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Enantioselective synthesis of acyclic allylic esters catalyzed by a palladium/BINAP(S) system

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Abstract—The synthesis of chiral nonracemic acyclic allylic pivalates via the Pd-catalyzed allylic substitution of racemic allylic carbonates is presented. Good to excellent enantioselectivities (up to 90%) were observed in several cases. An extraordinarily high preference for the production of the branched regioisomeric product is seen when starting from 3-buten-2-yl and crotyl substrates. A significant kinetic resolution (k_{rel} = 38) of the 1,3-dimethylallyl substrate was also observed, leading to the production of esters of both enantiomers of an allylic alcohol with a single enantiomer of catalyst.
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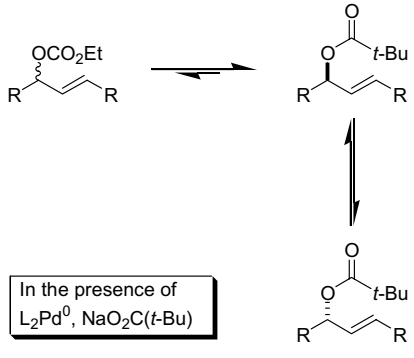
The palladium-catalyzed asymmetric allylic substitution reaction is a powerful synthetic method for the formation of C–C, C–N, C–S, and C–O bonds.[1,2] These reactions constitute a means of transforming an achiral or racemic allylic ester into a different, enantiomerically enriched allylic functionality determined by the nucleophile chosen. However, if the desired product is an enantiomerically enriched allylic alcohol, a different approach is often taken. Asymmetric additions to allylic aldehydes[3–6] and kinetic resolutions of the allylic esters[7–13] or alcohols[14–17] are both viable options. However, the former method is often less selective when an aliphatic allylic alcohol is desired, and the latter method has an intrinsic 50% maximum yield.

Through the use of a carboxylate as nucleophile in the palladium-catalyzed asymmetric allylic substitution reaction, chiral nonracemic allylic esters can be produced from racemic allylic esters. This method, though attractive, suffers from an inherent chemoselectivity problem. Since the product of this reaction can also serve as the substrate, the rate of reaction of the starting allylic ester must be significantly greater than that of the produced allylic ester. If the rates are similar, not only may the reaction not proceed in the forward direction, but the produced allylic ester will racemize over the course of the reaction. This intrinsic selectivity issue can be at least partly overcome by the use of allylic carbonates as substrates, taking advantage of their greater propensity to oxidatively add to Pd^0 than the produced allylic ester (Scheme 1).

This methodology was initially reported by Trost[18] in the synthesis of cyclic allylic esters from their allylic carbonate counterparts with excellent enantioselectivities. We wish to report the successful extension of this methodology to acyclic allylic substrates with our Pd/BINAP(S) system.

Recently, we reported the palladium-catalyzed kinetic resolution of several acyclic allylic acetates and benzoates in the presence of the axially chiral (*S*)-BINAP(S) ligand **1** (Scheme 2).[19]



Scheme 1.

Keywords: Palladium; Asymmetric allylation; Catalysis.
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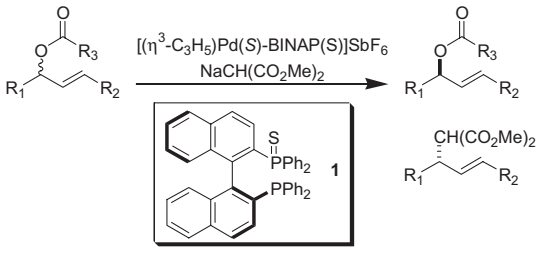


Scheme 2.

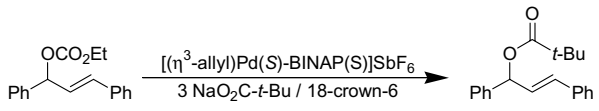
We were interested in the possibility of combining the high selectivity that this system had shown for addition of one enantiomer of starting allylic ester with the possible enantioselective synthesis of allylic esters from allylic carbonates. Initially, the desired outcome was to selectively consume a single enantiomer of allylic carbonate and produce a single enantiomer of allylic ester; in essence, a method of preparing both enantiomers of a given allylic ester with a single enantiomer of catalyst.

To establish general reaction conditions,[20] we began our investigation with the ethyl carbonate of 1,3-diphenylallyl alcohol **2a** (Table 1). Unfortunately, the sodium pivalate nucleophile proved exceedingly insoluble in thf, and no reaction was observed. Addition of the cation-solubilizing 18-crown-6 ether to the reaction mixture did result in conversion to the pivalate product with good enantioselectivity; however, no kinetic resolution of the starting allylic carbonate was observed during the course of the reaction. As the concentration of 18-crown-6 was increased, a corresponding increase in reaction rate was observed, with no loss of enantioselectivity. This increase in rate can be attributed to an higher concentration of nucleophile being in solution. Optimal results were found with 1 equiv of 18-crown-6 at 0 °C, which gave (−)-**2b** in 90% ee. It should be noted that these reactions must be carefully monitored with respect to percent conversion, and were generally quenched prior to full conversion to avoid the possibility of racemization.

With our conditions in hand, we then examined the scope of the reaction with several other allylic carbonates (Table 2). Interestingly, a kinetic resolution was observed with symmetrical substrate **3a**. The selectivity of a kinetic resolution is measured as the ratio of the rate constants of the two enantiomers of substrate in question, and is known as the selectivity factor, or k_{rel}. A k_{rel} of 38 was observed for **3a**, which is comparable to the best reported values[8] for derivatives of this allylic alcohol. Additionally, the signs of the optical rotations for product and reactant are opposite, which suggests that this reaction constitutes a separation of the two enantiomers of allylic alcohol with high enantioselectivity. It is not obvious why this particular substrate should give rise to a kinetic resolution as opposed to the other substrates tested, although we can say with certainty that the Pd catalyst must oxidatively add (−)-**3a** at a greater rate than it adds (+)-**3a** or (−)-**3b**.

Isomeric unsymmetrically substituted substrates **4a** and **5a** can give rise to both linear and branched allylation products **4b/4c** and **5b/5c**. In most Pd-catalyzed reactions, these substrates proceed to give the achiral, linear substitution product rather than the chiral, branched regioisomer.[21–24] Previously, we have reported that the Pd/(*S*)-BINAP(S) catalyzed alkylation of these substrates with sodium dimethylmalonate gave rise to the branched regioisomeric product in up to a 79:21 ratio. We were pleased to find that reaction of substrate **4a** under our current conditions gave **4b/4c** in a 92:8 regioisomeric ratio, with high ee in the branched isomer. We attribute this preference for formation of the branched product to both the electronic and steric effects of the BINAP(S) ligand. Steric effects would tend to place the more substituted allylic terminus *cis* to sulfur and *trans* to phosphorus. The electronic preference for nucleophilic attack *trans* to phosphorus then gives rise to formation of the branched product. Substrate **5a** also gave **5b/5c** with virtually identical regioisomeric distribution (entry 3); however, the reaction only proceeded to 27% conversion under our standard conditions, even after prolonged reaction times. Doubling the reactant

Table 1. Optimization of reaction conditions

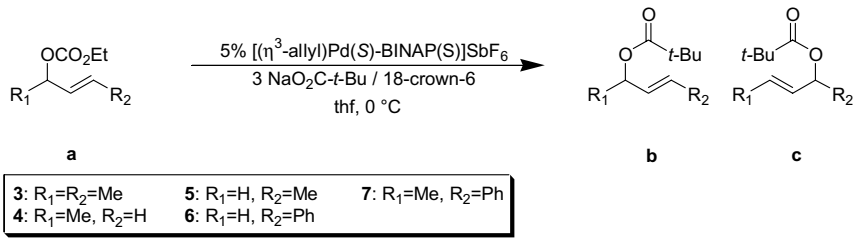


2a **2b**

Entry	Catalyst loading[a]	18-c-6[a]	*T*, °C	Time, h	% C[b]	% ee[c]	Optical rotation[d,28] (2b)
1	0	100%	rt	24	0	—	—
2	5%	0	rt	24	0	—	—
3	1%	5%	rt	23.5	76	77	(—)
4	5%	5%	0	47	88	87	(—)
5	5%	25%	0	7	90	89	(—)
6	5%	100%	0	2.5	85	90	(—)

[a] Mol% with respect to substrate.
[b] Percent conversion as determined by ^{1}H NMR.
[c] Determined by chiral shift experiments with (+)-Eu(hfc)$_3$.
[d] Sign of rotation measured at 20 °C and 589 nm.

Table 2. Reaction scope



Entry	Substrate	18-c-6[a]	Time, h	% C[b]	Ratio *b*:*c*[b]	% ee product[c] (optical rotation)[d]	% ee starting material[c] (optical rotation)[d,28]
1	**3a**	100%	12	45	—	87 (−)	73 (+) k_{rel} = 38
2	**4a**	100%	0.5	97	92:8[f]	85 (+)	—
3	**5a**	100%	22	27	9:91[f]	0	—
4	**5a**[e]	100%	0.5	91	13:87[f]	0	—
5	**5a**[e]	25%	1	97	9:91[f]	71 (+)	—
6	**6a**	100%	1	91	100:0	—	—
7	**7a**	100%	0.33	51	100:0	43 (−)	24 (+) k_{rel} = 2

[a] Mol% with respect to substrate.
[b] Percent conversion as determined by ^{1}H NMR.
[c] Determined by chiral shift experiments with (+)-Eu(hfc)$_3$.
[d] Sign measured at 20 °C and 589 nm.
[e] Reactant concentrations were doubled.[20]
[f] Note that **4b** = **5c**, which are the branched products.

concentration (entry 4) increased the conversion, but led to a racemic product. By doubling the concentration of the reactants and reducing the percentage of 18-crown-6 (entry 5), we were able to achieve full conversion to the pivalate, but the ee was lower than with **4a**. This is an unanticipated result because isomeric **4a** and **5a** are often presumed to yield identical π-allyl intermediates; therefore, they would be expected to give rise to identical regio- and stereoselectivities in the product. Partial isomerization or racemization might account for this. In order to verify that the product ester **5c** had not partially racemized over the course of the reaction, the reaction was quenched at various percent conversions *under the conditions for entry 5*. Consistent enantioselectivities were observed at all stages of the reaction under these conditions.

Thus reaction conditions for appropriate relative rates of oxidative addition of linear **5a** and subsequent racemization of **5c** must be carefully controlled in order to achieve high ee's in the product.

Cinnamyl-based substrates **6a** and **7a** were substituted exclusively in the less sterically hindered position, which is contrary to our expectations based on the above interpretation of ligand effects. Regiochemical analysis of the product dictates that the less substituted allylic position (H or Me) must be *cis* to sulfur and *trans* to phosphorus. This effectively removes steric arguments from consideration, as the two larger substituents must be *cis* to one another in the square-planar metal geometry. A relative change in the charge distribution of the allylic termini may be responsible for the observed regioselectivity. Several reports have documented the preference for Pd-catalyzed allylic substitution at the more remote terminus from the most electron-withdrawing group.[25–27]

In summary, we have shown that the Pd/(*S*)-BINAP(S) system is effective for the catalytic synthesis of allylic pivalates from the corresponding racemic carbonates with high regio- and stereoselectivity. Of particular interest is the formation of predominantly branched products from **4a**/**5a** in good to high ee, and the highly selective kinetic resolution of **3a**. Future work will focus on the many interesting mechanistic facets of this transformation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.105.

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20. General experimental procedure: sodium pivalate (36 mg, 290 μmol), 18-crown-6, and [(η^3-allyl)Pd(*S*)-BINAP-(S)]SbF_6 (5 mg, 4.81 μmol) were placed under inert atmosphere and 2 mL dry thf was added. The dark solution was stirred at the desired temperature for 10 min. A solution of allylic carbonate (96.3 μmol) in 1 mL dry thf at the desired temperature was then added, and the reaction mixture stirred for the given amount of time. The reaction was quenched by adding excess pentane. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. Column chromatography over silica gel (25:1 pentane:Et_2O) provided first the pure allylic pivalate, followed by the allylic carbonate. Column pretreatment with 3% v/v Et_3N/solvent mixture was necessary to prevent decomposition with **2a**. All products were satisfactorily characterized by comparison of their ^1H NMR spectrum with literature values.
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