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Hydroxy-rhodium(I) catalyzed regioselective Michael addition of cyclic enones

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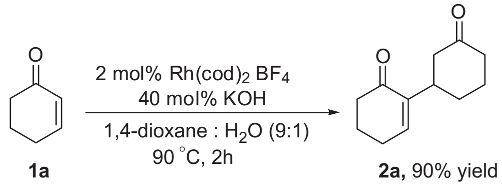
Hydroxy-rhodium catalyzed dimerization of various cyclic enones to the corresponding α-enone adducts is developed. The key feature of this method is that the base-sensitive, highly substituted enones also undergo dimerization and the resultant products are obtained in moderate to good yields.

Transition metal catalyzed carbon–carbon bond formation is a powerful approach in organic synthesis.[1] Varied families of transition metal complexes have been shown to catalyze a diverse array of reactions involving carbon–carbon and carbon-heteroatom bond formation. Among the variety of transition metal catalyzed reactions, rhodium-catalyzed conjugate addition reactions proceed under mild conditions with high regioselectivity as well as good yields.[2] This strategy provides a complement to the frequently used technique that involves a base-catalyzed addition procedure for enones. While examining the rhodium(I)-catalyzed[3] stereoselective 1,4-addition of an arylboronic acid to a cyclic enone **1a** in the presence of 5 mol % of Rh(cod)$_2$BF$_4$ in dioxane/water heating at 100 °C for 2 h., surprisingly, after work-up, together with the expected product 3-phenyl hexanone, a substantial amount of adduct **2a** was also isolated (30%).[3] When the reaction was performed without arylboronic acid under similar conditions, it also resulted in **2a** in a similar yield (30%). In another set of reactions, when the KOH loading was increased to 40 mol %, the reaction proceeded smoothly to yield the required product in a 90% yield (Scheme 1).

When the molar ratio of the Rh catalyst was reduced to 2 mol % and with similar KOH loading (40 mol %), the reaction proceeded smoothly without compromising the yield (90%).[4] The same reaction in the absence of the catalyst under otherwise similar conditions did not yield the desired compound **2a**. Other important methods for the synthesis of enone adduct **2a** that were reported in the literature include employing inorganic bases,[5] organic bases,[6] and a phase transfer catalytic method.[7]



Scheme 1. Hydroxy-rhodium catalyzed regioselective dimerization of cyclohexenone.

Among the solvents surveyed, dioxane/water turned out to be the solvent of choice (Table 1). Aqueous 1,2-dichloroethane and toluene did not yield the desired product **2a**. Interestingly, experiments were conducted with other metal salts (RuCl$_3$, CuCl$_2$, CuCl, CuBr, CuI and FeCl$_2$, and PdCl$_2$) as the catalyst in combination with KOH for this transformation, but none could catalyze the desired reaction, whereas RhCl$_3$·H$_2$O/KOH initiated the reaction and the corresponding product **2a** was obtained albeit in low yield (50%). The pre-catalyst system generated with 2 mol % of Rh(cod)$_2$BF$_4$/LiOH also showed comparable activity toward the synthesis of **2a**.

To check the generality of this protocol, the experiment was extended to various enone substrates under optimized conditions, and the results are summarized in Table 1.

Five-substituted cyclohexenone **1b** and **1c** smoothly underwent dimerization and gave the desired products **2b** and **2c** with 85% and 70% yields (Table 1, entries 1 & 2), respectively. Similarly, 5-(4-methylphenyl) cyclohexenone **1d** and 5-(4-methoxyphenyl) cyclohexenone **1e** were subjected to standard protocol and the respective products **2b**, **2c** were furnished in good yield (Table 1,

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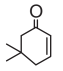
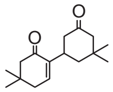
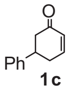
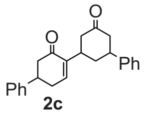
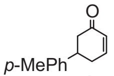
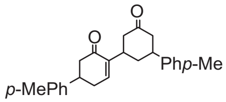
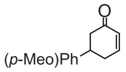
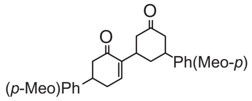
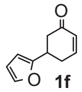
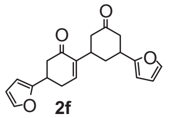
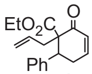
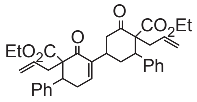
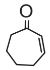
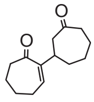
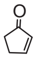
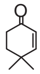
Table 1
Hydroxy-rhodium catalyzed dimerization of various cyclic enones to the corresponding α-enone adducts

Entry	Substrate	Product[a,b]	Time/h	% Yield
1	 **1b**	 **2b**	2	85
2	 **1c**	 **2c**	3	70
3	 **1d**	 **2d**	3	85[d]
4	 **1e**	 **2e**	2	88[d]
5	 **1f**	 **2f**	3	65[d]
6	 **1g**	 **2g**	3	68[d]
7	 **1h**	 **2h**	2	73
8	 **1i**	NR[c]		
9	 **1j**	NR[c]		

[a] All reactions were carried out in 1 mmol scale with 2 mol % of $Rh(cod)_2BF_4$, in dioxane/H_2O (9:1).

[b] Yields refer to isolated after column chromatography.

[c] NR = No reaction.

[d] Diastereoselectivity was not determined.

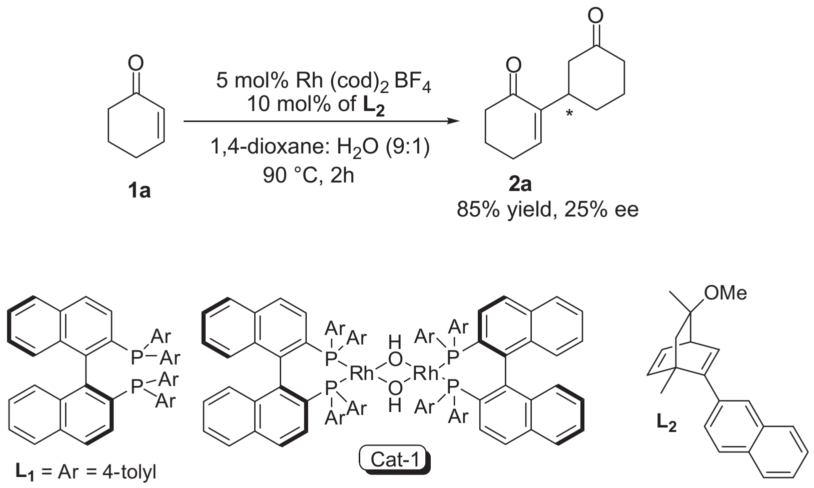
entries 3 & 4). Heteroaromatic five-substituted cyclohexenone **1f** as well resulted in Baylis–Hillman adduct **2f** in moderate yield (Table 1, entry 5). Ester containing 5,6-disubstituted cyclohexenone **1g** tolerated the reaction conditions and the desired product **2g** was afforded in a 68% yield (Table 1, entry 6). However, we did not succeed in obtaining dimerized α-enone adducts of cyclopentenone **1i** and 4,4-dimethyl cyclohexenone **1j** under the optimized conditions (Table 1, entries 8 & 9). In the case of **1i**, the substrate appears to undergo polymerization under the reaction conditions. In the case of **1j**, presumably, the proton abstraction of Rh-enolate of dimeric intermediate (**C**, Scheme 3) could not be achieved due to restricted conformation thereby making the catalytic cycle unfeasible.

Having identified the suitable conditions, we have focused our efforts on obtaining asymmetric induction in the above reaction by means of chiral diphosphines $\mathbf{L_1}$, **Cat-1** and chiral diene $\mathbf{L_2}$ as chiral inducers. To this end, cyclic enone **1a** in the presence of 5 mol % of $Rh(cod)_2BF_4$ and 10 mol % of $\mathbf{L_1}$ in dioxane/water heating 90 °C for 1 h resulted in **2a** as racemic in an 83% yield. Replacing $\mathbf{L_1}$ and $Rh(cod)_2BF_4$ with **Cat-1** under otherwise identical conditions that lead to the desired product **2a** with 15% ee and a 75% yield. Slight increase in the ee value of **2a** (25% ee)[8] was observed, while employing 10 mol % of $\mathbf{L_2}$[9] along with 5 mol % of $Rh(cod)_2BF_4$ under typical conditions (Scheme 2).

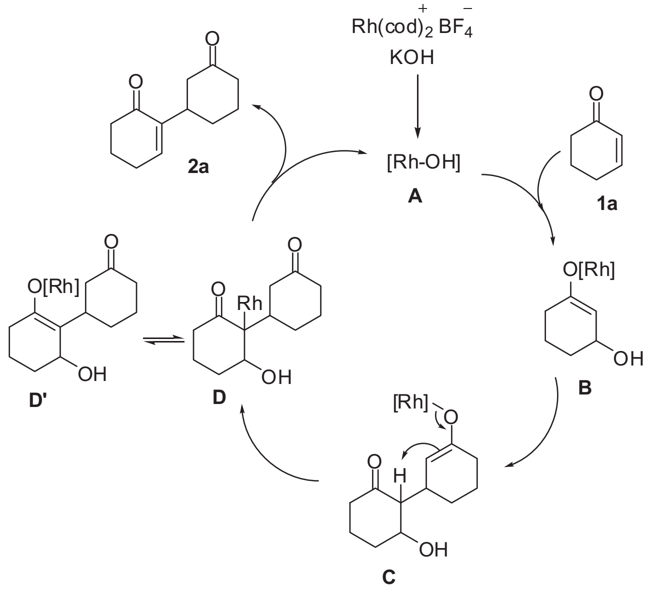
A plausible mechanism to rationalize the observed transformation is shown in Scheme 3.

Initially, the cationic Rh(I) in the presence of KOH generates Rh-OH **A** which could insert enone double bond **1a** resulting in vinylogous Rh-enolate **B**. The Rh-enolate **B** on electrophilic attack on a second molecule of enone could generate **C**, followed by the abstraction of proton giving rise to **D** which upon β-hydroxyelimination leads to the Baylis–Hillman adduct **2a**.

In conclusion, we have developed a practical procedure for the synthesis of cyclic α-enone adducts. This efficient protocol is



Scheme 2. Asymmetric hydroxy-rhodium catalyzed regioselective dimerization of cyclohexenone.



Scheme 3. A plausible mechanism of regioselective dimerization of cyclohexenone.

initiated with 2 mol % of Rh(I) catalyst and it also facilitates rapid synthesis of various dimerized enone adducts possessing pharmacophores which could be screened for biological activity.[10] Presently, this methodology, presently restricted to the dimerization of six and seven-membered cyclic enones, to the best of our knowledge, there is no report wherein, the Rh-OH pre-catalyst performing the carbon–carbon bond formation α- to enone. Further work is under progress for efficient enantioselective catalytic version.

Acknowledgments

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Supplementary data

Supplementary data associated (analytical data and copies of spectra's of 2**a**–**h**) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.057.

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4. *Typical reaction procedure for the synthesis of* ***2a***: Two-necked flask (10 mL) equipped with a septum, magnetic stir bar, condenser, and a three-way stopcock connected to nitrogen-balloon system and subjected to evacuated protocol was charged with Rh(I)(cod)$_2$BF$_4$ (9 mg, 0.02 mmol). To this, 2 ml of 1,4-dioxane and water (9:1) was added followed by cyclohexenone (1 mmol). The resulting reaction mixture was stirred for 5 min and KOH solution (2 M, 20 μL, 0.41 mmol) is added. The combined contents were heated to 90 °C for 2 h. Thereafter, the reaction was cooled to ambient temperature and filtered through a plug of Celite and washed with EtOAc (3 × 5 mL). The filtrate was concentrated under reduced pressure to give crude residue which was purified by silica gel column chromatography eluting with hexane/EtOAc (9:1) furnished **2a** 174 mg (90%) as dense liquid.
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