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Efficient Syntheses of Crispine A and Harmicine by Rh-Catalyzed Cyclohydrocarbonylation

Wen-Hua Chiou,*,† Gau-Hong Lin,† Che-Cheng Hsu,† Stephen J. Chaterpaul,‡ and Iwao Ojima‡

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan, R.O.C, and Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

wchiou@dragon.nchu.edu.tw

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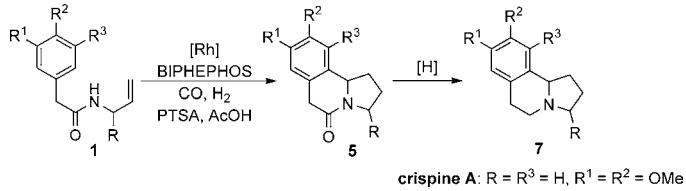
ABSTRACT



The first examples of Rh-catalyzed cyclohydrocarbonylation-bicyclization of *N*-allylic amides of arylacetic acids are reported. This novel carbonylative bicyclization process was successfully applied to the rapid syntheses of crispine A and its analogues (tricyclic indolizidine alkaloids) as well as harmicine (tetracyclic *β*-carboline alkaloid).

Transition-metal-catalyzed cyclization reactions provide powerful tools for the syntheses of complex fused ring systems.[1] In this regard, a suitable design of this process in a cascade manner will furnish a greener and more economical process by minimizing reaction steps and waste, since such a domino process would dramatically reduce the consumption of solvents, reagents, and energy, as compared to stepwise reactions.[2] We have shown that the cyclohydrocarbonylation (CHC)[3] of unsaturated dipeptide derivatives, bearing intramolecular heteroatom nucleophiles such as hydroxyl, carbamate, and thiol, proceeds efficiently to give the corresponding 1-azabicyclo[*x*.*y*.0]alkane amino acids with extremely high diastereoselectivity.[4,5] We envisioned that the utility and scope of this carbonylative bicyclization process would be further expanded if aromatic ring nucleophiles could be used, which would instantly increase the complexity of the products.[6] Then, we have found that electron-rich aromatic moieties indeed act as the intramolecular nucleophiles in the CHC process.

Figure 1 illustrates this novel CHC-bicyclization process.[3] This domino process commences with an extremely linear-selective hydroformylation of *N*-allylic amide of phenylacetic acid **1** to yield aldehyde **2**, which undergoes the first cyclization to form hemiaminal **3** in the presence of an acid. Dehydration of **3** generates an *N*-acyliminium ion **4**, followed by the second cyclization with an electron-rich aromatic nucleophile to afford bicyclization product **5**. This process is applicable to *N*-allylamide of indole-3-acetic acid **1f**, yielding **5f**.

† National Chung Hsing University.
‡ State University of New York at Stony Brook.

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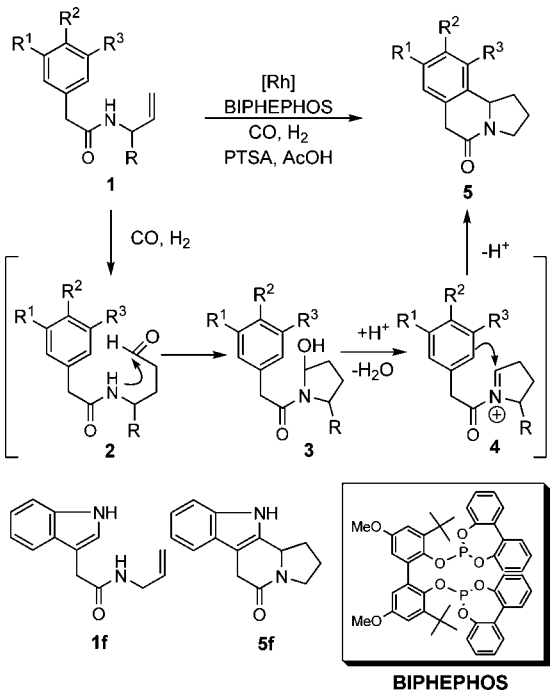

Figure 1. New CHC-bicyclization process.

We report here the first CHC-bicyclization process, involving aromatic carbon nucleophiles, for the rapid construction of naturally occurring alkaloids, crispine A and its analogues, as well as harmicine. It has been shown that indolizidine alkaloid crispine A, isolated from *Carduus crispus*,[7] is a potent antitumor agent against SKOV3, KB, and HeLa human cancer cell lines,[7] while β-carboline alkaloid harmicine, isolated from *Kopsia griffithii*, possesses strong antileishmania activity.[8]

N-Allylamides **1a**−**f** were readily prepared from the corresponding acid or acid chloride and allylamines (see the Supporting Information). The CHC reactions of **1a**−**f** were carried out in the presence of catalytic amounts of Rh−BIPHEPHOS complex and PTSA under CO and H_2. First, **1a** was chosen as the substrate to investigate suitable reaction conditions, which could be used as the standard conditions for other substrates. Results are summarized in Table 1.

Table 1. Optimization of the CHC-Bicyclization Reaction of **1a**[a]

entry	solvent	PTSA (%)	CO (atm)	H_2 (atm)	T (°C)	yield[b] (%)
1	toluene	10	2	2	60	dec
2	THF	10	2	2	60	dec
3	MeOH	10	2	2	60	dec
4	MeCN	50	2	2	60	32
5	AcOH	10	2	2	60	85
6	AcOH	50	2	2	60	66
7	AcOH	100	2	2	60	67
8	AcOH	10	6	6	60	60
9	AcOH	10	2	2	40	44
10	AcOH	10	2	2	60	77[c]

[a] Reagents and Conditions: All reactions were run with 1.0 mmol of **1a** (0.05 M in 20 mL solvent), $Rh(acac)(CO)_2$ (0.5 mol %), and BIPHEPHOS (1 mol %) for 16 h. [b] Isolated yield. [c] Reaction was run at 0.01 M substrate concentration.

Reaction of **1a** in toluene (entry 1), THF (entry 2), and MeOH (entry 3) gave only a messy mixture, including decomposition products. Use of acetonitrile as the solvent led to the formation of bicyclization product **5a**, but only in 32% isolated yield (entry 4). Employment of acetic acid as the solvent was a breakthrough and the reaction gave **5a** in 85% yield (entry 5) accompanied by a small amount of branched aldehyde **2a′** (7%) (see Scheme 1). The use of a smaller amount (<10 mol %) of PTSA often resulted in lower conversion to **5a** and substantial formation of uncyclized linear aldehyde **2a**. Thus, the presence of PTSA was found to be essential for the cyclization to proceed even when acetic acid was used as the solvent. However, the use of a larger amount of PTSA (50 and 100 mol %) did not have any beneficial effect and rather lowered the yield of **5a** (entries 6 and 7). Increasing the pressure of CO (6 atm) and H_2 (6 atm) did not show any favorable effect either (entry 8). Lowering the reaction temperature to 40 °C resulted in the appearance of **2a** in addition to **5a** after the standard 16 h reaction time (entry 9). The reaction at a lower substrate concentration (0.01 M) gave **5a** in somewhat lower yield (77%), but without **2a** (entry 10). Thus, we concluded that the use of 10 mol % of PTSA at 60 °C, 4 atm of CO/H_2 (1/1), and 0.05 M substrate concentration would be the optimal conditions so far, which would be used as the standard conditions for the subsequent reactions with other substrates.

It should be noted that even though there were two possible regioisomers in the second cyclization step, i.e., from **4** to **5** (see Figure 1), **5a** was the only product formed, which was supported by 2-D NMR analyses and comparison with reported NMR data for **5a**.[7f]

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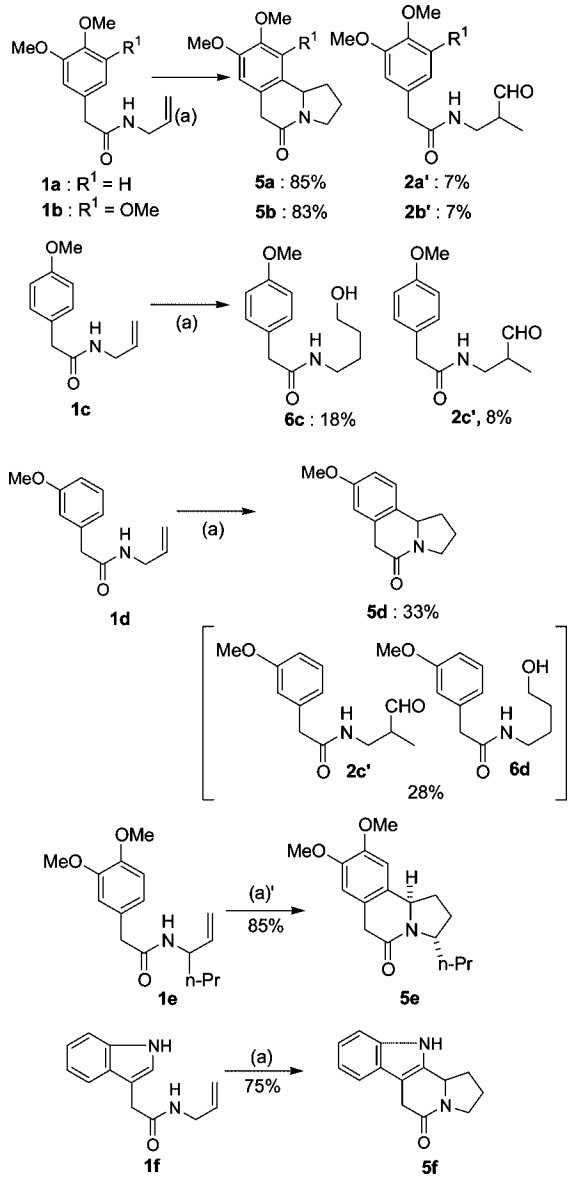
Scheme 1. CHC-Bicyclization of **1a**−**f**[a]



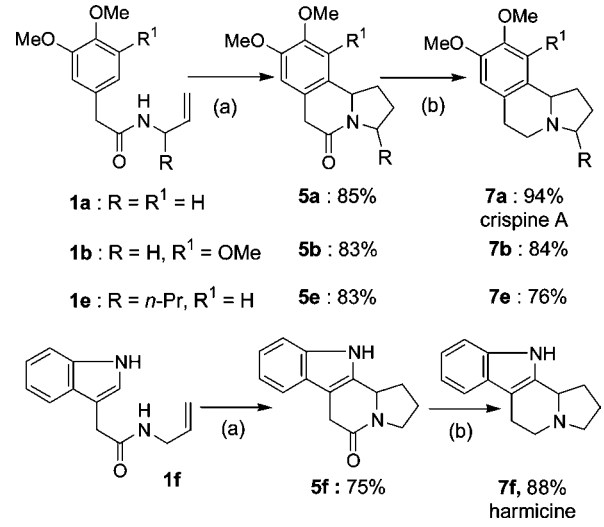
[a] Reagents and conditions: (a) **1** (0.05 M), Rh(acac)$(CO)_2$ (0.5 mol %), BIPHEPHOS, (1 mol %), and PTSA (10 mol %) in AcOH at 60 °C and 4 atm of CO/H_2 (1/1), 16 h. (b) Same as (a) except for the temperature and pressure, i.e., at 80 °C and 20 atm of CO/H_2 (1/1). (c) Same as (a) except for the concentration; i.e., 0.01 M substrate concentration was used.

Reaction of *N*-allylamide **1b**, bearing a 3,4,5-trimethoxyphenyl moiety, proceeded smoothly to give **5b** in 83% yield, accompanied by **2b′** (7%) (Scheme 1). The result is virtually the same as that of **1a** described above.

Next, we investigated the reactions of **1c** and **1d**, bearing only one methoxy group in the phenyl moiety, i.e., 4-methoxyphenyl and 3-methoxyphenyl, respectively (Scheme 1). As anticipated,[9] the reaction of **1c**, wherein the methoxy group is *meta* to the reacting C2 position, gave a mixture of

(9) AM1 calculation results carried out by *Spartan 06′* show the largest coeffecients in HOMO of **4d** is at the carbon *para* to the methoxy group, while that in **4c** is at the carbon *ortho* to the methoxy group, as anticipated.

Scheme 2. Bicyclization−Reduction Sequence to Crispine A, Its Analogues, and Harmicine[a]



[a] Reagents and Conditions: (i) Rh(acac)$(CO)_2$ (0.5 mol %), BIPHEPHOS (1 mol %), and PTSA (10 mol %) in AcOH at 60 °C and 4 atm of CO/H_2 (1/1) for 16 h; (ii) $LiAlH_4$−Et_3NHCl (5 equiv) in THF at 0 °C to rt overnight.

branched aldehyde **2c′** (8%) and alcohol **6c** (18%), accompanied by a complex mixture of unidentified side products. In contrast, the reaction of **1d**, wherein the methoxy group is *para* to the reacting C6-position, underwent CHC-bicyclization to give **5d** (33%), and a mixture of linear alcohol **6d** and branch aldehyde **2d′** (28%, **6d**/**2d′** = 5:2). The formation of alcohols **6c** and **6d** indicates that the reduction of aldehydes **2c** and **2d** competes with the first cyclization in these reactions because of the weak nucleophilicity of the monomethoxyphenyl moieities.

The formation of branched aldehydes **2a**−**d′** in spite of the use of extremely linear selective Rh−BIPHEPHOS catalyst[3,10,11] may be ascribed to a partial amide-directed chelation control[12] that favors the formation of branched aldehyde in the reactions of *N*-allylamides.

The reaction of *N*-hex-1-en-3-ylamide **1e** was found to require more forced conditions than the standard conditions used for those of **1a**−**d** to proceed. This is likely due to the steric bulk at the allylic position imposed on the hydroformylation step catalyzed by a bulky Rh−BIPHEPHOS complex. Thus, the reaction of **1e** was carried out at 80 °C and 20 atm of CO/H_2 (1/1) for 16 h to give **5e** in 83% yield as a single diastereomer (Scheme 1). The 2-D NMR analysis of **5e** on the basis of HSQC and ROESY clearly indicated 2,5-*trans* stereochemistry of the pyrrolidine moiety (see the Supporting Information).

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In addition to *N*-allylic amides of methoxy-substituted phenylacetic acids **1a**−**e**, *N*-allylamide of indole-3-acetic acid **1f** was employed as a substrate. The reaction of **1f** under the standard conditions afforded the corresponding bicyclization product **5f** in 64% yield, which was improved to 75% when the reaction was run in more dilute conditions (0.01M) (Scheme 1).

To convert tricyclic lactam **5a** and tetracyclic lactam **5f** to crispine A and harmicine, respectively, the lactam moiety needs to be reduced. It was well-known that alane−triethylamine complex[13,14] was an excellent reagent for this purpose, but we modified the procedure to generate this reducing agent in situ just by mixing equal amounts of $LiAlH_4$ and $Et_3N{\cdot}HCl$ in THF (see the Supporting Information).

Reductions of **5a** and **5f** with $LiAlH_4$ and $Et_3N{\cdot}HCl$ in THF gave crispine A (**7a**) and harmicine (**7f**) in 94% and 88% yields, respectively. In the same manner, crispine A analogues **7b** and **7e** were obtained in 84% and 76% yields from **5b** and **5e**, respectively. Results are summarized in Scheme 2.

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In summary, we reported the first examples of Rh-catalyzed CHC-bicyclization of *N*-allylic amides of arylacetic acids, wherein an electron-rich aromatic moiety acts as the intramolecular nucleophile to undergo the second cyclization. This novel carbonylative bicyclization process was successfully applied to the rapid syntheses of a tricyclic indolizidine alkaloid, crispine A, and its analogues as well as a tetracyclic β-carboline alkaloid, harmicine. Further studies on the exploration and applications of cyclohydrocarbonylation reactions are actively underway in these laboratories.

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Supporting Information Available: Experimental procedures, characterization data, as well as ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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