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An expedient route to diaza-spirocycles utilizing a sequential multicomponent α-aminoallylation/ring-closing metathesis strategy

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Abstract—A general method for the preparation of diaza-spirocycles is reported. This method used an olefin metathesis in order to construct the desired spirocyclic framework. Beginning with commercially available protected amino ketones, this strategy ultimately produced pharmacologically relevant diaza-scaffolds in an efficient and high-yielding process.

The continuing demand for novel lead compounds has led to the development of our scaffold-oriented synthesis program that targets pharmaceutically-attractive molecular skeletons primed for subsequent manipulation and derivatization. In this context, our group became interested in the synthesis of diaza-spirocycles due to their presence in a variety of biologically active compounds. Compounds containing these frameworks have proven to possess anesthetic,[1] antiinflammatory,[2] and antioxidant[3] properties. In addition, they have served as NK_1 receptor antagonists,[4] glycoprotein antagonists[5] and CNS agents.[6] Furthermore, the clinically useful dopamine antagonists such as spiperone and fluspiperone are spiroannulated piperidine derivatives.[7] This notable pharmacological profile has initiated a number of synthetic approaches toward diamino-spirocycles (and related compounds)[8] and warrants the continued communication of novel methods toward their synthesis. Along these lines, we now report on a ring-closing metathesis-based strategy for the preparation of these pharmacologically interesting diamino scaffolds.

Multicomponent reactions (MCRs) continue to attract considerable interest from the scientific community due to their ability to construct diversely functionalized molecules via simple, one-step transformations.[9] One such example is the α-aminoallylation of carbonyl compounds, a three-component reaction of aldehydes/ketones, amines, and an allylating agent.[10]

Herein, we report on efforts on the α-aminoallylation reaction of aminoketones as the carbonyl component followed by a ring-closing metathesis as a route to spirocyclic diamines. The general strategy is outlined in Figure 1. The reaction of an aminoketone with allylamine generates a ketimine, which is followed by the addition of the allyl group from pinacol allylboronate to provide the homoallylic/allylic secondary amine.

The synthesis of spirocyclic frameworks from cyclic ketones by the addition of allylmagnesium bromide to preformed ketimines generated from allylamine, followed by a ring-closing metathesis reaction (RCM) has previously been reported by Wright and co-workers.[11]

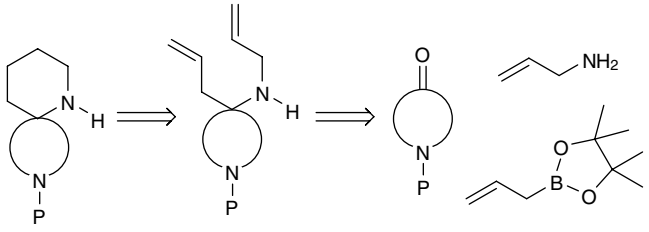

Figure 1. General strategy to spirocyclic diamines.

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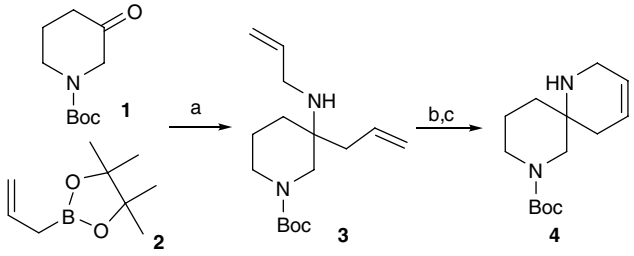
Our method uses a concise one-pot procedure for the addition of the allyl group to the in situ generated ketimine using pinacol allylboronate. Pinacol allylboronates represent an attractive allylating agent considering their commercial availability, stability, functional group tolerance and the non-toxic nature of boronic acids/esters.

Briefly, 1-*N*-boc-3-piperidone **1**, allylamine and the boronic ester **2** were heated in toluene at 80 °C with 4 Å mol sieves for 8 h to provide the amine substrate **3** in 75% yield (Scheme 1). Following purification, intermediate **3** was subjected to RCM conditions. It was observed that **3** had to be pretreated with 1.0 equiv of *p*-TsOH prior to the RCM reaction with the second generation Grubbs catalyst.[12] In the absence of the pretreatment the reaction failed to undergo ring-closure. Thus reaction of **3** with 1.0 equiv of *p*-TsOH in CH_2Cl_2 for 30 min at reflux followed by the addition of the Grubbs catalyst (5 mol %) gave **4** in 90% yield.[13] Under these conditions, it was observed that the RCM reaction was complete within 2 h. Alternatively, the amines could be adequately protected for the RCM reaction as the trifluroacetamide via treatment of the free amine with trifluoroacetic anhydride (TFAA) in pyridine, vida infra.[14]

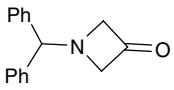
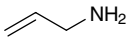
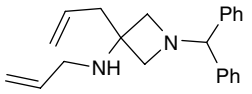
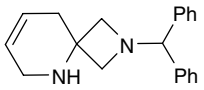
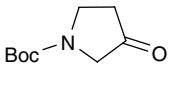
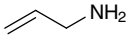
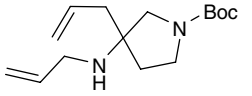
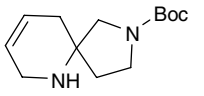
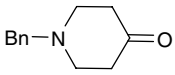
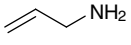
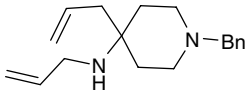
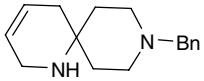
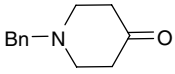
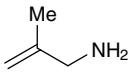
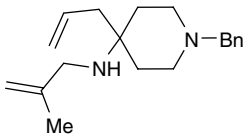
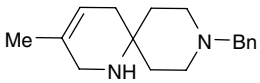
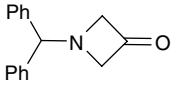
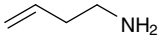
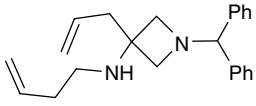
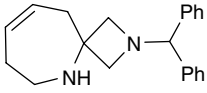
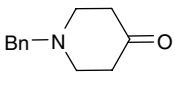
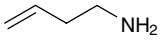
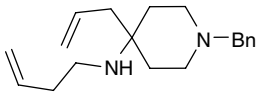
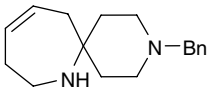
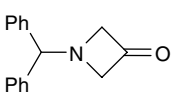
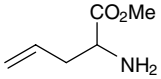
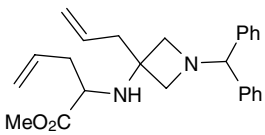
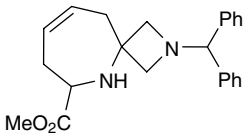


Scheme 1. Reagents and conditions: (a) $CH_2{=}CHCH_2NH_2$, toluene, 4 Å mol sieves, 80 °C, 75%; (b) *p*-TsOH, CH_2Cl_2; (c) 5 mol % $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, 90%.

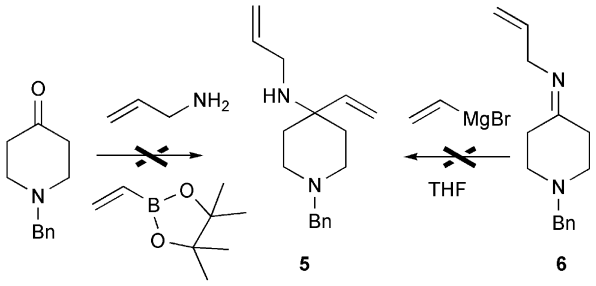
The generality of the α-aminoallylation reaction was demonstrated by the synthesis of a number of secondary amines (Table 1). The reaction was found to be quite general for both the amine and ketone substrates, as yields ranged from moderate (47%) to excellent (96%). It is noteworthy to mention that by simply varying the length (allylic vs homoallylic) of the amine component used in the MCR, both six- and seven-membered rings could be accessed in the subsequent RCM.

Attempts were made to access five-membered rings via the RCM of **5**. Unfortunately, however, both the Petasis boronic acid Mannich reaction[15] with pinacol vinylboronate and the addition of vinylmagnesium bromide to imine **6** failed to give any of the desired product (Scheme 2).

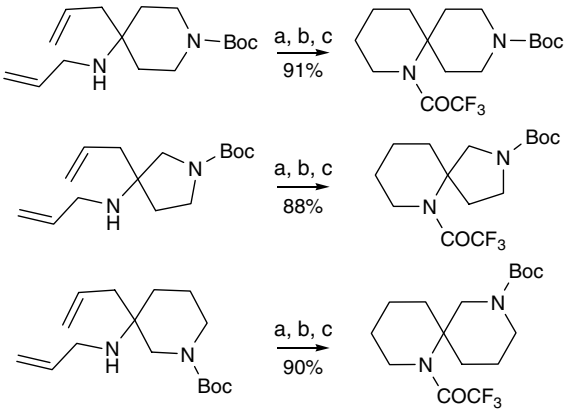
Table 1. α-Aminoallylation and RCM products

Entry	Ketone	Amine	α-Aminoallylation product	Yield (%)	RCM product	Yield (%)
1				74		88
2				76[a]		95
3				58		75
4				82		96
5				96		80
6				62		94
7				47		74

[a] 1.0 equiv of *p*-TsOH was used prior to the RCM, for all other examples in this table, 2.0 equiv of *p*-TsOH was used.



Scheme 2. Attempts toward five-membered systems.



Scheme 3. Reagents and conditions: (a) TFAA, pyridine; (b) 1 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; (c) H_2 Pd/C, MeOH, 60 psi.

As an extension of this chemistry, a series of trifluoroacetate-protected RCM adducts were subjected to hydrogenation conditions to provide the corresponding, fully saturated spirocyclic framework in excellent yield (Scheme 3).

In conclusion, we have developed a two-step reaction sequence using a one-pot α-aminoallylation reaction followed by the RCM reaction to make a diverse collection of spirocyclic diamines. The reaction sequence uses readily available starting materials to afford products in an efficient and concise process. The use of amino ketones in the α-aminoallylation reaction represents a valuable extension of this chemistry. The final products represent structural chemotypes that are useful scaffolds for lead generation. The diversification of this diamine collection is currently under way and will be reported in due course.

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13. A representative procedure is demonstrated by the preparation of *tert*-butyl 1,8-diazaspiro[5.5]undec-3-ene-8-carboxylate (**4**). 1-*N*-Boc-3-piperidone **1** (500 mg, 2.5 mmol), allylamine (0.94 mL, 12.5 mmol) and boronic ester **2** (420 mg, 2.5 mmol) were heated in toluene (5 mL) at 80 °C with 4 Å sieves (850 mg) for 8 h. The reaction mixture was cooled, filtered through a pad of celite. The

organic layer was concentrated and purified by flash chromatography (60% EtOAC/hexane) to afford 524 mg (75%) of **3** as a clear yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.52–1.66 (m, 6H), 2.13–2.28 (m, 2H), 3.09–3.51 (m, 4H), 5.07–5.22 (m, 4h), 5.82–5.92 (m, 2H); MS (ESI): *m*/*z* 281 (M+H); To a solution of **3** (167 mg, 0.6 mmol) in CH_2Cl_2 (20 mL) was added *p*-TsOH (114 mg, 0.6 mmol) and the reaction mixture was heated at reflux for 30 min. The reaction was cooled to room temperature and the Grubbs catalyst (25 mg, 0.03 mmol) was added and the reaction mixture was refluxed for an additional 2 h (TLC indicated disappearance of the starting material). The reaction was quenched by adding aq satd K_2CO_3 and extracted with EtOAc. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by flash chromatography (90-9-1: CH_2Cl_2–CH_3OH–NH_3) to afford 136 mg (90%) of **4** as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.52–1.66 (m, 4H), 3.14–3.57 (m, 8H), 5.70 (s, 2H); MS (ESI): *m*/*z* 253 (M+H).

14. For examples of the utilization of trifluoroacetate as an amine protecting group prior to ring-closing metathesis, see: (a) Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542–1543; (b) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, *1*, 138–144.
15. Maraccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005, Chapter 7.