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Practical Gram Scale Asymmetric Catalysis with Boroxinate Brønsted Acids Derived from the VAPOL and VANOL Ligands

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ABSTRACT: Our laboratories have been engaged in utilizing catalysts derived from the VAPOL and VANOL ligands towards the development of efficient asymmetric processes over the last several years. Subsequent to their development, practical scale-up of these methodologies to gram scale has always been deemed necessary to demonstrate. This article will report on such successful gram scale asymmetric catalysis that has been realized in our laboratories using the boroxinate Brønsted acid catalysts derived from the VAPOL and VANOL ligands. The processes reviewed will be the catalytic asymmetric aziridination of imines and the direct catalytic asymmetric aminoallylation of aldehydes.

INTRODUCTION

In the preceding article (DOI 10.1021/op200088b), we have detailed practical synthetic procedures for the preparation of the chiral ligands VAPOL and VANOL. These procedures start from cheap and readily available starting materials and, via streamlined synthetic routes, furnish multigram quantities of VAPOL and VANOL in an efficient manner and with high yields and absolute optical purity.

These vaulted ligands, VAPOL and VANOL, were introduced by our research group in 1993.[1] They, and their various derivatives, have since then been utilized in our group to construct a variety of efficient and general catalytic asymmetric processes. Self-assembled boroxinate Brønsted acid catalysts prepared from VAPOL and VANOL have been extensively applied by our group towards the development of a universal asymmetric aziridination system,[2−5] an asymmetric hetero-Diels−Alder reaction,[6] and a direct asymmetric aminoallylation of aldehydes.[7] VAPOL/VANOL catalysts containing aluminum or zirconium have been shown by us to successfully catalyze asymmetric Diels−Alder reactions,[1,8] imino-aldol reactions,[9] and Baeyer−Villiger reactions.[10] VAPOL and VANOL ligands have been also used in asymmetric catalysis by other research groups worldwide. Phosphoramidite derivatives of VAPOL and VANOL have been shown to be effective ligands in rhodium-catalyzed enantioselective intramolecular hydroarylation of alkenes.[11] VAPOL as a standalone species can mediate asymmetric Petasis reactions, affording chiral α-amino acid esters with high asymmetric inductions.[12] An increasing number of systems in recent years have showcased the use of the chiral phosphoric acid catalysts prepared from VAPOL and VANOL. Imine amidations,[13] imino ester reductions,[14] imine imidations,[15] as well as desymmetrization of *meso*-aziridines to afford vicinal diamines[16] and vicinal amidophenylthioethers[17] have all been shown to proceed with excellent levels of asymmetric inductions under their catalysis.

Over the years of practicing asymmetric catalysis especially with the self-assembled boroxinate Brønsted acid catalysts derived from VAPOL and VANOL,[2−7] a recurring theme in our research has been to demonstrate the practicality of these methodologies. Scale-up to furnish multigram quantities of final products with no or minimal use of column chromatography was set as a benchmark for such demonstrations. This benchmark has been successfully accomplished by us in our studies on the asymmetric aziridination of imines and the direct asymmetric aminoallylation of aldehydes. With the practical and scalable syntheses of VAPOL and VANOL outlined in the preceding article (DOI 10.1021/op200088b), access to these ligands by the larger synthetic community should be greatly facilitated. The purpose of the present article is to highlight the gram scale practical asymmetric catalysis that has been demonstrated in our laboratories by utilizing the self-assembled boroxinate Brønsted acid catalysts of VAPOL and VANOL.

GRAM SCALE CATALYTIC ASYMMETRIC AZIRIDINATION

Aziridines are important three-membered heterocycles found in numerous natural products with promising biological activities.[18] Aziridines are also invaluable building blocks in organic synthesis; by virtue of their inherent ring strain, they participate readily in a multitude of stereoselective ring-opening and ring-expansion reactions.[19,20] The field of catalytic asymmetric aziridination has seen impressive growth in the past decade, and this growth has been extensively reviewed.[21]

Efforts in our group over the past decade have resulted in the development and fundamental understanding of a universal asymmetric catalytic aziridination system.[2−5] Our original report, published in 2000,[2b] detailed the preparation of a wide variety of *cis*-aziridines from the reactions of benzhydryl imines and ethyl diazoacetate, catalyzed by boroxinate[5] Brønsted acids prepared from the VAPOL and VANOL ligands. Extensive studies on the original system in subsequent years led to a full report in 2008.[2h]

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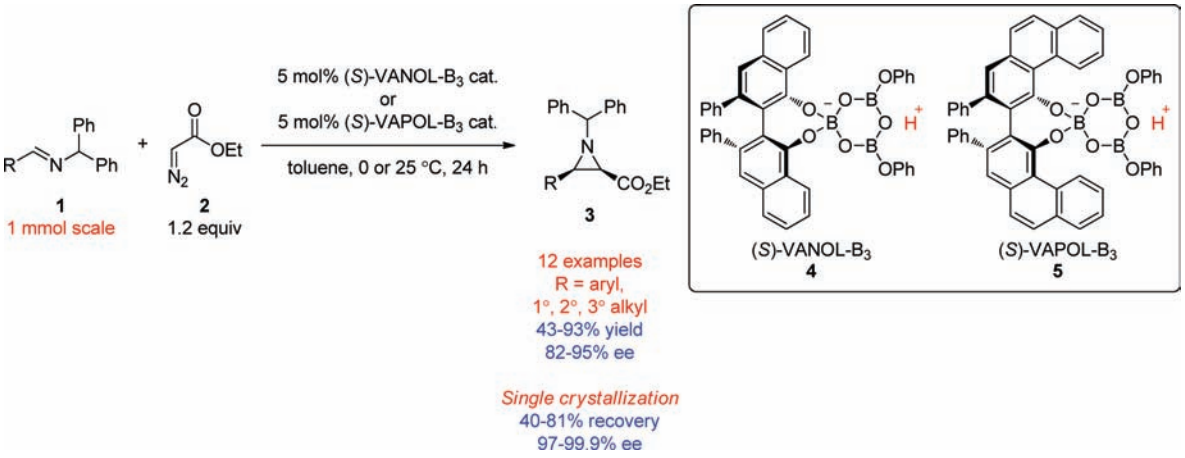
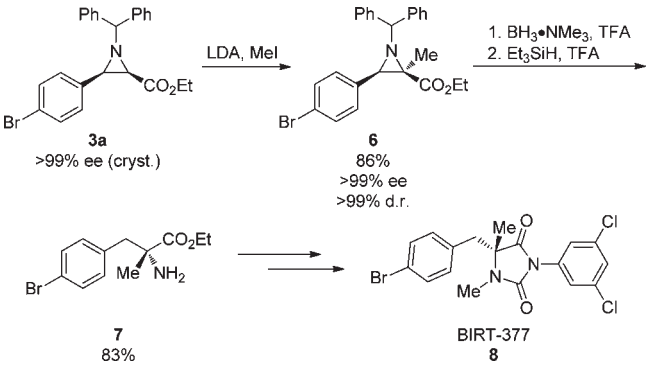
Scheme 1. Original Benzhydryl Catalytic Asymmetric cis-Aziridination System[2h]



Scheme 2. Synthesis of LFA-1 Antagonist BIRT-377[2e]



All the imines in our benzhydryl cis-aziridination system were prepared in a straightforward manner in multigram quantities from commercially available aromatic/aliphatic aldehydes and benzhydryl amine, in the presence of $MgSO_4$.[2h] All imines were purified by crystallization with good to excellent recoveries, with the exception of the 1° aliphatic imine which was used in its crude form. Scheme 1 captures the generality of this protocol over a broad spectrum of benzhydryl imines prepared from aromatic as well as 1°, 2°, and 3° aliphatic aldehydes.[2h] Remarkably, catalysts prepared from both the VAPOL and VANOL ligands gave essentially the same asymmetric inductions over all 12 of the substrates with an average difference of only 1.2% ee. All 12 of the benzhydryl aziridines depicted in Scheme 1 are solids and could be readily crystallized up to almost optical purity by a single crystallization with good to excellent recovery in all cases.

Thus, in looking for a substrate to demonstrate a practical scale-up of our original benzhydryl system, we chose the *p*-bromobenzhydryl aziridine **3a**. In addition to the attraction of the *p*-bromo functional group as a useful synthetic handle for various cross coupling transformations, we had also previously showcased this aziridine **3a** enroute to the total synthesis of LFA-1 antagonist BIRT-377 (Scheme 2).[2e] This total synthesis featured a diastereoselective alkylation of the aziridine ring which proceeded with complete retention of stereochemistry, a reductive ring opening of the aziridine ring, and a subsequent deprotection of the benzhydryl group to get to α-amino ester **7**, which was taken on to the final product BIRT-377 **8** in a further two steps. It was thus desired to develop a practical and efficient synthesis for aziridine **3a**, at a multigram scale, without the use of any column chromatography purification. This goal was subsequently borne out successfully and reproducibly in our laboratory and was also verified and reproduced by an independent research group (Scheme 3).[2l]

The requisite imine **1a** was prepared on a multigram scale from commercially available benzhydryl amine **9** and *p*-bromobenzaldehyde **10** (Scheme 3).[2l] The reaction proceeded at room temperature in the presence of $MgSO_4$ and afforded 84−85% yield of pure imine **1a** after crystallization in a single crop. The actual aziridination reaction was carried out in the presence of only 0.5 mol % of the boroxinate Brønsted acid catalyst **4** prepared from the VANOL ligand (corresponding to only 44 mg of the ligand being used) and proceeded to full conversion at room temperature in only 8 h (Scheme 3). Thus, 20 mmol or 7 g of imine **1a** was reacted with 1.2 equiv of ethyl diazoacetate **2** to afford the crude aziridine product. A single crystallization of the crude aziridine afforded *optically pure* (99% ee) *cis*-aziridine **3a** in 62−64% yield (5.4−5.6 g). After the second crop, the overall yield of the reaction was 89% (7.8 g), and the overall asymmetric induction was 92−93% ee. Note that *no* column chromatography has been used during the entire process, thus making it more attractive from the process chemistry perspective. The choice of VANOL as the ligand here rather than VAPOL was governed by a catalyst loading study during this scale-up work which revealed that the catalyst prepared from VANOL gave approximately four times as many turnovers as that prepared from VAPOL. We have also previously published a 10.9 g (40 mmol) scale aziridination of imine **1b** (R = Ph) with 0.25 mol % VAPOL boroxinate catalyst **5** in carbon tetrachloride solvent which gave the corresponding aziridine in 64% yield and 98% ee after collection of the first crop.[2h]

Our group has invested significant time and effort over the last many years to fine-tune and optimize our aziridination methodology. In an effort to map the active site of our catalyst, numerous N-protecting groups for the imine were screened.[2i] These studies revealed that while the use of a diphenylmethyl group on the imine was essential for the success of the aziridination reaction it did not represent the optimal substituent since it was found that various diarylmethyl groups were far more effective.

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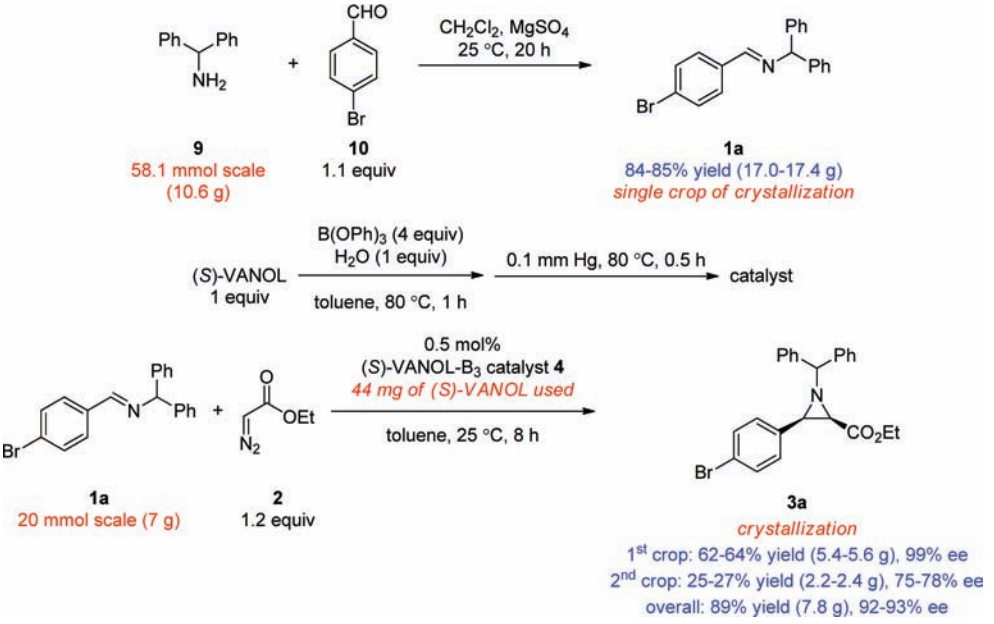
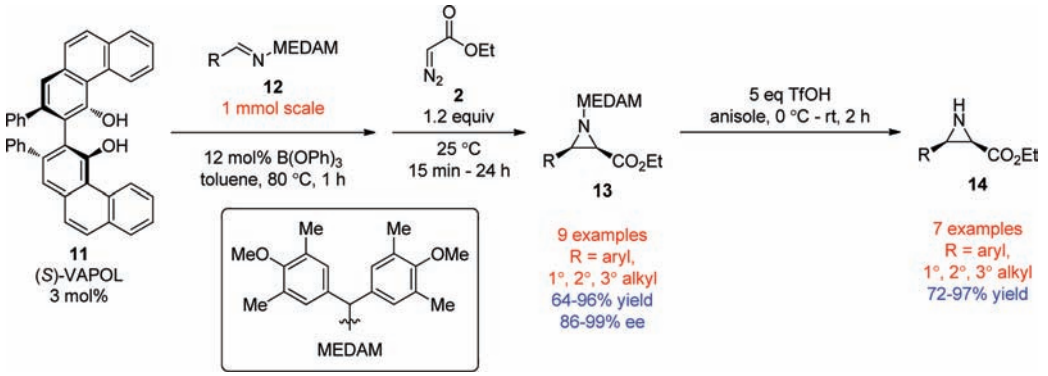
Scheme 3. Gram Scale Catalytic Asymmetric Synthesis of Benzhydryl Aziridine 3a[21]



Scheme 4. MEDAM Catalytic Asymmetric cis-Aziridination System[2j]



Seeking passé-partout for the *N*-substituent, we have recently demonstrated that the tetramethyldianisylmethyl (MEDAM) group is the optimal N-substituent for our universal catalytic asymmetric aziridination system.[2j,22]

Scheme 4 provides a high level overview of our cis-selective aziridination system with the MEDAM protecting group on the imine nitrogen.[2j] Using only 3 mol % of the boroxinate Brønsted acid catalyst prepared from VAPOL, exquisite levels of asymmetric inductions and yields for the most part were obtained for a broad range of *cis*-aziridines. The results from the VANOL ligand (not shown) were quite similar,[2j] as was the case in the benzhydryl *cis*-aziridination system (Scheme 1).[2h] We have performed a large scale catalytic asymmetric aziridination on an imine closely related to **12** according to the method shown in Scheme 4. This imine was derived from an amine with a dianisylmethyl (DAM) protecting group and benzaldehyde. This reaction gave the aziridine in 66% yield and 97% ee after collection of the first crop from 11.6 g (35 mmol) of the imine and from the boroxinate catalyst **4** prepared from 39 mg of the VANOL ligand.[2g]

Furthermore, in most of the examples for the MEDAM cis-aziridination system, we were also able to demonstrate smooth TfOH-induced cleavage of the MEDAM group to reveal the corresponding *N*-H aziridines (Scheme 4). Getting to the *N*-H aziridine is important to harness the utility of the chiral aziridine as an invaluable building block.[19,20] This is especially true in those transformations that involve nucleophilic ring opening of the aziridine under basic conditions since this type of reaction usually requires an electron-withdrawing group on the nitrogen.

An additional and significant improvement in the aziridination system was the development of a much simpler and easier method for active catalyst generation. For all of our early aziridination studies, the active boroxinate Brønsted acid catalyst was generated utilizing conditions depicted in Scheme 3.[3] These involve the use of a high vacuum (0.1 mmHg) to remove all volatiles during an intermediate unit operation, which was unattractive from a process chemistry and scale-up perspective. This unit operation can be eliminated as is exemplified in our MEDAM aziridination system (Scheme 4); the active boroxinate catalyst was generated by simply heating the ligand, $B(OPh)_3$, and the

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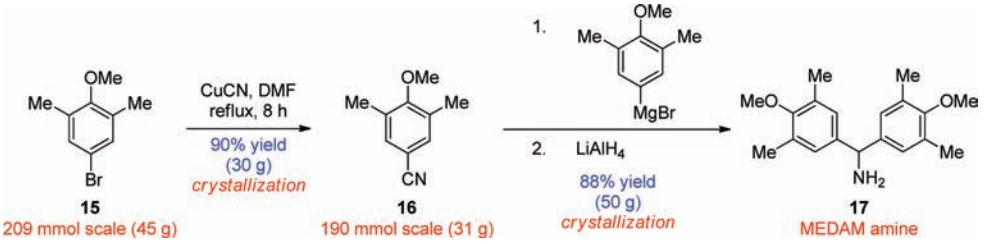
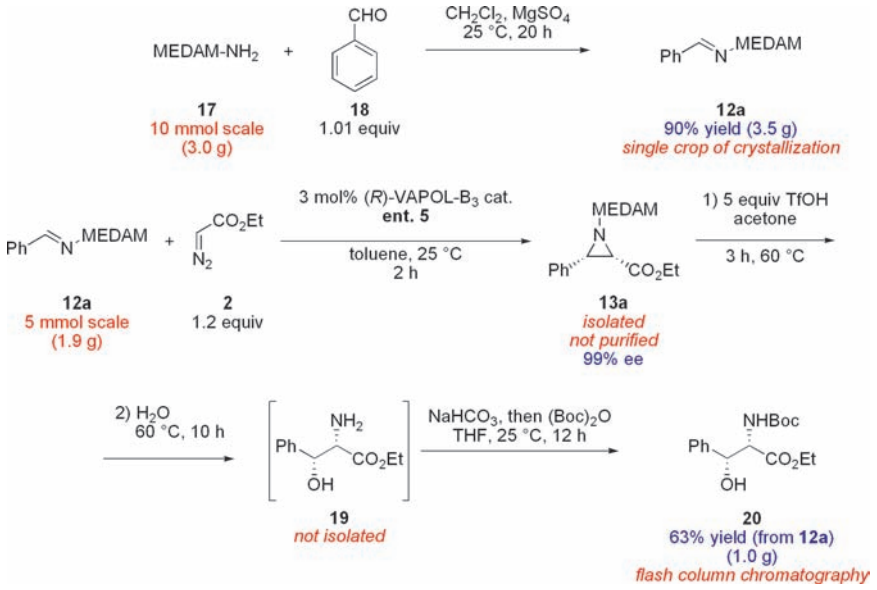
Scheme 5. Gram Scale Preparation of the MEDAM Amine 17[2j]



Scheme 6. Gram Scale MEDAM cis-Aziridination/Deprotection/Ring Opening



imine in toluene at 80 °C for 1 h. The mixture was cooled, and the actual aziridination reaction proceeded smoothly at room temperature with the addition of ethyl diazoacetate to afford the crude aziridine product.

Thus, our MEDAM cis-aziridination system had proved to be the most general and efficient system amongst all the generations of cis-aziridination systems developed in our laboratories over the past decade, at least from the perspective of the asymmetric inductions and yields obtained over the entire range of *cis*-aziridines. It was therefore subsequently desired to demonstrate the practicality of this methodology by scaling up the entire process to multigram scales, with a minimal or no use of column chromatography purifications.

As an initial step towards this goal, demonstrating an efficient and practical synthesis for the MEDAM amine was deemed to be of the utmost significance. This aim was realized successfully on a 50 g scale for the final product, the MEDAM amine **17** (Scheme 5).[2j] Thus, the MEDAM amine **17** could be prepared in one step from the commercially available bromide **15** and the commercially available nitrile **16**, through the reaction of the nitrile **16** with the Grignard reagent generated from the bromide **15** followed by an in situ LAH reduction of the resulting imine adduct. The nitrile **16** although commercially available is expensive; we were able to demonstrate a facile preparation of **16** from the cheaper bromide **15** by the Shechter modification of the Rosenmund−Van Braun reaction.[23] Thus, the entire process for the preparation of the MEDAM amine **17** can be carried out efficiently on a multigram scale, without the use of any column chromatography purification.

Utilizing the MEDAM amine **17** and commercially available aromatic/aliphatic aldehydes, all the imines **12** in our MEDAM cis-aziridination system (Scheme 4) were prepared in a straightforward manner in multigram quantities, in the presence of $MgSO_4$.[2j] All imines were purified by crystallization with good to excellent recoveries, with the exception of the 1° aliphatic imine which was used in its crude form. A representative MEDAM imine preparation is depicted in Scheme 6, for the Ph-MEDAM imine **12a**.

For the practical gram scale demonstration of our MEDAM cis-aziridination system, it was envisioned that the crude aziridine product could be directly subjected to a deprotection−ring-opening sequence under TfOH/water conditions. Such a process would directly yield, without any intermediate isolations and purifications, the corresponding optically pure β-hydroxyl-α-amino ester—a valuable building block in organic synthesis. This was realized successfully in our hands, and the entire process is depicted in Scheme 6. Thus, the imine **12a** was subjected to the aziridination reaction at a 5 mmol or 1.9 g scale, under catalysis by only 3 mol % of the chiral boroxinate Brønsted acid prepared from the VAPOL ligand according to conditions depicted in Scheme 4. This reaction proceeded to complete conversion in only 2 h at room temperature to afford the essentially optically pure crude aziridine **13a**. This was then subjected to a TfOH

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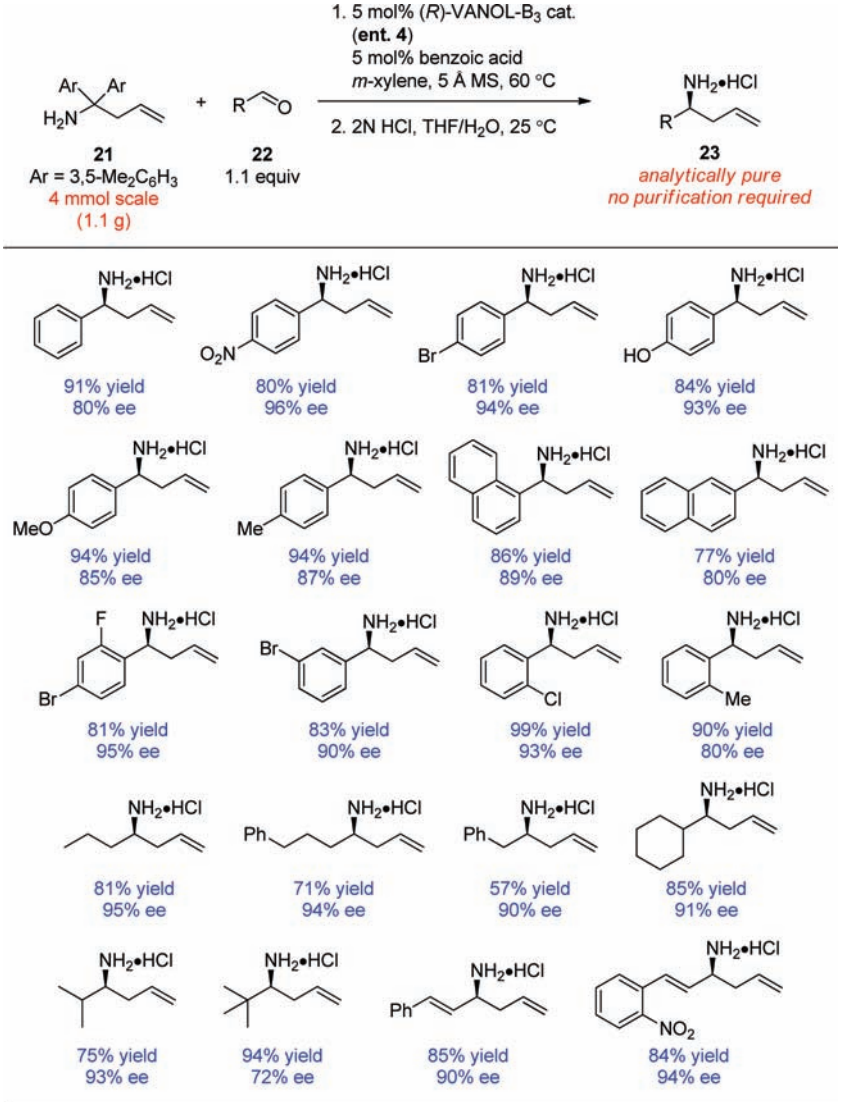
Table 1. Comparative Analysis of the Benzhydryl and MEDAM cis-Aziridination Systems

benzhydryl cis-aziridination system	MEDAM cis-aziridination system
significantly lower relative asymmetric inductions and yields	significantly higher relative asymmetric inductions and yields
benzhydryl amine is commercially available	MEDAM amine is not commercially available but can be made in one step from commercially available starting materials
aziridines are crystalline; optical purity can be enhanced in most cases to >99% ee with a single crystallization	aziridines are not crystalline
system of choice for crystalline aziridines	system of choice for noncrystalline aziridines
removal of the benzhydryl group, important for aziridine applications, is not efficient if aryl imine is used	removal of the MEDAM group, important for aziridine applications, is straightforward and general for all aziridines
relative rates of aziridinations are significantly slower	relative rates of aziridinations are significantly faster

Scheme 7. Gram Scale Catalytic Asymmetric Direct Aminoallylation of Aldehydes[7]



deprotection, a water induced ring opening, and a Boc protection sequence—*without any intermediate isolations*—to afford the pure β-hydroxyl-α-amino ester **20** in a 63% overall yield (1.0 g) from imine **12a**.

In the work reported above, we have demonstrated the practical and efficient scale-up at multigram quantities of our benzhydryl and MEDAM catalytic asymmetric cis-aziridination systems. Thus, this juncture merits a dialogue on the choice between these two aziridination systems that a practitioner would have to make should he or she embark on a quest to prepare chiral *cis*-aziridines. Both systems have inherent advantages as well as disadvantages, and these are drawn out in a comparative analysis in Table 1.

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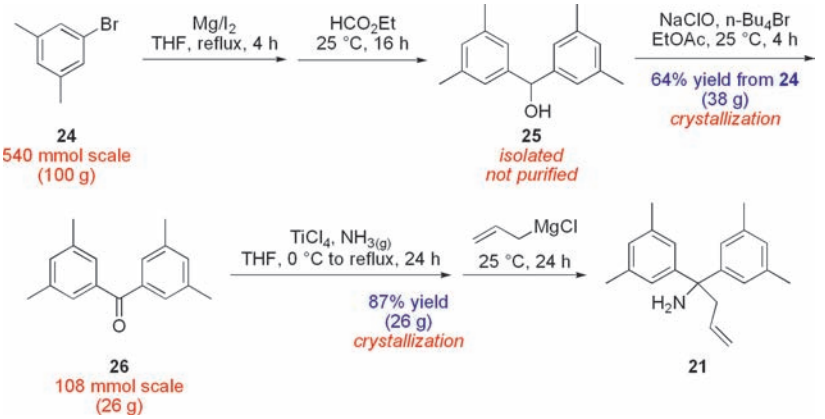
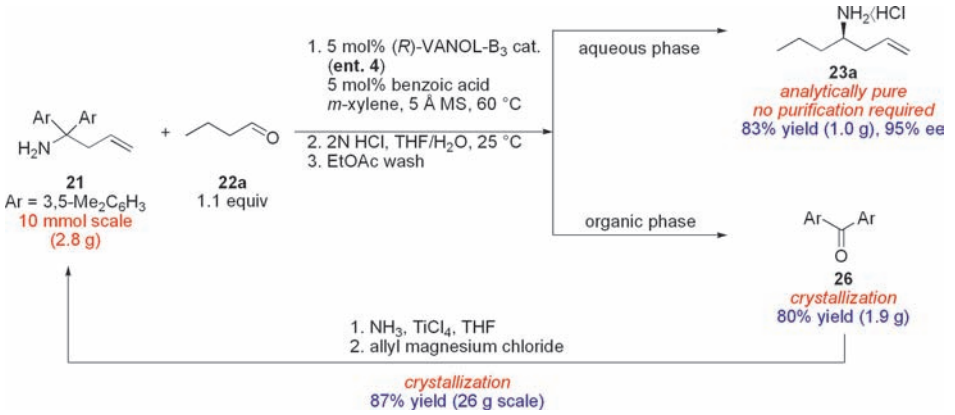
Scheme 8. Gram Scale Preparation of the Homoallylic Amine Starting Material 21[7]



Scheme 9. Recycle of the Homoallylic Amine Starting Material 21 from the Aminoallylation Reaction[7]



GRAM SCALE DIRECT AMINOALLYLATION OF ALDEHYDES

Chiral amines are ubiquitous motifs in the pharmaceutical and fine chemical industry and in the field of natural products.[24] Within the world of chiral amines, chiral homoallylic amines comprise an important subclass. These are invaluable building blocks in organic synthesis, and an incredible body of work has been devoted to their construction.[25]

Our group has recently communicated the development of a practical and general direct catalytic asymmetric aminoallylation of aldehydes, catalyzed by a synergistic cocktail of the chiral boroxinate Brønsted acid prepared from the VANOL ligand and a nonchiral Brønsted acid (benzoic acid).[7] The VANOL boroxinate Brønsted acid catalyst used here is identical to that utilized in our catalytic asymmetric aziridination work (vide supra). *The entire methodology has been developed on a gram scale and allows for the direct isolation of unprotected analytically pure chiral homoallylic amines.* The aminoallylation reaction is initiated from commercially available aldehydes and a homoallylic amine that is prepared on a multigram scale in three practical steps. An efficient single-step recycle of the homoallylic amine starting material has also been demonstrated. The methodology is general over a broad range of aromatic, 1°, 2°, and 3° aliphatic, benzylic, and alkenyl aldehydes, affording the corresponding analytically pure unprotected homoallylic amines in high yields and with excellent asymmetric inductions. *Of particular significance in this methodology is that all the individual steps are conducted without the use of any column chromatography purification, thus making the entire process simple and extremely attractive from the perspective of process chemistry and scale-up.* This includes the preparation of the starting homoallylic amine, the actual direct catalytic asymmetric aminoallylation reaction, as well as the recycle of the starting homoallylic amine.

The generality of our gram scale catalytic asymmetric direct aminoallylation methodology is depicted in Scheme 7.[7] A gamut of different aldehydes undergo aminoallylation to afford the corresponding homoallylic amine hydrochloride salts directly, in analytically pure form without any purification. These salts are suitable either for prolonged storage under ambient conditions or for immediate use. The boroxinate Brønsted acid catalyst was prepared under conditions similar to those depicted in Scheme 3. The VANOL ligand is distinctly superior to VAPOL in this methodology, quite unlike our aziridination methodology where VAPOL and VANOL give identical profiles for asymmetric inductions and yields.

The starting homoallylic amine **21** was prepared in multigram quantities in a three-step synthetic sequence starting from the bromide **24**, which was converted into a Grignard reagent and reacted with ethylformate to afford the alcohol **25** (Scheme 8). The crude product **25** was directly subjected to an oxidation

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reaction with commercially available Clorox bleach to provide ketone **26** in an overall yield of 64% from the bromide **24** after crystallization. The diaryl ketone **26** was then converted to the desired homoallylic amine **21** in a one-pot reaction where allyl magnesium chloride was added directly to the in situ generated *N*-H imine of ketone **26**. After crystallization, the amine **21** was obtained in 87% isolated yield (26 g scale for **21**).

Finally, we were able to also demonstrate a facile and practical recycle of the homoallylic amine starting material **21** from the direct aminoallylation reaction. This was done in the reaction of *n*-butanal **22a** and is depicted in Scheme 9. The diaryl ketone **26** was isolated from the organic phase of the aminoallylation reaction workup and purified by crystallization in 80% yield. This could then be recycled back to the homoallylic amine starting material **21** in 87% yield according to conditions depicted in Scheme 8.

CONCLUSION

In the preceding article (DOI 10.1021/op200088b), we have detailed practical and efficient gram scale syntheses for the chiral ligands, VAPOL and VANOL. In this article, we have detailed the use of the boroxinate Brønsted acid catalysts prepared from these ligands towards the gram scale preparation of chiral *cis*-aziridines and chiral homoallylic amines. These methodologies have been developed with a focus on the practicality, scalability, and simplicity of the reaction processes. In addition to the actual asymmetric catalysis, practical and gram scale processes for the preparation of starting materials, applications of the chiral products, and recycle of the starting materials have also been developed. Reaction telescoping and process intensification have been incorporated as much as possible. Crude products have been taken forward where possible, and crystallization has been employed as the purification method of choice; column chromatography purifications have been kept to a minimum. All reaction processes have been shown to proceed with excellent yields and asymmetric inductions, providing multigram quantities of the desired chiral products in an efficient manner. We anticipate that this body of work will find significant applications for the preparation of chiral N-containing compounds in the discovery and process development groups of various pharmaceutical and fine chemical industries, as well as in the research laboratories of the academia.

EXPERIMENTAL INFORMATION

For the gram scale catalytic asymmetric benzhydryl aziridination process (Scheme 3), see ref 2l. For the gram scale preparation of the MEDAM amine **17** (Scheme 5), see ref 2j. For all the gram scale work in the catalytic asymmetric direct aminoallylation of aldehydes methodology (Schemes 7, 8, and 9), see ref 7.

The experimental details for the gram scale catalytic asymmetric MEDAM aziridination process (Scheme 6) are given below.

Preparation of Imine 12a, *N*-Phenylmethylidenebis(4-methoxy-3,5-dimethylphenyl)methylamine[2j]. To a 50 mL flame-dried round-bottom flask filled with argon was added the MEDAM amine [bis(2,6-dimethyl-4-methoxyphenyl)methylamine] **17** (2.99 g, 10.00 mmol), $MgSO_4$ (2.0 g, 16.8 mmol, freshly flame-dried), and dry CH_2Cl_2 (30 mL). After stirring for 10 min, benzaldehyde **18** (1.08 g, 10.1 mmol, 1.01 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite, and the Celite bed was washed with CH_2Cl_2 (20 mL × 3). Then the filtrate was concentrated by rotary evaporation to give the crude imine as an off-white solid. Crystallization (1:9 CH_2Cl_2/hexanes) and collection of the first crop afforded imine **12a** as a white solid (mp 144−146 °C) in 90% isolated yield (3.50 g, 9.0 mmol). Spectral data for **12a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 3.66 (s, 6H), 5.35 (s, 1H), 6.99 (s, 4H), 7.39−7.41 (m, 3H), 7.80−7.82 (m, 2H), 8.35 (s, 1H); ^{13}C ($CDCl_3$, 125 MHz) δ 16.22, 59.59, 77.41, 127.86, 128.46, 128.49, 130.61, 130.63, 136.45, 139.22, 155.84, 160.28; IR (thin film) 2944w, 1643vs, 1483vs cm^{-1}. Mass spectrum: *m*/*z* (% rel intensity) 387 M+ (3), 283 (100), 40 (17). Anal. calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.42; H, 7.24; N, 3.55. These spectral data match those previously reported for this compound.[2j]

Preparation of Aziridine 13a, (2*S*,3*S*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate. To a 25 mL flame-dried homemade Schlenk flask equipped with a stir bar and flushed with argon was added (*R*)-VAPOL (81 mg, 0.15 mmol) and $B(OPh)_3$ (174 mg, 0.60 mmol) and aldimine **12a** (1.94 g, 5 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (10 mL) was added through the top of the Teflon valve to dissolve the reagents. The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (622 μL, 6.0 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 1 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the completion of the reaction. The reaction was diluted by addition of hexane (30 mL). The reaction mixture was then transferred to a 500 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (30 mL × 2), and the rinse was added to the 500 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.1 mmHg) for 2 h to afford the crude aziridine as an off-white solid. The crude aziridine was used in the next step without any further purification.

Preparation of Hydroxyl Amino Ester 20, (2*S*,3*R*)-Ethyl 2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate. To a solution of the crude aziridine **13a** obtained above in acetone (250 mL) was added trifluoromethanesulfonic acid (2.21 mL, 25 mmol, 5.0 equiv) at room temperature. The flask was then equipped with an air condenser and a nitrogen balloon at the top of the condenser through a rubber septum. The solution was stirred at 60 °C for 3 h under nitrogen atmosphere. The reaction was monitored by TLC. To the solution was then added water (50 mL), and the resulting mixture was stirred at 60 °C for 10 h. The solution was then cooled to room temperature, and the volume was reduced to half by rotary evaporation. Water (200 mL) was added to the resulting mixture. The mixture was washed with ether (40 mL × 3). To the water layer was added solid sodium bicarbonate until pH ∼ 9. To the resulting mixture was added THF (85 mL) and di-*tert*-butyl dicarbonate (1.75 g, 8.5 mmol, 1.6 equiv). The mixture was stirred at room temperature for 12 h. The mixture was then extracted with ethyl acetate (100 mL × 4). The combined organic layer was washed with saturated aqueous NaCl solution (40 mL × 2) and dried over anhydrous $MgSO_4$. The ethyl acetate was removed by rotary evaporation. Purification by flash silica gel chromatography (1:2 ether/hexanes as eluent) afforded **20** as colorless oil in 63% isolated yield (975 mg, 3.15 mmol). Spectral data for **20**:

R_f = 0.49 (2:1 Et_2O/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J = 7.1 Hz), 1.32 (br s, 9H), 2.79 (br s, 1H), 4.17 (q, 2H, J = 7.3 Hz), 4.49 (br d, 1H, J = 7.1 Hz), 5.16−5.19 (m, 1H), 5.28 (br s, 1H), 7.25−7.37 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.05, 28.14, 59.51, 61.67, 74.15, 80.03, 126.06, 128.02, 128.34, 139.80, 170.83 (one sp^2 carbon not located); $[\alpha]^{20}_D$ −7.0 (*c* 1.1, EtOH).

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