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Highly Enantioselective Syntheses of Functionalized α-Methylene-γ-butyrolactones via Rh(I)-catalyzed Intramolecular Alder Ene Reaction: Application to Formal Synthesis of (+)-Pilocarpine

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The α-methylene-γ-butyrolactone unit is an important motif of many natural products, such as (+)-pilocarpine, (+)-isopilocarpine, and (+)-isopilosine.[1] The exocyclic double bond is considered not only to be responsible for the interesting biological properties of γ-lactones but also to serve as a functional group for further manipulations in organic synthesis.[2] (+)-Pilocarpine, one of the most important imidazole alkaloids, serves as the leading therapeutic reagent in the treatment of narrow- or wide-angle glaucoma.[3] Due to its extensive pharmacological properties such as diaphoretic effects, miotic action, and particular application in ophthalmology,[4] considerable effort has been devoted to its synthetic studies.[5] In the synthesis of (+)-pilocarpine reported by Büchi, the key intermediate (4*R*)-(*Z*)-dehydrohomopilopic aldehyde was obtained in five steps from 2-acetylbutyrolactone in 92% ee and 20% overall yield (Scheme 1).[5b]

Several reviews on the synthesis of α-methylene-γ-butyrolactones have been published.[6] Most of them focus on the formation of the C−O bond to construct the γ-lactone unit. Recently, palladium (II)-catalyzed C−C formation via carbocyclization of enynes to form γ-lactones has shown its potential efficiency.[7] Extensive studies on transition metal-catalyzed Alder ene reactions have also been carried out.[8] However, only a Rh(I) system has been used to make γ-lactones.[9] Furthermore, there are only few examples dealing with the formation of chiral γ-lactones.[10] Herein we report a highly enantioselective Rh-catalyzed intramolecular Alder ene reaction for the synthesis of functionalized γ-lactones.

We previously reported a novel procedure using $[RhL_2Cl]_2$ as the catalyst precursor in a Rh-catalyzed Alder ene reaction.[9,11] It was found that the conversion is low when BINAP was used as the ligand. To make γ-lactones, we investigated the Rh(I)-catalyzed Alder ene reaction of **1a** and found that the reactivity is low with $[Rh(rac\text{-BINAP})Cl]_2$ as the precursor (Table 1, entry 1). However, when the reaction was heated at 65 °C, 100% conversion and 65% isolated yield were obtained (Table 1, entry 2). Furthermore, high yields and reactivities were also achieved when the catalyst was prepared in situ at 65 °C or room temperature (rt) (Table 1, entries 3−4). When other cationic rhodium precursors were used at rt, no product was detected (Table 1, entries 5−8). Addition of cyclooctadiene is found to inhibit the reaction (Table 1, entries 9−10).

The asymmetric Rh-catalyzed Alder ene reactions were carried out in the presence of $[Rh(COD)Cl]_2$, (*R*)- or (*S*)-BINAP, and $AgSbF_6$ at rt. Extraordinarily high enantioselectivity (>99% ee) and high yields (90−98%) were obtained for a wide range of substituents (Table 2, entries 1−8).

To further extend the utility of our methodology, we introduced various functional groups at the allylic position (Table 3). If R^2 is an acetyl group, the desired product is a vinyl acetate-substituted γ-lactone. If R^2 is an alkyl group, a vinyl ether is the corresponding product. Due to the wide applications of vinyl acetates and vinyl ethers, this transformation is particularly interesting and valuable for organic synthesis. All of the reactions in Table 3 were completed within 5 min at rt. Both vinyl acetate and vinyl ether-substituted γ-lactone were formed in high yields (91−98%) with excellent enantioselectivities (>99%) (Table 3, entries 1−11).

When the substrates with alcohol at allylic position **5** were used, the resulting products **6** contained an aldehyde. Again, high yields (91−99%) and enantioselectivities (>99%) were obtained (Table 4, entries 1−5). Further study shows the reaction of **5c** takes place smoothly with 2% catalyst loading without compromising the enantioselectivity. The aldehyde (*R*)-(+)-**6a** is especially interesting since it is the key intermediate in Büchi's synthesis of (+)-pilocarpine.[5b] To determine the absolute configuration, we have correlated the product **6a** with the literature results by determining the optical rotation [(+)-**6a** has *R*-configuration].[5b]

A formal synthesis of (+)-pilocarpine is an excellent example to demonstrate the synthetic utility of our method for making functionalized γ-lactones. In comparison to Büchi's synthesis,[5b] a

Scheme 1. Synthesis of (+)-Pilocarpine

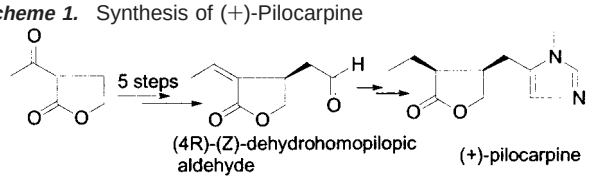
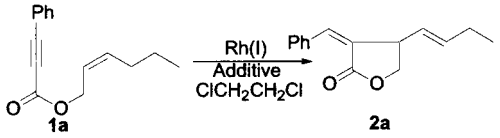


Table 1. Rh-catalyzed Alder Ene Reaction of **1a**[a]



entry	Rh(I)	temp	additive	time	conv.(%)[b,c]
1	$[Rh(rac\text{-BINAP})Cl]_2$	rt	$AgSbF_6$	1 h	0
2	$[Rh(rac\text{-BINAP})Cl]_2$	65 °C	$AgSbF_6$	12 h	100(65)
3	$[Rh(COD)Cl]_2$/*rac*-BINAP	65 °C	$AgSbF_6$	10 min	>99(90)
4	**$[Rh(COD)Cl]_2$/*rac*-BINAP**	**rt**	**$AgSbF_6$**	**10 min**	**95(92)**
5	$Rh(COD)_2SbF_6$/*rac*-BINAP	rt	none	10 min	0
6	$Rh(NBD)_2SbF_6$/*rac*-BINAP	rt	none	10 min	0
7	$Rh(COD)_2PF_6$/*rac*-BINAP	rt	none	10 min	0
8	$Rh(NBD)_2BF_4$/*rac*-BINAP	rt	none	10 min	0
9	$[Rh(COD)Cl]_2$/*rac*-BINAP	rt	100 mol % COD $AgSbF_6$	10 min	0
10	[Rh(COD)Cl]2/*rac*-BINAP	rt	10 mol % COD $AgSbF_6$	10 min	<2

[a] All reactions were performed using 10 mol % Rh(I) and12 mol % *rac*-BINAP in 0.2 mmol scale. [b] Conversion was detected by GC, and isolated yield is in parentheses. [c] The stereochemistry of **2a** was established by NOE.

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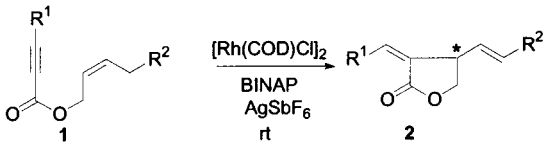
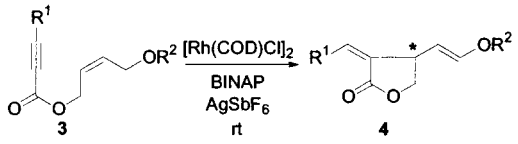
Table 2. Asymmetric Rh(I)-Catalyzed Intramolecular Alder Ene Reaction[a]



	substrate				product		
entry	1	R^1	R^2	BINAP	**2**[d]	yield(%)[b]	ee (%)[c]
1	**1a**	Ph	Et	*S*-BINAP	(*S*)-(+)-**2a**	93	>99
2	**1b**	Ph	H	*R*-BINAP	(*R*)-(−)-**2b**	94	>99
3	**1c**	Ph	Me	*R*-BINAP	(*R*)-(−)-**2c**	92	>99
4	**1c**	Ph	Me	*S*-BINAP	(*S*)-(+)-**2c**	93	>99
5	**1d**	Me	H	*R*-BINAP	(*R*)-(−)-**2d**	92	>99
6	**1e**	Me	Me	*R*-BINAP	(*R*)-(−)-**2e**	98	>99
7	**1f**	*n*-C_5H_{11}	H	*S*-BINAP	(*S*)-(+)-**2f**	90	>99
8	**1g**	*n*-C_5H_{11}	Me	*S*-BINAP	(*S*)-(+)-**2g**	95	>99

[a] All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrate/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1:0.05:0.11:0.20. This reaction finished within 2−10 min. [b] Isolated yield. [c] ee value was detected by GC or HPLC. [d] (*R*) and (*S*) were compared with known compounds **6a**.

Table 3. Asymmetric Rh(I)-Catalyzed Alder Ene Reactions of **3** to Form Functionalized Lactones[a]



	substrate				product		
entry	3	R^1	R^2	BINAP	**4**[d]	yield (%)[b]	ee (%)[c]
1	**3a**	Ph	Ac	*R*-BINAP	(*R*)-(−)-**4a**	96	>99
2	**3b**	Ph	Me	*S*-BINAP	(*S*)-(+)-**4b**	96	>99
3	**3c**	Ph	Bn	*S*-BINAP	(*S*)-(+)-**4c**	92	>99
4	**3d**	Me	Ac	*R*-BINAP	(*R*)-(−)-**4d**	93	>99
5	**3d**	Me	Ac	*S*-BINAP	(*S*)-(+)-**4d**	98	>99
6	**3e**	Me	Me	*S*-BINAP	(*S*)-(−)-**4e**	95	>99
7	**3f**	Me	Bn	*S*-BINAP	(*S*)-(+)-**4f**	91	>99
8	**3 g**	*n*-C_5H_{11}	Ac	*S*-BINAP	(*S*)-(+)-**4g**	97	>99
9	**3h**	*n*-C_5H_{11}	Me	*S*-BINAP	(*S*)-(−)-**4h**	96	>99
10	**3i**	*n*-C_5H_{11}	Bn	*R*-BINAP	(*R*)-(−)-**4i**	91	>99
11	**3i**	*n*-C_5H_{11}	Bn	*S*-BINAP	(*S*)-(+)-**4i**	92	>99

[a] All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrate/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1: 0.05:0.11:0.20. This reaction finished within 2−10 min. [b] Isolated yield. [c] ee value was detected by GC or HPLC. [d] (*R*) and (*S*) were compared with known compounds **6a**.

two-step synthesis from commercially available 2-butynic acid and (*Z*)-2-buten-1,4-diol using our method provided the intermediate (*R*)-(+)-**6a** in over 99% ee and 91% overall yield. (+)-Pilocarpine can be prepared in two additional steps from (*R*)-(+)-**6a** according to the literature method (Scheme 1). [5b]

In conclusion, we developed an atom-economic, highly efficient Rh(I)-catalyzed intramolecular Alder ene reaction, by which various functionalized α-methylene-γ-butyrolactones were formed in high yields with over 99% ee. Highly enantioselective syntheses of functionalized carbocycles and heterocycles such as lactams, pyrroles, and *tetra-H*-furans are currently in progress.

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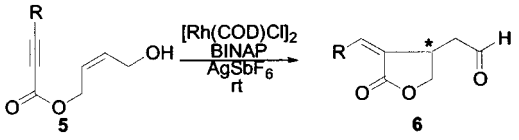
Table 4. Asymmetric Rh(I)-Catalyzed Alder Ene Reactions of **5** to Form Aldehyde Substituted Lactones[a]



entry	R	5	BINAP	**6**[d]	yield(%)[b]	ee(%)[c]
1	Me	**5a**	*R*-BINAP	(*R*)-(+)-**6a**	99	>99
2	Me	**5a**	*S*-BINAP	(*S*)-(−)-**6a**	98	>99
3	*n*-C_5H_{11}	**5b**	*S*-BINAP	(*S*)-(−)-**6b**	95	>99
4	Ph	**5c**	*R*-BINAP	(*R*)-(+)-**6c**	92	>99
5	Ph	**5c**	S−BINAP	(*S*)-(−)-**6c**	91	>99

[a] All the reactions were carried out in 2 mL of $ClCH_2CH_2Cl$ in 0.2 mmol scale. The ratio of substrates/$[Rh(COD)Cl]_2$/BINAP/$AgSbF_6$ was 1: 0.05:0.11:0.20. This reaction finished within 2−10 min. [b] Isolated yield. [c] ee value was detected by GC. [d] (*R*) and (*S*) were compared with known compounds **6a**.

Supporting Information Available: Spectroscopic data, GC, HPLC spectra, and experiments details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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