Synthesis of allyl selenides by palladium-catalyzed decarboxylative coupling†

Shelli R. Waetzig and Jon A. Tunge*

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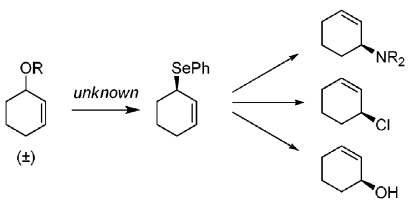
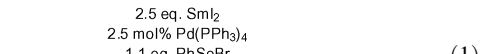
This communication details the Pd-catalyzed decarboxylation of selenocarbonates; use of a chiral nonracemic catalyst affords enantioenriched allyl selenides which undergo stereospecific [2,3]-sigmatropic rearrangements to form enantioenriched allylic amines and chlorides.

Alkyl selenides are versatile synthetic intermediates that undergo well-known 1,2-elimination upon oxidation or reduction upon treatment with radical initiators.[1] Furthermore, allyl selenides undergo [2,3]-sigmatropic rearrangements under a variety of conditions to afford allylic amines,[2] chlorides,[3] and alcohols.[4] Given the stereospecific nature of the [2,3]-sigmatropic rearrangement, one should be able to access enantioenriched allylic amines, chlorides, and alcohols, provided that the corresponding C-chiral enantiopure allyl selenides are available.[5] Although the addition of chiral selenium electrophiles has been well established in the literature,[6] a limited number of examples describe catalytic, asymmetric C–Se bond formation using nucleophilic selenium sources.[7] This is rather surprising given the numerous reports on asymmetric allylation of heteroatom nucleophiles.

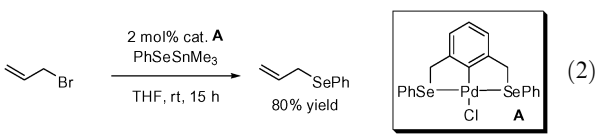


Several methods are known for the synthesis of racemic allyl selenides,[8] including the palladium-catalyzed addition of selenium nucleophiles to allylic acetates.[9] These methods, however, employ strong reducing agents, such as SmI_2 (eqn (1)), or require transmetalation from a stoichiometric toxic tin reagent ($PhSeSnMe_3$, eqn (2)). Furthermore, our attempts to reproduce the synthetic protocol for the synthesis of 2-cyclohexenyl phenylselenide using SmI_2 were unsuccessful.[10]

Previously, we have utilized Pd-catalyzed decarboxylation as a tool for carbon–carbon and carbon–heteroatom bond formation.[11] In these reactions decarboxylation replaces transmetalation, thus we expected that decarboxylative coupling would allow us to avoid the use of SmI_2 or $PhSeSnMe_3$ reagents that were previously required for allylic selenylation.[9] Such a

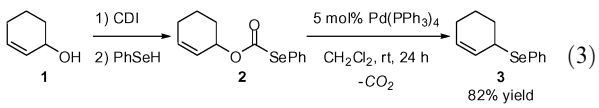


(1)



(2)

method is also appealing since the only byproduct generated is gaseous CO_2. Toward this end, allyl selenocarbonate **2** was synthesized from allylic alcohol **1** and treated with $Pd(PPh_3)_4$ in CH_2Cl_2 at room temperature (eqn (3)). The mixture cleanly converted to the desired allyl selenide (**3**), which was isolated in 82% yield.



(3)

Upon successful decarboxylation of allyl selenocarbonate **2**, various substituted allyl selenocarbonates were synthesized and treated under the conditions of catalysis (Table 1). While reaction of unsubstituted selenocarbonate **4a** afforded the allyl selenide **5a** in only moderate yield (49%), substituted allyl selenides were obtained in good to excellent yields. As expected for a reaction involving π-allyl palladium intermediates, the reactions of monosubstituted allyl selenocarbonates were highly regioselective and provided linear allylation products (**5c**, **5e**). Finally, the stereochemical course of the reaction was probed using racemic *cis*-allyl selenocarbonate **4g**. Overall retention of configuration was observed, providing the *cis*-substituted allyl selenide (**5g**) in high yield. This type of stereospecificity has been demonstrated previously with other soft nucleophiles, and is indicative of a double-inversion mechanism.[12]

The success of these reactions suggested that decarboxylative selenylation was a potentially viable coupling strategy for the asymmetric synthesis of allyl selenides. To begin, selenocarbonate **2** was used as a model substrate to screen chiral ligands for their ability to induce enantioselectivity in the reaction (Table 2). While bidentate P–N ligands failed to promote the reaction (entries 1, 2), the Trost ligand, and variants thereof, provided products with varying enantioselectivities (entries 3–5). A survey of solvents (entries 6–8) revealed that the (*S,S*)-Naphthyl-Trost ligand in toluene provided the highest enantioselectivity (89% ee). It was noted, however, that the reactions had problems with incomplete conversion;

Department of Chemistry, The University of Kansas, 2010 Malott Hall 1251 Wescoe Hall Drive, Lawrence KS, USA.
E-mail: tunge@ku.edu

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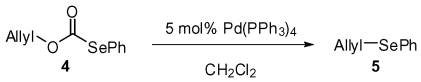
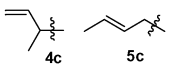
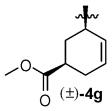
Table 1 Palladium-catalyzed decarboxylative selenylation



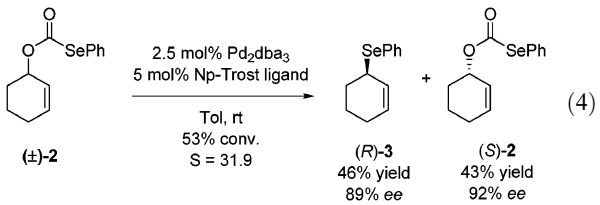
Allyl	Yield (%)	Allyl	Yield (%)
 **4a**	49[a]	 **4e**	83
 **4b**	66	 **4f**	72[c]
 **4c** **5c**	95[b]	 (±)-**4g**	99
 **4d**	90		

[a] 2.5 mol% catalyst used. [b] Isolated linear product with $E:Z$ ratio = 3.9 : 1. [c] E/Z = 10 : 1.

the reactions often reached ~50% conversion within the first 2 h followed by a drastic decrease in rate, such that the reaction would only reach ~55–80% completion after 24 h. Furthermore, forcing the reaction to proceed past 50% conversion by heating the reaction or extending the reaction time had a deleterious effect on the enantioselectivity (entries 9, 10).

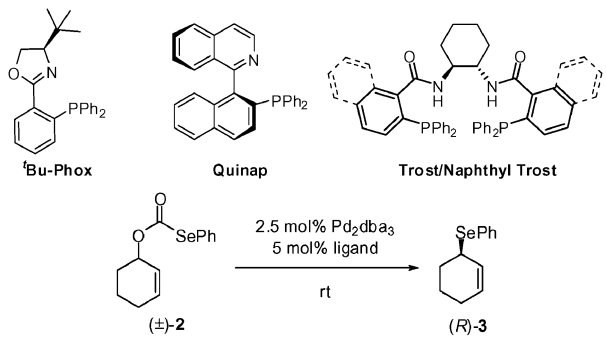
The low conversions and high enantioselectivities were initially attributed to two possible scenarios. First, selenium-containing ligands have been shown to coordinate transition metals as ligands and we thought it might be possible that the product could inhibit the reaction by binding to the catalyst.[13] This could explain slower rates at higher conversions, and could affect enantioselectivity by creating some achiral catalyst. However, product inhibition was not a problem when the reactions were run with racemic catalyst.

Alternately, the partial conversion could be attributed to a kinetic resolution of the racemic substrate. To test for this latter mechanism, selenocarbonate **2** was treated under our standardized reaction conditions (entry 7). The reaction completely stopped at 53% conversion, at which time the starting material and the product were both isolated (eqn (4)). The product allyl selenide was afforded in 46% yield and 89% ee. The unreacted selenocarbonate (*S*)-**2** was isolated with high enantiopurity (92% ee), showing that, indeed, an efficient kinetic resolution was taking place. With the ee of the reactant and the conversion of the reaction, the selectivity factor (*S*) calculated for the decarboxylative selenylation is 31.9, which is characteristic of a quite efficient kinetic resolution. In fact, similar kinetic resolutions have been demonstrated for allylations of allylic carbonates and acetates with other soft nucleophiles, where allylic carbonates in the presence of sulfur nucleophiles have shown very similar conversions and selectivity factors.[12,14] However, this is the first example that utilizes selenium nucleophiles for the palladium-catalyzed kinetic resolution of allyl-LG species.



(4)

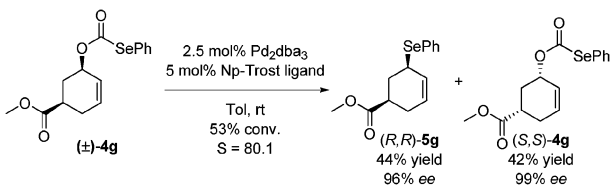
Table 2 Optimization of enantioselective allylic selenylation



Entry	Ligand	Solvent	Conv. (%)	ee **3** (%)
1	^{t}Bu-Phox	C_6D_6	12	ND
2	Quinap	C_6D_6	0	N/A
3	Trost	C_6D_6	78	28
4	Np-Trost	C_6D_6	60	73
5	Bicyclic-Trost[a]	C_6D_6	88	14
6	Np-Trost	THF	50	69
7	Np-Trost	Tol-d_8	54	89
8	Np-Trost	CD_2Cl_2	92[b]	60
9	Np-Trost	C_6D_6	100[c]	34
10	Np-Trost	Tol-d_8	63[d]	69

[a] See ESI† for ligand structure. [b] Run at 50 °C. [c] Run for 48 h. [d] Run at 0 °C.

Treatment of selenocarbonate (±)-**4g** under the same conditions resulted in the identical conversion as (±)-**2** (eqn (5)). The enantioselectivities obtained for the starting material and products were higher than those observed for unsubstituted cyclohexenyl selenocarbonate **2**. The selectivity factor calculated for this reaction was remarkably high at 80, showing that just the addition of the ester functional group had a dramatic impact on the reaction.

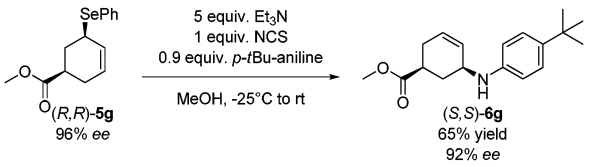


(5)

With the ability to synthesize enantioenriched allyl selenides, it seemed that the transformation of the allyl selenides to the corresponding allylic chlorides and amines *via* a [2,3]-sigmatropic rearrangement to give enantioenriched allylic amines and chlorides would be also be synthetically useful. Sharpless published a report in 1979 on the oxidation of achiral allyl selenides with *N*-chlorosuccinimide (NCS) or Chloramine-T.[3] Although the reported yields for the allylic aminations are

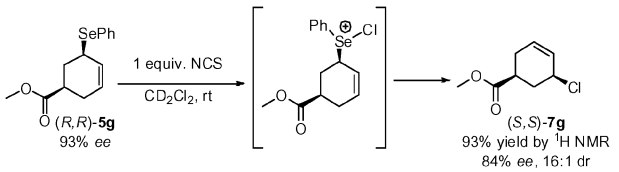
relatively low, these reactions are known to proceed through a cyclic transition state, which should facilitate the transfer of chirality to the products.[15] While this principle has been demonstrated with related aminations of chiral allyl selenides, the authors distinctly point out that the stereochemical integrity of the allylic rearrangement "must await methods for the preparation of stereohomogenous allylic selenides."[2]

To this end, we treated the isolated enantioenriched allyl selenide (*R*,*R*)-**5g** under the conditions reported for allylic amination (eqn (6)).[2] We were pleased to find the reaction provided the desired allylic amine in good yield and very high enantioselectivity. The conservation of enantiomeric excess (cee) of this reaction was 96% and absence of the corresponding diastereomer supports the hypothesis of a highly ordered cyclic transition state for this stereospecific reaction.



(6)

Enantioselective formation of carbon–halogen bonds is an important synthetic challenge. While the enantioselective halogenation of ketones *via* chiral enolates or chiral halogenating reagents is well known,[16] the enantioselective halogenation of less activated allylic systems still represents an obstacle in synthesis. In light of the high retention of stereochemistry for the [2,3]-sigmatropic rearrangement to form allylic amine (*S*,*S*)-**6g**, we were curious if similar chirality transfer would be possible from a chloroselenide derived from NCS. Therefore, allyl selenide (*R*,*R*)-**5g** was treated with 1 equivalent of NCS in CD_2Cl_2. We were pleased to find that mixture provided clean conversion of allyl selenide (*R*,*R*)-**5g** to the allylic chloride in 1 h at room temperature (eqn (7)). Due to the volatility of the allylic chloride, the yield was determined by ^{1}H NMR spectroscopy based on an internal standard. Following reaction completion, the reaction mixture was subjected to chiral-phase gas chromatography, where the product was found to have 84% ee and a diastereomeric ratio of 16 : 1 in favor of the desired product.



(7)

In conclusion, we have developed a palladium-catalyzed decarboxylative selenylation reaction that affords allyl selenides in good yields. Employing a chiral palladium catalyst results in the kinetic resolution of selenocarbonates to provide both the allyl selenide and selenocarbonate in high enantioselectivities. The synthesis of enantioenriched allyl selenides allows for further manipulations of these products, demonstrating that chiral, nonracemic allylic amines and chlorides can be readily obtained by a [2,3]-sigmatropic rearrangement from a common allyl selenide precursor.

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