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Rh(III)-catalyzed C–H activation-desymmetrization of diazabicycles using enol as directing group: A straightforward approach to difunctionalized cyclopentenes

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ABSTRACT

A Rh(III)-catalyzed C–H activation-desymmetrization of diazabicycles with *o*-vinylphenols as an efficient approach to alkenyl-substituted aminocyclopentenes is reported. This protocol represents another classic example for direct C–H activation of terminal alkenes using enol as directing group. The reaction features the ease of the preparation of starting materials, fast and high efficiency, broad substrate scope and 100% atom economy, thus provides a valuable entry to synthesize novel substituted cyclopentenes.

Introduction

Some 5-membered carbocyclic nucleosides are key intermediates for the synthesis of numerous natural or synthetic biologically active compounds (Fig. 1).[1] For example, adecypenol[2] and neplanocin A[3] are polyhydroxycyclopentitol-containing natural products, carbovir and abacavir are powerful nucleoside reverse transcriptase inhibitor used to treat HIV and AIDS, and other cyclopentenylamines act as thromboxane A2 inhibitor and human neurokinin-1 receptor antagonist.[4] As a consequence, direct synthetic approaches to novel di- or polysubstituted cyclopentenes possessing features of simple starting materials and high efficiency, remain of continuous interest and importance.

The most representative strategies adopted to obtain functionalized aminocyclopentenes relies on the transition-metal catalyzed ring-opening/desymmetrization of diazabicyclic alkenes with various nucleophiles,[5] which are versatile synthons for the construction of various functionalized cyclopentenes with extensive structural diversity. On the other hand, directing groups assisted Rh(III)-catalyzed functionalization of sp^2 C—H bond has been well developed owing to its wide application in the rapid constructing of many biointeresting molecular structures,[6,7] which features direct C—H functionalization and avoiding prefunctionalization of substrates.

Recently, Gulías reported an elegant work for the preparation of benzoxepines by the first metal-catalyzed (5+2) cycloaddition between *o*-vinylphenols and alkynes (Scheme 1a).[8] However, the Rh(III)-catalyzed desymmetrization has rarely been investigated.[9] Li reported the pioneering work on the Rh(III)-catalyzed coupling of arenes with 7-oxa/azabenzonorbornadienes via a desymmetrization method.[10] Later, Cui reported another Rh(III)-catalyzed C—H activation-desymmetrization of diazabicycles with arenes, using heterocycles and oximes as directing groups (Scheme 1b).[11] In continuation of our interest in Rh(III)-catalyzed C—H functionalization for the synthesis of biologically interesting small molecules,[12] herein, we report a Rh(III)-catalyzed desymmetrization of diazabicycles with *o*-vinylphenols toward the construction of alkenyl-substituted aminocyclopentenes, with features of easily prepared materials, high efficiency and broad substrate scope (Scheme 1c).

Results and disccusion

We commenced our study by investigating the coupling of 2-vinylphenol **1a** and diazabicycle **2a** with $[Cp^*RhCl_2]_2$ as catalyst. When the reaction was conducted in MeCN at 80 °C for 2 h in conjunction with $Cu(OAc)_2$ as additive, gratifyingly, the expected (2-hydroxy)phenethyl cyclopentenylhydrazine **3aa** was obtained in

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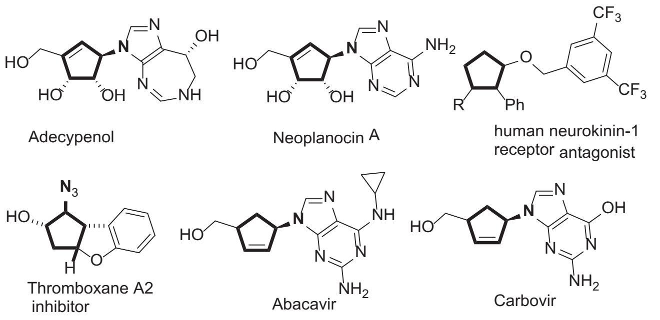
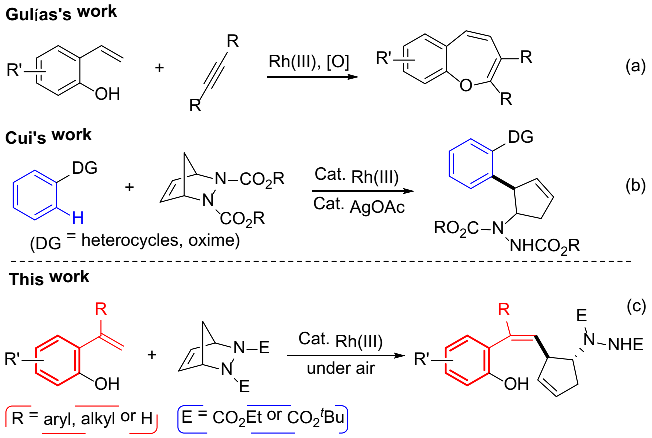


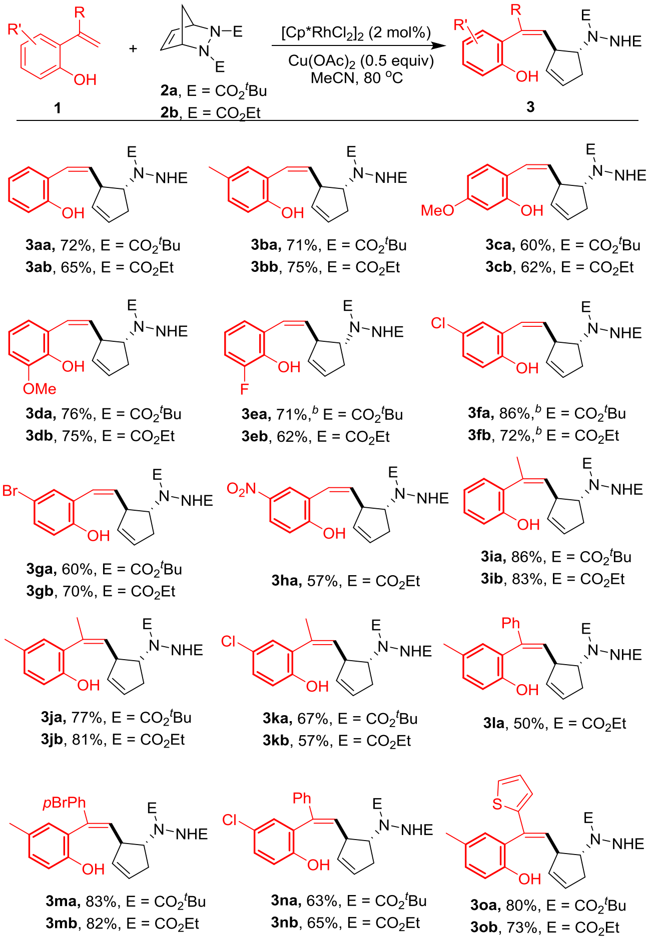
Fig. 1. Selected examples of natural products and drugs containing aminocyclopentanes or aminocyclopentanes.



Scheme 1. Design for Rh(III)-catalyzed ring-opening of diazabicycles using enol as directing group.

65% yield (Table 1, entry 1). This result encouraged us to further optimize the reaction condition. A survey of the additives and solvents showed that the combination of $Cu(OAc)_2$ and MeCN was optimal, and the product could be isolated in 72% yield (Table 1, entry 3). We found that lower $Cu(OAc)_2$ loading would also lead to the formation of product in a comparable yield (Table 1, entry 7), but 0.5 equiv is necessary. Moreover, the reaction could not go to completion at room temperature (Table 1, entry 9), and omission of rhodium completely shut down the reactivity, demonstrating its importance. Of note, the structure of this *cis* disubstituted

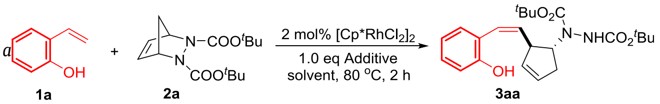
Table 2
Substrate Scope.[a]



[a] Isolated yields are given. Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (0.1 mmol), MeCN (2 mL), 2 h, 80 °C.

[b] DCE as solvent is better.

Table 1
Optimization of the reaction conditions.[a]



Entry	Additive	Solvent	Yield (%)[b]
1	AgOAc	MeCN	65
2	CsOAc	MeCN	14
3	$Cu(OAc)_2$	MeCN	72
4	$Cu(OAc)_2$	MeOH	56
5	$Cu(OAc)_2$	THF	0
6	$Cu(OAc)_2$	DCE	68
7[c]	**$Cu(OAc)_2$**	**MeCN**	**70**
8[d]	$Cu(OAc)_2$	MeCN	55
9[e]	$Cu(OAc)_2$	MeCN	10

[a] Reaction Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), solvent (2.0 mL), $[Cp^*RhCl_2]_2$ (2 mol%) and additive, 80 °C, 2 h.

[b] Yields of isolated products.

[c] 0.5 eq $Cu(OAc)_2$.

[d] 0.3 eq $Cu(OAc)_2$.

[e] Reaction run at room temperature.