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Efficient Syntheses of Functionalized Piperidines Through Extremely Regioselective Rh-Catalyzed Cyclohydrocarbonylation of Amido-ω,ω'-dienes

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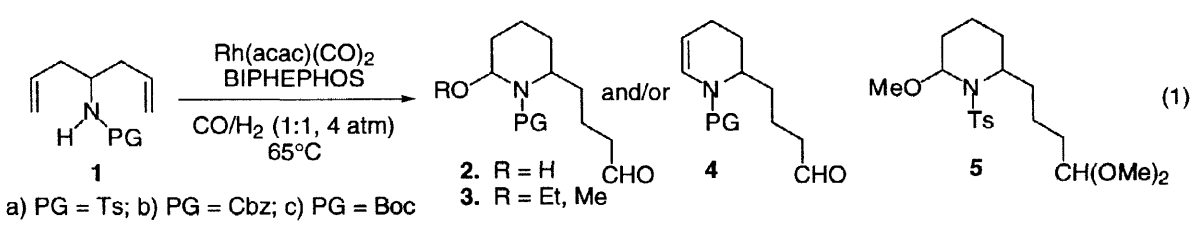
Abstract: The highly regioselective cyclohydrocarbonylation of 4-amido-1,6-heptadienes catalyzed by Rh-BIPHEPHOS complex gives functionalized piperidines quantitatively, which serve as versatile intermediates for the syntheses of a variety of piperidine and quinolizidine alkaloids. Reaction of 3-Boc-amino-1,5-hexadiene affords the corresponding dehydropiperidine-aldehyde exclusively via site and regioselective hydroformylation. Possible mechanisms for these reactions are proposed. © 1998 Elsevier Science Ltd. All rights reserved.

Functionalized piperidine alkaloids have attracted considerable interest because of their diverse biological activities.[1] We have been applying carbonylation reactions in the key steps for the syntheses of piperidine and izidine alkaloids.[2] Now, we report here the syntheses of functionalized piperidines through the extremely regioselective cyclohydrocarbonylation of amido-ω,ω'-dienes and their applications toward the construction of quinolizidine and indolizidine alkaloids.

The cyclohydrocarbonylation of 4-amido-1,6-heptadiene **1** catalyzed by Rh(acac)$(CO)_2$-BIPHEPHOS[3] at 65 °C and 4 atm of CO and H_2 (1:1) in THF gave 2-hydroxyl-6-(3-formylpropyl)piperidine **2** and/or 6-(3-formylpropyl)-5,6-didehydropiperidine **4** (eq. 1). On the other hand, the reaction in ethanol under the same conditions afforded 2-ethoxyl-6-(3-formylpropyl)piperidine **3** (PG = Ts, R = Et) exclusively (eq. 1). As Table 1 shows, when the reaction was run at 65 °C for 2 h (entry 1), hemiamidal **2** was formed exclusively. Hemiamidal **2** is converted to dehydropiperidine **4** with prolonged reaction time under the reaction conditions. Thus, a mixture of **2** and **4** was obtained at 7 h period (entry 2), and **4** became the sole product after 18 h (entry 3). Hemiamidal **2** can also be converted to **4** just by passing through a silica gel column. Typical N-protecting groups (PG), e.g., tosyl (Ts), carbobenzoxy (Cbz), and *tert*-butoxycarbonyl (Boc) groups, can be used in this reaction without appreciable difference in the yields. It should be noted that the reaction of **1a** in methanol gave 1-tosyl-2-methoxy-6-(3,3-dimethoxybutyl)piperidine (**5**) in quantitative yield, i.e., the aldehyde moiety of the initially formed cyclohydrocarbonylation product (**3**: PG = Ts, R = Me) was converted to the corresponding dimethylacetal under the reaction conditions.



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It has been shown that 1-alkoxy-6-(substituted)piperidines such as **3** and **5** serve as key intermediates for the diastereoselective syntheses of a variety of biologically active piperidine and indolizidine alkaloids.[4] Accordingly, the present cyclohydrocarbonylation of amido-ω,ω'-dienes **1** provides highly efficient and convenient routes to these versatile key intermediates for alkaloid syntheses.

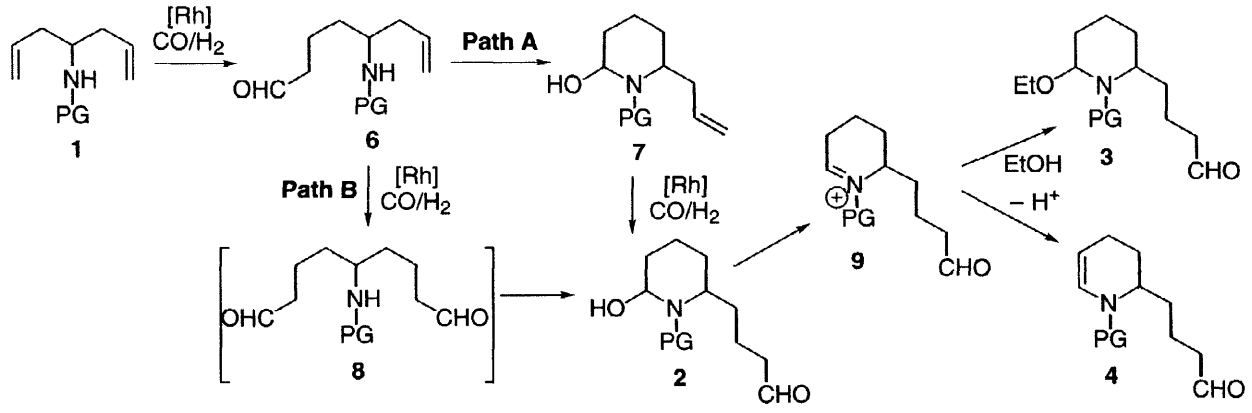
Table 1. Cyclohydrocarbonylation of Protected 4-amido-1,6-heptadienes **1**.[a)]

Entry	amidodiene	PG	Solvent	Time (h)	Product	Yield(%)[b)]
1	**1a**	Ts	THF	2	**2a**	100
2	**1a**	Ts	THF	7	**2a** + **4a** (7:3)	100
3	**1a**	Ts	THF	18	**4a**	100 (88)
4	**1b**	Cbz	THF	18	**4b**	100 (65)
5	**1c**	Boc	THF	18	**4c**	100 (71)
6	**1a**	Ts	EtOH	18	**3a**	100
7	**1c**	Boc	EtOH	18	**3c**	100 (93)
8	**1a**	Ts	MeOH	15	**5**	100 (73)

[a)]All reactions were run with **1** (0.22 mmol), $Rh(acac)(CO)_2$ (0.002 mmol), and BIPHEPHOS (0.004 mmol) in 1.5 mL solvent at 65 °C and 4 atm of CO and H_2 (1:1). Conversion was 100% in all cases based on ^1H NMR analysis. [b)] NMR yields. The values in parentheses are isolated yields after chromatography on silica gel.

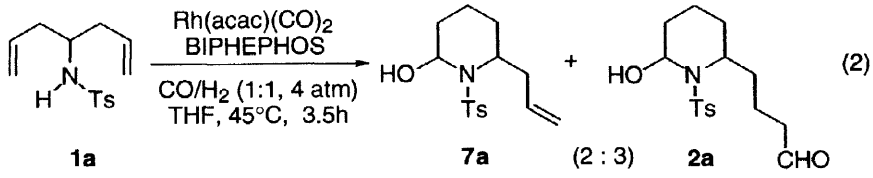
Proposed reaction pathways for the formation of **3** and **4** are shown in Scheme 1. Extremely linear-selective hydroformylation of one of the two olefin moieties of **1** gives **6**, which undergoes cyclization forming alkenyl-hemiamidal **7**, and subsenquent regioselective hydroformylation of the remaining olefin moiety of **7** affords hemiamidal-aldehyde **2** (Path A). Alternatively, another regioselective hydroformylation of **6** gives dialdehyde **8**, and the subsequent cyclization yields **2** (Path B).

Scheme 1. Proposed reaction pathways.



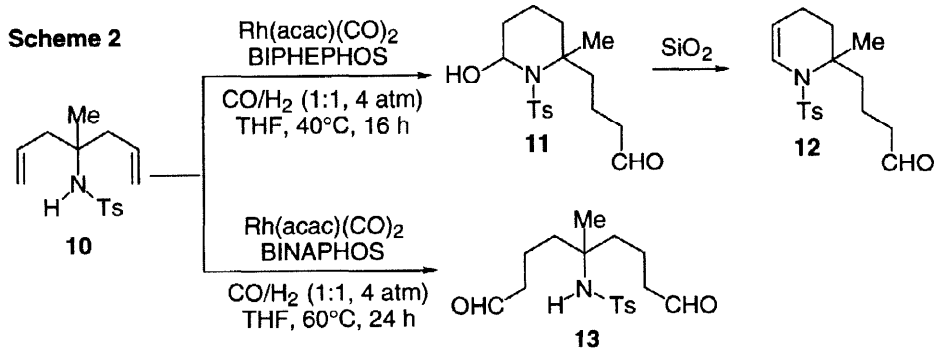
Elimination of hydroxyl anion from **2** generates reactive acyliminium intermediate **9**. Addition of ethanol to **9** gives **3**, while deprotonation, i.e., net elimination of water from **2**, affords **4**. Intermediate **2** was indeed isolated as mentioned above, and thus the intermediary of **2** has been confirmed. In order to determine which pathway is operative under the reaction conditions, the reaction was carried out at 45 °C for 3.5 h otherwise under

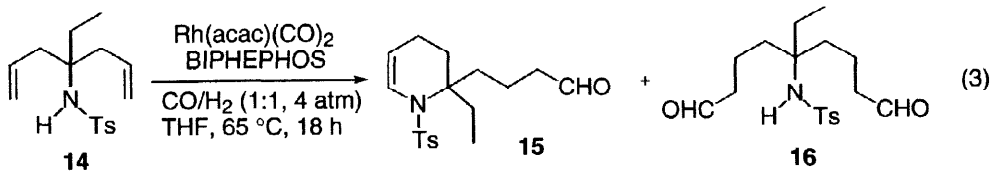
the standard conditions (see footnote a) of Table 1). This reaction gave a mixture of **7a** and **2a** (**7a/2a** = 2:3) in quantitative yield at 70% conversion (eq. 2). This result clearly supports Path A in that the cyclization of **6** giving **7** is faster than the second hydroformylation.



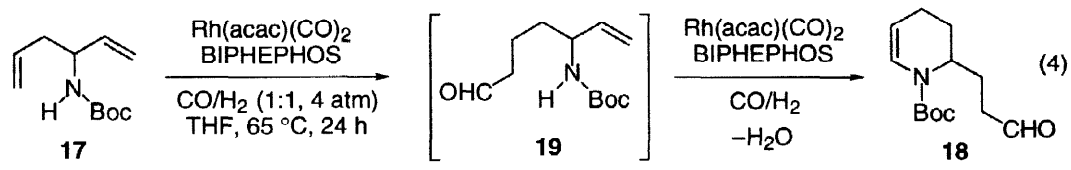
The influence of an alkyl substituent at the C-4 position of 4-amido-1,6-heptadienes was next investigated. The reaction of 4-methyl-4-tosylamino-1,6-heptadiene (**10**) catalyzed by the Rh-BIPHEPHOS complex at 40 °C gave hemiamidal-aldehyde **11** in nearly quantitative yield, which dehydrated upon passing through a silica gel column to afford dehydropiperidine **12** quantitatively (Scheme 2). Thus, the C-4 methyl does not affect the course of the reaction. However, when (*R,S*)-BINAPHOS[5] was used as the ligand, the reaction of **10** gave non-cyclized dialdehyde **13** as the predominant product (>95% yield) with small amounts of branched dialdehydes, i.e., no cyclization took place (Scheme 2). It should be noted that the nature of the ligand used exerts marked effects on the course of the reaction.[6] The reaction of 4-ethyl-4-tosylamino-1,6-heptadiene (**14**) catalyzed by the Rh-BIPHEPHOS complex at 65 °C for 18 h gave a mixture of dehydropiperidine-aldehyde **15** and dialdehyde **16** (**15**:**16** = 1:3) in quantitative yield (eq. 3). Prolonged reaction time led to the increase in the amount of **15**. These results suggest that the C-4 substitution does influence the course of the reaction, favoring Path B.

Scheme 2

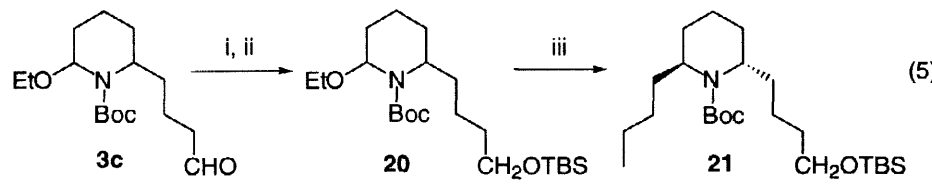




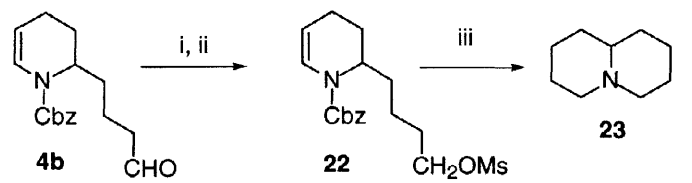
The reaction of unsymmetrical amidodiene **17** catalyzed by the Rh-BIPHEPHOS complex under the standard conditions gave dehydropiperidine-aldehyde **18** as the sole product, i.e., no pyrroline was formed (eq. 4). Thus, this reaction is extremely site and regio-selective in that the hydroformylation takes place at the homoallylic olefin moiety exclusively, only yielding the linear aldehyde intermediate **19**.



A preliminary feasibility study on the applications of functionalized piperidines **3** and **4**, thus obtained, to alkaloid syntheses has been successfully carried out. Two examples are shown below: (i) the diastereoselective alkylation of hemiamidal **20** derived from **3c**, giving **21** (eq. 5) and (ii) the construction of the basic framework of quinolizidine alkaloids **23** from **4b** (eq. 6).



(i) $NaBH_4$, EtOH, quant.; (ii) TBS-Cl, imidazole, THF, 90%; (iii) *n*-BuCu•BF_3, 83%.



i) $NaBH_4$, MeOH, 90%; ii) MsCl, DMAP, py, CH_2Cl_2, 80%; iii) H_2, Pd/C, EtOH, 60%.

Further investigations on the applications of this work as well as the development of asymmetric cyclohydrocarbonylations of amido-ω,ω'-dienes are actively underway.

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[6] The reaction of **1a** catalyzed by Rh-BINAPHOS complex at 60 °C and 4 atm of CO and H_2 (1:1) for 24 h gave a mixture of **2a** and **4a** (**2a**:**4a** = 3:7) in quantitative yield. Thus, BINAPHOS behaved in the same manner as BIPHEPHOS for **1a**.