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First rhodium/phosphoramidite complex-catalyzed enantioselective isomerization of allylic alcohols into aldehydes

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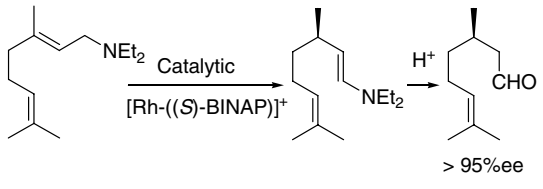
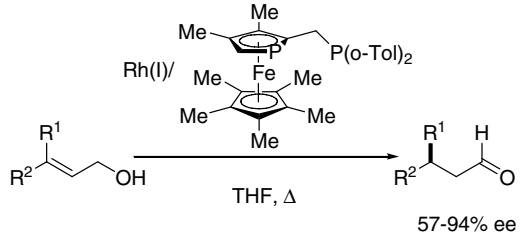
Abstract—Primary allylic alcohols are converted into chiral aldehydes in the presence of a catalytic amount (7 mol %) of a monodentate phosphoramidite rhodium catalyst. The aldehydes are isolated in high yields (84–89%) and moderate to good ee's (38–70%). A preliminary mechanistic study showed that the reaction proceeds through a 1,3-H migration pathway.

The double bond enantioselective isomerization of an allylic amine, allylic ether or allylic alcohol is a powerful reaction. A very efficient process was developed two decades ago starting from allylic amines.[1] It proved to be particularly useful as it has been applied at an industrial scale for the synthesis of (−)-menthol (Scheme 1).[1b]

The version starting from allylic alcohol is very interesting as it is a full atom economy process.[2] But, this reaction appears somewhat difficult to achieve efficiently. Indeed, while the racemic version was extensively studied,[3] the asymmetric version was less studied and the results obtained in term of reactivity and enantioselectivity were moderate[3,4] until the recent results reported by Fu.[5] Fu reported a very efficient isomerization reaction of primary allylic alcohols to aldehydes using Rh/phosphaferrocene complexes (Scheme 2) and consequently made an outstanding breakthrough.



Scheme 1. Enantioselective isomerization of diethylgeranylamine catalyzed by Rh–BINAP complex.



Scheme 2. Enantioselective isomerization of allylic alcohols to aldehydes using a Rh/phosphaferrocene complex.

More recently, Ikariya reported a novel asymmetric isomerization via Cp*Ru(PN) catalyzed kinetic dynamic resolution of secondary allylic alcohols. Optically active ketones were isolated with decent ee's (62–74%).[6] Nevertheless, it remains interesting to find alternate readily accessible, cheap ligands that can perform the reaction and extend its scope.

Phosphoramidites proved to be particularly efficient in a wide range of catalyzed reactions such as Rh-catalyzed hydrogenation of olefins,[7] Cu-catalyzed asymmetric conjugate addition of diorganozinc reagents,[8] Pd-catalyzed enantioselective hydrosilylation of alkenes,[9] Ir-catalyzed enantioselective allylation of ketone enolates.[10] Moreover, these are easily tunable and accessible ligands and their use in the isomerization of allylic alcohols is at the present time not described in the literature.

We started a study to evaluate the efficiency of this class of ligands in the enantioselective isomerization of allylic alcohols and we are reporting here that the monodentate

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ligand **L1** (Fig. 1) performs efficiently the reaction. Indeed, optically active aldehydes are isolated with decent ee's.

Allylic alcohols **1**–**5** were first synthesized according to known procedures (Ref. 5 and references cited therein). Ligands **L1**[11] and **L2**[12] were synthesized following the procedure described in the literature. The catalyst was prepared by adding two equivalents of the monodentate ligand to commercial $Rh(COD)_2BF_4$ followed by hydrogenation (1 atm) of the solution.[13] To the catalyst solution thus obtained was then added the substrate.

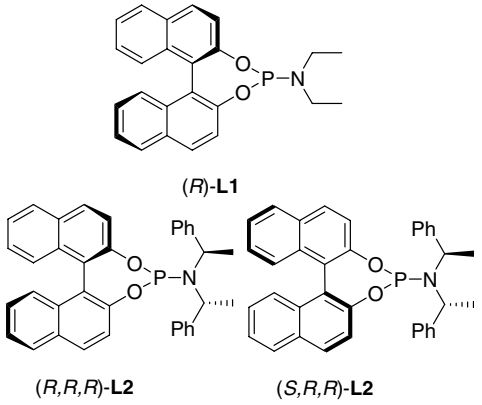


Figure 1. Monodentate phosphoramidite ligands **L1** and **L2**.

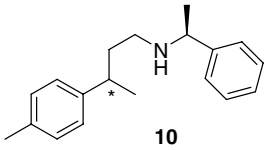
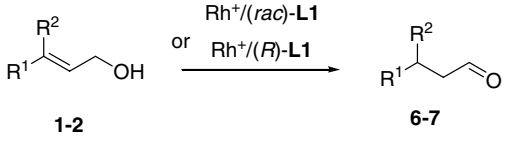


Figure 2. Amine **10**.



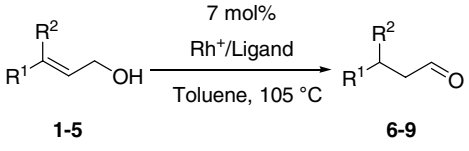
Scheme 3. Determination of optimal conditions.

The optimal conditions for the reaction were first determined using alcohol **1** or **2** as the substrate and (*rac*)-**L1** or (*R*)-**L1** as the ligand (Scheme 3 and Table 1). Toluene as the solvent, a temperature of 105 °C and 7 mol % of Rh proved to be the optimal condition.[16] In such conditions, Alcohol **1** was completely converted into aldehyde **6**, which was isolated in a very good yield (87%) and an encouraging (64%) ee (entry 6). The reaction can be completed with only 3 or 5 mol % of the catalyst (entries 7–9). Nevertheless, using such an amount of catalyst led to an increase of the reaction duration. For instance, the reaction was completed after 72 h when 5 mol % was used, but only 31% and 45% conversions were, respectively, obtained after 24 and 48 h. For this reason, we decided to use 7 mol % of the catalyst for further experiments.

Various allylic alcohols were then screened to evaluate the scope of the reaction (Scheme 4 and Table 2). In each case, a total conversion was obtained after 30 h and the aldehyde was isolated in high yield. The reactivity and the ee were not affected by the nature of the substituents (alkyl–aryl (entries 1, 4 and 5) or alkyl–alkyl (entry 2)) on the double bond.

Aldehydes were isolated with encouraging ee's starting from (*E*) allylic alcohols, while the opposite enantiomer was obtained with a moderate ee when the (*Z*) isomer **3** was used (entry 3). This observation is in agreement with the results obtained by Fu.[5]

We then tried to increase the enantioselectivity by using ligand (*R*,*R*,*R*)-**L2** bearing a chiral amine element. It has indeed been observed that the presence of a chiral amine can have a dramatic effect on the enantioselectivity in some metal-phosphoramidite catalyzed reactions.[8,9] When allylic alcohol **1** was reacted in the presence of 10 mol % of Rh and (*R*,*R*,*R*)-**L2** ligand, a conversion of only 30% was observed after 96 h at 105 °C. Moreover, the aldehyde was isolated as an almost racemic mixture (7% ee). A similar result was obtained with the diastereo-



Scheme 4. Extension to various aldehydes.

Table 1. Determination of optimal conditions via Scheme 3

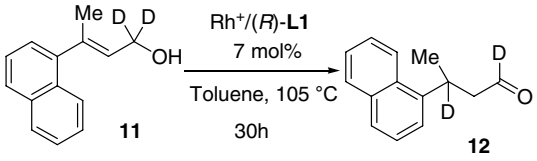
Entry	R^1	R^2	Ligand	Solvent	Temperature (°C)	Rhodium amount (mol %)	Duration (h)	Conversion (%)[a]	Yield (%)
1	Ph	*i*-Pr	(*rac*)-**L1**	THF	65	5	24	11	
2	Ph	*i*-Pr	(*rac*)-**L1**	THF	85	10	14	55	
3	Ph	*i*-Pr	(*rac*)-**L1**	Dioxane	25	10	24	0	
4	Ph	*i*-Pr	(*rac*)-**L1**	Dioxane	105	10	24	31	
5	Ph	*i*-Pr	(*rac*)-**L1**	Toluene	110	10	24	100	
6	Ph	*i*-Pr	(*R*)-**L1**	Toluene	105	7	30	100	87
7	Ph	*i*-Pr	(*R*)-**L1**	Toluene	105	5	24	31	
8	Ph	*i*-Pr	(*R*)-**L1**	Toluene	105	5	72	100	74
9	Cy	Me	(*R*)-**L1**	Toluene	105	3	72	100	68

[a] The reaction conversion was obtained from GC analysis on a HP-1 column and ^1H NMR.

Table 2. Extension to various allylic alcohols via Scheme 4

Entry	R^1	R^2	Alcohol	Ligand	Duration (h)	Conversion (%)	Aldehyde	Isolated yield (%)	ee %
1[a]	Ph	*i*-Pr	**1**	(*R*)-**L1**	30	100	**6**	87	70 (*R*)
2[b]	Cy	Me	**2**	(*R*)-**L1**	30	100	**7**	84	66 (*R*)
3[a]	*i*-Pr	Ph	**3**	(*R*)-**L1**	30	100	**6**	85	38 (S)
4[c]	*p*-Tol	*i*-Pr	**4**	(*R*)-**L1**	30	100	**8**	86	60 (*R*)
5[a]	Ph	Me	**5**	(*R*)-**L1**	30	100	**9**	89	64 (*R*)
6	Ph	*i*-Pr	**1**	(*R*,*R*,*R*)-**L2**	96	30[d]	**6**	—	7 (*R*)
7[a]	Ph	*i*-Pr	**1**	(*S*,*R*,*R*)-**L2**	96	30[d]	**6**	—	6 (*R*)

[a] The ee was analyzed on a Lipodex E column (25 m).
[b] The ee was analyzed on a Chiraldex G-TA column (30 m).
[c] The ee was analyzed from NMR analysis after conversion of the enantiomeric mixture to the diastereoisomeric mixture of amine **10**.[17]
[d] 10 mol % of the catalyst was used.



Scheme 5. Reaction of labelled compound **11**.

isomeric (*S*,*R*,*R*)-**L2** ligand. This disappointing result shows that the efficiency of the reaction is dramatically decreased by a sterically demanding ligand.

Finally, we started preliminary mechanistic studies. The 1,1-dideuterated allylic alcohol **11** was synthesized according to known procedures.[5] Then, it was reacted with 7% catalyst. A clean formation of aldehyde **12** was observed. Compound **12** bears a deuterium atom on C-sp^2 carbon and more interestingly a second deuterium atom on C-3 carbon (Scheme 5).[18] This result demonstrates that the reaction proceeds through a 1,3-H migration pathway.

To conclude, we demonstrate for the first time that phosphoramidites are valuable ligands for the enantioselective Rh-catalyzed isomerization of allylic alcohols to chiral aldehydes. The isolated yields are high and the ee's encouraging. The search for better mono- and bidentate phosphoramidite ligands for this isomerization reaction is now actively underway.

Acknowledgements

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16. General procedure for the isomerization of allylic alcohols using rhodium/phosphoramidite complex catalysts: In a N_2-filled glovebox, a solution of monodentate phosphoramidite (0.04 mmol) in toluene (2 mL) was added to a stirred suspension of $[Rh(COD)_2]BF_4$ (8 mg, 0.02 mmol) in toluene (2 mL), and the resulting yellow solution was stirred for 15 min at room temperature. The catalyst solution was taken out of the glovebox and after three vacuum/H_2-refill cycles, the solution was stirred for 1 h at room temperature. Then, under an argon atmosphere, allylic alcohol (0.285 mmol) in toluene (3 mL) was added to the catalyst solution and the reaction mixture was stirred for 30–35 h at 105 °C. The solution was then concentrated, and the product was purified by silica gel column chromatography to give the chiral aldehyde.
17. Amine **10** (Fig. 2) was obtained from aldehyde **8** by a reductive amination process using (*S*)-α-methylbenzylamine and $NaBH(OAc)_3$.
18. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 3H, CH_3), 2.74 (d, 1H, $J = 16$ Hz, CH_2), 2.85 (d, 1H, $J = 16$ Hz, CH_2), 7.25–7.82 (m, 7H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 34.4 (t, $J = 20.0$ Hz), 51.8 (t, $J = 3.6$ Hz), 125.4, 125.8, 126.0, 126.2, 126.5, 128.0, 128.0, 128.8, 132.7, 134.0, 143.2, 202.0 (t, $J = 26.0$ Hz); HRMS (EI): calcd for $C_{14}H_{12}D_2O$ (M^+): 200.1170, found: 200.1159.