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Catalytic Asymmetric Synthesis of Chiral Allylic Esters

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Abstract: A broadly useful catalytic enantioselective synthesis of branched allylic esters from prochiral (*Z*)-2-alkene-1-ols has been developed. The starting allylic alcohol is converted to its trichloroacetimidate intermediate by reaction with trichloroacetonitrile, either *in situ* or in a separate step, and this intermediate undergoes clean enantioselective S_N2' substitution with a variety of carboxylic acids in the presence of the palladium(II) catalyst (R_p,*S*)-di-μ-acetatobis[(η^5-2-(2′-(4′-methylethyl)oxazolinyl)cyclopentadienyl-1-C,3′-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium, (R_p,*S*)-[COP-OAc]$_2$, or its enantiomer. The scope and limitations of this useful catalytic asymmetric allylic esterification are defined.

Introduction

Branched allylic alcohols (1-alken-3-ols) are versatile intermediates for the synthesis of a wide variety of organic compounds.[1,2] When chiral, these alcohols are often accessed in enantioenriched form by kinetic resolution,[3,4] although their synthesis using enantioselective chemical catalysts is becoming increasingly important. For example, they can be assembled enantioselectively by forming allylic C−H or C−C bonds by catalytic asymmetric reduction of enones[5] or catalytic asymmetric addition of vinyl nucleophiles to aldehydes.[6,7] Alternatively, branched allylic alcohols can be prepared in enantioselective fashion by formation of the allylic C−O bond. Numerous catalytic asymmetric allylic alkylations of alkoxides, phenoxides, or carboxylates with Pd(0),[8−10] Ir(I),[11] Rh(III),[12] Cu(II),[13] and Ru(II)[14] catalysts have been described.[15] Of these, the iridium-catalyzed methods are of particular importance because iridium(I) η^3-allyl intermediates react preferentially with nucleophiles at the more-substituted end of the allyl fragment.[16] Using phosphoramidite ligands, Hartwig has shown that Ir-catalyzed allylation of phenoxides and alkoxides can generate the corresponding allylic ethers in high enantiomeric purity and up to 99:1 branched to linear selectivity. In principle, this method could deliver branched allylic alcohols in high enantiomeric purity; however, conversion of an allylic benzyl ether or related intermediate to the parent allylic alcohol is complicated by the presence of the C=C π-bond.

With Ir-phosphoramidite catalysts, Carreira recently reported the two-step conversion of allylic carbonates to enantioenriched

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(1) Enantioenriched allylic esters are ubiquitous intermediates in the synthesis of complex molecules. Selected recent examples include the following: (a) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103–1106. (b) Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695–2698. (c) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776.

(2) For a comprehensive review of the synthesis of allylic alcohols, see: Hodgson, D. M.; Humphreys, P. G. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Clayden, J. P., Ed.; Thieme: Stuttgart, 2007; Vol. 36, pp 583−665.

(3) Enzymatic kinetic resolution: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354. (b) Carrea, G.; Riva, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2226–2254. (c) *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; VCH: Weinheim, Germany, 1995. (d) Faber, K. *Biotransformations in Organic Chemistry*, 3rd ed.; Springer: Berlin, 1997; pp 201−205.

(4) Palladium-catalyzed kinetic resolution: (a) Ebner, D. C.; Bagdanoff, J. T.; Ferreira, E. M.; McFadden, R. M.; Caspi, D. D.; Trend, R. M.; Stoltz, B. M. *Chem.—Eur. J.* **2009**, *15*, 12978–12992. (b) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854–3867. (c) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 15957–15966. (d) Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817–14824.

(5) (a) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(6) (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645–5648.

(7) A novel catalytic asymmetric approach involving Cu-catalyzed catalytic asymmetric allylic alkylation was described recently: (a) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025–1037. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.

(8) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320–10321.

(9) For comprehensive reviews see: (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.

(10) Direct palladium-catalyzed allylic C−H oxidation to provide 3-acyloxy-1-alkenes in modest enantioselectivity has been reported by the White group: Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448–6451.

(11) (a) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918–8920. (b) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928–1931. (c) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794–4797. (d) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426–3427.

(12) (a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883. (b) Evans, P. A.; Leahy, D. K.; Slieker, L. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3613–3618.

(13) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

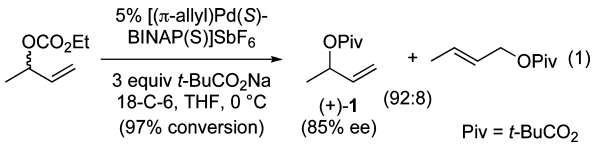
(14) (a) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206–1207. (b) Onitsuka, K.; Okuda, H.; Sasai, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1454–1457.

(15) For a recent review of enantioselective allylation reactions, see: Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.

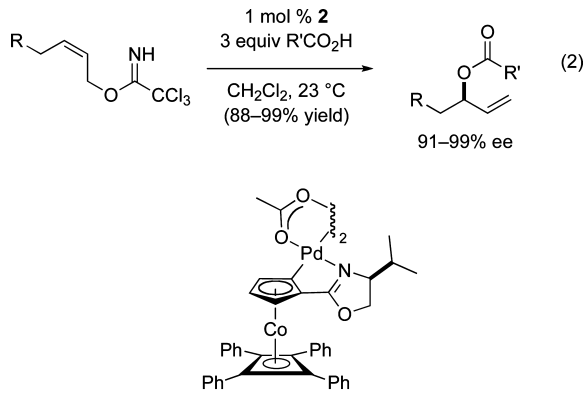
(16) For a recent review, see: Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691.

branched allylic alcohols using silanolates as hydroxide equivalents.[17] In this case, the allylic silyl ether product is transformed in high yield to the parent allylic alcohol by reaction with 30% aqueous NaOH in methanol.

Branched allylic esters are particularly convenient precursors of branched allylic alcohols and also important synthetic intermediates in their own right. Prior to our report in 2005, there was only a single example of the catalytic asymmetric synthesis of 3-acyloxy-1-alkenes by forming the allylic C−O bond.[18] In that disclosure, the reaction of sodium pivalate with racemic 3-buten-2-yl ethyl carbonate and a palladium-BINAP(*S*) catalyst was reported to take place with a branched-to-linear ratio of 92:8 to give (+)-3-buten-2-yl *tert*-butyl carbonate (**1**) in 85% ee (eq 1).



In 2005, we described the most general catalytic asymmetric allylic esterification reaction yet reported. In this process, trichloroacetimidate derivatives of prochiral (*Z*)-allylic alcohols were shown to react with carboxylic acids in the presence of 1 mol % of the Pd(II) catalyst $[(R_p,S)$-COP-OAc$]_2$ (**2**)[19] or its enantiomer to give a variety of 3-acyloxy-1-alkenes in high yields and high enantiomeric purity (eq 2).[20] These reactions proceeded at room temperature with exceptionally high branched-to-linear ratios (up to 800:1) to give ester products, which are easily transformed to the parent branched allylic alcohol. In this article, we delineate the scope and limitations of this new catalytic asymmetric synthesis of chiral allylic esters. In the accompanying paper, we describe experiments that provide insight into the mechanism of this transformation.[21]



Scheme 1. Discovery of Palladium-Catalyzed 3-Acyloxy-1-alkene Synthesis

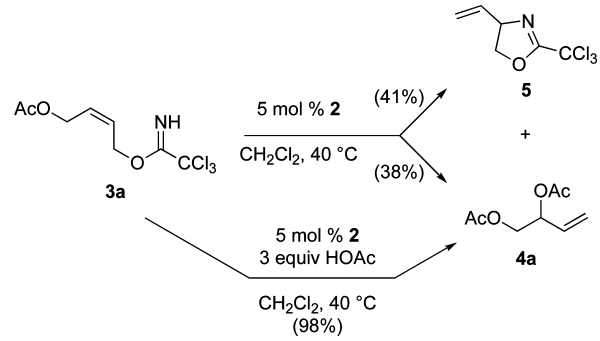
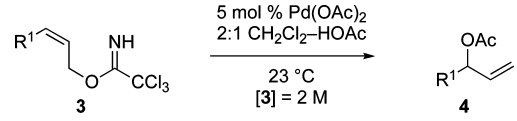


Table 1. Palladium Acetate-Catalyzed Formation of Racemic 3-Acetoxy-1-alkenes

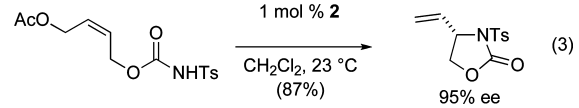


entry	R^1	temp (°C)	time (h)	4	yield (%)[a]
1	*n*-Pr	23	5	**4b**	96
2	*n*-Pr	38	1	**4b**	52
3[b]	$(CH_2)_2$Ph	23	10	**4c**	70
4	*i*-Bu	23	2	**4d**	85
5	CH_2OH	23	2	**4e**	82
6	CH_2OAc	23	2	**4a**	99
7	CH_2OPMB	23	5	**4f**	91
8	$(CH_2)_3OTBS$	23	4	**4g**	83

[a] Yield of pure product. [b] 1 mol % catalyst loading.

Results and Discussion

Initial Studies and Optimization. Several years ago we reported that $[(R_p,S)$-COP-OAc$]_2$ (**2**) was a preferred catalyst for catalytic asymmetric intramolecular aminopalladation of (*Z*)-allylic *N*-tosylcarbamates to form 3-tosyl-4-vinyloxazolidin-2-ones (eq 3).[22] It was in attempting to extend this reaction to the formation of enantioenriched 4-vinyloxazolidines that the catalytic asymmetric allylic esterification reaction was discovered. In a key early experiment, exposure of acetoxybutenyl trichloroacetimidate **3a** to 5 mol % of COP catalyst **2** at room temperature formed a ~1:1 mixture of 4-vinyloxazolidine **5** and 1,2-diacetoxy-3-butene (**4a**) (Scheme 1). This result suggested that S_N2' displacement of the imidate by acetic acid was occurring competitively with intramolecular cyclization of the imidate nitrogen. Indeed, in the presence of excess acetic acid, imidate **3a** was converted into butenyl diacetate **4a** in 98% yield, with no competing intramolecular cyclization being observed.



Palladium acetate was identified as an effective catalyst for the synthesis of racemic 3-acetoxy-1-alkenes from trichloroacetimidate derivatives of (*Z*)-2-alkene-1-ols (Table 1). These reactions were optimally carried out at room temperature and proceeded within hours in the presence of 5 mol % $Pd(OAc)_2$. No conversion to allylic acetate products was observed in the absence of palladium acetate. At 38 °C, trichloroacetimidate

(17) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204–6207.
(18) Faller, J. W.; Wilt, J. C. *Tetrahedron Lett.* **2004**, *45*, 7613–7616.
(19) (a) Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; Watson, M. P. *Org. Synth.* **2007**, *84*, 148–155. (b) Anderson, C. E.; Overman, L. E.; Richards, C. J.; Watson, M. P.; White, N. S. *Org. Synth.* **2007**, *84*, 139–147. (c) Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346–1348.
(20) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867.
(21) Cannon, J.; Kirsch, S. F.; Overman, L. E.; Sneddon, H. F. *J. Am. Chem. Soc.* **2010**, *132*, http://dx.doi.org/10.1021/ja106688j, following paper in this issue.
(22) Kirsch, S. F.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 2859–2861.

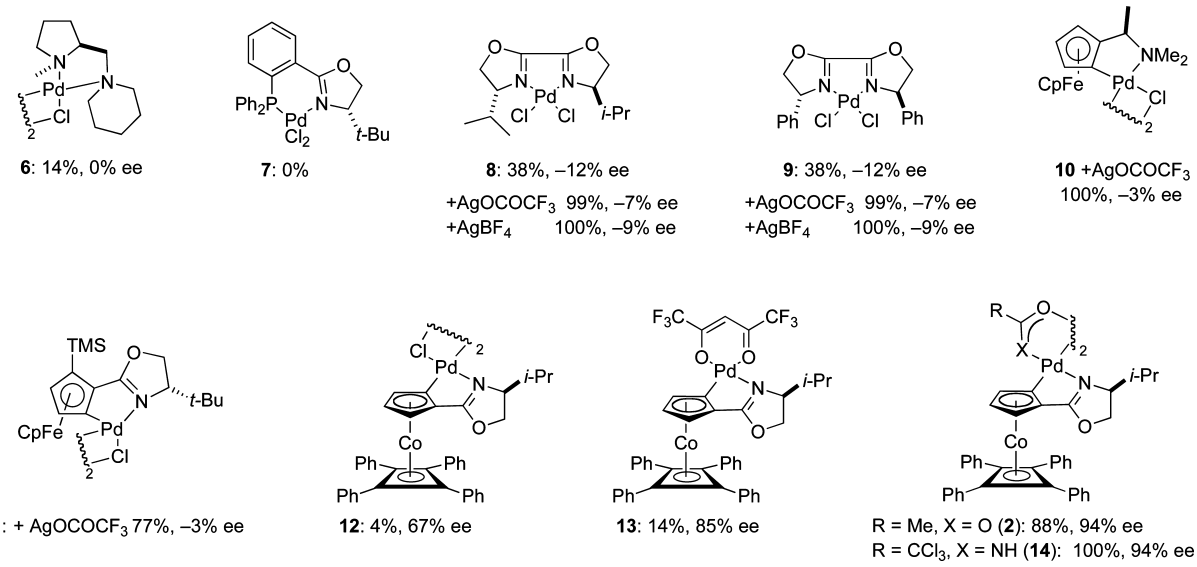
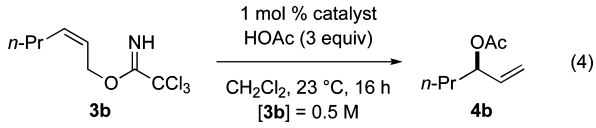


Figure 1. Yield and enantioselectivity in forming (*R*)-3-acetoxy-1-hexene (**4b**) using enantiomerically pure palladium(II) complexes under the conditions specified in eq 4.[23]

3b (R^1 = *n*-Pr) gave allylic acetate **4b** in lower yield, as rapid precipitation of palladium black was observed (entry 2). Although not extensively investigated in these early experiments, catalyst loadings as low as 1 mol % could be employed (entry 3). Selectivity for forming the branched allylic acetate was high, as signals diagnostic of the linear allylic acetate product were not detected by ^{1}H NMR analysis of crude reaction products.



In light of these initial discoveries, the reaction of (*Z*)-2-hexenyl imidate **3b** with acetic acid to form 3-acetoxy-1-hexene (**4b**) was examined in the presence of a variety of enantiomerically pure Pd(II) complexes (eq 4 and Figure 1).[23] Cationic palladium diamine complex **6**[24] and palladium dichloride PHOX complex **7** were kinetically ineffective catalysts for this transformation, as were palladium dichloride bis-oxazoline complexes **8** and **9**. Catalysis rate increased markedly when complexes **8** and **9** were pretreated with 4 equiv of silver salts; however, the enantioselectivity in forming **4b** was very low with these cationic palladium(II) complexes. Cationic complexes generated from the palladacyclic halide-bridged dimeric complexes **10**[25] and **11**[26] also showed good catalytic rates but negligible enantioselectivity. Higher enantioselectivities were realized with the palladacyclic COP complexes **12**, [(R_p,*S*)-COP-Cl]$_2$,[19] and **13**, (R_p,*S*)-COP-hfacac;[27] however, catalytic rates were poor. The optimal combination of enantioselectivity and rate was achieved with acetate-bridged COP complex **2**, [(R_p,*S*)-COP-OAc]$_2$, and the amidate-bridged (R_p,*S*)-COP complex **14**,[28] both of which formed the (*S*)-allylic ester **4b** in 94% ee and high yield. Because COP complexes **2** and **14** readily interconvert in the presence of excess acetic acid[21] and because both enantiomers of [COP-OAc]$_2$ are commercially available, [COP-OAc]$_2$ (**2**) was chosen for further investigation.

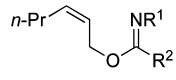
Several studies were carried out to optimize this catalytic asymmetric synthesis of allylic esters. Under standard conditions—1 mol % [(R_p,*S*)-COP-OAc]$_2$ (**2**), 3 equiv of HOAc, 0.5 M imidate, 23 °C—the conversion of (*Z*)-2-hexen-1-yl trichloroacetimidate (**3b**) to (*R*)-3-acetoxy-1-hexene (**4b**) was studied in various solvents with the following results: CH_2Cl_2 (88%, 17 h), THF (69%, 16 h), benzene (43%, 16 h), MeCN (8%, 17 h). With the exception of the coordinating solvent MeCN, the enantiopurity of ester product **4b** was nearly identical in the solvents surveyed (91−94% ee). Trichloroacetamide was identified as a product by GC analysis.

The effect of temperature on the transformation of **3b** → **4b** was surveyed in CH_2Cl_2 using 1 mol % [(R_p,*S*)-COP-OAc]$_2$ (**2**), 3 equiv of HOAc, and an imidate concentration of 0.5 M. The reaction was quite slow at 0 °C, with (*R*)-allylic ester **4b** being formed in only 17% yield (96% ee) after 17 h. Under identical conditions, (*R*)-3-acetoxy-1-hexene (**4b**) was produced in 88% yield (94% ee) at room temperature and 94% yield at 38 °C, albeit with reduced enantioselectivity (87% ee). We conclude that, in terms of both rate and enantioselectivity, this catalytic enantioselective allylic esterification is best carried out at room temperature; however, for slow reactions, increasing the reaction temperature to 38 °C to increase the catalysis rate would only slightly decrease the enantioselectivity.

We also briefly examined other carboxyl nucleophiles and imidate leaving groups. The use of sodium or ammonium acetate, instead of acetic acid, led to no product formation, which is not surprising, as protonation of the imidate would presumably be required to generate the competent leaving group, trichlo-

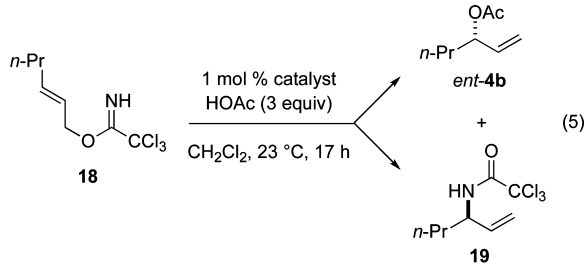
(23) (a) Cationic complexes were generated from chloride-bridged dimer precursors by pretreatment at room temperature with 4 equiv of the silver salt specified in Figure 1. (b) A negative sign before the % ee indicates that ***ent*-4b** was produced in excess.
(24) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449–1456.
(25) (a) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837–8840. (b) Sokolov, V. I.; Troitskaya, L. L.; Reutov, J. *J. Organomet. Chem.* **1977**, *133*, C28–C30.
(26) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933–2934.
(27) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101–8104.
(28) Olson, A. C.; Overman, L. E.; Sneddon, H. F.; Ziller, J. W. *Adv. Synth. Catal.* **2009**, *351*, 3186–3192.

roacetamide.[29] *N*-Arylimidate **15**, which is a good substrate for [COP-Cl]$_2$-catalyzed allylic imidate rearrangement,[30] did not react with acetic acid in the presence of [COP-OAc]$_2$, nor did allylic trifluoroacetimidates **16** or **17**. Thus, allylic trichloroacetimidates are the preferred substrates, which is attractive, as they are the most convenient imidates to prepare from allylic alcohols.[31]



15: R^1 = *p*-MeOC$_6$H$_4$, R^2 = Ph
16: R^1 = Ph, R^2 = CF_3
17: R^1 = H, R^2 = CF_3

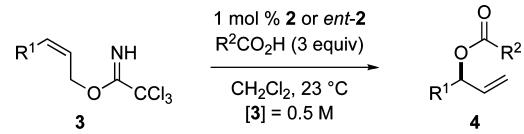
This catalytic asymmetric synthesis of allylic esters is not useful with *E* allylic imidate precursors. For example, reaction of (*E*)-trichloroacetimidate **18** with acetic acid catalyzed by 1 mol % of [(R_p,*S*)-COP-OAc]$_2$ (**2**) gives the allylic ester product, in this case *ent*-**4b**, in only 66% ee (eq 5). The [COP-Cl]$_2$-catalyzed asymmetric rearrangement of allylic trichloroimidates to give allylic trichloroacetamides is known to proceed significantly faster with the *E* stereoisomer of an allylic imidate,[31] a trend that is also seen with [COP-OAc]$_2$. Thus, the yield of allylic ester is lower in the *E* series, as allylic trichloroacetimidate rearrangement to form allylic amide **19** becomes a competing process (eq 5).[32] It was recently discovered that the amidate-bridged COP catalyst **14** enabled the formation of branched allylic aryl ethers from (*E*)-allylic trichloroacetimidates, because the allylic imidate rearrangement is somewhat slower with this catalyst.[28] However, catalyst **14** also performed poorly in the reaction depicted in eq 5.[33]



catalyst	products
[(R_p,*S*)-COP-OAc]$_2$ (**2**)	*ent*-**4b** 82% (66% ee) + **19** 10%
[(R_p,*S*)-COP-NHCOCCl$_3$]$_2$ (**14**)	*ent*-**4b** 58% (66% ee) + **19** 26%

Scope and Limitations of Catalytic Enantioselective Allylic Esterification. Using the conditions identified in our optimization studies, a series of trichloroacetimidates of (*Z*)-2-alkene-1-ols were allowed to react with acetic or benzoic acid in the presence of 1 mol % of [(R_p,*S*)-COP-OAc]$_2$ (**2**) or its enantiomer *ent*-**2** (Table 2). With but one exception, the branched product was formed with high selectivity, with the linear product not being observed by ^{1}H NMR analysis of the crude reaction product. 3-Acetoxy- (entry 1) and 3-benzoyloxy-1-hexene (entry 2) were produced in identical enantiomeric purities of 94% ee. The yield was somewhat higher (98%) for the latter, likely reflecting the lower volatility and associated higher recovery of this product

Table 2. Catalytic Enantioselective Synthesis of 3-Acyloxy-1-alkenes[a]



entry[a]	R^1	R^2	**3**	time (h)	**4**	yield (%)[b]	ee (%)[c] (config)
1	*n*-Pr	Me	**3b**	17	**4b**	88	94 (*R*)[d]
2[e]	*n*-Pr	Ph	**3b**	16	**4b**	98	94 (*R*)[f]
3	*i*-Bu	Me	**3c**	14	**4d**	96	93
4	Cy	Me	**3d**	48	**4h**	45	90
5	$(CH_2)_2$Ph	Ph	**3e**	17	**4i**	85	93[g]
6	CH_2OH	Me	**3f**	17	**4e**	92	97 (*S*)[h]
7	CH_2OAc	Me	**3g**	8	**4a**	90	99 (*S*)[h]
8	CH_2OPMB	Me	**3h**	16	**4f**	93	99 (*S*)[h]
9	$(CH_2)_3$OTBS	Me	**3i**	17	**4g**	98	93 (*R*)[i]
10[j]	$(CH_2)_3$OTBS	Ph	**3i**	20	**4j**	93	99 (*S*)[d,g]

[a] [(R_p,*S*)-COP-OAc]$_2$ (**2**), except for entry 10, which used *ent*-**2**. [b] Yield of pure product. [c] Determined by GC analysis unless otherwise indicated; results of duplicate experiments agreed within ±2%. [d] Absolute configuration determined by analysis of the Mosher ester.[34] [e] [**3**] = 0.17 M. [f] Absolute configuration by optical rotation.[35] [g] Determined by HPLC analysis. [h] Absolute configuration by synthesis from (*S*)-3-butene-1,2-diol. [i] Absolute configuration by optical rotation.[36] [j] Catalyst was *ent*-**2**.

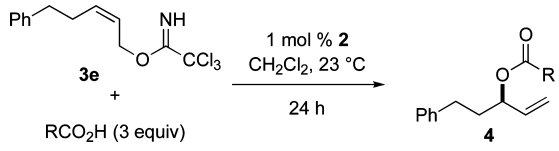
from chromatographic purification. Branching at the 5-position was well tolerated (entry 3), but branching at the 4-position resulted in a marked decrease in catalysis rate (entry 4). Furthermore, in the reaction of cyclohexyl substrate **3d**, the branched-to-linear ratio was reduced to 92:8. Imidate **3f**, bearing a hydroxyl group, was a suitable substrate for this reaction, producing acetate **4e** in 92% yield and 97% enantiomeric excess (entry 6). Ester, ether, and silyl ether substituents were also well tolerated (entries 7−10). The absolute configuration was established experimentally for seven of the allylic ester products reported in Table 2. In all cases, the (R_p,*S*) enantiomer of [COP-OAc]$_2$ provided the allylic ester enantiomer depicted in eq 2. The opposite enantiomer was produced with the enantiomeric catalyst *ent*-**2** (entry 10).

With the exception of the reaction reported in entry 4, the [COP-OAc]$_2$-catalyzed synthesis of allylic esters produces branched products in excellent yield and high enantiomeric excess; no significant byproduct other than traces of the COP catalyst was apparent by ^{1}H NMR analysis of the concentrated crude reaction mixture (see figure in Supporting Information). Capillary GC analysis failed to detect linear products [(*E*)- or (*Z*)-2-hexen-1-yl acetate] in the reaction of entry 1 under conditions whereby 1 part in 800 of the linear product would have been observed. However, at high acetic acid concentrations (>4 M in CH_2Cl_2), the branched-to-linear ratio decreases markedly. In the presence of water (>0.01% v/v), (*Z*)-hex-2-enyl trichloroacetate, which results from hydrolysis of the trichloroacetimidate, was identified as a minor byproduct in the reaction of entry 1. This byproduct was not formed when commercial glacial acetic acid was used without distillation.

Prior to further surveying the scope of this catalytic asymmetric synthesis of allylic esters, a series of ^{1}H NMR experiments were conducted to determine the relative reactivity of ten diverse carboxylic acids with imidate **3e** (Table 3). Not

(29) Estimated pK_a = 12.8; calculated using Advanced Chemistry Development (ACD/Labs) Software, version 8.14.
(30) Overman, L. E.; Owen, C. E.; Pavan, M. M. *Org. Lett.* **2003**, *5*, 1809–1812.
(31) Carpenter, N. E.; Overman, L. E. *Org. React.* **2005**, *56*, 1–107.
(32) Under identical conditions, allylic trichloroacetamide is not detected in the corresponding reaction of (*Z*)-imidate **3b**.
(33) This result is not surprising in light of the rapid interconversion of catalysts **2** and **14** in the presence of acetic acid.
(34) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
(35) Martin, V. S.; Ode, J. M.; Palazón, J. M.; Soler, M. A. *Tetrahedron: Asymmetry* **1992**, *3*, 573–580.
(36) Enders, D.; Nguyen, D. *Synthesis* **2000**, 2092–2098.

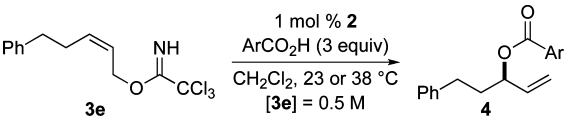
Table 3. Relative Reactivity of Carboxylic Acids with Allylic Imidate **3e** in the Presence of 1 mol % of COP Catalyst **2**[a]



entry	R	pK_a	% conversion[b] 10 h	% conversion[b] 24 h
1	*o*-$ClC_6H_4CH_2$	4.1	55	79
2	Me	4.8	65	89
3	Ph	4.2	62	84
4	*p*-MeC_6H_4	4.4	42	67
5	*t*-Bu	5.0	24	40
6	$MeOCH_2$	3.6	13[d]	38[d]
7	1-adamantyl	6.8	16	26
8	$ClCH_2CH_2$	4.0	18[c]	21
9	*o*-ClC_6H_4	2.9	16[d]	18[d]
10	Cl_2CH	1.3	18[d]	18[d]

[a] 3 equiv of RCO_2H, 1 mol % **2**, rt, [**3e**] = 0.5 M. [b] Determined by ^1H NMR analysis of ester product **4** using an internal standard. [c] % conversion at 3 h was 12%. [d] The major product of these reactions was the linear allylic acetate.

Table 4. Scope of the Enantioselective Reaction of Aromatic Carboxylic Acids with Imidate **3e** To Form 3-Acyloxy-1-alkenes



entry	Ar	time (h)	temp (°C)	4	yield (%)[a]	ee (%)[b]
1	*p*-MeC_6H_4	17	23	**4k**	85	93
2[c]	2-naphthyl	17	23	**4l**	87	96
3	*p*-$MeOC_6H_4$	22	38	**4m**	79	86
4[d]	*p*-$MeOC_6H_4$	22	23	**4m**	46	95
5	*p*-PhC_6H_4	19	38	**4n**	95	97[e]
6	*p*-ClC_6H_4	16	38	**4o**	86	97
7	*p*-$NO_2C_6H_4$	22	38	**4p**	65	87
8	*o*-ClC_6H_4	18	38	**4q**	24	46−53

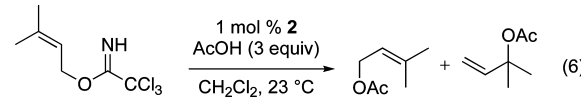
[a] Yield of pure product after silica gel chromatography. [b] Determined by HPLC analysis unless otherwise noted; results of duplicate experiments agreed within ±3%; absolute configuration assigned in analogy with the products reported in Table 2. [c] **3b** used as substrate, [**3b**] = 0.17 M. [d] 10:1 CH_2Cl_2/THF used as solvent. [e] Determined after conversion to benzoate ester **4i**.

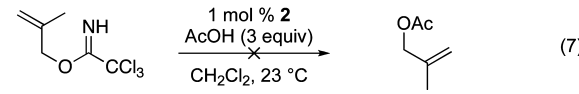
surprisingly, the reaction was slower with the bulky carboxylic acids pivalic acid and 1-adamantanecarboxylic acid (Table 3, entries 5 and 7). There was no apparent correlation between percent conversion and pK_a for the less sterically demanding acids. However, for carboxylic acids of pK_a 4 or lower, conversion to allylic ester **4** was unsatisfactory. In three of these cases (entries 6, 9, and 10), the major product was the linear (*E*)-allylic ester, with the allylic imidate disappearing within hours in the presence of the strongest acid (entries 9 and 10). Control experiments show significant formation of linear esters when imidate **3e** is exposed to methoxyacetic, *o*-chlorobenzoic, or dichloroacetic acid without catalyst **2** present.

We next examined the [COP-OAc]$_2$-catalyzed reaction of a series of aromatic carboxylic acids with (*Z*)-trichloroacetimidate **3e** (Table 4). Only *p*-toluic acid and 2-napthoic acid were appreciably soluble in CH_2Cl_2, allowing catalysis reactions to be carried out conveniently under our standard conditions (entries 1 and 2): 1 mol % [(R_p,*S*)-COP-OAc]$_2$ (**2**), 3 equiv of HOAc, 0.5 M imidate, 23 °C.[37] To increase the solubility of the acid, reactions with other substituted benzoic acids were conducted at 38 °C. Benzoic acids with both electron-donating and electron-withdrawing groups provided allylic ester products **4k**−**p** in high yield (79−95%) and excellent enantioselectivity (93−97% ee) (entries 1−3 and 5−7). Only the reaction of *o*-chlorobenzoic acid was unsatisfactory, providing allylic ester **4q** in poor yield and low enantioselectivity (entry 8). With this sterically hindered, more acidic (pK_a = 2.94) acid, the uncatalyzed background reaction occurred at a competitive rate.[38] In an attempt to improve the solubility of the carboxylic acid nucleophile at room temperature, the reaction of imidate **3e** with *p*-methoxybenzoic acid was carried out in 10:1 CH_2Cl_2/THF (entry 4). Although the enantioselectivity was slighly higher (97 vs 95% ee) than that of the corresponding reaction conducted at 38 °C in CH_2Cl_2, the yield after a reaction time of 22 h was considerably lower.

A variety of aliphatic carboxylic acids can be successfully employed in this enantioselective construction of 3-acyloxy-1-alkenes (Table 5). Phenylacetic acid and isobutyric acid react in high yield at room temperature to give the corresponding ester products **4r** and **4s** in high yield and enantioselectivity (entries 1 and 2). Reactions with bulkier carboxylic acids (entries 3 and 4), or less soluble carboxylic acids (entries 5 and 6), were optimally conducted at 38 °C to give ester products **4t**−**w** in useful yields (68−95%) and good enantioselectivities (86−96% ee). The successful use of indole-3-acetic acid and TBS-protected cholic acid (entries 5 and 6) suggest the potential broad scope of this method. Only the reaction with acrylic acid was unsatisfactory, providing branched allylic ester product in low yield (entry 7).

Several additional limitations to this method have been identified. Attempts to employ α-amino acids or nicotinic acid failed; the former is likely the result of the low solubility of the zwitterionic nucleophile, and the latter is likely from competitive nitrogen−palladium coordination.[39] Allylic imidates with additional alkyl substituents at C2 or C3 were also unsuitable substrates for the [COP-OAc]$_2$-catalyzed allylic ester synthesis. Substitution at C3 is not tolerated, because the uncatalyzed background reaction dominates, resulting in the formation of mixtures of the linear and racemic-branched tertiary allylic ester products (e.g., eq 6). 2-Methyl-2-propenyl trichloroacetimidate does not react with carboxylic acids in the presence of [COP-OAc]$_2$, undoubtedly because the oxypalladation step is disfavored in this case (eq 7).

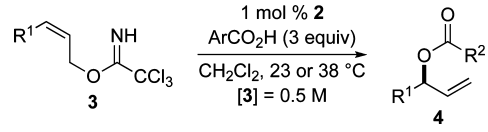


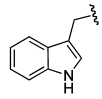
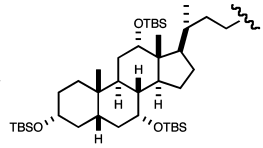


The conversion of prochiral (*Z*)-2-alkene-1-ols to enantioenriched 3-acyloxy-1-alkenes can be accomplished in a

(37) None of the reactions reported in Table 4 were homogeneous.
(38) In the absence of catalyst **2**, reaction of **3e** with *o*-chlorobenzoic acid provided ~20% conversion to the linear *o*-chlorobenzoate ester after 24 h.
(39) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031–5044.

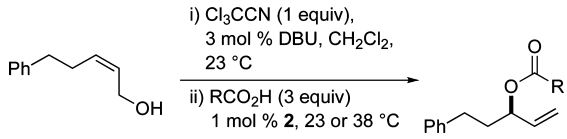
Table 5. Scope of the Enantioselective Reaction of Aliphatic Carboxylic Acids with Imidate **3** To Form 3-Acyloxy-1-alkenes

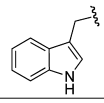


entry	R^1	R^2	**3**	time [h]	temp [°C]	**4**	yield [%][a]	ee [%][b]
1[c]	*n*-Pr	CH_2Ph	**3b**	20	23	**4r**	90	91
2	*n*-Pr	*i*-Pr	**3b**	21	23	**4s**	89	92[d]
3	$(CH_2)_2Ph$	*t*-Bu	**3e**	48	38	**4t**	95	94[e]
4	$(CH_2)_2Ph$	1-adamantyl	**3e**	48	38	**4u**	68	86[f]
5	$(CH_2)_2Ph$		**3e**	17	38	**4v**	65	96
6	$(CH_2)_2Ph$		**3e**	48	38	**4w**	91	91[e]
7	$(CH_2)_2Ph$	$CH{=}CH_2$	**3e**	48	38	**4x**	37	nd

[a] Yield of pure product after silica gel chromatography. [b] Determined by HPLC analysis unless otherwise noted; results of duplicate experiments agreed within ±3%; absolute configuration assigned in analogy with products reported in Table 2. [c] [**3**] = 0.17 M. [d] Determined by GC analysis. [e] Determined after conversion to benzoate ester **4h**. [f] Determined by analysis of the Mosher ester.[34]

Table 6. One-Pot Enantioselective Synthesis of Branched Allylic Esters



entry	R	temp [°C]	**4**	yield [%][a]	ee [%]
1	Me	23	**4c**	76	92[b]
2	Ph	38	**4i**	72	80[c]
3	*p*-$MeOC_6H_4$	38	**4m**	94	90[c]
4		38	**4v**	64	87[d]

[a] Yield of pure product after silica gel chromatography. [b] Determined by GC analysis. [c] Determined by SFC analysis. [d] Determined by HPLC analysis.

one-pot reaction, as allylic trichloroacetimidates are conveniently prepared in CH_2Cl_2 from the DBU-catalyzed addition of allylic alcohols to trichloroacetonitrile.[40] In the one-pot sequence, the allylic trichloroacetimidate is generated by reaction of the allylic alcohol with 1 equiv of Cl_3CCN in the presence of 3 mol % DBU; after imidate formation is complete, 3 equiv of a carboxylic acid and 1 mol % (R_p,*S*)-[COP-OAc]$_2$ (**2**) are added, and the allylic esterification is allowed to proceed either at room temperature or at 38 °C (Table 6). This process provided the 3-acyloxy-1-alkene products **4c**, **4i**, **4m**, and **4v** in useful yields and enantiomeric excesses that are slightly lower than those realized in the two-step sequence (Tables 2, 4, and 5). One important consideration is the necessity for complete consumption of trichloroacetonitrile prior to addition of the catalyst. Addition of the carboxylic acid and [COP-OAc]$_2$ (**2**) to reactions in which imidate formation was incomplete provided the allylic ester in low yield and unconsumed allylic trichloroacetimidate **3e**.[41] In order to achieve consistent results, the *in situ* generation of the trichloroacetimidate intermediates was carried out for 7 h to ensure full consumption of trichloroacetonitrile before the carboxylic acid and palladium catalyst were added.

Conclusion

A useful catalytic enantioselective synthesis of branched allylic esters from prochiral (*Z*)-2-alkene-1-ols has been developed. The starting allylic alcohol is converted to its trichloroacetimidate intermediate by reaction with trichloroacetonitrile, either *in situ* or in a separate step, and this intermediate suffers clean enantioselective S_N2' substitution with a variety of carboxylic acids in the presence of the palladium(II) catalyst, [COP-OAc]$_2$. The allylic substitution reaction proceeds at, or just slightly above, room temperature, using catalyst loadings of 1 mol % to provide a variety of 3-acyloxy-1-alkenes in good yields (60−98%) and excellent enantiomeric purities (86−99% ee). Either enantiomer of the allylic ester product can be prepared, as both enantiomers of

(40) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1927–1947.

(41) We have found that the addition of alcohols to trichloroacetonitrile is catalyzed by [COP-OAc]$_2$ (**2**) at room temperature. However, this reaction is low yielding because the catalyst becomes poisoned, presumably from the formation of a minor byproduct.

$[COP\text{-}OAc]_2$ are commercially available. A variety of carboxylic acids, including ones containing additional heteroatom functionalities, react successfully. However, carboxylic acids having pK_a's much lower than 4 cannot be used, because acid-promoted ionization of the allylic trichloroacetimidate is a competitive side reaction with these acids. The reaction is limited also to primary (*Z*)-2-alkene-1-ols having disubstituted double bonds.

Exceptionally high branched-to-linear ratios are a distinctive feature of the catalytic enantioselective allylic esterification reaction discussed herein: typically, only the branched product can be detected by ^{1}H NMR analysis of crude reaction products, with b/l ratios of >800 being documented. This feature alone suggests a novel mechanism for this Pd(II)-catalyzed substitution reaction, which is the subject of the accompanying article.[21]

The utility of this synthesis of enantioenriched allylic esters has been illustrated recently in the construction of 1,3-polyol arrays[42] and the total synthesis of the 12-membered macrolide (+)-chloriolide.[43]

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Supporting Information Available: General methods, experimental procedures, and NMR, HPLC, SFC, and GC data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA106685W

(42) (a) Menz, H.; Kirsch, S. F. *Org. Lett.* **2009**, *11*, 5634–5637. (b) Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164–4166.
(43) Haug, T. T.; Kirsch, S. F. *Org. Biomol. Chem.* **2010**, *8*, 991–993.