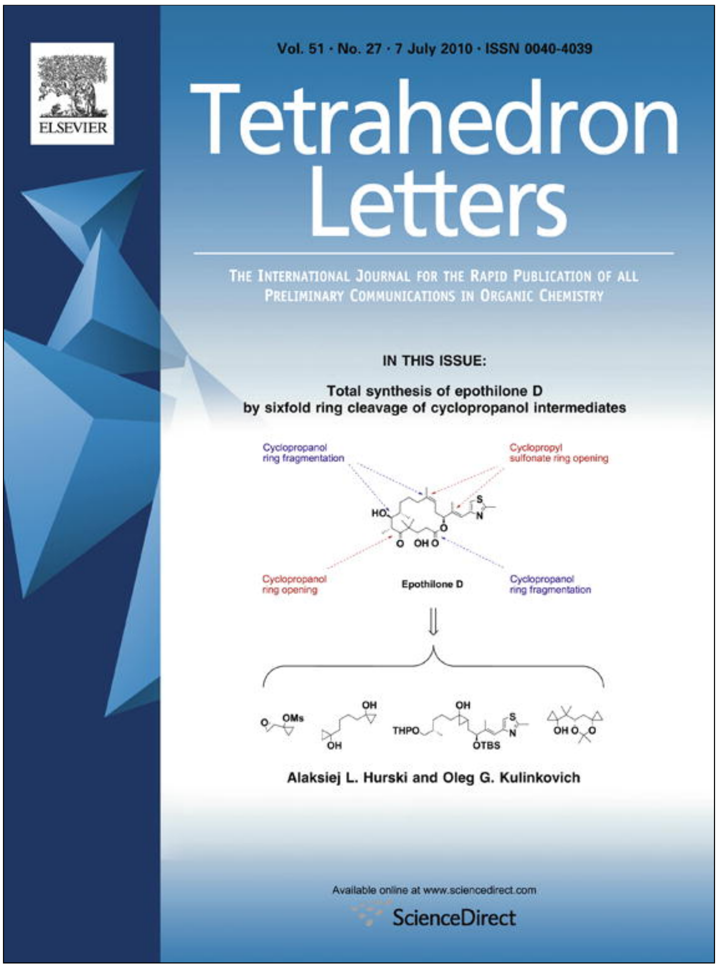
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Palladium(II)-catalyzed dicarboxymethylation of chiral allylic alcohols: chirality transfer affording optically active diesters containing three contiguous chiral centers

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ABSTRACT

This manuscript describes the extension of Stille's palladium-catalyzed olefin dicarbonylation reaction to chiral allylic alcohols with chirality transfer to afford the corresponding chiral alcohol functionalized with bis-carbomethoxy esters, containing three contiguous chiral centers, in good to excellent diastereoselectivities (78–98%).

1. Introduction

Enantiopure chiral materials are of key importance, particularly in the preparation of bioactive pharmaceuticals and more recently in liquid crystals, and palladium catalysis can be used in the construction of new asymmetric centers, either asymmetric catalysis or through the intramolecular transfer of existing chirality within a molecule. The directing influence of the hydroxyl group has been demonstrated for a number of reactions of chiral allylic alcohols,[1–9] and stereoselectivities of over 98% have been demonstrated for some reactions.[10–13] We presently wish to report the extension of chirality transfer from chiral allylic alcohols utilizing Stille's palladium-catalyzed olefin dicarbonylation reaction.[14] In this context is it noteworthy that a number of groups have explored the use of chiral catalysts with the Stille bis-alkoxycarbonylation for the asymmetric construction of chiral bis-esters. Inomata and coworkers recently reported the palladium-catalyzed asymmetric bis(alkoxycarbonylation) of cyclic olefins in the presence of copper triflate.[15] Liang et al. have described a palladium-catalyzed asymmetric biscarbonylation of terminal olefins using chiral *S*,*N*-heterobidentate ligands.[16] Takeuchi described a palladium-catalyzed asymmetric bis(alkoxycarbonylation) reaction of terminal olefins in the presence of copper(I) triflate using a chiral bioxazoline ligand to give optically active mono-substituted succinates with enantioselectivities up to 66% ee,[17] while Sperrle reported the enantioselective bis-alkoxycarbonylation of 1-olefins to substituted succinates using cationic palladium(II) complexes with C2 symmetric chelating ligands, and also the use of cationic palladium(II) complexes to catalyze multiple carbonylation of 1-olefins to 2-oxopentanedioates and to butanedioates.[18] The dicarbonylation reaction is catalyzed by a $PdCl_2$–$CuCl_2$ system in methanol under basic conditions at low CO pressures (3 atm) to give diesters with an overall *syn* addition.[19–27] While chirality transfer generally involves transfer of optical activity from one carbon to another, this allylic dicarbonylation that we now report involves a double insertion of CO to give diesters containing three contiguous chiral centers.

2. Results and discussion

The bis-carbonylation with chirality transfer was first tested with the chiral cyclic allylic alcohol (*R*)-(+)-cyclopent-2-en-1-ol[28] (**1**). Cyclopent-2-enone underwent clean 1,2-reduction to afford compound (*R*)-(+)-**1** in 78.3% isolated yield and 71% ee by reduction with chiral (*R*)-oxazaborolidine[29–31] and borane. Kita reported a similar asymmetric reduction of a cyclic enone with an oxazaborolidine[32] and Matusuo recently reported the oxazaborolidine-catalyzed asymmetric reduction of α-methylene ketones using borane-diethylaniline as a stoichiometric reducing agent.[33] The absolute configuration of **1** was determined based upon measurement of rotation and comparison with literature values.[34] Treatment of (*R*)-(+)-**1** with $PdCl_2$ and $CuCl_2$ in methanol at room temperature under an atmosphere of CO (3 atm) in the presence of trimethyl orthoformate to remove adventitious water gave two products in 65% and 35% relative yields as determined by gas chromatography. The two products were identified by ^{1}H and ^{13}C NMR to be (1*S*,2*S*,3*R*)-dimethyl 3-hydroxycyclopentane-1,2-dicarboxylate (**2**) and (*S*)-methyl 3-oxocyclopentanecarboxylate (**3**), respectively (Scheme 1). The ee of **2** was established to be 69.7% as determined by ^{1}H NMR in the presence of lanthanide shift reagent Eu(hcf)$_3$, thus the reaction proceeded in 98% diastereoselectivity (Table 1), representing the efficiency of chirality transfer from the asymmetric carbinol center. As noted, allylic alcohol (*R*)-(+)-**1** was utilized with 71% ee, such that complete diastereoselectivity

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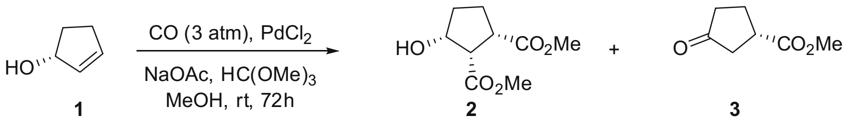
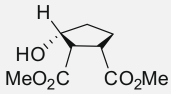
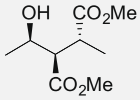
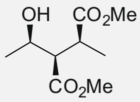
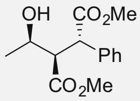
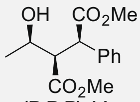


Scheme 1. Dicarbonylation of (*R*)-(+)-**1**.

Table 1
Stereochemistry of dicarbonylated products from various allylic alcohols

Substrate	%ee of substrate	Dicarbonylated product	%Yield	%ee of Dicarbonylated product[a]	Diastereo-selectivity[b]
(*R*)-(+)-Cyclopent-2-en-1-ol (**1**)	71	 (1*S*,2*S*,3*R*)-**2**	45	69.7	98
R-(+)-(*Z*)-Pent-3-en-2-ol [(*Z*)-**9**]	86	 **(R,R,R)-10**	52	82.7	96
(*R*)-(−)-(*E*)-Pent-3-en-2-ol [(*E*)-**9**]	83	 **(R,R,S)-10**	29	64.7	78
(*R*)-(*Z*)-4-Phenyl-3-butene-2-ol [(*R*)-(*Z*)-**13**]	87	 **(R,R,S)-14**	41	80.7	93
(*R*)-(*E*)-4-Phenyl-3-buten-2-ol [(*R*)-(*E*)-**13**]	75.3	 **(R,R,R)-14**	36	64.7	86

[a] Average of three ee values determined for each of the three asymmetric centers by ^{1}H NMR using the chiral shift reagent Eu(hcf)$_3$.
[b] Diastereoselectivity (efficiency of chirality transfer) = product ee/ee of substrate × 100%.

in the bis-alkoxycarbonylation would yield diester of ee identical to the starting allylic alcohol. The relative stereochemistry of the dicarbonylation product **2** was established by ^{1}H NMR, and NOE studies. The *J* values of H_b with H_a and H_c, respectively are 8.0 and 15.6 Hz. These values are consistent with the *syn* stereochemistry between H_a, H_b and H_c. Since the absolute configuration at C-1 is known to be *R*, the absolute configuration at C-1 and C-2, bearing the carbomethoxy groups, must both be *S*. The relative stereochemistries of H_a, H_b and H_c were also confirmed on the basis of NOE studies (Fig. 1). The all-*syn* relative stereochemistry evident by the 10.2% enhancement of the signal for H_a upon irradiation of H_b and the 13.3% enhancement of the signal for H_c. The cis stereochemistry is as predicted for the double-carbonylation reaction.[35]

The product distribution and relative stereochemistries are consistent with the proposed mechanism (Scheme 2), similar to the mechanism proposed by Uenishi[13] for an intramolecular palla-

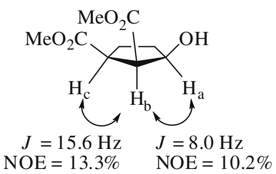
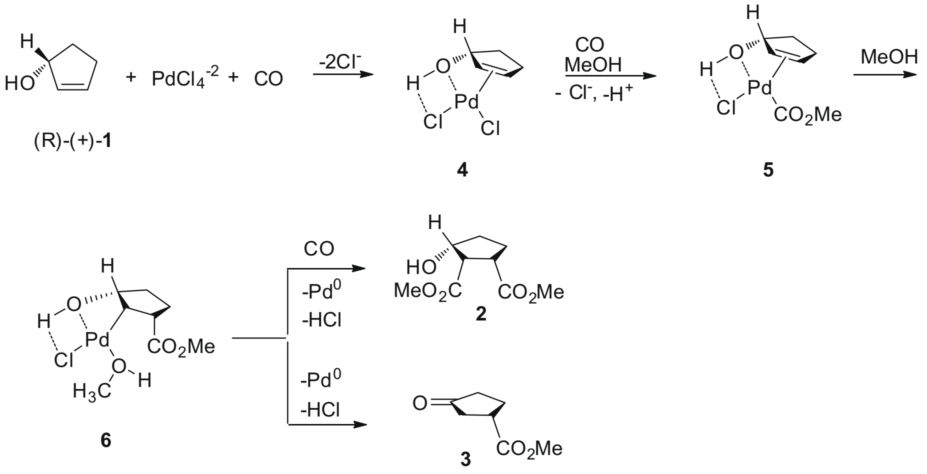


Figure 1. Confirmation of all-*cis* stereochemistry of dicarbonylated product **2** based on vicinal coupling constants and NOE correlations.

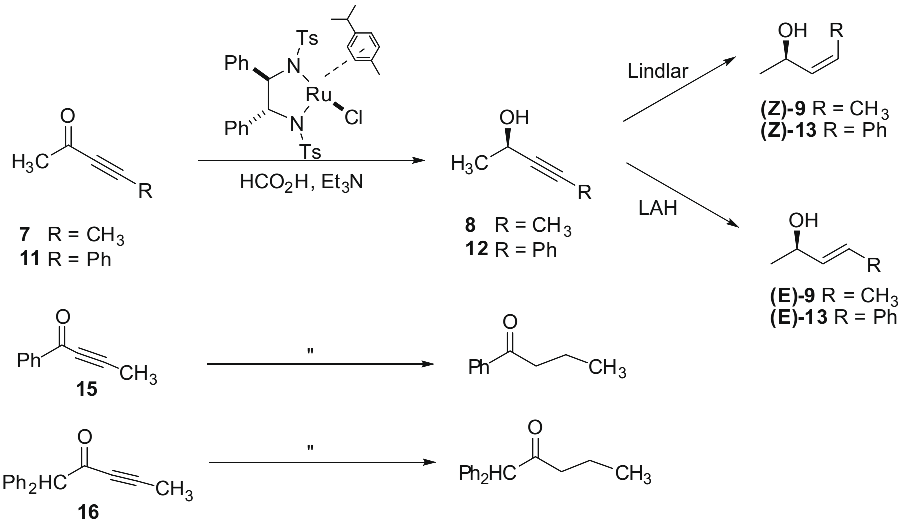
dium(II)-catalyzed oxypalladation and 1,3-chirality transfer. Thus, the hydroxyl group directs the palladium to the face that produces the most stable π-complex **4**, which in turn depends on the absolute configuration of the starting allylic alcohol **1**.[4,10–13] Addition of carbon monoxide to complex **4** followed by insertion of methanol yields the olefin-carbomethoxypalladium intermediate **5**, which undergoes insertion of the carbomethoxy group to produce the σ-complex **6**.[14,19] Adduct **6** then either undergoes further *syn* addition of CO to give desired **2**, or loses a proton and eliminates palladium yielding an enol which tautomerizes to ketone **3**.

Next we examined the carbomethoxylation of (*R*)-(*Z*)-pent-3-en-2-ol [(*Z*)-**9**] and (*R*)-(*E*)-pent-3-en-2-ol [(*E*)-**9**]. Both isomers were prepared from the reduction of (*R*)-(+)-pent-3-yn-2-ol (**8**) (Scheme 3). (*R*)-(+)-pent-3-yn-2-ol (**8**) was prepared in 85% yield by the reduction of 3-pentyn-2-one **7** with chiral (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)] reagent in formic acid/triethylamine isotropic mixture according to the general method of Bogliotti.[36] A sample of (*R*)-(*Z*)-**9** was prepared in 86% ee by reduction of the triple bond with Lindlar's catalyst[37] while (*R*)-(*E*)-**9** was prepared in 83% ee by reduction with $LiAlH_4$.[38] GLC and ^{1}H NMR analysis showed that each sample was greater than 95% of the desired double bond geometric isomer.

Dicarbomethoxylation of each geometric isomer of **9** independently was carried out in the same manner as for the substrate (*R*)-(+)-**1** (Table 1). (*R*)-(*Z*)-**9** afforded three products as shown by GLC, which were identified by NMR spectroscopy to be the desired (2*R*,3*R*)-dimethyl 2-((*R*)-1-hydroxyethyl)-3-methylsuccinate [(*R*,*R*,*R*)-



Scheme 2. Proposed mechanism for the palladium-catalyzed bis-alkoxycarbonylation of allylic alcohols with chirality transfer.



Scheme 3. Preparation of *Z* and *E* allylic alcohols **9** and **13**.

10] in 80% relative yield, plus 4-methoxy-pentan-2-one in 10% yield, and 4-acetoxy-pentan-2-one in 10% yield. A pure sample of (*R*,*R*,*R*)-**10** was obtained by gas chromatography and the enantiomeric excess was determined by ^{1}H NMR in the presence of chiral shift reagent Eu(hfc)$_3$ to be 82.7%, thus the diastereoselectivity was 96%. The dicarbonylation of (*R*)-(*E*)-**9** afforded the desired dicarboxymethylation product (2*R*,3*S*)-dimethyl 2-((*R*)-1-hydroxyethyl)-3-methylsuccinate, (*R*,*R*,*S*)-**10**, in 45% relative yield, plus 4-methoxy-pentan-2-one, 4-acetoxy-pentan-2-one, and 4-carbomethoxy-pentan-2-one, and 5%, 20%, and 30% relative yields, respectively. A pure sample of (*R*,*R*,*S*)-**10** was collected by GLC and analyzed by ^{1}H NMR in the presence of the lanthanide shift reagent Eu(hcf)$_3$ to establish an ee of 64.7%, representing a diastereoselectivity of 78%. The relative configurations of stereogenic centers in the carbonylated products (**10**) of (*R*)-(*Z*)-**9** and *R*-(*E*)-**9** were confirmed by NOE. NOE has been used previously to assign absolute configurations of cyclic systems[39] and the theory for acyclic systems such as **9** with restricted rotation has also been presented.[40] Shown in Figure 2 are the NOE assignments for the most stable rotamers of the two products. These assignments are in agreement with all the information from ^{1}H–^{1}H NOESY NMR. The assignment of absolute configuration is consistent with the expected initial *syn* addition of the elements of the carbomethoxy-Pd(II) moiety shown in Scheme 2.

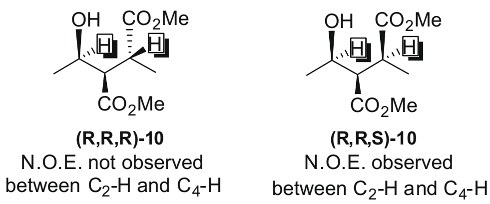


Figure 2. Assignment of relative stereochemistry of stereoisomers of **10** based on NOE.

Carbonylation of allylic alcohols (*R*)-(*Z*)-4-phenyl-but-3-ene-2-ol [(*R*)-(*Z*)-**13**] and (*R*)-(*E*)-4-phenyl-3-buten-2-ol [(*R*)-(*E*)-**13**] were then evaluated. Propargyl alcohol **12** was prepared in 87% ee with (*R*) absolute configuration by the reduction of propagyl ketone **11** again using (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)] as outlined in Scheme 3. Allylic alcohol (*R*)-(*Z*)-**13** was prepared in 87% ee by the reduction of the propagyl alcohol (*R*)-4-phenyl-but-3-yne-2-ol (**12**) using Lindlar's catalyst. Allylic alcohol (*R*)-(*E*)-**13** was prepared in 75% ee by the reduction of **12** using LiAlH$_4$.

Carbomethylation of (*R*)-(*Z*)-**13** afforded three products that were isolated and purified by flash chromatography. NMR analysis showed the compounds to be 4-methoxy-4-phenylbutan-2-one, 4-acetoxy-4-phenyl-butan-2-one, and the desired (2*R*,3*S*)-dimethyl 2-((*R*)-1-hydroxyethyl)-3-phenylsuccinate (*R*,*R*,*S*)-**14**, in 41% yield. The ee of (*R*,*R*,*S*)-**14** was determined by ^{1}H NMR in the presence of the lanthanide shift reagent Eu(hcf)$_3$ to be 80.7%, representing a diastereoselectivity of 93%. Dicarbomethoxylation of (*R*)-(*E*)-**13** also produced three products, which were isolated and purified by flash chromatography. ^{1}H NMR analysis showed the compounds to be 4-methoxy-4-phenylbutan-2-one, 4-acetoxy-4-phenyl-butan-2-one, and the (2*R*,3*R*)-dimethyl 2-((*R*)-1-hydroxyethyl)-3-phenylsuccinate (*R*,*R*,*R*)-**14** in 17%, 27% and 56% yield, respectively. The diastereomeric ratio for (*R*,*R*,*R*)-**14** was determined by ^{1}H NMR in the presence of the lanthanide shift reagent Eu(hcf)$_3$ to be 64.7%, thus the dicarbomethoxylation proceeded in 86% diastereoselectivity.

We also attempted to prepare (*R*)-1-phenyl-3-butyn-1-ol and (*R*)-1,1-dipheny-4-pentyne-2-ol utilizing (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine)(*p*-cymene)] from the corresponding propargyl ketones **15** and **16**, but only clean 1,4-reduction occurred as shown in Scheme 3. These results indicate that 1,2-reduction of propargyl ketone to chiral allylic alcohol using this chiral ruthenium reagent may be limited to propargyl ketones with a non-bulky group on the α carbon.

In summary, we have demonstrated the utilization of asymmetric dicarboxymethylation of allylic alcohols for the preparation of materials containing three contiguous asymmetric centers in good to excellent (78–98%) diastereoselectivities.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.105.

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