Cyclizations

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$[Pd(PPh_3)_4]$-Catalyzed Diastereoselective Synthesis of *trans*-1,2-Diazetidines from 2,3-Allenyl Hydrazines and Aryl Halides**

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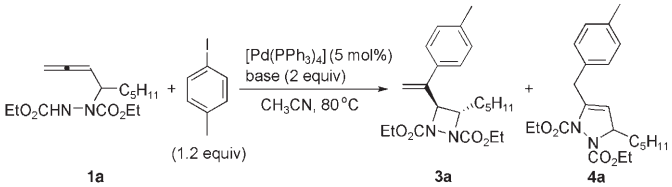
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Four-membered cyclic compounds are found in many biologically active natural and unnatural compounds.[1] Accessing such compounds is a synthetic challenge for synthetic organic chemists because of the intrinsic ring strain.[2] Diazetidines are a type of four-membered ring, which contains two nitrogen atoms, and can be dated back to the 1850's; however, most of the early synthetic reports were later shown to be incorrect.[3] In addition, the discovery of penicillin in 1929 stimulated ongoing interest in this type of structure from physical, polymer, theoretical, and medicinal chemists. Notably, the methods for the synthesis of 1,2-diazetidines are limited: (1) the [2+2] cycloaddition reaction of azodicarboxyl compounds react only with the electron-rich olefins, lacking allylic hydrogens, in very poor selectivity affording also the six-membered [4+2] cycloaddition byproduct;[4] (2) the direct bisalkylation of 1,2-dibromoethane with 1,2-dialkylhydrazines afforded simple nonfunctionalized diazetidines in very low yield;[5] (3) the intramolecular cyclization of 1-(1-hydroxy-propan-2-yl)hydrazine-1,2-dicarboxylate derivatives was reported by Ma and co-workers in 2006.[6] Thus, new methods for a highly selective and high yielding synthesis of functionalized 1,2-diazetidines are still of current interest.

Recently, there has been much attention focused on the coupling/cyclization reaction of organic halides with functionalized allenes for the synthesis of some potentially important carbo- and heterocyclic compounds.[7–9] However, a highly selective formation of four-membered rings still remains a challenge; for example, Hiemstra and co-workers and Tanaka, Ibuke, and co-workers, as well as Kang et. al. reported the palladium-catalyzed coupling/cyclization reaction of 3,4-dienyl amide derivatives with organic halides[10,11] or hypervalent iodonium salts[12] to form azetidines and/or tetrahydropyridines albeit with poor selectivity. We recently showed that the $[Pd(PPh_3)_4]$-catalyzed coupling/cyclization reaction of nonsubstituted or 5-substituted-3,4-allenyl amides with organic halides afforded a mixture of four- and six-membered ring products, however, the selectivity and yield for the formation of four-membered products were low.[13] Herein, we describe a highly efficient regio- and diastereoselective synthesis of *trans*-1,2-diazetidines through the cyclization reaction of 2,3-allenylic hydrazines with aryl halides.

In our initial attempt, we synthesized 2,3-allenylic hydrazine **1a**[14] and chose $[Pd(PPh_3)_4]$ as the catalyst. During screening, it was observed that the reaction of **1a** with 4-iodotoluene in MeCN with Na_2CO_3 as the base afforded 1,2-diazetidine **3a** in 11% yield (Table 1, entry 1). Additional studies indicated that NaOH, KO*t*Bu, Et_3N, and Cy_2NMe were poor bases for this reaction (Table 1, entries 2–5). However, Cs_2CO_3, Ag_2CO_3, K_2CO_3, CsF, or KOH all provided four-membered ring **3a** in 53–74% yield (Table 1, entries 6–10); the reaction with K_2CO_3 (Table 1, entry 8) or CsF (Table 1, entry 9) provided the desired product with low stereoselectivity. Thus, reaction conditions (Conditions A:

Table 1: $[Pd(PPh_3)_4]$-catalyzed reaction of allenyl hydrazine **1a** and 4-iodotoluene under different reaction conditions.



1a **3a** **4a**

Entry	Base	*t* [h]	Yield of **3a** [%][a]	*trans*:*cis* ratio of **3a**	Yield of **4a** [%][a]
1	Na_2CO_3	24	11[b]	100:0	0
2	NaOH	5	n.d.		
3	KOBu^t	2	n.d.		
4	Et_3N	20	5[c]	100:0	0
5	Cy_2NMe	30.5	trace		
6	Cs_2CO_3	2	74	100:0	<7
7	Ag_2CO_3	2	53	100:0	<10
8	K_2CO_3	6	74	20:1	trace
9	CsF	24	64	17:1	trace
10	KOH	2	59	100:0	<6
11	Cs_2CO_3[d]	2	77	100:0	<7

[a] Yield of isolated product. [b] Recovered 82% of **1a**. [c] Recovered 87% of **1a**. [d] Used 1.1 equiv of Cs_2CO_3. n.d. = not determined becasue of complicated reaction mixture.

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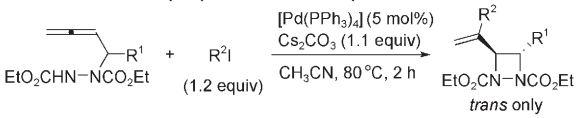
organic halide (1.2 equiv), $[Pd(PPh_3)_4]$ (5 mol%), Cs_2CO_3 (1.1 equiv), MeCN, 80 °C) were defined as the optimal set of conditions for the cyclization (Table 1, entry 11). Compound **3a** was fully characterized by NMR, IR, MS, and HRMS methods. From the ^{1}H NMR spectrum the coupling constant between the two methine protons is approximately 5.2 Hz, which led to the assignment of a *trans* stereochemistry.[4a–c,f,h] Careful analysis revealed that the yield for five-membered ring regioisomer **4a** is less than 7% when the optimal reaction conditions were used.[15]

The scope of the diastereoselective 1,2-diazetidine-forming reaction was then investigated by using the optimal reaction conditions, and some of the results are listed in Table 2. Noteworthy are: (1) in all the cases the diastereoselectivity is very high with only the *trans*-**3** products being formed, (2) the yields range from moderate to good.

Table 2: $[Pd(PPh_3)_4]$-catalyzed synthesis of *trans*-1,2-diazetidines by the cyclization of 2,3-allenyl hydrazines with aryl halides.



1 **2** **3**

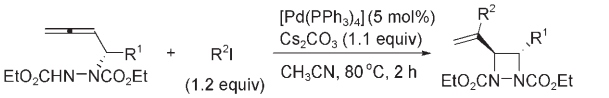
Entry	R^1 (**1**)	R^2 (**2**)	Yield of **3** [%][a]
1	*n*-C_5H_{11} (**1a**)	*p*-MeC_6H_4	77 (**3a**)
2	*n*-C_5H_{11} (**1a**)	*m*-MeC_6H_4	71 (**3b**)
3	*n*-C_5H_{11} (**1a**)	Ph	70 (**3c**)
4	*n*-C_5H_{11} (**1a**)	*p*-$MeOC_6H_4$	73 (**3d**)
5	*n*-C_7H_{15} (**1b**)	*p*-MeC_6H_4	75 (**3e**)
6	*n*-C_7H_{15} (**1b**)	*m*-MeC_6H_4	70 (**3f**)
7	*n*-C_7H_{15} (**1b**)	Ph	63 (**3g**)
8	*n*-C_7H_{15} (**1b**)	*p*-$MeOC_6H_4$	75 (**3h**)
9	*n*-C_8H_{17} (**1c**)	*p*-MeC_6H_4	72 (**3i**)
10	*n*-C_8H_{17} (**1c**)	*m*-MeC_6H_4	71 (**3j**)
11	*n*-C_8H_{17} (**1c**)	Ph	66 (**3k**)
12	*n*-C_8H_{17} (**1c**)	*p*-$MeOC_6H_4$	74 (**3l**)
13	$PhCH_2$ (**1d**)	*p*-MeC_6H_4	68 (**3m**)
14	$PhCH_2$ (**1d**)	*m*-MeC_6H_4	68 (**3n**)
15	$PhCH_2$ (**1d**)	Ph	62 (**3o**)
16	$PhCH_2$ (**1d**)	*p*-$MeOC_6H_4$	71 (**3p**)

[a] Yield of isolated product.

By using the protocol for the diastereoselective synthesis of *trans*-1,2-diazetidine, additional studies were conducted to investigate the possibility of synthesizing optically active *trans*-1,2-diazetidines. Optically pure (*R*)-1,2-nonadien-4-ol and (*R*)-1,2-undecadien-4-ol were readily prepared by the Crabbé reaction of (*R*)-1-octyn-3-ol and (*R*)-1-decyn-3-ol, respectively,[16] which are easily made from the kinetic enzymatic resolution of the corresponding racemic propargylic alcohols.[17] Optically active (*S*)-**1** can be easily prepared by the reaction of optically pure 2,3-allenols with diethyl azodicarboxylate.[14] The reaction of optically active (*S*)-**1a** or (*S*)-**1b** with aryl halides afforded optically active 1,2-diazetidines (*S*,*S*)-**3** diastereoselectively with high enantiopurities (Table 3).

In conclusion, we have developed a mild and highly diastereoselective methodology for the synthesis of *trans*-1,2-diazetidines in good yields. By using the readily accessible enantiomerically enriched 2,3-allenyl hydrazines, optically active vinylic 1,2-diazetidines with high *ee* values can be synthesized. Because of the importance of 1,2-diazetidines[18] and the ready access to the starting materials, this reaction will have applications in organic synthesis. Additional studies in this area are being conducted in our laboratory.

Table 3: Diastereoselective synthesis of optically active vinylic 1,2-diazetidines.



(*S*)-**1a**,**1b** >99% *ee* **2** (3*S*,4*S*)-**3**

Entry	R^1 ((*S*)-**1**)	R^2 (**2**)	Yield of (3*S*,4*S*)-**3** [%]	*ee* [%][a]
1	*n*-C_5H_{11} (**1a**)	*p*-MeC_6H_4	74 (**3a**)	99.4
2	*n*-C_5H_{11} (**1a**)	*p*-$MeOC_6H_4$	74 (**3d**)	99.4
3	*n*-C_7H_{15} (**1b**)	*p*-MeC_6H_4	68 (**3e**)	98.5
4	*n*-C_7H_{15} (**1b**)	*p*-$MeOC_6H_4$	75 (**3h**)	98.5

[a] The *ee* values were determined by HPLC analysis (see the Supporting Information).

Experimental Section

Synthesis of **3a**: Under an atmosphere of argon, Cs_2CO_3 (90 mg, 0.28 mmol), 4-iodotoluene (65 mg, 0.30 mmol), $[Pd(PPh_3)_4]$ (15 mg, 0.013 mmol), **1a** (76 mg, 0.25 mmol), and CH_3CN (3 mL) were added sequentially to an oven-dried Schlenk tube equipped with a stirring bar. The reaction mixture was stirred at 80 °C for 2 h, at which time the reaction was complete as determined by TLC analysis. The resulting mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ether = 10:1) to afford 7 mg of an unidentified mixture and 76 mg (77%) of **3a**: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.3$ Hz, 2H), 7.13 (d, $J = 8.3$ Hz, 2H), 5.60 (s, 1H), 5.44 (s, 1H), 4.81 (d, $J = 5.2$ Hz, 1H), 4.34–4.17 (m, 4H), 3.85 (dt, $J = 5.2$ and 6.9 Hz, 1H), 2.33 (s, 3H), 1.86–1.62 (m, 2H), 1.33–1.12 (m, 12H), 0.81 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 161.1$, 160.6, 144.2, 137.9, 134.5, 129.1, 126.3, 113.7, 69.4, 69.1, 62.4, 62.2, 34.5, 31.2, 24.0, 22.3, 21.0, 14.3, 14.2, 13.8 ppm; MS (EI) *m*/*z* (%) 388 (M^+, 23.29), 144 (100); IR (neat) 2932, 1752, 1713, 1626, 1513, 1466, 1322, 1099 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{32}N_2O_4$ [M^+] 388.2362. Found 388.2365.

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