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Stereospecific Overman Rearrangement of Substituted Cyclic Vinyl Bromides: Access to Fully Substituted α-Amino Ketones

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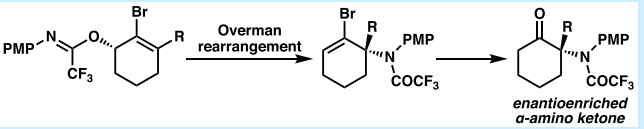
Supporting Information

ABSTRACT: A versatile thermal Overman rearrangement of enantioenriched, cyclic allylic alcohols providing tertiary allylic amines has been developed. The vinyl bromide used to control enantioselectivity in a preceding CBS reduction is utilized as a synthetic handle for the preparation of tertiary α-amino ketones and related derivatives in an asymmetric fashion.



The synthesis of amine-containing stereocenters has been researched extensively owing to the presence of this moiety in a number of bioactive and synthetically useful molecules (Figure 1).[1] Despite this interest, the preparation of

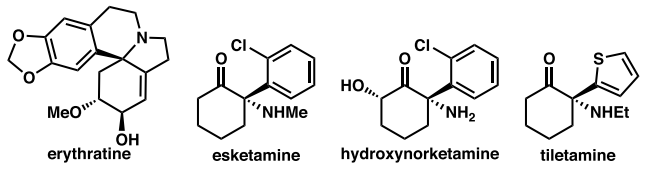
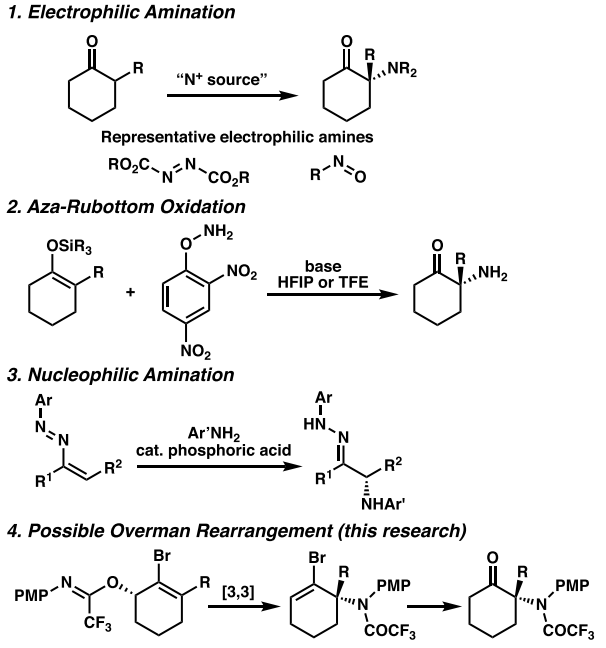


Figure 1. Representative structures containing fully substituted amino stereocenters.

this motif in some situations remains a challenge, particularly with respect to enantioenriched fully substituted α-amino ketones.[2] Many of the reported asymmetric strategies toward this specific motif rely on the functionalization of enolates with electrophilic amine sources, primarily nitroso[3] and azodicarboxylates[4] derivatives (Scheme 1). Recently, however, other unique strategies have arisen such as aza-Rubottom type reactions[5] or those based on nucleophilic amine sources.[6]

In continuation of these studies, the development of new strategies would allow for more varied methods to build this important structural motif. Given our interest in fully substituted stereocenters,[7] we sought to employ a strategy that would specifically allow the synthesis of tertiary amine stereocenters in an asymmetric fashion. Sigmatropic rearrangements have proven to be among the most reliable methods for forming hindered stereocenters, with the ability to transfer starting asymmetry to the product in a stereospecific manner. Thus, we decided to target the use of an Overman rearrangement[8] of enantioenriched, substituted allylic alcohols bearing functionality that would ultimately allow the synthesis of an α-amino ketone. The asymmetric aspect of this overall transformation is therefore simplified to the preparation of an enantioenriched allylic alcohol, for which there are numerous reliable preparative procedures. Notably, a related strategy was

Scheme 1. Synthetic Strategies toward α-Amino Ketones



recently reported by researchers from Janssen for the synthesis of esketamine via a cyanate sigmatropic rearrangement utilizing an asymmetric transfer hydrogenation to provide the requisite enantioenriched allylic alcohol.[9]

To begin we first investigated different strategies toward the synthesis of chiral, enantioenriched allylic alcohols. Ultimately, the Corey–Bakshi–Shibata (CBS) reduction was identified as ideal for our strategy since it is known to reliably reduce substituted cyclic enones in high enantioselectivity.[10] In particular, bromo-enones are common substrates for CBS reductions, with the bromide imparting enhanced facial bias of

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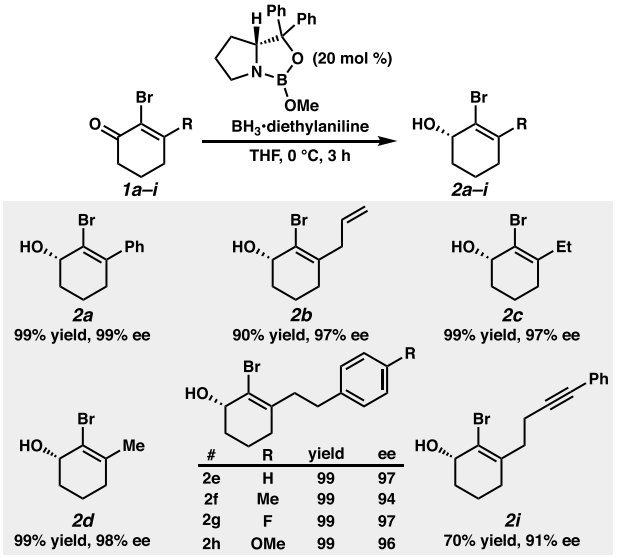
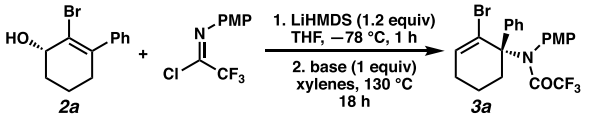
the ketone leading to increased enantioselectivities. Often, however, the bromide is solely used as a means of obtaining increasing enantioselectivity and is subsequently removed via a debromination step following the reduction. In this case, we wondered whether the vinyl bromide functionality could instead be further utilized as a synthetic handle toward the synthesis of additional chiral amine building blocks, in particular α-amino ketones. We were pleased to find that a number of β-substituted α-bromo-enones, containing various aryl and alkyl substituents, could be selectively reduced via the *in situ* formation of the CBS catalyst (Scheme 2),[11] setting the stage for the subsequent stereospecific Overman rearrangement.

Scheme 2. Synthesis of Alcohols via CBS Reduction



Our initial interest in this transformation focused on aryl-substituted systems owing to their prevalence in pharmaceuticals (e.g., esketamine). Thus, we chose cyclohexenol **2a** as a standard substrate for examination of the reaction conditions. While transition-metal catalyzed rearrangements[12] were not successful in our hands, standard thermal conditions affected the desired transformation (Table 1). Starting from the allylic alcohol, an intermediate trifluoroacetimidate could be prepared by treatment with LiHMDS and an imidoyl chloride reagent. This material could then be carried on crude through the rearrangement by heating to 130 °C in xylenes with the addition of a base to prevent material decomposition. A variety of bases for the rearrangement were examined, with inorganic bases generally proving to be superior. Potassium carbonate was identified as the optimal base providing the desired rearranged product in 45% yield and 97% ee (entry 6).

Table 1. Overman Rearrangement Base Screen

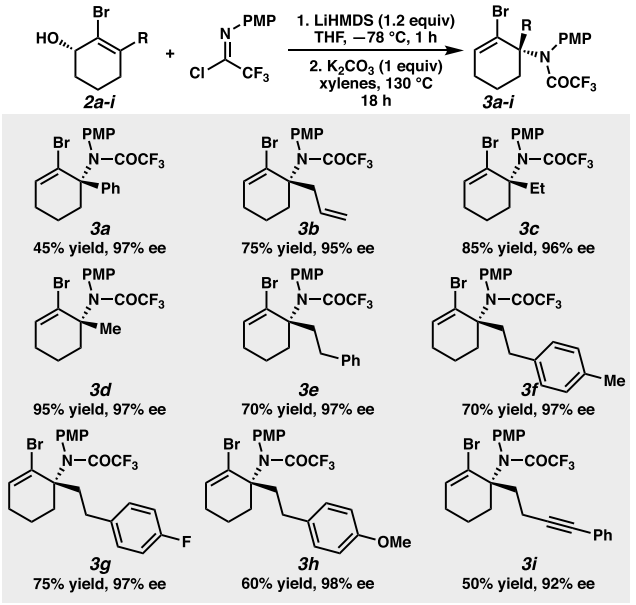


entry	base	yield (%)[b]	ee (%)[c]
1	DBU	15	96
2	Et_3N	33	97
3	NaOAc	36	97
4	NaOH	40	96
5	Li_2CO_3	33	96
6	K_2CO_3	45	97

[a]Conditions: 0.2 mmol of **2a**, 0.2 mmol of base, 2 mL of solvent. [b]Yield of isolated product. [c]Determined by chiral SFC.

Unfortunately, attempts to increase the yield above this point proved to be unsuccessful. Modifying variables such as solvent/temperature combinations and amine protecting group afforded suboptimal results. Additionally, differentially substituted aromatic substituents (e.g., *para*-fluoro) as well as other substrates bearing directly connected sp^2 functionality (e.g., vinyl) failed to provide any of the desired product. We wondered how other substrates might perform in this transformation and decided to continue forward with examining a substrate scope (Scheme 3). We were pleased to find that the use of alkyl substituents indeed proved to be more successful. Allyl substituted **3b** was obtained in 75% yield and 95% ee. Small alkyl groups such as ethyl (**3c**) and methyl (**3d**) were also tolerated, furnishing the products in 80% and 95% yield, respectively, both in high enantiopurity. The rearrangement performed well with phenylethyl groups bearing various *para*-substituents leading to products **3e**–**3h** in moderate 60–75% yield. Lastly, an alkyne was also tolerated in the transformation (**3i**), albeit in a diminished 50% yield. In all cases, minimal to no erosion of allylic alcohol enantiopurity was observed following the rearrangement.[13]

Scheme 3. Reaction Scope of Overman Rearrangement[a]



[a]Conditions: 0.2 mmol of **2a**, 0.2 mmol of base, 2 mL of solvent. [b]Yield of isolated product. [c]Determined by chiral SFC.

With a scope of the rearrangement examined, we next turned toward derivatizations of the obtained products. Using allyl substituted **3b** as a test substrate, sequential amine deprotections could be performed (Scheme 4).[10] First, removal of the trifluoroacetate group was realized under reductive conditions with sodium borohydride providing substituted aniline **4**. Next, oxidative removal of the *p*-methoxy phenyl substituent could be affected under standard oxidative

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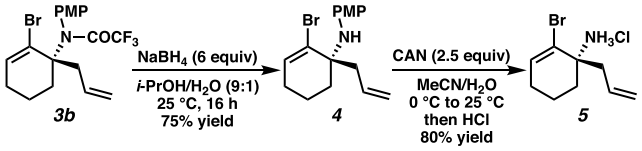
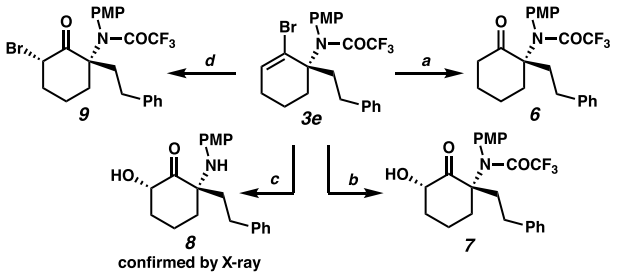
Scheme 4. Sequential Removal of Amine Protecting Groups



conditions, furnishing the desired tertiary amine **5** as its hydrochloride salt, following treatment with HCl in ether.

Next, our original strategy of targeting fully substituted α-amino ketones was realized upon exposure of vinyl bromide **3e** to a variety of conditions (Scheme 5). Treatment with

Scheme 5. Derivatization of Rearrangement Product[a]



[a]Conditions: (a) $Co(acac)_2$ (1 equiv), Et_3SiH (5 equiv), O_2 (1 atm), *i*-PrOH, 50 °C, 2 h, 75% yield. (b) O_3, pyridine (2.5 equiv), CH_2Cl_2, −78 to 25 °C, 85% yield. (c) O_3, MeOH, then DMS, −78 to 25 °C, 80% yield. (d) $RuCl_3$ (2 mol %), $NaIO_4$, MeCN/EtOAc/H_2O, 25 °C, 16 h, 60% yield.

$Co(acac)_2$ and Et_3SiH under an atmosphere of oxygen affords the corresponding ketone **6** in 75% yield.[14] This transformation is proposed to occur via a Mukaiyama hydration followed by loss of bromide. Surprisingly, during attempts to oxidatively cleave the vinyl bromide under ozonolysis conditions in CH_2Cl_2 with pyridine, cyclic α-hydroxy ketone **7** was obtained instead as a single diastereomer in 85% yield, potentially via the intermediacy of an epoxide.[15] This compound is particularly interesting as this substituent pattern mirrors that which is believed to be the active human metabolite of esketamine (hydroxynorketamine) that is essential for the parent molecule's antidepressant activity.[16] When the ozonolysis is performed in methanol, with a dimethylsulfide quench, the α-hydroxy ketone is again obtained; however, in this case concomitant removal of the trifluoroacetate protecting group occurs providing ketone **8** in 80% yield. The identity and stereochemistry of ketone **8** was confirmed by X-ray diffraction (see Supporting Information for details). Lastly, treatment with $RuCl_3$ and sodium periodate interestingly affords the α-bromoketone **9** as a single diastereomer. We were pleased to find that these experiments validate our original hypothesis that the vinyl bromide handle could lead to a variety of α-amino ketone derivatives through relatively straightforward transformations.

In summary, we have developed a versatile asymmetric method for the synthesis of fully substituted allylic amines in good yields and excellent enantioselectivities via the combination of a CBS reduction and a stereospecific Overman rearrangement. Subsequent transformations allow the preparation of stereochemically rich and biologically important α-amino ketone derivatives bearing multiple reactive sites poised to undergo further functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03347.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1955048 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This manuscript is dedicated to Professor Larry E. Overman (UC Irvine) for being an inspirational force in organic synthetic chemistry.

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