Regio- and Stereocontrolled Synthesis of 3-Substituted 1,2-Diazetidines by Asymmetric Allylic Amination of Vinyl Epoxide

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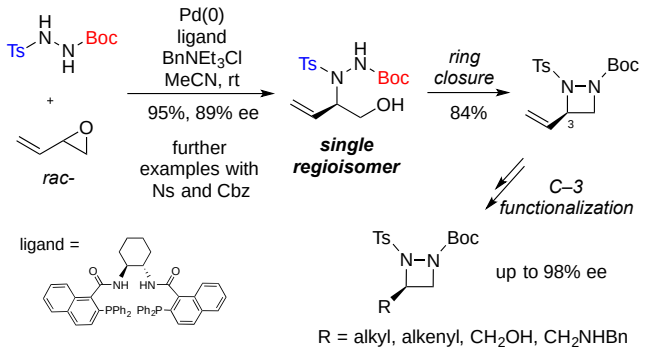
Supporting Information Placeholder



ABSTRACT: Pd-catalyzed asymmetric allylic amination of *rac*-vinyl epoxide with unsymmetrical 1,2-hydrazines proceeds with excellent regio- and stereocontrol, which after further ring closure provides differentially protected 3-vinyl-1,2-diazetidines in good yields. The chirality at C–3 exerts stereocontrol over the nitrogen centers in the 1,2-diazetidine with all substituents orientating themselves *trans* to their neighbours. Efficient functionalization without rupture of the strained ring is demonstrated (e.g. by cross-metathesis), establishing the first general route to C–3 substituted 1,2-diazetidines in enantioenriched form.

Four-membered heterocycles such as oxetanes[1] and azetidines[2] are important substructures in drug discovery. For example, the azetidine-containing MEK inhibitor Cobimetinib was recently approved for the treatment of melanoma.[3] Consequently, there is interest in the development of other four-membered heterocyclic templates for drug discovery programs.[4] One potentially interesting scaffold is the 1,2-diazetidine nucleus **1** that contains a hydrazine subunit within a saturated four-membered ring (Figure 1). This framework has significant potential for diversification by facile substitution at the two nitrogen atoms. Moreover, by introduction of a substituent at C–3, as well as increasing structural diversity, stereochemical control over the nitrogen centers *via* pyramidal inversion might be realized such that all three substituents orientate themselves *trans* to their neighbors to minimize repulsive interactions.

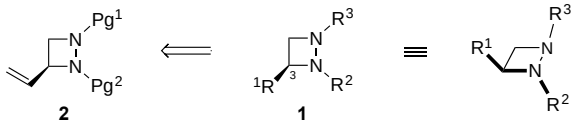
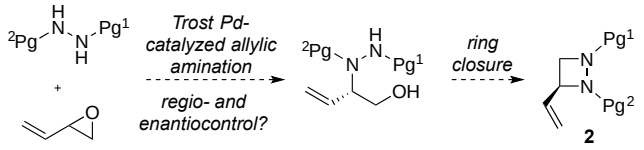


Figure 1. 3-Substituted 1,2-diazetidines as stereochemically defined scaffolds for medicinal chemistry

With these ideas in mind, we sought to develop an efficient, stereocontrolled route to 1,2-diazetidine **2** in either enantiomeric form, bearing a vinyl group at C–3 and orthogonal protection of the two nitrogen atoms ($Pg^1 \neq Pg^2$). Such a molecule would allow ready introduction of different groups on each nitrogen, and allow diversification at C–3 by way of synthetic manipulations of the double bond (cross-metathesis, ozonolysis/reductive amination, etc.).

Currently, the synthesis of enantiomerically-enriched 3-substituted 1,2-diazetidines is poorly developed.[5-8] Ma reported the diastereoselective synthesis of 3,4-disubstituted 1,2-diazetidines *via* Pd-catalyzed cyclization of chiral 2,3-allenyl hydrazines with aryl halides in good yields.[5] Alternatively, Iacobini *et al.* made 3-methyl-1,2-diazetidines by Rh-catalyzed asymmetric hydrogenation of 3-methylene-1,2-diazetidines.[6] However, neither method is well suited for the synthesis of **2**, which crucially requires differentiation of the two nitrogen atoms. Here, we describe a concise approach to **2** that exploits the asymmetric allylic amination of vinyl epoxide with differentially protected hydrazines, followed by ring closure to produce the four-membered ring (Scheme 1). Manipulation of **2** to produce a variety of 3-substituted 1,2-diazetidines is further demonstrated.

Scheme 1. Planned approach to 1,2-diazetidine 2



At the outset, it was unclear whether it would be possible to identify conditions/substrates that would realize the highly challenging allylic amination step. High regio- and enantiocontrol is needed in the opening of the epoxide *via* the internal carbon atom. Encouragingly, Mangion *et al.* have shown that 1,2,2-trisubstituted hydrazines open vinyl epoxide at the internal carbon with high levels of control under Pd catalysis.[9] Moreover, the identification of suitable *N*-protecting groups (Pg^1 and Pg^2) to achieve chemoselective opening by a single nitrogen of the hydrazine was required. To address this question, we targeted hydrazines with appreciable differences in nitrogen pKa's, by substituting one end with a carbamate (Pg^1 = Cbz, Boc) and the other with a sulfonamide (Pg^2 = Ts, Ns).

Initially, we examined the dynamic kinetic resolution of *rac*-vinyl epoxide (**3**) with hydrazine **4** to give alcohol **5** under palladium catalysis. Promisingly, only the sulfonamide bearing nitrogen acts as nucleophile in this transformation. Optimization studies explored the impact of variation in ligand, solvent, catalyst loading and additives on the yield and enantioselectivity of the conversion (Table 1). Three ligands developed by Trost for the enantiodiscrimination of Pd complexed π-allyl intermediates were evaluated, namely **6**-**8** (Figure 2).[10] Using 1 mol % of Pd and 5 mol % of (*R*,*R*)-**6**, alcohol (*S*)-**5** was produced in good yield and encouraging ee (Table 1, entry 1). Previous reports suggested that halide additives can influence the selectivity.[9,11] Gratifyingly, addition of tetrabutylammonium bromide markedly improved the enantioselectivity (entry 2). Use of ligands **7** and **8** proved less effective (entries 3-4). Use of chloride salts led to further improvements in both yield and enantioselectivity (entries 5-6) although iodide proved less effective (entry 7). Changes in cation structure had minimal effect (entry 8). Reduced ligand loadings led to incomplete conversion (entry 9) and addition of Cs_2CO_3 led to lower yield and enantioselectivity (entry 10). Solvent optimisation suggested that the highly polar aprotic solvent, acetonitrile, gave better yields and better enantioselectivity than CH_2Cl_2, THF or toluene (entries 11-13). Thus, the optimized conditions involve reaction of *rac*-**3** (1.1 equiv) with hydrazine **4** using $Pd_2(dba)_3$ (1 mol %), **6** (5 mol %) in acetonitrile as solvent at room temperature with either 1 equiv of Bu_4NCl or $BnN(Et)_3Cl$ as additive. Under these conditions, hydrazine **5** was produced in excellent yield and ee. Moreover, products derived from nucleophilic attack through the carbamate protected nitrogen or by opening of the epoxide at the unsubstituted carbon were not observed. The gross structure of **5** and the stereochemistry were confirmed by X-ray diffraction (XRD) (see Supporting Information). The formation of (*S*)-**5** using (*R*,*R*)-**6** being deduced by the small value of the Flack parameter.

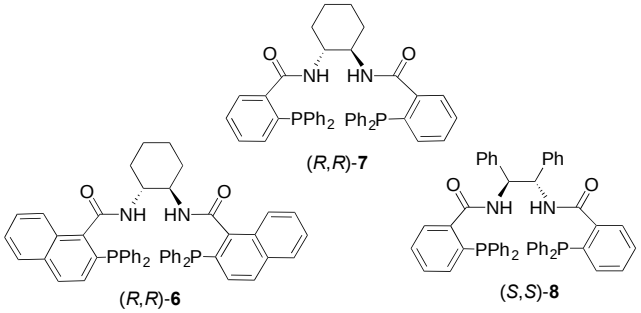
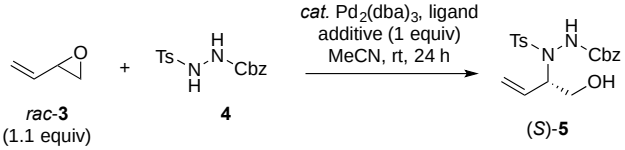


Figure 2. Ligands used in asymmetric allylic amination

Table 1. Optimisation of asymmetric allylic amination

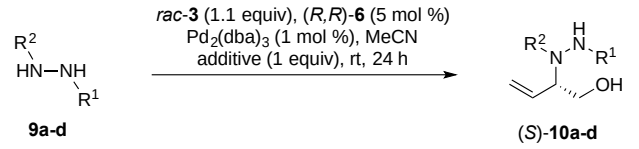


entry	$Pd_2(dba)_3$ (mol %)	ligand (mol %)	additive	product yield (%)[a]	ee (%)[b]
1	1	**6** (5)	--	80	66
2	1	**6** (5)	Bu_4NBr	84	87
3	1	**7** (5)	Bu_4NBr	79	77
4[c]	1	**8** (5)	Bu_4NBr	80	85
5	1	**6** (5)	Bu_4NCl[d]	92	93
6[e]	1	**6** (5)	$BnN(Et)_3Cl$	92	93
7	1	**6** (5)	Bu_4NI	82	69
8	1	**6** (5)	Bu_4PBr	80	87
9	1	**6** (2.5)	Bu_4NBr	--[f]	n.d.
10[g]	0.5	**6** (2.5)	Bu_4NBr	70	57
11[h]	1	**6** (5)	Bu_4NBr	89	85
12[i]	1	**6** (5)	Bu_4NBr	80	25
13[j]	1	**6** (5)	Bu_4NBr	77	73

[a]After column chromatography. [b]By chiral HPLC. [c](*S*,*S*)-**8** as ligand producing (*R*)-**5**. [d]Contains 15% Bu_4NBr. [e](*S*,*S*)-**6** as ligand producing (*R*)-**5**. [f]Reaction not completed after 2 days. [g]5 mol % of Cs_2CO_3 added. [h]In CH_2Cl_2. [i]In toluene. [j]In THF, reaction took 7 days.

Four additional hydrazines **9a-d** with different *N*-protecting groups were subjected to these reaction conditions (Table 2). Interestingly, no control could be achieved using symmetrical 1,2-*bis*-tosyl hydrazine **9a**, with both singularly and doubly alkylated hydrazine products seen (entry 1). This finding is consistent with our early observations that sulfonamides are highly reactive nucleophiles in this transformation. Thus, somewhat counter-intuitively, better results were achieved with the more complex hydrazine substrates **10b-d** where an additional element of chemoselectivity was required. Substrates bearing one sulfonamide (Ts or Ns) and one carbamate (Cbz or Boc) group on the hydrazine gave excellent conversions and enantioselectivities in this process (entries 2-4). The assignment of configuration of **10b-d** was made by analogy with that seen with (*S*)-**5**. In the case of **10b**, recrystallization further improved the product ee (entry 2).

Table 2. Use of other 1,2-disubstituted hydrazines

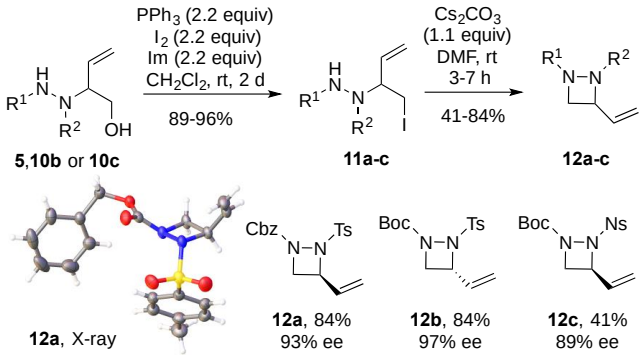


entry	substrate	additive	yield (%)[a]	ee (%)[b]	product
1	**9a** R^1 = Ts, R^2 = Ts	Bu_4NBr	--[c]	n.d.	**10a** R^1 = Ts, R^2 = Ts
2[d,e]	**9b** R^1 = Boc, R^2 = Ts	$BnN(Et)_3Cl$	95	89 (96)[f]	**10b** R^1 = Boc, R^2 = Ts
3	**9c** R^1 = Boc, R^2 = Ns	Bu_4NCl	98	89[g]	**10c** R^1 = Boc, R^2 = Ns
4	**9d** R^1 = Cbz, R^2 = Ns	Bu_4NCl	93	92	**10d** R^1 = Cbz, R^2 = Ns

[a]After column chromatography. [b]By chiral HPLC. [c]Both single and double alkylation observed. [d]Using (*S,S*)-**6** as ligand providing (*R*)-**10b**. [e]Reaction took 48 h. [f]After recrystallization from hexane/CH_2Cl_2. [g]Determined after conversion to diazetidine **12c**.

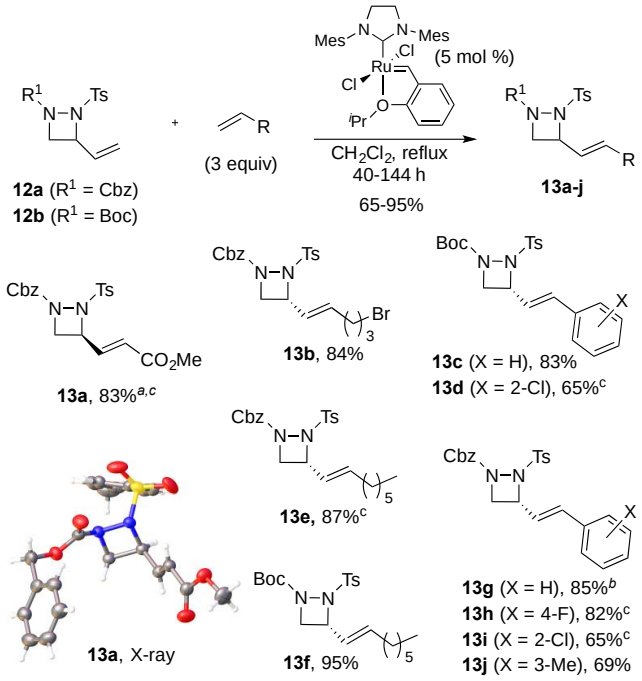
Next, we explored ring closure to the 1,2-diazetidine ring. In such cyclizations, the use of a soft leaving group is important to suppress competitive six-membered 1,3,4-oxadiazine ring formation *via* closure through the carbamate oxygen atom.[8] Thus, alcohol **5** was first converted to iodide **11a** prior to base-induced closure to **12a** (Scheme 2). Use of Cs_2CO_3 in DMF proved most effective for this step. Three differentially protected 1,2-diazetidines were successfully synthesized using this two-step method in high ee (see Supporting Information). Tosyl derivatives **12a** and **12b** bearing Cbz and Boc groups on the second nitrogen were produced in excellent yields, with lower yields seen for the corresponding nosyl derivative **12c**. Single crystal X-ray diffraction confirmed the gross structure of 1,2-diazetidine **12a** and the (*S*)-configuration at C–3. Encouragingly, all three substituents within **12a** orientate themselves *trans* to their neighbors to minimize repulsive interactions in the solid state, in accordance with our hypothesis.

Scheme 2. Synthesis of 3-vinyl-1,2-diazetidines 12a-c



Next, we explored if these chiral building blocks could be successfully functionalized at C–3. Initial work focused on homologation by way of Ru-catalyzed cross-metathesis (CM) (Scheme 3).[12] Although strained 1,2-diazetidines are known to tolerate a number of Pd-,[5,6c] Rh-[6a] and Cu-catalyzed[6c] bond forming processes, it was uncertain whether they would make good substrates for Ru-catalyzed cross-metathesis. Using the Hoveyda-Grubbs catalyst, good to excellent yields of **13a-j** were obtained upon reaction with a variety of terminal alkenes (3 equiv) (Scheme 3). One exception was **13a** where the second-generation Grubbs catalyst was used. For less reactive alkenes, the addition of a second aliquot of catalyst and alkene proved necessary to drive the reactions to completion. Reactive functional groups such as esters and halogens were well tolerated. In every example, only the *E*-alkene was observed. For **13a**, the structure and *E*-configuration were confirmed by XRD. Using **13g**, we confirmed that no racemization occurred during the CM process.

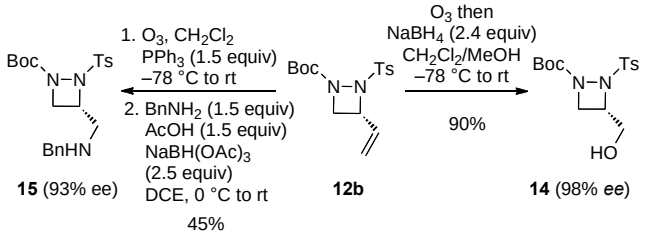
Scheme 3. Cross-metathesis using 3-vinyl-1,2-diazetidine



[a] Grubbs-II catalyst used, whose structure is provided in the Supporting Information. [b]92% ee by chiral HPLC. [c]After 48 h, additional catalyst (5 mol %) and alkene (3 equiv) added.

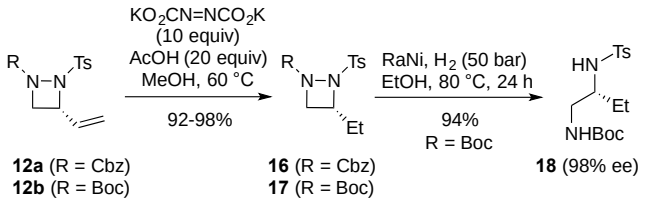
The C–3 vinyl group can be oxidatively cleaved to the corresponding aldehyde by ozonolysis, and efficiently converted *in situ* to alcohol **14** by reduction, or amine **15** by reductive amination using sodium triacetoxyborohydride (Scheme 4). Both products were produced in high ee, indicating that the intermediate aldehyde is not prone to racemization under these conditions. We speculate that the four membered ring may play a role in inhibiting any such racemization, since the formation of the requisite enol/enolate intermediate would result in the introduction of an energetically disfavoured sp^2–hybridized carbon with the four-membered ring.

Scheme 4. Functionalization of 3-vinyl-1,2-diazetidine



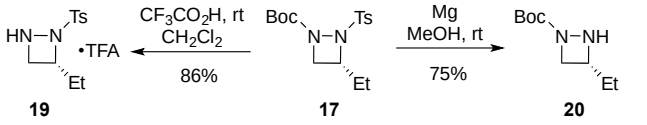
Reduction of the alkene functionality is also possible. Diimide proved to be an effective method for the formation of the corresponding saturated 1,2-diazetidines (Scheme 5).[13] Thus, *N*-ethyl derivatives **16** and **17** could be readily made without concomitant reductive opening of the strained ring.[14] Controlled cleavage of the N–N bond to yield enantiomerically enriched 1,2-diamines is also demonstrated. Using Raney Ni as catalyst at 50 bar hydrogen pressure, saturated 1,2-diazetidine **17** was successfully converted into differentially protected 1,2-diamine **18** in excellent yield and ee (Scheme 5). The reductive cleavage of **14** was also achieved in 86% yield and 97% ee (see Supporting Information for details). This methodology could potentially be used to develop a new route to chiral 1,2-diamines.[15]

Scheme 5. Reduction of 3-vinyl-1,2-diazetidines



Selective removal of the protecting groups within **17** was possible (Scheme 6). The Boc group being removed with TFA to give **18** in excellent yield. Separately, the tosyl group was cleaved using Mg in MeOH to provide **20** in 75% yield.

Scheme 6. Selective deprotection of 1,2-diazetidine 17



In summary, a three-step asymmetric synthesis of enantioenriched 3-vinyl-1,2-diazetidines has been developed in which the two nitrogen atoms are differentially substituted with carbamate and sulfonamide protecting groups. In the key asymmetric allylic amination reaction, only the sulfonamide-bearing nitrogen acts as nucleophile. Crystallography evidence suggests that the chirality at C–3 exerts stereocontrol over both nitrogen centers such that all substituents orientate themselves *trans* to their neighbours. The chemical integrity of the strained 1,2-diazetidines was maintained during a range of chemical transformations including: (i) Ru-based cross-metathesis; (ii) ozonolysis followed by hydride reduction; (iii) alkene reduction using diimide; and (iv) treatment with TFA. However, they can be reductively cleaved to 1,2-diamines or selectively deprotected under appropriate conditions. Taken together, these findings suggest that C–3 substituted 1,2-diazetidines may make excellent building blocks for drug discovery and/or asymmetric catalysis, avenues of work which are being actively explored in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, copies of ^{1}H and ^{13}C NMR spectra, chiral HPLC traces and X-ray data in cif format. This Supporting Information is available free of charge on the ACS Publications website.

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14. Hydrogenations using metal catalysts led to partial over-reduction. For example, reduction [10% Pd/C, H_2 (1 atm.), MeOH, rt] of **12b** led to formation of **17** (27%) alongside quantities of $TsNH–N(Boc)(CH_2)_3CH_3$ resulting from concomitant reduction of the C(3)–N bond of the diazetidine ring.
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