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Kinetic Resolution and Unusual Regioselectivity in Palladium-Catalyzed Allylic Alkylations with a Chiral P,S Ligand

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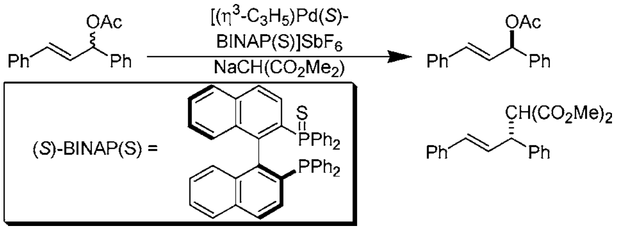
ABSTRACT



Effective kinetic resolutions of acyclic allylic acetates and benzoates have been obtained using a palladium/(S)-BINAP(S) catalyst system. Unusually large preferences for the formation of branched alkylation products from 3-but-2-enyl and crotyl substrates have been observed.

The palladium-catalyzed asymmetric allylic alkylation reaction has emerged as an extremely versatile C−C bond forming tool.[1,2] Numerous efficient ligand systems have been developed for this transformation, including many chiral bisphosphines, chiral P,N ligands,[3,4] and, less commonly, chiral P,O and P,S ligands.[5−9]

Although the usual synthetic target has been the product from a nucleophilic addition, several reports have recently appeared documenting the kinetic resolution of allylic acetates and carbonates in the course of these reactions.[9−14]

This report describes the kinetic resolution of some allylic substrates (see Scheme 1) with the readily prepared axially chiral (*S*)-BINAP(S) ligand **1**.[15−17] The regiochemistry of reactions using ligand **1** are unusual, as it promotes the

Scheme 1

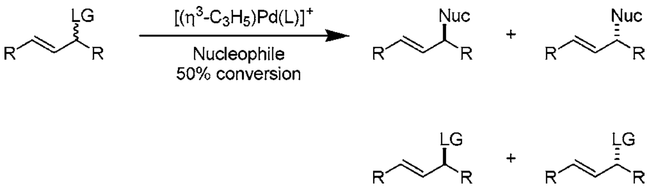


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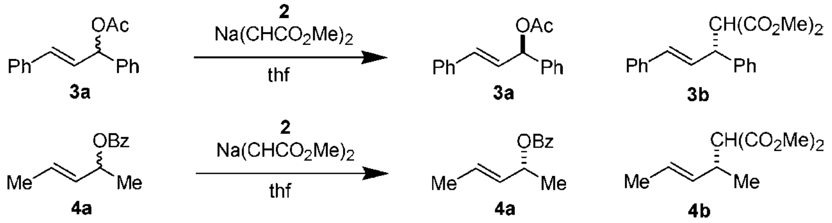
Table 1. Kinetic Resolution of Symmetrically Substituted Allylic Substrates



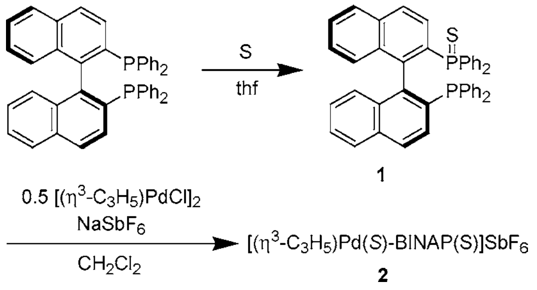
entry	substrate	**2** (mol %)[a]	T	% conv[b]	ee[c] of unreacted substrate (R)[d]	ee[c] of alkylated product (X)[d]
1	**3a**	5	25	23	27	68 (S)
2	**3a**	5	25	55	>98	74 (S)
3	**3a**	5	25	69	>98	72 (S)
4	**3a**	5	25	100		72 (S)
5	**3a**	5	−30	62	>98	80 (S)
6	**3a**	1	25	51	46	19 (S)
7	**4a**	5	25	44	52	56 (R)
8	**4a**	5	−30	40	54	67 (R)

[a] With respect to substrate. [b] Determined by ^{1}H NMR ($CDCl_3$) of the quenched reaction mixture. [c] Determined by ^{1}H NMR chiral shift experiments with (+)-Eu(hfc)$_3$. [d] Assigned by comparison of optical rotation values with published values.

formation of branched isomers in reactions that would otherwise be expected to yield linear products. Although catalysis with other metals can yield branched products with 3-buten-2-ol and crotyl alcohol derivatives, palladium-catalyzed reactions usually yield a preponderance of linear products.[1,2]

Ligand **1** and its corresponding palladium complex **2** are prepared as shown in Scheme 2. Significant kinetic resolution of racemic 1,3-diphenylallyl acetate, *rac*-**3**, was initially observed when using sodium dimethylmalonate as nucleophile. Alkylation of this substrate proceeded rapidly at room temperature (<5 min), and it proved to be easier to control the progress of the reaction by adjusting the loading of the nucleophile than by quenching the reaction after a certain period of time (Table 1). Upon reaching a conversion of 55%, the (*S*)-alkylation product was obtained in modest enantiomeric purity (60% ee), but more importantly unreacted (*R*)-allylic acetate was recovered in >98% ee.

Scheme 2



Encouraged by these results, we began to examine the scope of the kinetic resolution (Table 2). From a practical standpoint, benzoate esters were preferred over acetate esters owing to their lower volatility and ease of chromatographic separation. For example, entry 3 was performed on a 300-mg scale with comparable optical purity for the materials produced at that conversion. This was an important finding since the most recent advances in kinetic resolutions of this type have achieved excellent selectivity results with cyclic carbonates but acyclic carbonates have yielded products with lower selectivity.

The selectivity factor (the ratio of relative rate constants for the reaction of the two enantiomers) determines the % conversion required to achieve an acceptably high ee. Generally a value >10 gives a synthetically useful system. Prior to 2001 the best published systems gave values for *rac*-**3** of $k_{rel} \approx 5$. Gais[18] has recently developed one of the best systems based on palladium, which uses *tert*-butylsulfinate as the nucleophile. For *rac*-**3** this system gave 51% ee at 36% conversion (these values imply a $k_{rel} \approx 30$ *if one assumes pseudo-first-order kinetics*), and ~99% ee was observed at 73% conversion. Our results show a >98% ee at 55% conversion at 25 °C and 27% ee at 23% conversion, suggesting a value for $k_{rel} \approx 26$ at 25 °C.

The selectivity of this BINAP(S)/Pd system suggested its potential use with unsymmetrically substituted allylic alcohols. Low molecular weight secondary allylic alcohols, such as 3-buten-2-ol, are particularly difficult substrates for effective use of the Sharpless kinetic resolution procedure. Although the procedure yields the allylic alcohol in high enantiomeric purity in the case of the higher molecular weight 3-octen-2-ol, the reaction takes 6−12 days.[18] Furthermore, low molecular weight alcohols are difficult to separate from the reaction mixture. The Sharpless protocol has been successfully used for the preparation of the epoxy alcohol derived from 3-buten-2-ol; however, the allylic

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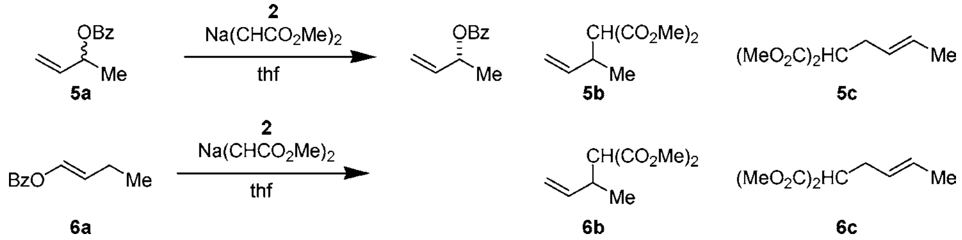
Table 2. Reaction of Unsymmetrically Substituted Allylic Substrates^a



entry	substrate	T	% conv^b	ee^c of unreacted substrate (R)^d	ee^c of alkylated product (R)^d	branched:linear product ratio^b
1	**5a**	25	53	59	10	60:40
2	**5a**	−30	47	58	12	71:29
3	**5a**	−30	63	81	14	76:24
4	**5a**	−30	100		16	79:21
5	**6a**	−30	100		20	64:36

^{a} All reactions performed with 5 mol % catalyst to substrate. ^{b} Determined by ^{1}H NMR (CDCl$_3$) of the quenched reaction mixture. ^{c} Determined by ^{1}H NMR chiral shift experiments with (+)-Eu(hfc)$_3$. ^{d} Configuration assigned by comparison of sign of optical rotation with published values.

alcohol was not isolated in this case.[19] Generally, successful kinetic resolution of low molecular weight allylic alcohols are conspicuous by their absence in reviews of the Sharpless epoxidation.[20] Hence, synthetic procedures for natural products often use alternatives, such as preparations from lactic acid.[21]

This suggests that a viable alternative kinetic resolution route to 3-buten-2-ol derivatives may be especially useful.[22] Our results show that 3-buten-2-yl benzoate may be kinetically resolved conveniently using the BINAP(S)/Pd system (see Table 2).

Interestingly, the unsymmetrically substituted substrate *rac*-**5** exhibited an unusually high ratio of branched to linear alkylation product. There are examples of other metal allyl species (Mo, Rh, Ir) and achiral palladium catalysts providing a high branched to linear product ratio; however, in most palladium-catalyzed allylic alkylation reactions, the linear alkylation product is observed predominantly.[23−27]

Alkylation of linear substrate **6** also proceeded with a regiochemical preference for the branched alkylation product but in a smaller ratio than when starting from substrate *rac*-**5**. This phenomenon is termed a regiochemical memory effect, whereby the position of the leaving group determines the regiochemistry of the alkylated product to some extent.[28−34]

The observation of a regiochemical preference for the branched product has generally been attributed to steric effects in some cases and electronic effects in others. Larger bite angles and steric crowding can produce a lower energy transition state in the incipient formation of the less encumbered terminal olefin bound to the metal when a branched isomer is formed. Thus on rare occasions when higher branched to linear ratios have been observed, they are often with higher coordination number metals, such as molybdenum[35] or ruthenium.[36,37] High branched to linear ratios have also been observed with iridium[38,39] and rhodium[40,41] catalysis wherein Ir(III) and Rh(III) complexes are produced upon oxidative addition and tend to be six-coordinate; hence, steric factors can also be more important in these systems than with Pd(II) complexes that tend to be four-coordinate. Thus, when high branched to linear ratios have been observed for palladium catalysis, they have often been promoted by larger bite angle ligands.[42−45] With unsymmetrical ligands, in particular, electronic effects can

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also direct regiochemistry by varying the charge distribution at allylic termini trans to particular donors.[46−48] We believe that the electronic asymmetry of the BINAP(S) ligand plays a more important role in the regiocontrol in the system discussed here, since we would anticipate a normal bite angle of ~88°, assuming *P,S* binding is involved. The steric effects in BINAP(S) would tend to place the more sterically congested terminus of the η^3-allyl cis to sulfur and trans to phosphorus. Attack trans to phosphorus is preferred electronically,[49−51] which would favor branched products. One should also note that anion effects that change rates of interconversion or enhance the production of η^1-allyls could be important.[52] In this context one expects that the leaving group departs trans to palladium and the benzoate does not necessarily immediately bind to the metal. Hence, an anion bound in an intermediate might well be one from the pool of anions in solution. Although we intend to investigate the mechanism in greater detail, a subtle interplay of the possible interactions[53] may be responsible for the regiocontrol observed in this system.

In summary, we have shown that ligand **1** is effective for the kinetic resolution of allylic acetates and benzoates for palladium-catalyzed allylic alkylation. Unsymmetrically substituted allylic substrates show a high degree of selectivity for the branched regioisomer with this catalytic system.

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Supporting Information Available: Preparation of catalyst and general procedure for catalytic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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