Communication

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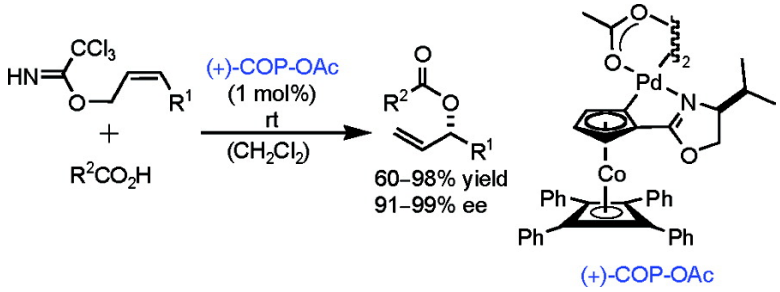

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Catalytic Asymmetric Synthesis of Chiral Allylic Esters

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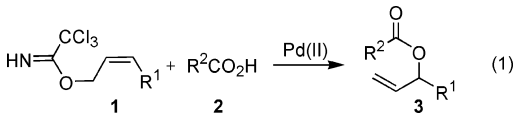
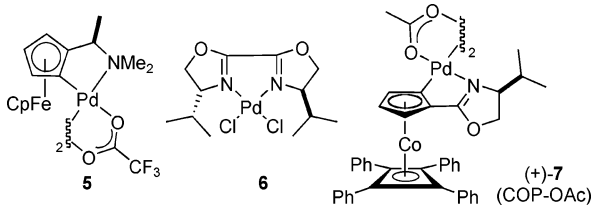
Chiral allylic alcohols and their derivatives are important intermediates in the synthesis of many biologically active compounds. The most widely used method to prepare 1-alken-3-ols, or their ester derivatives, in high enantiomeric purity is by kinetic resolution.[1−3] An alternative enantioselective approach involves formation of the carbon−oxygen bond. Transition-metal-catalyzed allylic substitution has been used to prepare enantioenriched allylic ethers from the reaction of achiral allylic carbonates with phenoxides[4] or aliphatic alkoxides,[5] although these products are not readily converted into the corresponding enantioenriched allylic alcohols. In this communication, we report the first catalytic asymmetric synthesis of 3-acyloxy-1-alkenes, products readily transformed to enantioenriched allylic alcohols.

Recently, we reported that prochiral (*E*)-allylic trichloroacetimidates can be transformed into chiral allylic trichloroacetamides, and the corresponding amines, of high enantiopurity by a palladium(II)-catalyzed asymmetric allylic rearrangement.[6] In this reaction, the catalyst is believed to activate the carbon−carbon π-bond for attack by the internal nitrogen nucleophile, with the trichloroacetimidate functional group eventually serving also as a leaving group by undergoing carbon−oxygen bond cleavage. We report herein that prochiral (*Z*)-allylic trichloroacetimidates **1**, which only slowly undergo palladium(II)-catalyzed allylic imidate rearrangements,[6] react efficiently with carboxylic acids to give chiral allylic esters **3** (eq 1). When the palladium(II) catalyst is COP-OAc [(+)-**7**][7,8] or its enantiomer, *ent*-COP-OAc [(−)-**7**], the 3-acyloxy-1-alkene products **3** are produced in high enantiopurity.



1 **2** **3** (1)

The reaction of (*Z*)-allylic trichloroacetimidates **1**[9] and acetic acid to give racemic allylic acetate **3** (R^2 = Me) is catalyzed by palladium(II) acetate (**4**) at room temperature [5 mol % catalyst **4**, CH_2Cl_2/HOAc (2:1 v/v; 1 M)];[10] in the absence of $Pd(OAc)_2$, the formation of allylic acetates **3** is not observed under these conditions. The transformation of prochiral trichloroacetimidate **1a** to enantioenriched acetate **3a** (R^1 = *n*-Pr) was examined using 1 mol % of a variety of chiral palladium(II) complexes (CH_2Cl_2, 1.5 M, room temperature, 3 equiv of glacial acetic acid). Of the 12 catalysts screened, complexes **5**−**7** proved to be the most effective. Cyclopalladated catalyst **5**[11] displayed excellent reactivity (100% conversion after 16 h); however, acetate **3a** was formed in low enantiopurity (~3% ee). Bisoxazoline complex **6**[12] exhibited lower reactivity (38% conversion after 16 h) and slightly improved enantioselectivity (12% ee). By far, the best catalyst was COP-OAc [(+)-**7**], which provided (*R*)-allylic acetate **3a** in 88% yield and 94% ee. Solvent had a marked influence on catalytic efficiency. Reactions of allylic imidate **1a** with 3.0 equiv of HOAc in the presence of 1 mol % COP-OAc at room temperature followed the order: CH_2Cl_2 (88%, 17 h) > THF (69%, 16 h) > benzene (43%, 16 h) > MeCN (8%, 17 h). With the exception of MeCN, these reactions provided (*R*)-**3a** in high enantiopurity (91−94% ee).



The scope of the reaction of (*Z*)-allylic trichloroacetimidates **1** with carboxylic acids **2** (3 equiv) in the presence of 1 mol % COP-OAc, (+)-**7**, or its enantiomer, (−)-**7**, is summarized in Table 1. Imidate **1a** and acetic acid gave acetate **3a** with excellent enantioselectivity after 17 h at 0°C, albeit in low yield (entry 1). However, this reaction occurred at a practical rate at room temperature or at 38 °C, with higher enantioselectivity (94%) being realized at room temperature (entries 2−4). At room temperature, reactions of imidate **1a** with other aliphatic or aromatic carboxylic acids provided the corresponding allylic esters **3g**−**l** in 91−99% ee and good yield (60−98%)[13] (entries 5−11). The reaction of substrate **1b** (R^1 = *i*-Bu) with acetic acid also took place in high yield and with high enantioselection (entry 12). The presence of heteroatom substituents in the allylic imidate was well tolerated. Trichloroacetimidate **1c** containing a free hydroxyl group gave acetate **3c** in high yield and enantioselectivity (97% ee) (entry 13), as did substrates containing ester, ether, or silyl ether functional groups (entries 14−17).

Several additional observations merit note. The reactions reported in Table 1 were remarkably clean, taking place without the formation of any significant byproducts.[14] Of primary importance, the corresponding *Z* or *E* prochiral primary allylic esters were not seen by ^{1}H NMR analysis of crude reaction mixtures; for **3a**, capillary gas chromatography indicated the branched-to-linear ratio to be extremely high (800:1).[15,16] The reaction was slowed markedly when R^1 was branched [R^1 = cyclohexyl, 45% yield and 90% ee after 48 h in the presence of 2 mol % (+)-**7**]; in this case, the branched-to-linear ratio was 92:8. Primary allylic trichloroacetimidates containing a second alkyl substituent at C3 did not provide the corresponding enantioenriched tertiary allylic esters, forming instead mixtures of primary and racemic branched tertiary allylic esters. The use of sodium acetate or ammonium acetate instead of acetic acid resulted in no product formation. Reaction of the *E* stereoisomer of trichloroacetimidate **1a** with acetic acid in the presence of 5 mol % COP-OAc [(+)-**7**] provided (*S*)-**3a** in low yield and enantioselectivity (42%, 54% ee).

A plausible mechanism for the catalytic nucleophilic displacement reaction reported herein is shown in Scheme 1. Reversible coordination of COP-OAc to the imidate nitrogen produces complex **9**, which after loss of an acetate ligand, activates the prochiral olefin for attack by the external carboxylic acid nucleophile to give

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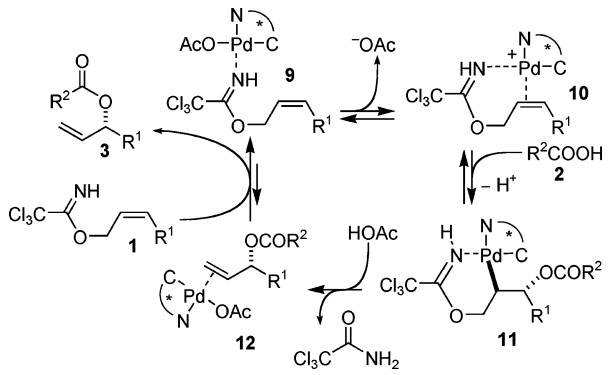
Table 1. Enantioselective Formation of Allylic Esters **3** from (*Z*)-Allylic Trichloroacetimidates **1** and Carboxylic Acids **2**[a]

entry	R^1 (**1**)	R^2 (**2**)	catalyst	time [h]	temp [°C]	**3**	yield [%][b]	ee [%][c] (config)
1	*n*-Pr (**1a**)	Me (**2a**)	(+)-**7**	17	0	**3a**	17[d]	96 (*R*)[e]
2	**1a**	**2a**	(+)-**7**	17	23	**3a**	88	94 (*R*)[e]
3	**1a**	**2a**	(+)-**7**	17	38	**3a**	94	87 (*R*)[e]
4[f]	**1a**	**2a**	(−)-**7**	20	23	*ent*-**3a**	91	94 (*S*)[e]
5[g]	**1a**	CH_2Ph (**2b**)	(+)-**7**	20	23	**3g**	90	91[h]
6	**1a**	*i*-Pr (**2c**)	(+)-**7**	21	23	**3h**	89	92
7[g]	**1a**	Ph (**2d**)	(+)-**7**	16	23	**3i**	98	94 (*R*)[i]
8[j]	**1a**	Ph (**2d**)	(−)-**7**	18	23	*ent*-**3i**	100	>99 (*S*)[i]
9[g]	**1a**	C_6H_4(*p*-NO_2) (**2e**)	(+)-**7**	26	23	**3j**	60	94[h]
10[g]	**1a**	C_6H_4(*o*-MeO) (**2f**)	(+)-**7**	10	23	**3k**	92	>99[h]
11[g]	**1a**	2-naphthyl (**2g**)	(+)-**7**	17	23	**3l**	87	96[h]
12	*i*-Bu (**1b**)	**2a**	(+)-**7**	14	23	**3b**	96	93
13	CH_2OH (**1c**)	**2a**	(+)-**7**	17	23	**3c**	92	97 (*S*)[k]
14	CH_2OAc (**1d**)	**2a**	(+)-**7**	8	23	**3d**	90	>99 (*S*)[k]
15	CH_2OPMB (**1e**)	**2a**	(+)-**7**	16	23	**3e**	93	>99 (*S*)[k]
16	$(CH_2)_3OTBS$ (**1f**)	**2a**	(+)-**7**	17	23	**3f**	98	93 (*R*)[l]
17	**1f**	**2d**	(−)-**7**	20	23	*ent*-**3m**	93	>99[h] (*S*)[e]

[a] Conditions: 0.15 mmol of **1**, 1 mol % **7**, 0.45 mmol of **2**, CH_2Cl_2 (1.5 M). [b] Yield of pure product after column chromatography. [c] Determined by GC analysis unless otherwise indicated. [d] The remainder of the mass was **1a**. [e] Absolute configuration by the Mosher method (ref 20). [f] With 4.1 mmol of **1a**, 1 mol % **7**, 13.5 mmol of **2a**, CH_2Cl_2 (0.5 M). [g] At 0.5 M. [h] Determined by HPLC analysis. [i] Absolute configuration by optical rotation (ref 2c). [j] With 0.6 mmol of **1a**, 1 mol % **7**, 1.8 mmol of **2d**, CH_2Cl_2 (0.2 M). [k] Absolute configuration by synthesis from (*S*)-3-butene-1,2-diol. [l] Absolute configuration by optical rotation (ref 1c).

Scheme 1. Mechanism (Illustrated for Catalysis by (+)-COP-OAc)



palladacyclic intermediate **11**. Deoxypalladation of this intermediate produces complex **12** and ultimately the 3-acyloxy-1-alkene and 2,2,2-trichloroacetamide.[17]

In summary, the first catalytic asymmetric allylic esterification reaction is described. This reaction proceeds with predictable high stereoinduction,[18] is accomplished at room temperature using low catalyst loadings, and likely proceeds by a novel mechanism. The use of trichloroacetimidates as leaving groups[19] is particularly convenient as these intermediates can be prepared in high yield by simple base-catalyzed condensation of allylic alcohols and trichloroacetonitrile.[9] We anticipate additional applications of this concept for catalytic asymmetric carbon−carbon and carbon−heteroatom bond formations.

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Supporting Information Available: Representative experimental procedures, copies of HPLC and GC traces used to determine enantiopurity, copies of ^{1}H NMR spectra and GC traces of crude **3a**, and copies of ^{1}H NMR spectra of **1a**−**f**, and ^{1}H and ^{13}C NMR of **3a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) COP-OAc can be generated from COP-Cl[7,8] by reaction in CH_2Cl_2 at room temperature with 2.5 equiv of AgOAc, followed by filtration through silica gel. (*S*)-COP-Cl is available from Aldrich Chemical Co. (64663−6); both (*S*)- and (*R*)-COP-OAc will soon be available commercially.

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(10) When carried out under these conditions, (*Z*)-allylic trichloroacetimidates **1a**−**g** provided the corresponding allylic acetates **3a**−**g** in 82−99% yields.

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(13) Low solubility of **2e** in CH_2Cl_2 is likely responsible for the moderate yield in forming **3j** (entry 9).

(14) In the presence of water (>0.01% v/v), (*Z*)-hex-2-enyl trichloroacetate was identified as a minor byproduct (**1a** + **2a** → **3a**). This byproduct was not formed when commercial glacial acetic acid (contains <0.01% acetic anhydride) was used.

(15) The limits of detection by this method are approximately 1000:1.

(16) With HOAc concentrations in CH_2Cl_2 >4.5 M, the branched:unbranched ratio decreases markedly.

(17) Trichloroacetamide was identified as a product by GC analysis.

(18) The changes in absolute configuration of products seen in Table 1 are a consequence of different CIP priorities of R^1.

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