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A Practical Catalytic Asymmetric Addition of Alkyl Groups to Ketones

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Literally hundreds of catalysts will promote additions of zinc alkyl groups to aldehydes with high enantioselectivities.[1−3] In sharp contrast, the use of ketones as alkyl and aryl group acceptors under similar conditions has proven much more challenging. This discrepancy is due to the greater reactivity of aldehydes over ketones, which is accentuated by the mild nature of dialkylzinc reagents.[4] As a result, only two catalysts have been shown to promote the asymmetric addition of aryl or alkyl zinc reagents to ketones. The addition of phenyl groups to ketones was reported in 1998 by Dosa and Fu[5] who employed Noyori's amino alcohol ligand DAIB, **1** (15 mol %, Figure 1).[6] The success of this addition can be attributed, in part, to the increased reactivity of diarylzinc reagents over their dialkylzinc counterparts. In the arylation reaction, enantioselectivities ranged from 36 to 75% for dialkyl ketones and 72−91% for aryl methyl ketones.[5]

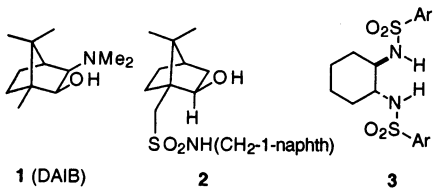

Figure 1. Structures of ligands for the asymmetric addition of alkyls to ketones.

In the same year, Ramón and Yus[7,8] reported the alkylation of ketones with dialkylzinc reagents and a titanium-based catalyst. They employed titanium tetraisopropoxide in combination with a camphor-based hydroxysulfonamide ligand, **2**.[7,8] They observed enantioselectivities from 16 to 89% and obtained good yields in most cases. However, the resulting catalyst showed low activity; at 20 mol % catalyst the additions required between 4 and 14 days for consumption of the substrate.

Our initial experiments in the asymmetric addition of alkyl groups to ketones involved the use of bis(sulfonamide) ligands[9] **3** (Figure 1) with titanium tetraisopropoxide and diethylzinc. This is one of the most efficient and enantioselective catalysts known for the additions of alkyl groups to aldehydes.[9] The catalysts for this process are believed to be bis(sulfonamido)Ti(O^iPr)$_2$.[9−11] In some cases, additions to aldehydes gave >98% ee and were complete in 15 min at −45 °C.[11] However, when we used ketones as substrates, reactions were slow, with 40% conversion after 2 days and 25% formation of reduction product. Additionally, the ee's were under 10%. We hypothesized that the reactivity of the catalysts could be increased by constraining the geometry of the ligand, which would result in a more open binding site. The first generation ligands were based on *trans*-1,2-diaminocyclohexane and camphor sulfonyl chloride, both of which are commercially available (Scheme 1).

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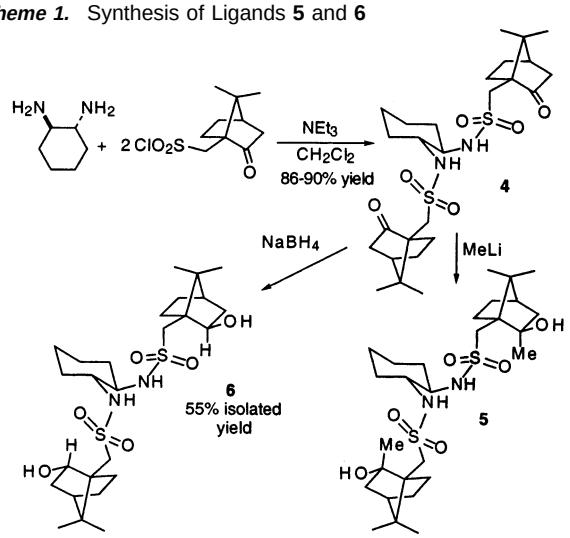
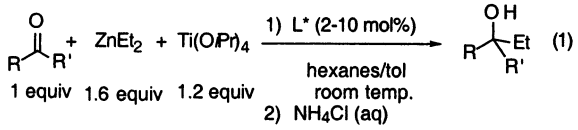
Scheme 1. Synthesis of Ligands **5** and **6**



Reaction of these reagents in the presence of Et_3N furnished the diketone **4**. Addition of methyllithium to **4** proceeded to give a single diastereomer of the diol **5** (Scheme 1).[12] Use of **5** in the asymmetric addition reaction (eq 1) resulted in formation of the tertiary alcohol addition products in 70−90% ee. Like those in the



Yus system,[7,8] the reactions were very slow; only 5−20% conversion was observed after 24 h. We believed that if the ligand bulk about the titanium center could be trimmed while maintaining the constrained geometry, the catalysts might be more active. Diketone **4** was reduced with $NaBH_4$ to form two diastereomers in a 3.5:1 ratio (Scheme 1). The diastereomers were easily separated by chromatography on silica. The major diastereomer, isolated in 55% yield, was shown to be the C_2-symmetric diol **6** (2D NMR). This two-step sequence has been used to prepare 6.7 g (12.2 mmol) of ligand **6**. To our delight, ligand **6** formed an efficient and highly enantioselective catalyst for the addition of alkyl groups to ketones.

The results of our study are shown in Table 1. Catalyst loadings as low as 2 mol % have been successfully used for the asymmetric addition reactions. Acetophenone and related derivatives are excellent substrates for this catalyst. The reactions of acetophenone and 3-methylacetophenone were complete in less than 30 h, and the addition products were formed in 96% and 99% ee. Reactions with 3-methylacetophenone employing 10 and 2 mol % catalyst gave product with the same ee's and similar yields (entry 2).

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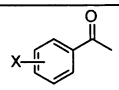
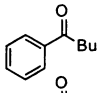
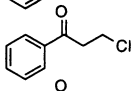
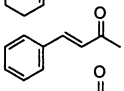
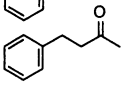
Table 1. Asymmetric Addition of Ethyl Groups to Ketones with Ligand **6** in Equation 1

entry		mol%	yield	time (h)	ee[a] (config)
					
1	X = H	2	71	29	96 (S)
2	X = 3-Me	10	82	12	99
		2	78	24	99
3	X = 4-OMe	10	85	111	94
4	X = 3-CF_3	2	56	14	98
5	X = 2-Me	10	24	48	96
6		10	35	22	>99
7		10	83	47	87
		2	79	102	88
8		10	82	44	89
9		2	56	46	96
10		2	80	26	90
11		10	68	68	70

[a] ee's determined by GC or HPLC. See Supporting Information for details.

Electron-donating and -withdrawing substituents have little effect on the ee of the product; 4-methoxy- and 3-(trifluoromethyl)-acetophenones gave 94 and 98% ee, respectively (entries 3 and 4). However, the substituent had a significant impact on reaction times for these substrates. The trifluoromethyl and methoxy derivatives required 14 and 111 h to complete, respectively. The results from the reaction of 2-methylacetophenone demonstrated that substitution of the 2-position does not adversely affect the enantioselectivity (96%) but does result in reduced reactivity and yield (24%, entry 5). α-Tetralone also gave excellent ee (>99%); however, the yield was low (35%). Yus also reported a low yield with this compound (25% yield).[7,8] In our case, two aldol products were isolated in 48% yield.

Other alkyl aryl ketones also proved to be very good substrates for the asymmetric addition reaction. Valerophenone and 3-chloropropiophenone underwent additions with enantioselectivities of 88 and 89%, respectively, in good yields (entries 7 and 8).

Reactions of α,*β*-unsaturated ketones in eq 1 provided tertiary allylic alcohols. 1-Cyclohexenyl methyl ketone gave product with 96% ee (entry 9). *trans*-4-Phenyl-3-buten-2-one proved to be an excellent substrate for the addition reaction, giving 90% ee (entry 10). The related dialkyl ketone, 4-phenyl-2-butanone, was envisioned to be a difficult substrate because the size of the methyl and the alkyl groups are comparable. Surprisingly, this substrate gave the addition product in 70% ee (entry 11). Note that care must be used when handling the enantiomerically enriched tertiary alcohols to avoid loss of ee (see Supporting Information).

We have also examined the addition of dimethylzinc to propiophenone using the same enantiomer of the ligand shown in Scheme 1 and employed in eq 1. Interestingly, the addition to propiophenone using dimethylzinc gave the (*R*)-enantiomer of 2-phenyl-2-butanol (2 mol % ligand, 83% yield, 94% ee) while the addition of diethylzinc to acetophenone gave the (*S*)-enantiomer of the same alcohol in 96% ee (Table 1, entry 1). Thus, employing the same enantiomer of the ligand one can obtain either enantiomer of 2-phenyl-2-butanol with excellent enantioselectivity.

To test the scalability of this process, the asymmetric addition reaction of 3-methylacetophenone was examined on a larger scale. Reaction of 5.0 g (37 mmol) of this ketone was conducted with 2 mol % ligand. After 40 h at room temperature, the reaction was worked-up with aqueous ammonium chloride, extracted into CH_2Cl_2, and purified on silica to provide 4.5 g (73% yield) of the addition product with 99% ee. The ligand was recovered in 84% yield. These results highlight the practicality of this system.

The construction of chiral quarternary centers remains one of the most challenging frontiers of asymmetric catalysis.[13,14] The catalyst system outlined here generates chiral tertiary alcohols and allylic alcohols with excellent ee's. The chiral ligand **6** is easily synthesized in two steps from commercially available materials and can be prepared on large scale. Furthermore, we have demonstrated that the reaction is easily scalable and can be conducted at room temperature.

We are currently examining the scope and mechanism of this efficient and enantioselective asymmetric C−C bond-forming reaction.

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Supporting Information Available: Procedures, characterization of **6** and chiral alcohols, and ee analyses (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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