ChemPubSoc Europe

DOI: 10.1002/chem.201500886

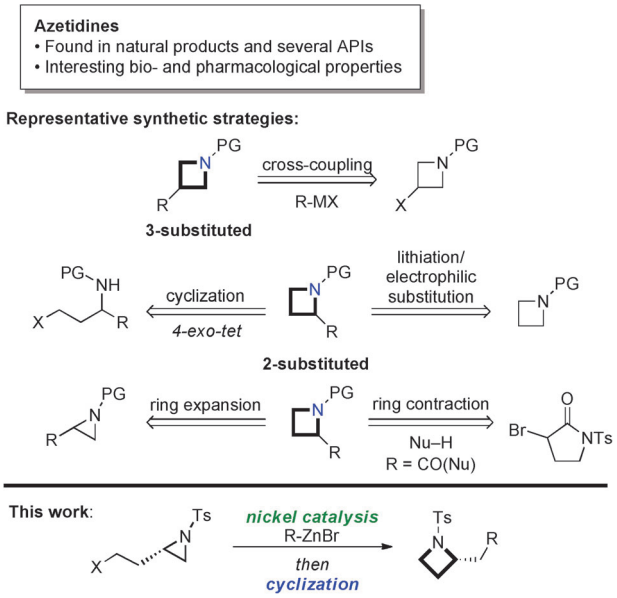
CHEMISTRY
A European Journal
Communication

Asymmetric Synthesis

A General Strategy for the Synthesis of Enantiomerically Pure Azetidines and Aziridines through Nickel-Catalyzed Cross-Coupling

Kim L. Jensen, Dennis U. Nielsen, and Timothy F. Jamison*[a]

Abstract: In this communication, we report a straightforward synthesis of enantiomerically pure 2-alkyl azetidines. The protocol is based on a highly regioselective nickel-catalyzed cross-coupling of aliphatic organozinc reagents with an aziridine that features a tethered thiophenyl group. Activation by methylation transforms the sulfide into an excellent leaving group and triggers the formation of the 2-substituted azetidine core structure by cyclization. In addition, we have expanded this concept to the synthesis of enantiomerically pure, terminal alkyl aziridines. Coupling of a TMS-protected aziridine alcohol, followed by acidic work-up to remove the silyl group, provides 1,2-amino alcohol products that are readily cyclized to aziridines. Both of these sequences display excellent functional group tolerance and deliver the desired azetidine and aziridine products in good to excellent yields.



Scheme 1. Synthetic strategies for 2- and 3-substituted azetidines. API = Active pharmaceutical ingredient.

Azetidines constitute an interesting class of molecules among the family of saturated nitrogen heterocycles. Besides being found in a number of naturally occurring molecules, the azetidine core has become an important target structure in the medicinal and agrochemical industries due to the remarkable biological and pharmacological properties displayed by molecules possessing this moiety.[1] Historically, azetidines have received considerably less attention than their five- and six-membered nitrogen heterocycle counterparts, largely because of profound challenges associated with their synthesis.[2] Nevertheless, a variety of strategies for the formation of azetidines have been evaluated in recent decades (Scheme 1).

Over the past few years, a number of protocols have been reported to synthesize 3-substituted azetidines through cross-coupling reactions from the corresponding 3-halo-azetidines.[3] However, this strategy is not applicable for the preparation of 2-substituted azetidines and, consequently, this isomer is synthesized using different methods.[4] Hodgson, for example, has developed a lithiation-electrophilic substitution sequence to functionalize azetidines at the 2-position.[5] Enantioselectivity of up to 84% *ee* was documented when a super-stoichiometric amount of a chiral ligand was employed.[5a] Examples of ring expansion of aziridines with dimethylsulfoxonium methylide have also been demonstrated.[1] Recently, a three-step protocol based on ring contraction of α-bromo pyrrolidinones to give racemic α-carbonylated azetidines was reported.[6] More common synthetic strategies rely on 4-*exo* cyclizations of open-chain structures.[1d] Although a number of successful asymmetric approaches have been reported,[7] many are of somewhat limited generality and result in moderate yields due to the kinetically unfavorable cyclization. In addition, many of these syntheses are greater than seven steps in length and require several functional group manipulations.[8] Finally, the 2-substituent is often introduced early in the synthetic sequence, thus making structure-activity relationship (SAR) studies troublesome. Consequently, we envisioned that a protocol for the synthesis of 2-substituted azetidines that allows for the incorporation of the substituent at a late stage in the synthesis would be of high value. Since stereochemistry plays such a vital role in medicinal chemistry, we undertook the development of an asymmetric synthesis.

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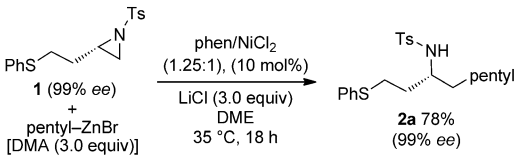
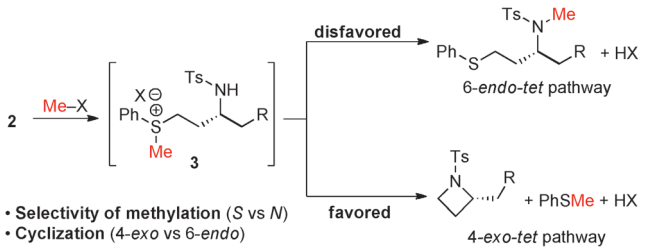
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500886.

We recently developed a highly regioselective nickel-catalyzed cross-coupling of aliphatic aziridines and aliphatic organozinc reagents to form sulfonamides in high yields.[9] The protocol uses an air- and moisture stable nickel(II)-phenanthroline precatalyst[10] and works well for both commercially available and in situ prepared organozinc reagents.[11] We hypothesized that an aziridine encompassing a tethered leaving group could easily be transformed into 2-substituted azetidines through a straightforward two-step protocol (Scheme 1). Furthermore, we knew from our previous study that the absolute stereochemistry of the aziridines is retained in the coupling reaction, thus making it possible to access the azetidines in enantiomerically pure form. At the outset of our studies, we targeted a substructure that could function as an excellent leaving group for the cyclization and at the same time display excellent stability during the coupling reaction. To this end, we selected sulfides for the following reasons: 1) Sulfides are stable under a variety of reaction conditions, 2) they function as excellent leaving groups upon activation with electrophiles, and 3) the corresponding aziridine starting material could be accessed readily from the α-amino acid methionine. Unfortunately, we found that the aziridine derived from methionine was unstable, undergoing rapid polymerization upon standing at ambient temperature. At this stage, we reasoned that a less nucleophilic sulfide in the form of an aryl sulfide would be more stable. Indeed, aziridine **1**, obtained in five steps from commercially available homoserine lactone, was stable. Moreover, despite the potential of catalyst inhibition by coordination of sulfur, the thiophenyl group was well-tolerated in the nickel-catalyzed cross-coupling. Accordingly, when **1** was treated with pentylzinc bromide using 1,10-phenanthroline/$NiCl_2$ (10 mol%, 1.25:1 ratio) precatalyst in 1,2-dimethoxyethane (DME) at 35 °C, full conversion was observed. Desired sulfonamide **2** was obtained in 78% isolated yield and with complete enantiomeric integrity (99% *ee*) [Eq. (1)].[12] Reduction of the catalyst loading to 5 mol% resulted in prolonged reaction times (>36 h), and thus for practical reasons 10 mol% of the Ni precatalyst was employed. As shown in our previous study, addition of LiCl is critical for reactivity, probably to accelerate transmetalation, as lithium chloride and organozinc reagents are known to form lithium organozincates, $RZnX_2Li$, which generally display improved nucleophilicity.[13]



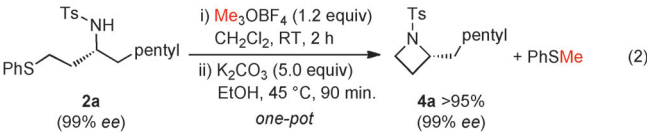
(1)

Next, we evaluated the azetidine formation by electrophilic activation of the sulfide. Sulfonium salts are known to induce kinetically unfavorable cyclization reactions, and thus we constructed **3** by methylation (Scheme 2).[14] It should be noted that, although 4-*exo*-*tet* cyclizations are kinetically challenging,[15] this mode of cyclization should still be favored over the alternative 6-*endo*-*tet* pathway that would lead to an irreversible transposition of the methyl group from the sulfur atom to the sulfonamide nitrogen atom.[16]



Scheme 2. Potential challenges associated with the methylation/cyclization sequence.

Consequently, in order for this strategy to be successful, we required conditions that allowed for selective methylation of the sulfide over the sulfonamide nitrogen atom. Gratifyingly, when coupling product **2a** was treated with 1.2 equivalents of Meerwein's salt (Me_3OBF_4) in CH_2Cl_2 at ambient temperature, the sulfide was selectively methylated to form **3a** (R = pentyl and X = BF_4) [Eq. (2)].

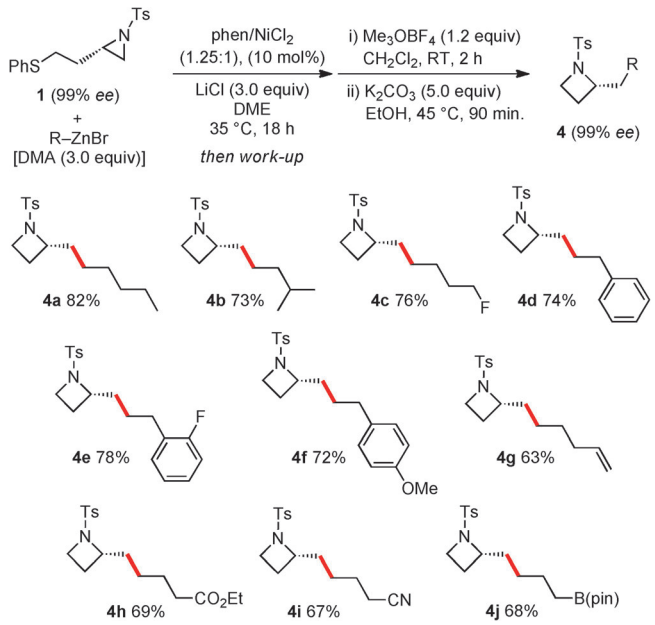


(2)

In order to prevent undesired methylation of the nitrogen atom by the remaining trimethyloxonium species during the cyclization step, we decided to use a protic solvent to quench any remaining Meerwein's salt. Accordingly, dilution of the reaction mixture with ethanol followed by addition of K_2CO_3 (5.0 equiv) and heating to 45 °C induced cyclization to form the desired azetidine product **4a** (<90 min), with PhSMe as the only observed byproduct.[17] Analysis by NMR spectroscopy indicated that the sulfonium salt had formed as a 1:1 mixture of diastereoisomers in the methylation step; nevertheless, both diastereoisomers were smoothly converted to enantiomerically pure (99% *ee*) azetidine **4a** in nearly quantitative yield.

After having identified optimal conditions for both the coupling reaction [Eq. (1)] and the subsequent one-pot methylation/cyclization sequence [Eq. (2)], we evaluated this two-step synthesis of azetidines over a range of organozinc reagents (Scheme 3).

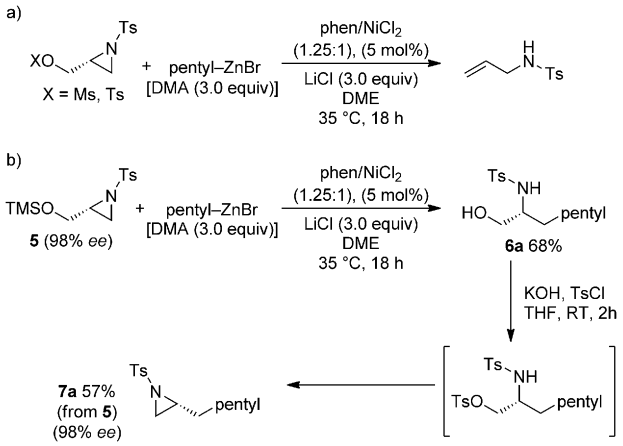
Performing the reaction with pentylzinc bromide provided the azetidine product **4a** in 82% isolated yield. The yield of this telescoped sequence is slightly better than the stepwise approach, which afforded **4a** in approximately 78% yield. The reaction also worked well for a branched and a fluoride containing organozinc reagent as demonstrated by the formation of product **4b** and **4c**. Application of homobenzyl nucleophiles furnished **4d–f** in similar high yields (72–78%). In order to expand the utility of this method we examined nucleophiles containing useful functional groups for subsequent structural diversification. Gratifyingly, the reaction worked well in the presence of an alkene and ester, providing products **4g** and



Scheme 3. Evaluation of organozinc reagents for the synthesis of 2-substituted azetidines. Yields shown are for entire sequence (overall isolated yield from **1**). DMA = *N*,*N*-dimethylacetamide.

4h in 63% and 69% yield, respectively. In addition, a cyano group was tolerated in the sequence furnishing **4i** in a similar yield (67%) and, notably, providing an entry to both ketones through organometallic additions and amines through reduction. Though a TBS-protected alcohol was tolerated in the coupling, unfortunately the following azetidine formation proved problematic, resulting in a low yield (not shown). We were able to circumvent this limitation by employing a masked alcohol in the form of a pinacol boronate (B(pin)) via a binucleophilic coupling reagent that afforded product **4j** in 68% yield.[18] Importantly, no products corresponding to transmetalation of the boronate were observed. It should be noted that in order to obtain reactivity similar to the other reagents, it was necessary to employ 1.5 equivalents of LiCl to the organozinc reagent. This requirement is presumably due to a reversible interaction of the boronate with the chloride ion that is required to enhance the nucleophilicity of the organozinc reagent, as noted above.[13]

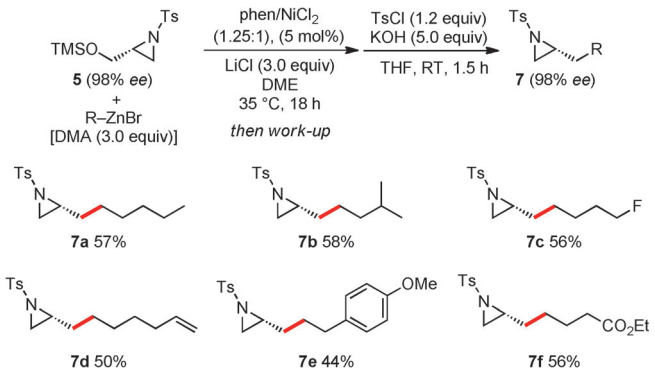
After having successfully developed the synthesis of enantiomerically pure 2-substituted azetidines, we decided to expand the reaction concept to the synthesis of terminal mono-substituted aziridines, which are of great importance in modern chemical synthesis.[19] Although numerous syntheses of aziridines have been reported,[20] only a few of the protocols have proven amenable to the synthesis of enantiomerically enriched, terminal aliphatic aziridines.[21] The majority are based on transition-metal-catalyzed aziridination of alkenes through nitrene insertion reactions. Moderate to good enantioselectivities have been achieved, but the reactions generally proceed in low to moderate yields.[22] Notably, Katsuki and co-workers used a Ru(CO)(salen) complex to furnish the aziridine products in good yields and enantioselectivities.[22c] Many approaches rely on routes from readily accessible 1,2-amino alcohols.[23] Jacobsen and co-workers reported a synthesis of enantioenriched terminal aziridines from the corresponding epoxides using a hydrolytic kinetic resolution (HKR),[24] followed by nucleophilic opening of the remaining enantioenriched epoxide with a sulfonyl-protected amine nucleophile.[25] As an alternative that would complement these protocols and with the above azetidine method in hand, we designed a general aziridine precursor that would serve as an entry to a wide range of enantiomerically pure aliphatic aziridines. At the outset we investigated a number of activated aziridine alcohols derived from the α-amino acid serine (Scheme 4). Interestingly and



Scheme 4. Evaluation of precursors for aziridine synthesis. Ms = mesyl sulfonyl, Ts = tosyl, phen = 1,10-phenanthroline.

somewhat surprisingly, we found that the tosylated and mesylated alcohols did not provide the desired cross-coupling products, instead affording *N*-allyl-tosylamide as the major product (Scheme 4a), possibly by way of oxidative insertion of Ni into the C–O bond, followed by ring-opening of the aziridine and concurrent formation of the olefin. Consequently, in order to temper the reactivity of the C–O bond and favor C–N bond insertion, we protected the alcohol as a TMS silyl ether (**5**) (Scheme 4b). This modification turned out to be successful, delivering the coupling product **6a** in 68% yield, even at 5 mol% catalyst loading. The TMS protecting group displayed excellent stability to chromatography on silica gel. However, when subjected to aqueous hydrochloric acid conditions during work-up, the silyl group was efficiently removed to yield the corresponding unprotected 1,2-amino alcohol. Subjecting this intermediate to cyclization conditions using TsCl and KOH in THF furnished the desired aliphatic terminal aziridine product **7a**. When performing the two-step protocol without purification of the amino alcohol intermediate, the aziridine **7a** was isolated in 57% overall yield from **5**. Furthermore, as anticipated, the reaction sequence proceeded with complete chirality transfer, giving the aziridines in high enantiomeric purity.

To demonstrate the utility of this sequence, a number of organozinc reagents were evaluated (Scheme 5). In general, the reaction furnished the desired products in moderate to good



Scheme 5. Representative examples of synthesized aliphatic aziridines. Yields shown are for entire sequence (overall isolated yield from **5**).

yields (44–58%). Both linear and branched aliphatic reagents worked smoothly (**7a**,**b**). More importantly, organozinc reagents containing functional groups such as a fluorine atom (**7c**), an alkene (**7d**), an aryl group (**7e**), and an ester (**7f**) were also tolerated. The alkene containing product **7d** complements nitrene-based aziridination approaches, as selective mono-aziridination is generally challenging.

In summary, we have developed general and straightforward approaches towards the syntheses of enantiomerically pure aliphatic 2-substituted azetidines and terminal aliphatic aziridines. Both strategies employ a highly regioselective nickel-catalyzed ring-opening reaction of enantiomerically pure terminal aziridines with aliphatic organozinc reagents. For the azetidines a methylation/cyclization sequence of a tethered thiophenyl group was used and, in the case of aziridines, a tosylation/cyclization sequence of the 1,2-amino alcohol intermediate was applied. Both sequences tolerate a broad range of organozinc reagents, giving the products in good overall yield and in enantiomerically pure form. These methods provide direct access to a wide variety of enantiomerically pure azetidines and aziridines, thus enabling further investigations of these important nitrogen heterocycles.

Acknowledgements

K.L.J. and D.U.N. would like to thank the Lundbeck Foundation for a postdoctoral fellowship and the Villum Foundation, respectively.

Keywords: asymmetric synthesis · azetidines · aziridines · nickel-catalysis · organozinc reagents

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Received: March 5, 2015
Published online on ■■ ■■, 0000

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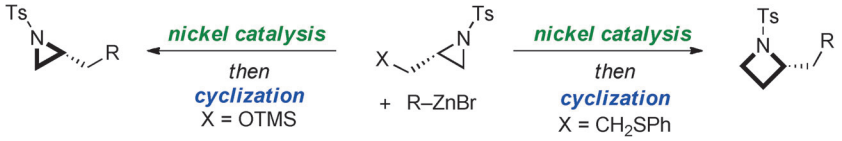

One ring to rule them both! General and straightforward procedures for the efficient synthesis of enantiomerically pure aliphatic 2-substituted azetidines and terminal aziridines were developed. The protocols are based on a highly regioselective nickel-catalyzed cross-coupling reaction followed by cyclization. The products are obtained in good yields for a broad selection of organozinc reagents.