Cyclic Amines

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Palladium-Catalyzed Ring-Contraction and Ring-Expansion Reactions of Cyclic Allyl Amines**

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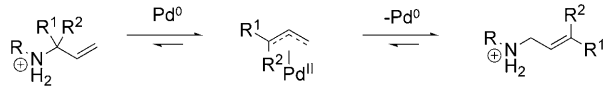
Cyclic allyl amines serve as useful tools in synthesis,[1] and are found in a vast number of naturally occurring alkaloids.[2] Preparation of cyclic allyl amines can be achieved by a number of classical methods such as the addition of allyl nucleophiles to cyclic imines and nitrones and subsequent reduction,[3] or Wittig reactions.[4] Such approaches, however, require harsh reaction conditions and have limited reaction scope. Milder methods include metal-catalyzed transformations such as intramolecular oxidative amination,[5] allylic amination,[6] and intramolecular hydroamination of allenes.[7] Ring-closing metathesis is perhaps the most convergent approach that renders itself well to rapid and modular assembly of a wide range of allyl amines. Herein, we show that allyl amines, which can be accessed using ring-closing metathesis and other straightforward methods, are convenient starting points for ring-contraction and ring-expansion reactions in which the conjugate acid of the nitrogen-containing nucleophile is enlisted as the leaving group.

Our interest in the field of allyl amine chemistry stems from earlier studies of regioselectivity in palladium-catalyzed allylic amination. This work revealed the thermodynamic origin of linear selectivity in that reaction.[8] It later transpired that the isomerization had occurred as a result of having active Pd^0 species and acid in solution, and followed the mechanistic rationale shown in Scheme 1. Although this intermolecular process is largely undesirable and can be avoided,[9] it does suggest that an amine can play a dual role by first acting as the leaving group, and then as the nucleophile.[10]

We envisioned straightforward access to complex allyl amines by skeletal isomerizations of readily accessible cyclic allyl amine scaffolds. This method can be strategically applied to late-stage modifications of complex amine-containing skeletons by using amine-containing fragments as both nucleophiles and as leaving group precursors.

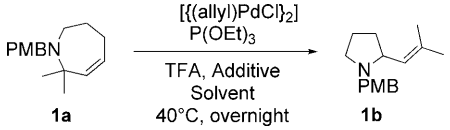
Amines that do not bear electron-withdrawing substituents have long been recognized for their reluctance to undergo palladium-catalyzed C–N bond scission.[10] In the course of our earlier studies of intermolecular allylic amination, we discovered that branched product selectivity is kinetic in origin when THF is used as the solvent, whereas linear products are formed as a result of acid-promoted branched-to-linear isomerization. High levels of branched selectivity were attained by introducing 1 equivalent of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) that prevented isomerization. We recently returned to this system and discovered that product isomerization was slow under these reaction conditions, and only 30% of product isomerized after one week. Unexpectedly, in dichloromethane, branched allyl amines fully isomerized to form linear products within four days, even in the presence of DBU.[11] In addition, we have also observed the effect of solvent on kinetic branched/linear ratios in allylic amination. High branched regioselectivities were recorded with THF, as well as THF/dichloromethane mixtures where there was at least 10% THF, whereas in dichloromethane both regioisomers were favored equally throughout the reaction, until full conversion was achieved.[12]

Intrigued by the fact that dichloromethane promotes formation of the more stable product from both kinetic and thermodynamic points of view, we wanted to test whether or not such isomerization can be used to rearrange cyclic allyl amines. Table 1 shows the results of isomerization-driven ring construction. We were encouraged that in dichloromethane



Scheme 1. Allylic isomerization promoted by a combination of palladium and protic acid.

Table 1: Evaluation of palladium-catalyzed isomerization reaction conditions.[a]



1a **1b**

Entry	Ligand	Solvent	Additive (10 mol%)	Conversion [%]
1	$P(OEt)_3$	THF	–	0
2	$P(OEt)_3$	CH_2Cl_2	–	50
3	$P(OEt)_3$	CH_2Cl_2	morpholine	quant.
4	–	CH_2Cl_2	morpholine	0
5	$P(OEt)_3$	THF	morpholine	0

[a] Reaction conditions: palladium catalyst/ligand/morpholine/substrate/TFA = 1:4:10:40:40 in solvent (0.5 M) at reflux, overnight. PMB = *p*-methoxybenzyl, THF = tetrahydrofuran.

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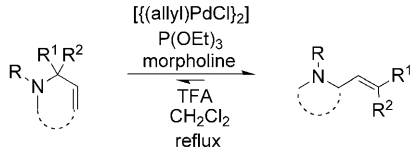
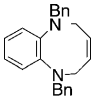
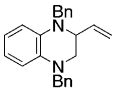
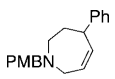
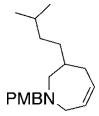
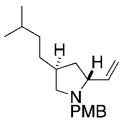
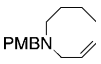
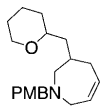
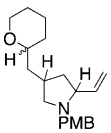
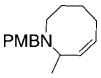
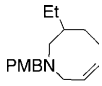
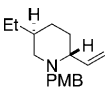
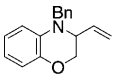
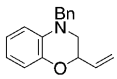
tetrahydroazepine **1a** gave the corresponding 2-prenyl pyrrolidine **1b** in 50% yield after 8 hours (Table 1, entry 2). Trifluoroacetic acid (TFA; 1 equiv) was employed in order to activate the amine. Interestingly, the addition of 10 mol% of morpholine pushed the reaction to completion (Table 1, entry 3). We think that in the presence of TFA, morpholine acts as a buffer and enables controlled protonation of the starting material. In addition, it can assist in the activation of the palladium catalyst. Importantly, replacing morpholine with *N*-methyl morpholine gave no change to the reaction efficiency. With no ligand present, the rearrangement of **1a** provided no conversion (Table 1, entry 4). In addition, uncatalyzed olefin isomerization was not observed when either **1a** or **1b** were used as starting materials. Switching the solvent to THF with or without the addition of morpholine gave no conversion (Table 1, entries 1 and 5). The reaction with 5 mol% of TFA (with morpholine added) gave little conversion.

The substrate scope of the reaction is shown in Table 2. It includes ring-contraction reactions of seven- and eight-membered allylic amines and a ring-expansion of allylic azetidine (Table 2, entry 13). All of the starting materials were prepared using metathesis protocols and other standard reactions.[12] When the optimized reaction conditions (Table 1, entry 3) were applied to **2a**, no conversion to the corresponding pyrrolidine **2b** was observed even when the solvent was switched to dichloroethane at 60°C (Table 2, entry 2). Placing substituents in a 2,4 relation and carrying out the reaction in dichloroethane did improve conversion; **3a** produced **3b** with a 2:1 diastereoselectivity in modest yield, with the unreacted starting material making up for the mass balance (Table 2, entries 3). Likewise, **4a** gave the corresponding pyrrolidine **4b** with both vinyl and isopentyl substituents in a *trans* relation. When the substituents were placed in a 2,5 relation in a larger ring, **6b** was produced in good yield and 3:1 diastereoselectivity (Table 2, entry 6). Because the reaction proceeds under the thermodynamic control, the product ratio is proportional to the difference in the ground-state stability of the possible diastereomers.

Fused heterocycles were shown to work as substrates during ring contraction (Table 2, entries 7 and 8), although competing allylic rearrangement of phenol ethers was also observed under the reaction conditions (Table 2, entry 7). Nonetheless, both **7a** and **8a** rearranged fully at 40°C in dichloromethane. Significantly, the substrates containing seven- and eight-membered rings led to ring contraction in high yields (Table 2, entries 9–12). As can be seen (Table 2, entries 1, 9, and 10), alleviation of ring strain overrides the substitution pattern of the olefin as the driving force. In cases

Table 2: Synthesis of cyclic allyl amines via ring rearrangement.[a]



Entry	Substrate	Product	Yield [%][b]	Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **1b**	97	8	 **8a**	 **8b**	78
2[c]	 **2a**	 **2b**	0	9	 **9a**	 **9b**	94 (*E*/*Z*=3.6:1)
3[c]	 **3a**	 **3b**	53 (2:1)	10	 **10a**	 **10b**	93
4[c]	 **4a**	 **4b**	50 (2:1)	11	 **11a**	 **11b**	97
5[c]	 **5a**	 **5b**	68 (1:1)	12	 **12a**	 **12b**	92 (*E*/*Z*=4.6:1)
6	 **6a**	 **6b**	71 (3:1)	13[d]	 **13a**	 **13b**	96
7	 **7a**	 **7b**  **7b'**	83 (1:1)				

[a] Reaction conditions: palladium catalyst/ligand/morpholine/substrate/TFA = 1:4:10:40:40 in CH_2Cl_2 (0.5 M) at reflux, overnight. [b] Yield of isolated product. [c] Palladium catalyst/ligand/morpholine/substrate/TFA = 1:4:10:20:20 in DCE (0.5 M) at reflux, overnight. [d] Palladium catalyst/ligand/morpholine/substrate/TFA = 1:4:10:100:100 in CH_2Cl_2 (0.2 M) at room temperature, overnight. Bn = benzyl, DCE = 1,2-dichloroethane.

where a disubstituted olefin could be formed, the *E* geometry is preferred (Table 2, entries 9 and 12).

In summary, we have demonstrated the use of acid-promoted palladium-catalyzed isomerization in the skeletal rearrangement of cyclic amines. As complex cyclic allyl amines can be prepared by a multitude of methods, our study should open up new retrosynthetic possibilities. One might be particularly excited about nontrivial disconnections that would involve functional group interconversions by allyl amine dehydrogenation as the first retrosynthetic step.

Experimental Section

Allyl palladium chloride dimer (0.01 mmol, 3.6 mg) was added to a flame-dried vial equipped with a stir bar. The complex was dissolved in anhydrous dichloromethane (0.80 mL) under nitrogen. A mixture of triethyl phosphite (0.04 mmol, 6.6 mg) and morpholine (0.05 mmol, 4.36 mg) were added to the reaction mixture, and it was stirred for 5 min. Then **1a** (0.40 mmol, 98 mg) was dissolved in anhydrous dichloromethane (1.0 mL) and was added to the reaction mixture, followed by the addition of TFA (0.40 mmol, 45.6 mg). The reaction vial was sealed and stirred at reflux for 10 h. The reaction mixture was cooled to RT, washed with saturated solution of sodium bicarbonate, extracted with dichloromethane, dried with sodium sulfate and concentrated. The crude material was purified by flash chromatography on silica gel (hexanes/EtOAc = 9:1, $R_f = 0.36$) to give **1b** (0.39 mmol, 96 mg, 97 %) as an orange oil.

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[12] See the Supporting Information.

