JOC*Note*

Regioselective Palladium-Catalyzed Formate Reduction of *N*-Heterocyclic Allylic Acetates

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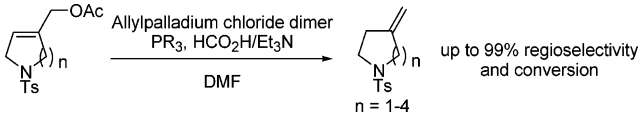
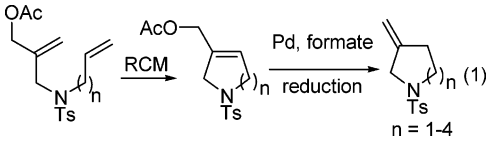


The regioselective palladium-catalyzed formate reduction of allylic acetates in five- to eight-membered heterocycles is reported. Reduction of allylic acetates under mild conditions using allylpalladium chloride dimer, phosphines, and formic acid/triethylamine in DMF gives the *exo*-cyclic olefins in good regioselectivities and high yields. Synthetic application in preparing *N*-tosyl-3-oxo-piperidine is also reported.

Ring-closing metathesis (RCM) has become one of the most effective methods to form heterocyclic compounds.[1] However, modification of the resulting *endo*-olefin is limited by the poor selectivity in discriminating between the two olefinic carbon atoms. For example, hydroboration and oxymercuration of an unsymmetrically disubstituted *endo*-olefin formed by RCM gave a mixture of regioisomers.[2,3] The lack of regioselectivity was also oberved in epoxidation, followed by nucleophilic ring opening of *endo*-olefins.[4]

Recently, Lautens' group reported palladium-catalyzed formate reduction of allylic carbonates to form terminal olefins with excellent regio- and diastereoselectivity.[5] This reaction was also used to prepare chiral fluoroalkylated compounds by Konno's group.[6] We felt that this methodology might also apply to solve the problem of regioselectivity in modifying the olefins formed by RCM.[7,8] Herein, we would like to report the palladium-catalyzed formate reduction of allylic acetates of five- to eight-membered *N*-heterocycles to transform the *endo*-olefin to the *exo*-position (eq 1).



The synthesis of the required allylic acetates of *N*-heterocycles **1a**−**d** is shown in Scheme 1. Alkylation of *N*-(alkenyl)-tosylamides **2a**−**d**[9,10] with 2-bromomethylallyl acetate (**3**)[11] provided the dienes **4a**−**d** for ring-closing metathesis. Grubbs' catalysts were used to perform the ring formation and gave the five- to eight-membered allyl acetates **1a**−**d** in good yields.

Palladium-catalyzed formate reductions of 2,5-dihydropyrrole **1a** are summarized in Table 1. Trialkylphosphonium salts R_3PHBF_4 were used instead of the air-sensitive trialkylphosphines to simplify the experimental operations.[5,12] Tributylphosphine, the most frequently used ligand in palladium-catalyzed formate reductions to generate linear, terminal olefins, was tested first with some common solvents (entries 1−4). We found that the effects of the solvents are significant. In THF and CH_2Cl_2, the *endo*-product **6a**[13] dominates; on the other hand, the desired *exo*-product **5a**[14] is more favored in acetonitrile and DMF. Therefore, DMF was used in the following studies. Raising the

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(3) Nguyen, G.; Perlmutter, P.; Rose, M. L.; Vounatsos, F. *Org. Lett.* **2004**, *6*, 893.

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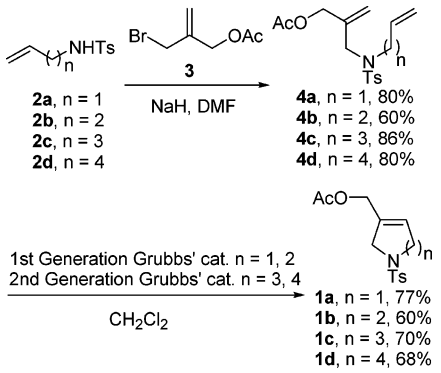
SCHEME 1. Synthesis of *N*-Heterocycles with Allylic Acetates



reaction temperature to 40 °C shortened the reaction time and gave similar selectivity (81−85% of the *exo*-olefin **5a**, entries 4 and 5). Extending the reaction time did not alter the ratio of the two olefins, which indicates that the alkenes **5a** and **6a** are kinetically stable under the reaction conditions (entry 6). However, when the reaction temperature was 60 °C, *endo*-olefin **6a** became the major product, indicating that the thermodynamically more stable *endo*-product **6a** is favored at high temperature.[15]

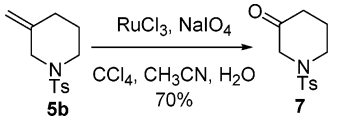
To achieve better regioselectivity, phosphine ligands with various electronic and steric properties were screened. Tricyclohexylphosphine (PCy_3) favors the *exo*-product **5a** in a nearly 9 : 1 ratio at room temperature (entry 8). We also found that the ratio of palladium to phosphine is important. The amount of *exo*-olefin **5a** increased as the ratios of PCy_3 to Pd increased from one to two (entries 8, 10, and 11). Although adding more phosphine (up to 4 equiv) slightly improved the regioselectivity (91%), the rate of conversion was decreased (entry 12). As seen in the reactions of P(*n*-Bu)$_3$, raising the reaction temperature to 40 °C was accompanied by lower selectivity (entry 13). Increasing the size of ligand to tri-*tert*-butylphosphine led to a disappointing conversion and selectivity. Triphenylphosphine only gave the *endo*-product **6a** (entry 15). The selectivity favored the *exo*-olefin **5a** as the size of the aryl groups increased to 1-naphthyl and *o*-tolyl (entries 15−17).[16] Interestingly, di-*tert*-butyl 2-biphenylphosphine, an aryl, alkyl mixed phosphine, provided the best regioselectivity (93%) among the phosphine ligands screened for **1a** (entry 18). The structurally similar dicyclohexyl 2-biphenylphosphine and di-*tert*-butyl 2-(2′-methylbiphenyl)phosphine provided better conversions but lower regioselectivities (entries 20−21). All the bidentate ligands with different bite angles gave mediocre selectivities (entries 22−27).[17] The ligand with a labile nitrogen donor afforded the better regioselectivity among these bidentates (entry 27). These results are consistent with Hayashi's observation that the use of monodentate phosphines is essential in asymmetric reductions of π-allylpalladium complexes, even though the optimal ratio of Pd : P is 1 : 2.[18]

The palladium-catalyzed formate reductions of tetrahydropyridine **1b** are summarized in Table 2. Tributylphosphine provided *exo*-olefin **5b**[19] exclusively at room temperature, but conversion was low. Attempts to increase the conversion by raising the temperature to 40 °C reduced the ratio (entry 2). In contrast to the reactions of **1a**, reactions using PCy_3 and P(*t*-Bu)$_3$ proceeded very poorly (entries 3 and 4). To our surprise, triphenylphosphine provides excellent regioselectivity, favoring *exo*-olefin **5b**, despite low conversion (entry 5). The other two analogs of triphenylphosphine, P(1-naphthyl)$_3$ and P(*o*-Tol)$_3$, gave even lower conversions and poor regioselectivity (entries 6−8). On the other hand, di-*tert*-butyl 2-biphenylphosphine provided both good regioselectivity (*exo* 96%) and conversion (94%, entry 9).

The results using seven- and eight-membered *N*-heterocycles **1c** and **1d** as the substrates are summarized in Tables 3 and 4. The *endo*-products **6c,d**, usually the minor component in the reactions and inseparable from the *exo*-products **5c,d**, were synthesized independently (see Supporting Information) to confirm their identity on ^{1}H NMR spectra. We noticed that the reaction rates of these medium rings are faster than those of **1a** and **1b**, which allow us to perform the reductions at 0 °C. Four selected phosphine ligands were used to effect the reduction. For both **1c** and **1d**, di-*tert*-butyl 2-biphenylphosphine gave complete conversion and no *endo*-product was detected on 500 MHz ^{1}H NMR. This aryl and alkyl mixed phosphine, instead of P(*n*-Bu)$_3$, is the choice of ligand for this regioselective reduction of these cyclic substrates.

Solvents, phosphines, and temperatures are important factors in our studies of the allylic reductions of *N*-heterocycles **1a**−**d**. The different reactivity among **1a**−**d** also indicates that this reaction is sensitive to the subtle conformational change between the five- to eight-membered rings.

The selective isomerization that we report here has potential applications in synthesis. Consider, for example, a preparation of *N*-tosyl-3-oxo-piperidine (**7**, eq 2), an intermediate in the synthesis of Aloperine and carbolines,[20,21] by way of RCM. Oxidation of the exocyclic alkene by ruthenium(III) chloride and sodium periodate affords **7** cleanly,[22] whereas a preparation that relies on hydration of an *endo*-alkene followed by oxidation would lead to mixtures of ketones.[2,3]



(2)

In conclusion, palladium-catalyzed formate reductions of allylic substrates is shown to be an effective method to isomerize the endocyclic olefin formed by RCM to the *exo*-position, thus providing one way to circumvent the problem of regioselectivity in further modification of the cycloalkenes formed by ring-

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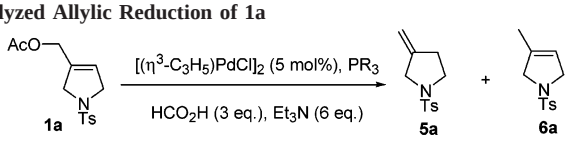
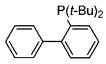
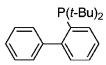
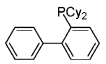
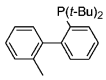
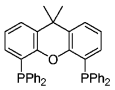
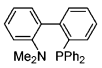
TABLE 1. Palladium-Catalyzed Allylic Reduction of 1a



entry	PR_3	solvent	Pd : P	temp. (°C)	time (h)	conv. (%)	ratios[a] (%) 5a	6a
1	P(*n*-Bu)$_3$	THF	1 : 2	25	24	38	n.d.[b]	>99
2	P(*n*-Bu)$_3$	CH_2Cl_2	1 : 2	25	6	58	28	72
3	P(*n*-Bu)$_3$	CH_3CN	1 : 2	25	6	>99	72	28
4	P(*n*-Bu)$_3$	DMF	1 : 2	25	16	>99	81	19
5	P(*n*-Bu)$_3$	DMF	1 : 2	40	6	>99	85	15
6	P(*n*-Bu)$_3$	DMF	1 : 2	40	24	>99	83	17
7	P(*n*-Bu)$_3$	DMF	1 : 2	60	21	>99	n.d.[b]	>99
8	PCy_3	DMF	1 : 2	25	15	93	89	11
9	PCy_3	DMF	1 : 2	40	16	>99	60	40
10	PCy_3	DMF	1 : 1	25	14	>99	6	94
11	PCy_3	DMF	1 : 1.5	25	14	>99	27	73
12	PCy_3	DMF	1 : 4	25	16	69	91	9
13	PCy_3	DMF	1 : 4	40	16	>99	34	66
14	P(*t*-Bu)$_3$	DMF	1 : 2	25	13	57	21	79
15	PPh_3	DMF	1 : 2	25	17	74	n.d.[b]	>99
16	P(1-naphthyl)$_3$	DMF	1 : 2	40	16	>99	18	82
17	P(*o*-Tol)$_3$	DMF	1 : 2	40	14	>99	73	27
18		DMF	1 : 2	25	25	81[c]	93	7
19		DMF	1 : 2	40	16	>99	84	16
20		DMF	1 : 2	25	3	>99	37	63
21		DMF	1 : 2	25	3	>99	81	19
22	dppm	DMF	1 : 2	25	16	75	63	37
23	dppe	DMF	1 : 2	40	20	59	25	75
24	dppp	DMF	1 : 2	40	20	0	–	–
25	dppf	DMF	1 : 2	25	16	33	52	48
26		DMF	1 : 2	40	14	>99	65	35
27		DMF	1 : 1	25	16	90	81	19

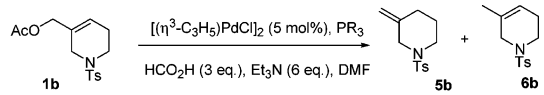
[a] Ratios were determined by 500 MHz ^{1}H NMR of crude reaction mixtures. [b] Not detected. [c] Isolated yield, 68%.

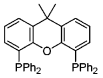
closing metathesis. Further application of this methodology to natural product synthesis is currently being explored.

Experimental Section

Procedure for Palladium-Catalyzed Formate Reduction. Triethylamine (54 μL, 0.39 mmol) and formic acid (7 μL, 0.19 mmol) were added to a solution of allylpalladium chloride dimer (1.2 mg, 3.3×10^{-3} mmol) and di-*tert*-butyl 2-biphenylphosphine (3.9 mg, 0.013 mmol) in DMF (200 μL) under an atmosphere of nitrogen. The solution was stirred at room temperature for 5 min. Acetate **1b** (19 mg, 0.063 mmol) in DMF (400 μL) was added to the solution of the palladium complex. After being stirred

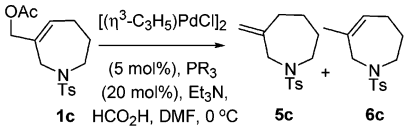
TABLE 2. Palladium-Catalyzed Allylic Reduction of 1b

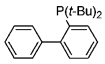
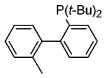


entry	PR_3	Pd:P	temp. (°C)	time (h)	conv. (%)	ratios[a] (%) 5b	6b
1	P(*n*-Bu)$_3$	1 : 2	25	21	38	>99	n.d.[b]
2	P(*n*-Bu)$_3$	1 : 2	40	4	>99	86	14
3	PCy$_3$	1 : 2	25	21	76	47	53
4	P(*t*-Bu)$_3$	1 : 2	25	21	0	–	–
5	PPh$_3$	1 : 2	25	21	59	97	3
6	P(*o*-Tol)$_3$	1 : 2	25	21	0	–	–
7	P(1-naphthyl)$_3$	1 : 2	25	21	22	18	82
8	P(1-naphthyl)$_3$	1 : 2	40	20	46	48	52
9		1 : 2	25	21	94[c]	96	4
10		1 : 2	25	21	85	29	71
11		1 : 1	25	21	62	85	15

[a] Ratios were determined by 500 MHz ^{1}H NMR of crude reaction mixtures. [b] Not detected. [c] Isolated yield, 80%

TABLE 3. Palladium Catalyzed Allylic Reduction of 1c

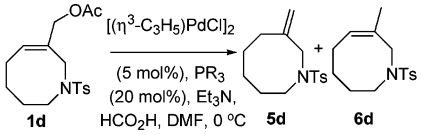


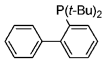
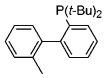
entry	PR_3	time (h)	conv. (%)	ratios[a] (%) 5c	6c
1	PPh$_3$	14	44	99	1
2	P(*n*-Bu)$_3$	14	9	>99	n.d.[b]
3		18	>99	>99[c]	n.d.[b]
4		18	>99	82	18

[a] Ratios were determined by 500 MHz ^{1}H NMR of crude reaction mixtures. [b] Not detected. [c] Isolated yield, 81%

at room temperature for 21 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (3 mL × 2) and saturated $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered, and concentrated to give the crude product. The crude product was analyzed by 500 MHz ^{1}H NMR to determine the ratio of **5b** to **6b**,[23] and further purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:9; R_f 0.43) to give pure compound **5b** (13 mg, 0.05 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.86 (s, 1H), 4.79 (s, 1H), 3.47 (s, 2H), 3.03 (m, 2H), 2.40 (s, 3H), 2.07 (m, 2H), 1.68−1.60 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 140.5, 133.0, 129.5, 127.7, 111.6, 52.4, 46.3, 31.9, 25.6, 21.5. The spectroscopic data of **5b** were consistent with those reported in literature.[18]

TABLE 4. Palladium Catalyzed Allylic Reduction of 1d



entry	PR_3	time (h)	conv. (%)	ratios[a] (%) 5d	6d
1	PPh$_3$	18	61	74	26
2	P(*n*-Bu)$_3$	18	46	69	31
3		18	>99	>99	n.d.[b]
4		18	92[c]	>99	n.d.[b]

[a] Ratios were determined by 500 MHz ^{1}H NMR of crude reaction mixtures. [b] Not detected. [c] Isolated yield, 80%.

Preparation of Allylic Acetate 1a. Diolefin **4a** (480 mg, 1.48 mmol) and first generation Grubbs' catalyst (20 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) were heated to reflux for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:1; R_f 0.52) to give compound **1a** (338 mg, 1.14 mmol, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (2 H, J = 8.2 Hz), 7.29 (2 H, J = 8.0 Hz), 5.58 (1H, s), 4.52 (2H, s), 4.10−4.09 (2H, m), 4.05 (2H, d, J = 3.8), 2.39 (3H, s), 2.01 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 143.6, 134.3, 134.1, 129.8, 127.4, 123.0, 60.2, 54.8, 54.7, 21.5, 20.6. HRMS (FAB): calcd for $[M + H]^+$ ($C_{14}H_{18}O_4NS$) 296.0957, found 296.0958.

***N*-Tosyl-3-oxo-piperidine (7).** Sodium periodate (35 mg, 0.16 mmol) and ruthenium(III) chloride (1 mg, 12 mol %) were added to the solution of compound **5b** (10 mg, 0.04 mmol) in CCl_4 (100 μL), acetonitrile (100 μL), and water (150 μL). After being stirred at room temperature for 2 h, the reaction mixture was diluted with water (1 mL), extracted with CH_2Cl_2 (2 mL × 4), dried over sodium sulfate, filtered, and concentrated to give the crude product. The crude ketone was further purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:1; R_f 0.57) to give pure **7** as a colorless solid (7 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.3 (d, J = 8.1 Hz, 2H), 3.58 (s, 2H), 3.27 (t, J = 5.8 Hz, 2H), 2.43 (s, 3H), 2.35 (t, J = 6.9, 2H), 2.02−1.99 (m, 2H).[20]

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Supporting Information Available: Experimental details for preparation and detailed spectroscopic data of compounds **1a**−**d**, **4a**−**d**, **5a**−**d, 6a**−**d**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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