Enantiomerically Enriched Tetrahydropyridine Allyl Chlorides

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Abstract: Enantiomerically enriched allyl halides are rare due to their configurational lability. Here we report stable piperidine-based allyl chloride enantiomers. These allyl chlorides can be produced via resolution, and undergo highly enantiospecific catalyst-free substitution reactions with C, N, O and S-based nucleophiles. Deuterium-labelled chloro-tetrahydropyridine, selectively prepared using the H/D primary kinetic isotope effect, and DFT calculations were used to investigate the mechanisms of the reactions. The allyl chlorides may also serve as valuable mechanistic tools for probing stereoselective reaction pathways.

The stereoselective synthesis of molecules with chloro-substituted stereogenic centres is challenging. Despite considerable effort, few asymmetric chlorination methods have been reported. Synthesis of enantiomerically enriched allyl halides has proven to be especially difficult as they are generally prone to fast isomerization and racemization (Scheme 1). Enantioenriched allyl chlorides are virtually unknown, except as a feature of diastereomeric compounds, where other stereogenic elements exert control over the observed stable allyl halide configuration. The selective preparation of enantiomerically enriched allyl chlorides could be important as stereogenic centers containing C-Cl bonds are found in pharmaceuticals, and the allyl halides may undergo stereospecific reactions.

1) Enantiomerically enriched allyl halides are difficult to access:
- Low stability
- Prone to isomerization
- Prone to racemization

2) This work:

Tetrahydropyridines (THPs) are a subgroup of nitrogen heterocycles found in biologically active molecules. THPs are also important precursors to functionalized piperidines. Piperidine is among the most common motifs found in licensed pharmaceuticals, and is frequently found in best-selling brand-name medicines. 3-substituted piperidine derivatives are at the core of many potent therapeutic agents (Figure 1) and methods for their preparation have attracted growing attention. However, asymmetric syntheses of 3-substituted piperidines via direct functionalization is scarce.

Figure 1. Examples of biologically active 3-substituted piperidines.

Due to the importance of THPs, racemic 3-chloro-1,2,3,6-tetrahydropyridines were examined in asymmetric allylic additions (AAAs) with Zr-nucleophiles and copper catalysts. To our surprise, we were able to isolate enantiomerically enriched allyl chlorides from the reaction mixture. The kinetic resolution of halides has received little attention, with resolution of allyl halides being limited to a single report of activated allyl fluorides. Here we report the synthesis of enantioenriched allylic 3-chloro-THPs via kinetic resolution and investigate alternative preparation methods. The chemically and configurationally stable allyl chlorides can be used to prepare a wide range of THP derivatives that may be useful in synthesis and medicinal chemistry (Scheme 1-2).

Initial exploration of Cu-catalyzed AAA with chloro-tetrahydropyridines showed recovery of scalemic allyl chloride, indicating slow (or indeed no) interconversion between starting material enantiomers during the reaction. The reaction of 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (rac-1) with 4-phenyl-1-buten-2 (2) was followed in time (Scheme 2). After 30 minutes at −10 °C the reaction reached 16% conversion, giving product 3a in 94% ee, with the ee of 3a then decreasing ~15% due to slow consumption of the less reactive starting enantiomer over time. The ee of 1 increased from 0 to 80% over 22 hours, where it remained unchanged (within experimental error).

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We then investigated conditions to optimize the ee of 1. With styrene, diluting the reaction conditions, and using DCM as solvent R-1 was obtained in useful yield with excellent selectivity (Scheme 3-1a). Kinetic resolution was found to be much faster on larger scales (Scheme 3-1b, c). These reactions also afforded alkylation product 3b in 49-65% yield and 84-88% ee. Conveniently, scalemic allylic chloride samples can be recycled, with resolution on such material giving up to 99% ee (Scheme 3-2).

R-1 shows remarkable thermal stability; in toluene heated to reflux for 24 hours only 3% ee erosion was observed without any detectable side product formation (Scheme 3-3).

Alternative routes to enantoienriched 1 were tested (see SI).

Though thermally stable, R-1 is a versatile chiral non-racemic building block and undergoes a variety of highly stereospecific substitution reactions. Using mild conditions we were able to access a variety of THP derivatives including ethers (6), esters (7), vinylogous ethers (8), thioethers (9), malonates (10), fluorides (11) and amines (13) with very high stereospecificity (94-99% es, Scheme 4).

The absolute configuration of R-1 was assigned by converting allyl fluoride 11 to 12, which has been determined by X-ray crystallographic analysis, and knowledge (vidia infra) that R-1 to 11 occurs via an S_{N}2 pathway.
To clarify the mechanism of stereospecific substitution we prepared isotopically labelled rac-1-d. Reduction of benzylpyridinium bromide in CD$_2$OD selectively adds D to the C3 position of 14-d, which was epoxidized to 15-d. We used the primary kinetic isotope effect of H/D deprotonation$^{11}$ as a strategy to prepare deuterium-labelled ally alcohol 5-d. This sequence gave a 2.4:1 D/H ratio at C5 after optimization.$^{12}$ Racco1-d was obtained with 61-65% D saturation as judged by $^1$H and $^2$H NMR spectroscopic experiments after chlorination (Scheme 5-1)$^{12}$ Acyclic allyl chlorides generally undergo S$_{2}$i substitutions as the carbon with the leaving group can freely rotate about the vicinal olefin,$^{13}$ but mechanistic studies with cyclic allyl chlorides suggests S$_{2}$i substitutions are generally favoured followed by anti-S$_{2}$i and syn-S$_{2}$i pathways.$^{13}$

Our results (Scheme 5-2) show that the D H saturation at C5 of rac-1-d is usually conserved throughout these substitutions, strongly suggesting S$_{2}$i reactions. An exception to this trend is seen with thioether 9-d which shows some D transfer to C3. As the es of R-1 to 9 is high (96% es), it suggests that the reaction occurs by a mixture of pathways, in favour of S$_{2}$i, with both S$_{2}$i and syn-S$_{2}$i leading to the same enantiomer. Density Functional Theory (DFT) calculations excluded transannular aziridinium ion formation due to the large free energy difference between an azabicyclic intermediate and $^1$ (37.8 kcal/mol).$^{14}$

Such levels of energy necessarily imply unfavourable transition structures to access it (TS $\geq$ 37.8 kcal/mol), thus eliminating the possibilities of an intra-nucleophilic reaction pathway with double inversion.

DFT studies were also used to probe the kinetic resolution of rac-1 (Scheme 6-1).$^{15}$ Starting from a Cu$^{+}$-complex in which the ligand n-alkyl groups were abbreviated in computational models,$^{15}$ rac-1 can bind to the metal centre at the N lone-pair. Two diastereomeric complexes can form with similar stabilities: of which S-C1 (0.8 kcal/mol) is slightly less favorable than R-C1 (-0.2 kcal/mol). Such a qualitative difference could potentially suggest a role in stereoselectivity and explain the specificity observed with N-benzyl-protected allyl chlorides.$^{15}$ For displacement of chloride by the catalyst, five possible pathways were investigated: syn- and anti- oxidative addition, anti-S$_{2}$i, S$_{2}$i and syn-S$_{2}$i.$^{15}$ Alternative conformations were considered for each possibility.$^{15}$ The syn-S$_{2}$i transition structure (TS) S-TS1 was the most favorable overall, proceeding from the reaction of S-1 with a barrier of 25.7 kcal/mol to give the (R)-product of alkylation. For the (S)-enantiomer, this was followed by the S$_{2}$i TS S-TS2 (28.4 kcal/mol). Copper-catalyzed allylic alkylations are often described as occurring through complexation of a Cu(I) complex to the allylic olefin followed by oxidative addition to generate an allyl-Cu(III)$^{15}$ complex, but here anti-S$_{2}$i, syn- and anti- oxidative addition were found to be comparatively unfavourable, except with the anti-S$_{2}$i-oxidative addition pathway (S-TS3) that is only 0.1 kcal/mol higher than S-TS2.$^{15}$

Our computational model is nevertheless qualitatively correct to disfavour S-TS3 over S-TS2 as it would otherwise give the opposite enantiomer than observed experimentally. Similarly to S-1, R-1 was found to preferentially react via a syn-S$_{2}$i pathway, with the barrier for R-TS1 at 26.5 kcal/mol. As found for S-1, the next most stable was S$_{2}$i TS R-TS2 at 27.9 kcal/mol. Based on these computations, the alkylation of R-1 is kinetically disfavored vs. S-1 ($\Delta\DeltaG^1$syn-S$_{2}$i = 0.8 kcal/mol) via dominant syn-S$_{2}$i pathways for both enantiomers. This is consistent with the absolute sense of enantioenrichment observed experimentally, in which the (R)-enantiomer of both substrate and product accumulates. In addition to the major syn-S$_{2}$i pathway, our
result possibly implicate involvement of a minor 3,2 mechanism to give the same product stereochemistry.

D-labelled rac-1-d was subjected to Cu-catalyzed resolution (Scheme 6-2), and in accordance with computation, both 3,2’ and 3,2 pathways are operative; product 3b-d shows D-incorporation at the C3 (49%) and C5 (13%) positions consistent with syn-3,2’ and then 3,2 being the most favourable pathways. No deuterium-isomerization of starting 1-d was observed and R-1-d was isolated from the reaction mixture with 73% ee.

We have found allyl chlorides that are thermodynamically stable and can be prepared in highly enantioenriched form. A rare kinetic resolution of allylic chlorides formed piperidine-based allyl chlorides with high ee. The allyl chloride enantiomers can be separated by chromatography using a chiral non-racemic stationary phase, or prepared by stereosepecific (with retention or inversion) chlorination of the corresponding alcohol. The allyl chlorides undergo highly enantiospecific substitution reactions with nucleophiles to give a wide range of tetrahydropyridine products which are important in biology and medicine. Experiments with D-labelled chloro-tetrahydropyridine and DFT calculations were used to investigate the mechanistic pathways of nucleophilic substitution and kinetic resolution reactions. This work provides new routes for the formation of enantiomERICally enriched tetrahydropyridine derivatives. Further, rac-1, R-, or S-, R-1-d and other configurationally stable allyl halides may serve as probe substrates for investigating reaction pathways in mechanistic studies of reactions.

Acknowledgements

Financial support from the UK Engineering and Physical Sciences Research Council (EP/N022246/1) is gratefully acknowledged. A. V. B. is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. T. P. thanks the People Programme (Marie Curie Actions) of the EU’s Seventh Framework Programme (FP7/2007-2013) under REA grant agreement 316955 for funding. The authors thank Dr. Nader Amin for assistance in D-NMR. We acknowledge the RMACC Summit supercomputer, which is supported by the National Science foundation (ACI-1532235 and ACI1532236), the University of Colorado Boulder and Colorado State University, and the Extreme Science and Engineering Discovery Environment (XSEDE) through allocation TGCHE180056.

Conflict of Interest

Oxford University Innovation has filed a patent application (GB1815018.5) with S.P.F. and S.K. named as inventors. The remaining authors declare no competing financial interests.

Keywords: allyl halides • kinetic resolution • stereoselective • primary kinetic isotope effect • mechanistic studies • mechanistic probes • tetrahydropyridines • Density Functional Theory

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