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Highly Enantioselective Catalytic Phenylation of Ketones with a Constrained Geometry Titanium Catalyst

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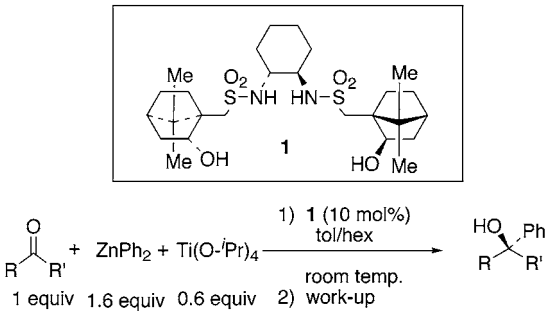
ABSTRACT



The catalytic asymmetric addition of phenyl groups from diphenylzinc to ketones is reported. The catalyst, generated from a dihydroxy bis(sulfonamide) ligand and titanium tetraisopropoxide, gives good to excellent enantioselectivities with a range of substrates.

The asymmetric addition of alkyl groups to aldehydes has been extensively studied, and many catalysts will promote this addition with high enantioselectivities.[1,2] In contrast, analogous addition reactions to ketones have proven to be a challenging problem.[3−8] This discrepancy is due to the reduced propensity of ketones to coordinate to Lewis acids, relative to aldehydes. Furthermore, to achieve high enantioselectivities, catalysts must readily distinguish between the lone pairs of the carbonyl oxygen. Differentiation of aldehyde lone pairs is simple; little steric hinderence is encountered on binding syn to the aldehydic hydrogen relative to binding syn to the alkyl substituent. With ketones, however, discrimination of the lone pairs is difficult due to their similar environments.

One of the goals of our research has been to develop catalysts capable of promoting the asymmetric alkylation of carbonyl groups. To this end, we have had a long-standing interest in the design of catalysts based on multidentate dihydroxy bis(sulfonamide) ligands incorporating *trans*-1,2-diaminocyclohexane.[6,7,9,10] These investigations culminated in our identification of the dihydroxy bis(sulfonamide) ligand **1** (Figure 1), which formed the first efficient and highly

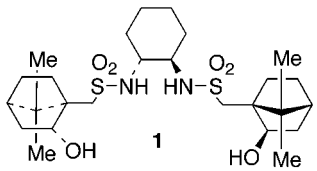


Figure 1. Ligand **1** based on the (*R*,*R*)-diamine and (*S*)-camphor.

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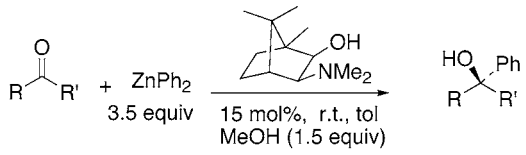
enantioselective catalyst for the addition of alkyl groups to aryl alkyl ketones[6] and α,β-unsaturated cyclic enones.[7]

Ligand **1** is readily synthesized in two steps from commercially available materials and can be used in as little as 2 mol % loading.[6] After our report detailing the synthesis and application of **1** to the catalytic asymmetric addition of alkyl groups to ketones,[6] Yus and co-workers published a similar study using the same ligand.[8] Our success with ligand **1** in the alkyl additions led us to examine the enantioselective arylation of ketones with $ZnPh_2$, and we were pleased to find that the results were again excellent across a range of substrates. The products of these reactions are tertiary alcohols that possess chiral quaternary centers. Such stereocenters are difficult to install in an asymmetric fashion with high enantioselectivity. During the preparation of the current manuscript, Yus published the use of **1** in the arylation of 4′-substituted acetophenones and 4′-bromopropiophenone,[11] prompting us to report our independent investigations that define the scope of the phenyl addition to ketones with ligand **1**.

The first catalytic enantioselective phenyl addition to ketones was reported by Dosa and Fu in 1998.[3] In this pioneering work, these authors employed Noyori's (+)-DAIB ligand[12,13] and diphenylzinc. Although direct use of diphenylzinc gave low yields, addition of methanol to the diphenylzinc solution resulted in formation of a mixed alkoxy phenyl zinc reagent that gave increased yields and enantioselectivities, as shown in Figure 2.[3] In contrast, diphenylzinc



R	R '	yield (%)	ee (%)
Me	4-C_6H_4-Br	53	80
Me	2-naphth	58	72
Et	3-C_6H_4-Br	91	91
Et	2-naphth	79	86
Et	4-C_6H_4-Br	83	90
Me	^{i}Pr	63	60
Me	C_6H_{11}	76	75

Figure 2. Results of Dosa and Fu in the asymmetric addition of phenyl groups to ketones.

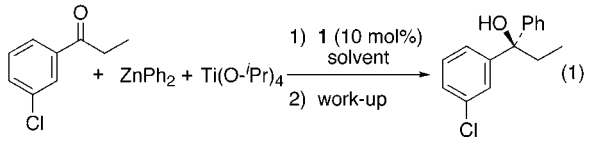
and alkyl phenyl zinc reagents can be used in the additions to aldehydes.[14−20]

In our study, we chose 3′-chloropropiophenone as the test substrate for optimization of the reaction parameters, as outlined in Table 1. In our initial experiments, we used conditions similar to those in our asymmetric alkylations of ketones. Employing 10 mol % **1**, 1.2 equiv of titanium tetraisopropoxide, and 1.6 equiv of diphenylzinc in a mixture of toluene and hexanes at room-temperature resulted in formation of the product with 99% isolated yield and in 87% enantioselectivity after 18 h (entry 1). Unfortunately, lowering the temperature to 0 °C led to significant decrease in both product ee and yield (entry 2). Use of toluene alone resulted in a slight increase in the product ee to 89%, while hexanes alone resulted in no change (entries 3 and 4). Diethyl ether gave product of 92% ee, but the yield dropped to 81%. Combination of diethyl ether and hexanes gave higher yield (88%) with little change in product ee (91%). No reaction was observed when the Lewis basic THF was employed or methanol was added in a fashion similar to the report of Dosa and Fu.[3] These studies indicate that the catalyst enantioselectivity remains high with a variety of solvents.

Table 1. Examination of the Effects of Solvents and Temperature on the Yield and Enantioselectivity of the Phenylation of 3′-Chloropropiophenone

entry	solvent	T (°C)	yield (%)	ee (%)[a]
1	toluene/hexanes	22	99	87
2	toluene/hexanes	0	57	65
3	toluene	22	99	89
4	hexanes	22	99	87
5	Et_2O	22	81	92
6	Et_2O/hexanes	22	88	91
7	THF/hexanes	22	NR	
8	THF/CH_2Cl_2	22	NR	
9	toluene/methanol	22	NR	

[a] Conditions for all ee determinations are in Supporting Information.



The next step in our optimization involved variation of the reagent stoichiometry, as detailed in Table 2. Using toluene and hexanes, we initially varied the amount of titanium tetraisopropoxide and ligand **1** (entries 1−7). Decreasing the titanium tetraisopropoxide to 0.6 equiv led

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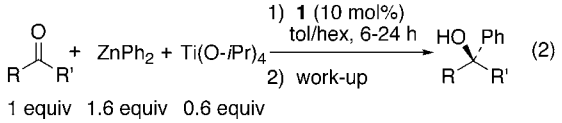
Table 2. Examination of the Effect of Reagent Stoichiometry on Yield and Enantioselectivity in the Phenylation of 3′-Chloropropiophenone

entry	mol % **1**	equiv Ti(O-^{i} Pr)$_4$	solvent	yield (%)	ee (%)
1	10	0.2	tol/hex	37	65
2	10	0.4	tol/hex	66	87
3	10	0.6	tol/hex	99	92
4	10	1.2	tol/hex	99	87
5	10	1.8	tol/hex	97	85
6	10	2.4	tol/hex	95	85
7	5	0.6	tol/hex	82	87
8	10	0.6	Et_2O/hex	80	91
9	10	0.6	Et_2O	59	92

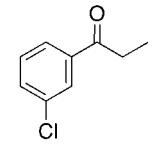
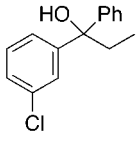
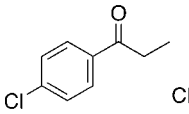
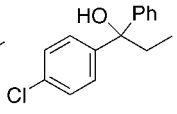
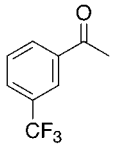
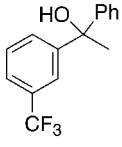
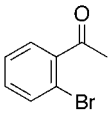
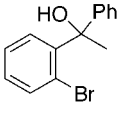
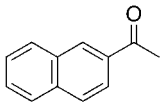
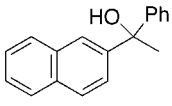
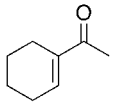
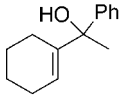
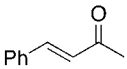
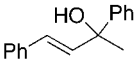
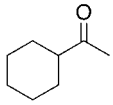
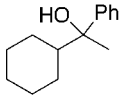
to the highest yield and product ee (99% yield, 92% ee, entry 3). Reducing the catalyst loading to 5 mol % resulted in a decrease in the enantioselectivity to 87% (entry 7). Reactions employing diethyl ether and 0.6 equiv of titanium tetraisopropoxide gave excellent enantioselectivities; however, yields were reduced (entries 8 and 9).

Employing the optimized reaction conditions in entry 3 of Table 2,[21] we examined the phenylation of a series of ketone substrates, as shown in eq 2 and Table 3. A slightly lower enantioselectivity was observed with 4′-chloropropiophenone than with the 3′-chloro derivative. Acetophenone derivatives are excellent substrates for this catalyst. The phenyl addition products from 3′-(trifluoromethyl)acetophenone, 2′-bromoacetophenone, and 2′-acetonaphthone were formed with high yields and enantioselectivities of 95−96% (entries 3−5). It is anticipated that the 2′-bromo benzene derivative in entry 4 can be further elaborated through cross-coupling reactions. Impressive enantioselectivities were also obtained with α,β-unsaturated enones (entries 6 and 7). 1-Acetyl-1-cyclohexene (entry 6) underwent addition with 94% yield and 93% enantioselectivity. The yield of the addition product with *trans*-4-phenyl-3-buten-2-one was 58%, but the enantioselectivity remained high (91%). The allylic alcohol products formed from α,β-unsaturated enones are useful chiral building blocks that can be readily functionalized at the double bond. Dialkyl ketones also proved to be good substrates for our catalyst, with cyclohexyl methyl ketone and 3-methyl-2-butanone giving 87 and 75% ee (entries 8 and 9, respectively). These data compare favorably with the results of Dosa and Fu[3] illustrated in Figure 2.



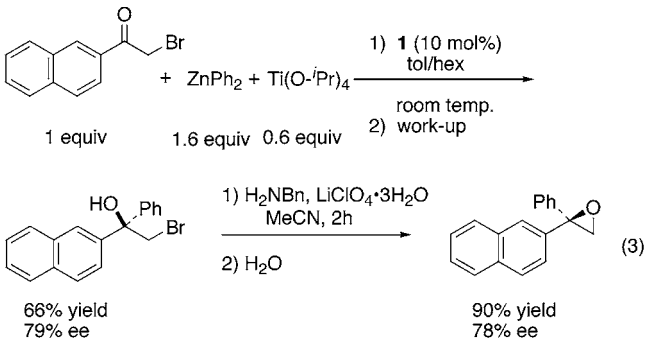
To further expand the scope of the asymmetric phenylation of ketones, we have investigated the use of an α-halo ketone. The products of such a reaction can be converted into epoxides, which are among the most useful chiral building blocks in organic synthesis. Subjecting α-bromo-2′-acetonaphthone to the phenylation conditions in eq 3 resulted in

Table 3. Yields and Enantioselectivities for the Phenylation of Various Ketone Substrates (Eq 2)

entry	substrate	product	yield (%)	ee (%)
1			99	92
2			99	88
3			93	95
4			76	95
5			99	96
6			94	93
7			58	91
8			81	87
9			55	75

formation of the product alcohol in 66% yield and 79% enantioselectivity. Cyclization proceeded cleanly, affording the epoxide in 90% yield with no loss of ee, within experimental error. Such chiral 1,1-diaryl epoxides are difficult to prepare by catalytic asymmetric methods, despite extensive research into epoxide-forming reactions.

(21) **General Procedure for the Preparation of Tertiary Alcohols. Preparation of 1-(3-Chlorophenyl)-1-phenyl-1-propanol.** The bis(sulfonamide) ligand **1** (5.4 mg, 10 mol %) was weighed into a well-dried Schlenk flask. A solution of diphenylzinc (35.1 mg, 0.16 mmol) in toluene (1 mL) was added, followed by titanium(IV) isopropoxide (50 μL, 1.2 M hexanes solution, 0.06 mmol). The homogeneous reaction mixture was stirred at room temperature for 15 min. 3′-Chloropropiophenone (17.2 mg, 0.1 mmol) was then added as a solution in toluene (0.5 mL). The reaction mixture was stirred at room temperature until TLC showed complete consumption of the ketone. The reaction was quenched with a 15% aqueous tartaric acid and extracted with CH_2Cl_2. The combined organic phases were dried using anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (hexanes/EtOAc 98:2) to give the tertiary alcohol (24.4 mg, 99% yield, 92% ee) as an oil: $[\alpha]_D^{20} = +21.4$ (*c* 0.81, $CHCl_3$).



In conclusion, we report an efficient and highly enantioselective catalyst for the phenylation of ketones. The reaction employs the readily available ligand **1**, a substoichiometric amount of titanium tetraisopropoxide, and commercially available diphenylzinc. The reactions are clean, affording high yields of the tertiary alcohol in less than 24 h at room temperature. These results represent a significant improvement over those obtained using the more synthetically challenging DAIB (Figure 2).[22,23] Additionally, a methanol additive is not necessary. Future studies will focus on expanding the scope of reactions catalyzed by our ligand **1** and studies directed toward understanding the mechanism of this synthetically useful reaction.

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Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0352963

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