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Fam–Ti Catalyzed Enantioselective Alkynylation of Aldehydes

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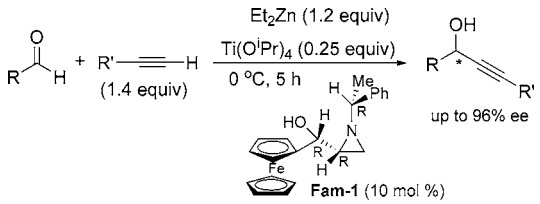
ABSTRACT



Ferrocenyl-substituted aziridinylmethanol (Fam-1) has been used as a chiral catalyst with titanium for enantioselective alkynylation of aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes to give the corresponding propargylic alcohols in up to 96% yield and 96% ee. The ligand can be prepared easily and recycled.

Development of new and practical chiral catalysts is a major interest of organic chemists. Ideal catalysts are the ones that can be synthesized easily in both enantiopure forms, can provide high yields and enantioselectivities in various reactions, and are inexpensive. Catalytic asymmetric carbon−carbon bond formation by addition of terminal acetylenes to aldehydes is highly important; the resulting propargylic alcohols are versatile building blocks for many chiral organic compounds.[1] Development of new and more efficient catalysts for alkynylation of aldehydes is of current interest.[2] Although impressive results have been obtained in this field, it is still desirable to develop a catalyst that can tolerate aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes and acetylenes other than phenylacetylene. Additionally, the reaction should not require higher concentration of zinc reagents or alkynes or longer reaction times.[2a,b,d,e,h] We recently developed a new set of chiral ligands, ferrocenyl-substituted aziridinylmethanols (Fam), and used one of them with zinc efficiently in enantioselective 1,3-dipolar cycloaddition reactions of azomethine ylides to obtain pyrrolidines in up to 95% ee.[3] These ligands were also used in diethylzinc addition reactions to aldehydes[4] to obtain secondary alcohols with up to 99% ee and enones[5] to obtain β-ethylated ketones in up to 80% ee. The performance of these ligands has also been tested in the enantioselective alkynylation of aldehydes. Herein we report the results of this study.

Chiral Fam ligands **1**−**4** (Figure 1) were prepared[3] in three easy steps starting with easily available acryloyl ferrocene[6] on a gram scale in enantiomerically pure forms by employing a Gabriel−Cromwell reaction.[7]

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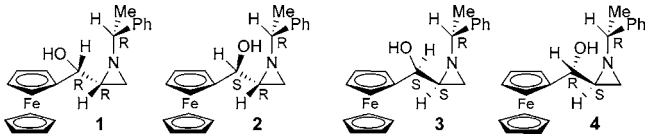
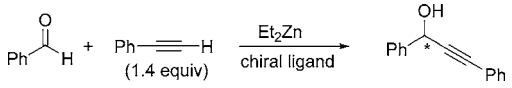


Figure 1. Structures of chiral Fam ligands **1**−**4**.

We first looked at the catalytic effect of all four ligands **1**−**4** in enantioselective alkynylzinc addition reactions. The results of these studies are summarized in Table 1. As can be seen 10 mol % of ligand with 2.0 equiv of diethylzinc and without Ti(O^{i}Pr)$_4$ gave the propargylic alcohols in 60−92% yields but low ees (entries 1−6) after reaction times of 18−28 h. Lowering the temperature to −20 °C (entry 3) or the amount of diethylzinc to 1.2 equiv (entry 7) improved the enantioselectivity, but it was still not satisfactory. The use of camphorsulfonamide−Ti complex by Wang et al.,[2d] BINOL−Ti complex by Pu et al.,[2h] and H$_8$-BINOL−Ti complex by Chan et al.[2g] in phenylacetylene addition to aromatic and aliphatic aldehydes showed high ee. Therefore we decided to evaluate Fam−Ti complex in enantioselective alkynylation of aldehydes. Using the same amount of chiral ligand **1** as before, 1.2 equiv of diethylzinc, and 0.5 equiv of Ti(O^{i}Pr)$_4$, the product was obtained in 91% yield and 96% ee after 18 h (entry 8). With this promising result, the effect of the amount of titanium and ligand and the reaction time on the yield and ee of the propargylic alcohol was explored.

Table 1. Optimization of Reaction Conditions



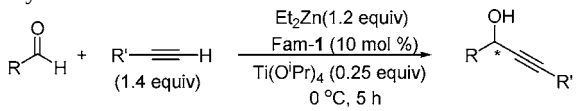
entry	ligand	Et_2Zn (equiv)	$Ti(O^iPr)_4$ (equiv)	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**1**	2.0		rt	18	92	22
2	**1**	2.0		0	20	90	26
3	**1**	2.0		−20	28	75	44
4	**2**	2.0		−20	28	78	32
5	**3**	2.0		−20	28	60	46
6	**4**	2.0		−20	28	72	34
7	**1**	1.2		0	28	93	38
8	**1**	1.2	0.50	0	18	91	96
9	**1**	1.2	0.25	0	18	91	92
10	**1**	1.2	0.25	0	5	92	94
11[c]	**1**	1.2	0.25	0	5	35	82
12[c]	**1**	1.2	0.25	0	10	66	82
13	**2**	1.2	0.25	0	5	53	70
14	**3**	1.2	0.25	0	5	71	86
15	**4**	1.2	0.25	0	5	57	8

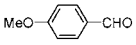
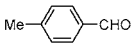
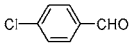
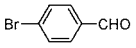
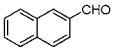
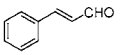
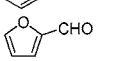
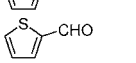
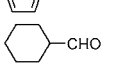
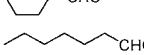
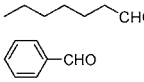
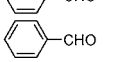
[a] Isolated yields. [b] Determined by chiral HPLC. [c] 5 mol % ligand was used.

Lowering the amount of Ti to 0.25 equiv (entry 9) or the reaction time to 5 h (entry 10), the yield and ee of the reaction were not affected significantly. However, at a lower ligand concentration both the yield and enantioselectivity decreased (entries 11 and 12). Best results were obtained with 10 mol % of ligand **1**, 0.25 equiv of Ti(O^{i}Pr)$_4$, 1.4 equiv of alkyne, and 1.2 equiv of diethylzinc in 5 h at 0 °C.

After determining the optimum reaction conditions, we examined the generality of this catalyst system, as summarized in Table 2. The catalytic system developed in this study works efficiently and cleanly for the alkynylation of a series of aromatic aldehydes (entries 1−9). Substitution at the *ortho*, *meta*, or *para* positions of the aldehydes did not show a considerable effect on the yield and enantioselectivity of the reaction. Similarly, enantioselective alkynylation of α,β-unsaturated and heteroaromatic aldehydes gave the corresponding propargylic alcohols in excellent enantioselectivities (entries 10, 11, and 12, respectively). Our catalyst also gave very good results with aliphatic aldehydes (entries

Table 2. Fam-**1** Catalyzed Asymmetric Alkynylation of Aldehydes



entry	aldehyde	alkyne	yield (%)[a]	ee (%)[b]
1			92[c]	96[c]
2			90	96
3			93	92
4			91 (89)[c]	94 (92)[c]
5			91	92
6			91	96
7			91	92
8			91	92
9			90 (90)[c]	96 (98)[c]
10			87	92
11[d]			93	96
12[d]			92	96
13			96	86
14			93	88
15[d]			84	94
16[d]			80	94

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Obtained with recovered ligand. [d] 2.0 equiv of Et_2Zn and alkyne were used, reaction time was 17 h for entries 15 and 16.

(7) Cromwell, N. H.; Babson, R. D.; Harris, C. E. *J. Am. Chem. Soc.* **1943**, *65*, 312.

13 and 14). Significantly, alkylacetylenes can also be used with this catalyst system to synthesize the corresponding propargylic alcohols in high enantioselectivities (entries 15 and 16), although longer reaction time and higher concentration of diethylzinc and alkylacetylene were required.[8] The ligand Fam-**1** can be recovered in more than 90% yield and recycled without losing its activity (entries 1, 4, and 9). We believe that the configuration at the aziridine center of the Fam ligands is important in determining the configuration of the product, the selectivity obtained with ligands **1** and **2** is opposite to that of ligand **3**, although the yield and ee are low for the last two ligands.

In summary, we developed a catalyst system that can be used in enantioselective alkynylzinc addition to aldehydes to give the propargylic alcohols in up to 96% ee. Besides the ease of synthesis of the ligand, the reactions can be run with a low concentration of diethylzinc and acetylenes at shorter reaction times as compared to similar studies reported in the literature. In addition, the catalyst developed in this study works with aromatic, heteroaromatic, aliphatic, and α,*β*-unsaturated aldehydes as well as alkylacetylenes. It is also worth mentioning that both enantiomers of the catalyst can be obtained easily starting from commercially available (*R*)-/(*S*)-methylbenzylamine. Furthermore, the catalyst can be recovered and recycled successfully. The catalytic effect of Fam ligands for other asymmetric reactions is under investigation in our laboratory and will be reported in due course.

(8) Under the standard conditions, 1-hexyne gave the product in 51% yield and 94% ee. 1-Heptyne gave the product in 61% yield and 92% ee.

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Supporting Information Available: Experimental procedures and characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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