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Highly Enantioselective Asymmetric Isomerization of Primary Allylic Alcohols with an Iridium–N,P Complex

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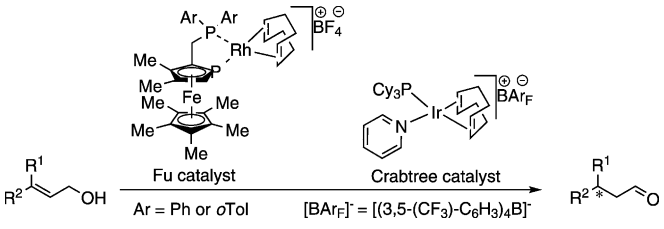
The asymmetric transformation of allylic amines to optically active enamines, catalyzed by rhodium-BINAP complexes, has been well studied and even applied in industry.[1] The related transition-metal-catalyzed isomerization of primary allylic alcohols is an atom-economical route to the corresponding aldehydes (Scheme 1). Various catalysts have



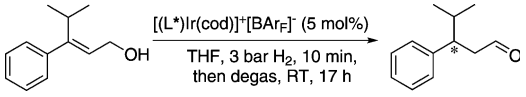
Scheme 1. Asymmetric isomerization of a primary allylic alcohol.

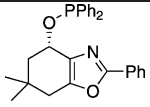
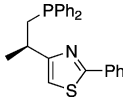
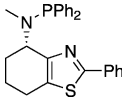
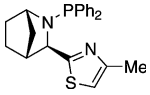
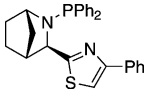
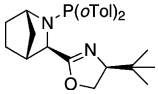
been developed for this reaction,[2] however, only a few asymmetric examples have been reported. Fu and co-workers obtained appreciable results using planar-chiral phosphaferrocene-based rhodium catalysts.[3] In 2009, Mazet and co-workers showed that Crabtree's catalyst isomerized a wide range of primary allylic alcohols.[4] They later developed three generations of chiral phosphine-oxazoline-based iridium-N, P catalysts that displayed high activities and selectivities in the asymmetric version of this reaction.[5] Recently, Quintard, Alexakis, and Mazet used the iridium-catalyzed asymmetric isomerization of primary allylic alcohols in sequence with the chiral-enamine-catalyzed functionalization of aldehydes to access α,β-chiral aldehydes with excellent diastereo- and enantioselectivity.[6]

The N,P-ligated iridium catalysts developed by Mazet and co-workers give excellent selectivities in the asymmetric isomerizations of *E*-trisubstituted primary allylic alcohols, but only moderate enantiomeric excess (*ee*) values for *Z*-trisubstituted and 3,3-dialkyl allylic alcohols. The similarities between Mazet's catalysts and those that perform well in the asymmetric olefin hydrogenation,[7] prompted us to apply the iridium-N,P complexes $[(L^*)Ir(cod)]^+[BAr_F]^-$ ($L^* = \mathbf{A}$–**F**, Table 1), which were developed in our group for that purpose,[8] to the asymmetric isomerization of allylic alcohols. The result was a highly enantioselective isomerization of both *E*- and *Z*-trisubstituted primary allylic alcohols to the corresponding chiral aldehydes.

We chose (*E*)-4-methyl-3-phenylpent-2-en-1-ol for the test substrate with which to screen our catalysts (Table 1). Catalysts with ligands **A**–**D** showed little activity for asymmetric isomerization (Table 1, entries 1 to 4). Surprisingly, a moderate yield and high enantioselectivity were delivered with the catalyst bearing Ligand **E** (Table 1, entry 5), despite its simi-

Table 1. Screening of catalysts for the asymmetric isomerization of (*E*)-4-methyl-3-phenylpent-2-en-1-ol.



Entry[a]	L*		Yield[b] [%]	*ee*[c] [%]
1		**A**	<5	n.a.[d]
2		**B**	<5	n.a.[d]
3		**C**	<5	n.a.[d]
4		**D**	<5	n.a.[d]
5		**E**	43	>99 (*S*)
6		**F**	88	>99 (*S*)

[a] Each result is the average from two reactions. [b] Isolated product yields. [c] Determined by chiral GC/MS. Absolute configurations were determined by comparing optical rotations to literature values (see Ref. [3b]). [d] Not applicable.

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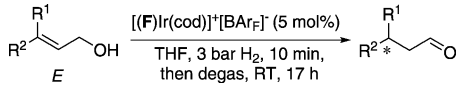
larities with **C** and **D**. Ligand **E** differs from **C** by virtue of its bulky bicyclic backbone, and from **D** in that it bears a bulkier phenyl group rather than a methyl group on the thiazole moiety. This is consistent with the observations of Mazet and co-workers that the reaction is highly sensitive to the catalyst structure,[9] hence the steric accessibility of the catalysts could be crucial to our system. A catalyst made from an even bulkier ligand **F** gave high yield while maintaining a high enantioselectivity (>99% *ee*, Table 1, entry 6) and was therefore tested in the isomerization of a broad range of primary allylic alcohols.

E-trisubstituted allylic alcohols were evaluated first (Table 2). Aromatic allylic alcohols with bulky alkyl substituents ($R^1 = i$Pr and Cy) gave excellent yields, as well as high enantioselectivities (Table 2, entries 1 and 2). An aromatic allylic alcohol with a linear alkyl group on the double bond (R^1 = Et) was isomerized with a similar enantioselectivity (97% *ee*), but the yield decreased dramatically (Table 2, entry 3). When the substituent was even smaller (R^1 = Me), the enantioselectivity was only marginally affected, but the aldehyde was recovered in poor yield (Table 2, entry 4). Thus the catalytic asymmetric isomerization of an allylic alcohol was significantly impacted by the size of its substituents (R^1). An aromatic group was not required, as a series of 3,3-dialkyl allylic alcohols were isomerized as well. Just as was the case for aromatic allylic alcohols, 3,3-dialkyl allylic alcohols with larger substituents were isomerized more effectively (Table 2, entries 5–8).

More challenging *Z*-trisubstituted allylic alcohols were isomerized using the same catalyst (Table 3). Aromatic allylic alcohols, interestingly, supplied the desired aldehydes in uniformly high enantioselectivities, regardless of the steric properties of their substituents (Table 3, entries 1–4). Yields were moderate for these substrates except when a very small substituent was present on the double bond (R^2 = Me, Table 3, entry 1), the yield was observed to be poor. The isomerization of 3,3-dialkyl allylic alcohols was also attempted. Nerol was a challenging substrate (Table 3, entry 5), but a substrate with a larger substituent (*Z*)-3-cyclohexylbut-2-en-1-ol was isomerized to the corresponding aldehyde in moderate yield and with excellent enantioselectivity (Table 3, entry 6).

In summary, $[(\mathbf{F})\mathrm{Ir(cod)}]^+[\mathrm{BAr_F}]^-$ catalyzed a highly enantioselective asymmetric isomerization of a range of *E*- and *Z*- trisubstituted primary allylic alcohols to the corresponding chiral aldehydes. Notably, the selectivity of this catalyst was less sensitive to steric effects in the asymmetric isomerization of *Z*-trisubstituted allylic alcohols than *E*-trisubstituted compounds.

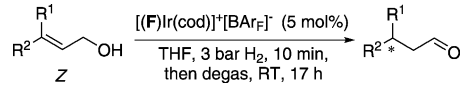
Table 2. Asymmetric isomerization of *E*-trisubstituted primary allylic alcohols.



Entry[a]	R^1	R^2	Yield[b] [%]	*ee*[c] [%]
1	Cy	Ph	86	>99 (*S*)
2	*i*Pr	Ph	88	>99 (*S*)
3[d]	Et	Ph	21	97 (*R*)
4[d]	Me	Ph	<5	91 (*R*)
5[d]	Me	$(CH_3)_2C{=}CH(CH_2)_2$	11	94 (*S*)
6[d]	Me	*t*BuCH$_2$	24	95 (*S*)
7	Me	Cy	79	96 (*R*)
8	Me	*t*Bu	40	>99 (*R*)

[a] Each result is the average from two reactions. No *E*/*Z* isomerization of the allylic alcohols was detected. [b] Isolated product yields. [c] Determined by chiral GC/MS. Absolute configurations were determined by comparing the optical rotations of the product to literature values (for details, see the Supporting Information). [d] Trace amounts of the α,β-unsaturated aldehyde were observed (ref. [3b]).

Table 3. Asymmetric isomerization of *Z*-trisubstituted primary allylic alcohols.



Entry[a]	R^1	R^2	Yield[b] [%]	*ee*[c] [%]
1	Ph	Me	14	>99 (*S*)
2	Ph	Et	38	>99 (*S*)
3	Ph	*i*Pr	42	>99 (*R*)
4	Ph	Cy	50	>99 (*R*)
5	$(CH_3)_2C{=}CH(CH_2)_2$	Me	n.a.[d]	n.a.[d]
6	Cy	Me	50	98 (*S*)

[a] Each result is the average from two reactions. No *E*/*Z* isomerization of the allylic alcohols was detected. [b] Isolated product yields. [c] Determined by chiral GC/MS. Absolute configurations were determined by comparing the optical rotations of the product to literature values (for details, see the Supporting Information). [d] Not applicable.

Experimental Section

General procedure: A 10 mL microwave tube containing the iridium catalyst $[(\mathrm{L^*})\mathrm{Ir(cod)}]^+[\mathrm{BAr_F}]^-$ (8 mg) and sealed with a septum was evacuated and refilled with N_2 three times. Thereafter, dry THF (2 mL) was added. The septum was pierced with a needle and the vessel was sealed in a hydrogenation bomb. After eight cycles of applying and venting 3 bar of argon, the tube was pressured to 3 bar with H_2 and allowed to react for 10 min, during which time the orange solution became yellow. The vessel was vented and removed from the bomb, and the solution was degassed through three freeze-pump-thaw cycles. Allylic alcohol (0.1 mmol) was then added as a stock solution (0.33 M) in dry THF, and the reaction was stirred under N_2 for 17 h.[10]

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Keywords: aldehydes · allylic alcohols · asymmetric catalysis · iridium · isomerization · N, P ligands

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[9] Mazet and co-workers reasoned that a bulky trialkylphosphine moiety might be crucial to this reaction (see Ref. [5a]) and that any variation of the Crabtree catalyst that combines a trialkylphosphine with an sp^2-hybridized N-donor ligand would be inactive for the isomerization reaction (see Ref. [5c])

[10] It was observed that if the solution containing the catalyst was not freeze-thawed at least three times prior to the addition of the substrate, competing hydrogenation took place resulting in trace amounts of saturated alcohols.

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