

Cyclizations

[Pd(PPh₃)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

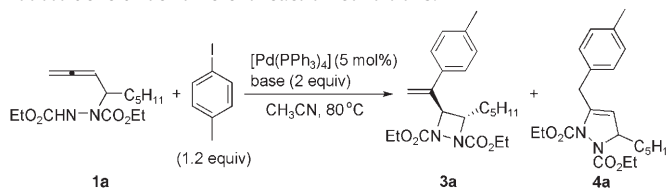
Four-membered cyclic compounds are found in many biologically active natural and unnatural compounds.^[1] Accessing such compounds is a synthetic challenge for synthetic organic chemists because of the intrinsic ring strain.^[2] Diazetidines are a type of four-membered ring, which contains two nitrogen 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, Iyube, 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(PPh₃)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-allenyl hydrazines with aryl halides.

In our initial attempt, we synthesized 2,3-allenyl hydrazine **1a**^[14] and chose [Pd(PPh₃)₄] as the catalyst. During screening, it was observed that the reaction of **1a** with 4-iodotoluene in MeCN with Na₂CO₃ as the base afforded 1,2-diazetidine **3a** in 11 % yield (Table 1, entry 1). Additional

Table 1: [Pd(PPh₃)₄]-catalyzed reaction of allenyl hydrazine **1a** and 4-iodotoluene under different reaction conditions.



Entry	Base	t [h]	Yield of 3a [%] ^[a]	<i>trans</i> : <i>cis</i> ratio of 3a	Yield of 4a [%] ^[a]
1	Na ₂ CO ₃	24	11 ^[b]	100:0	0
2	NaOH	5	n.d.		
3	KOBu ^t	2	n.d.		
4	Et ₃ N	20	5 ^[c]	100:0	0
5	Cy ₂ NMe	30.5	trace		
6	Cs ₂ CO ₃	2	74	100:0	< 7
7	Ag ₂ CO ₃	2	53	100:0	< 10
8	K ₂ CO ₃	6	74	20:1	trace
9	CsF	24	64	17:1	trace
10	KOH	2	59	100:0	< 6
11	Cs ₂ CO 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 Cs₂CO₃. n.d. = not determined because of complicated reaction mixture.

studies indicated that NaOH, KO^tBu, Et₃N, and Cy₂NMe were poor bases for this reaction (Table 1, entries 2–5). However, Cs₂CO₃, Ag₂CO₃, K₂CO₃, CsF, or KOH all provided four-membered ring **3a** in 53–74 % yield (Table 1, entries 6–10); the reaction with K₂CO₃ (Table 1, entry 8) or CsF (Table 1, entry 9) provided the desired product with low stereoselectivity. Thus, reaction conditions (Conditions A:

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

organic halide (1.2 equiv), [Pd(PPh₃)₄] (5 mol %), Cs₂CO₃ (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 ¹H 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-diazetidene-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(PPh₃)₄]-catalyzed synthesis of *trans*-1,2-diazetidines by the cyclization of 2,3-allenyl hydrazines with aryl halides.

$ \begin{array}{c} \text{EtO}_2\text{CHN}-\text{NCO}_2\text{Et} \\ \text{1} \end{array} + \begin{array}{c} \text{R}^2\text{I} \\ \text{(1.2 equiv)} \\ \text{2} \end{array} \xrightarrow[\text{CH}_3\text{CN, 80 }^\circ\text{C, 2 h}]{[\text{Pd}(\text{PPh}_3)_4] \text{ (5 mol\%)} \\ \text{Cs}_2\text{CO}_3 \text{ (1.1 equiv)}} \begin{array}{c} \text{EtO}_2\text{CHN}-\text{NCO}_2\text{Et} \\ \text{3} \end{array} $			
Entry	R ¹ (1)	R ² (2)	Yield of 3 [%] ^[a]
1	<i>n</i> -C ₅ H ₁₁ (1a)	<i>p</i> -MeC ₆ H ₄	77 (3a)
2	<i>n</i> -C ₅ H ₁₁ (1a)	<i>m</i> -MeC ₆ H ₄	71 (3b)
3	<i>n</i> -C ₅ H ₁₁ (1a)	Ph	70 (3c)
4	<i>n</i> -C ₅ H ₁₁ (1a)	<i>p</i> -MeOC ₆ H ₄	73 (3d)
5	<i>n</i> -C ₇ H ₁₅ (1b)	<i>p</i> -MeC ₆ H ₄	75 (3e)
6	<i>n</i> -C ₇ H ₁₅ (1b)	<i>m</i> -MeC ₆ H ₄	70 (3f)
7	<i>n</i> -C ₇ H ₁₅ (1b)	Ph	63 (3g)
8	<i>n</i> -C ₇ H ₁₅ (1b)	<i>p</i> -MeOC ₆ H ₄	75 (3h)
9	<i>n</i> -C ₈ H ₁₇ (1c)	<i>p</i> -MeC ₆ H ₄	72 (3i)
10	<i>n</i> -C ₈ H ₁₇ (1c)	<i>m</i> -MeC ₆ H ₄	71 (3j)
11	<i>n</i> -C ₈ H ₁₇ (1c)	Ph	66 (3k)
12	<i>n</i> -C ₈ H ₁₇ (1c)	<i>p</i> -MeOC ₆ H ₄	74 (3l)
13	PhCH ₂ (1d)	<i>p</i> -MeC ₆ H ₄	68 (3m)
14	PhCH ₂ (1d)	<i>m</i> -MeC ₆ H ₄	68 (3n)
15	PhCH ₂ (1d)	Ph	62 (3o)
16	PhCH ₂ (1d)	<i>p</i> -MeOC ₆ H ₄	71 (3p)

[a] Yield of isolated product.

By using the protocol for the diastereoselective synthesis of *trans*-1,2-diazetidene, 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-

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

$ \begin{array}{c} \text{EtO}_2\text{CHN}-\text{NCO}_2\text{Et} \\ \text{(S)-1a,1b >99\% ee} \end{array} + \begin{array}{c} \text{R}^2\text{I} \\ \text{(1.2 equiv)} \\ \text{2} \end{array} \xrightarrow[\text{CH}_3\text{CN, 80 }^\circ\text{C, 2 h}]{[\text{Pd}(\text{PPh}_3)_4] \text{ (5 mol\%)} \\ \text{Cs}_2\text{CO}_3 \text{ (1.1 equiv)}} \begin{array}{c} \text{EtO}_2\text{CHN}-\text{NCO}_2\text{Et} \\ \text{(3S,4S)-3} \end{array} $				
Entry	R ¹ (1)	R ² (2)	Yield of (<i>S,S</i>)- 3 [%]	ee [%] ^[a]
1	<i>n</i> -C ₅ H ₁₁ (1a)	<i>p</i> -MeC ₆ H ₄	74 (3a)	99.4
2	<i>n</i> -C ₅ H ₁₁ (1a)	<i>p</i> -MeOC ₆ H ₄	74 (3d)	99.4
3	<i>n</i> -C ₇ H ₁₅ (1b)	<i>p</i> -MeC ₆ H ₄	68 (3e)	98.5
4	<i>n</i> -C ₇ H ₁₅ (1b)	<i>p</i> -MeOC ₆ H ₄	75 (3h)	98.5

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

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.

Experimental Section

Synthesis of 3a: Under an atmosphere of argon, Cs₂CO₃ (90 mg, 0.28 mmol), 4-iodotoluene (65 mg, 0.30 mmol), [Pd(PPh₃)₄] (15 mg, 0.013 mmol), **1a** (76 mg, 0.25 mmol), and CH₃CN (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; ¹H NMR (300 MHz, CDCl₃): δ = 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); ¹³C NMR (75.4 MHz, CDCl₃): δ = 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 C₂₂H₃₂N₂O₄ [*M*⁺] 388.2362. Found 388.2365.

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