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A New 1,1′-Binaphthyl-Based Catalyst for the Enantioselective Phenylacetylene Addition to Aromatic Aldehydes without Using a Titanium Complex

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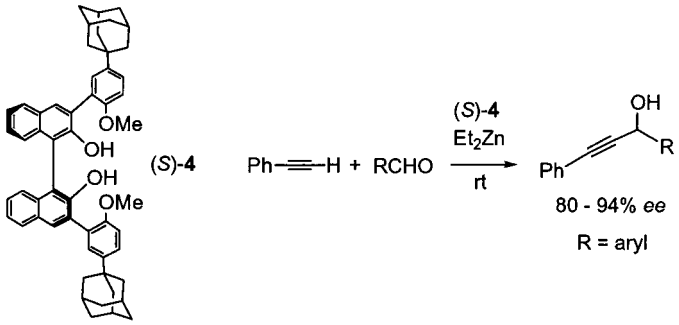
ABSTRACT



A novel 1,1′-binaphthyl compound containing bulky 3,3′-aryl substituents is found to catalyze the reaction of a terminal alkyne with various aromatic aldehydes under mild conditions to generate chiral propargyl alcohols with 80–94% ee. Unlike the previously reported 1,1′-binaphthyl catalysts, this new compound does not require the use of a titanium complex and the pre-preparation of an alkynylzinc. This has greatly simplified the experimental procedure for this reaction.

The asymmetric alkynylzinc addition to aldehydes[1−5] is very useful for the synthesis of chiral propargyl alcohols that are important precursors to many chiral organic compounds.[6−8] Among the catalysts developed for this reaction,[1−5] two types of chiral ligands have shown high enantioselectivity for various substrates. One is the amino alcohol ligand **1** reported by Carreira,[2] and the other is BINOL reported by us[3] and Chan.[4] Carreira's catalyst shows excellent enantioselectivity for the alkynylzinc addition to *aliphatic* aldehydes, and the BINOL catalyst shows excellent enantioselectivity for the

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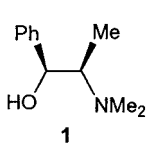
alkynylzinc addition to *aromatic* aldehydes.[3,4] We found that the BINOL-catalyzed reaction required the use of 0.5−1 equiv of $Ti(O^iPr)_4$ and a separated step for the preparation of an alkynylzinc reagent from a terminal alkyne and diethylzinc.[3] Herein, we report the discovery of a new 1,1′-binaphthyl-based catalyst for the enantioselective reaction of phenylacetylene with aromatic aldehydes *without using the titanium complex and pre-preparing the alkynylzinc*.



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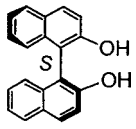
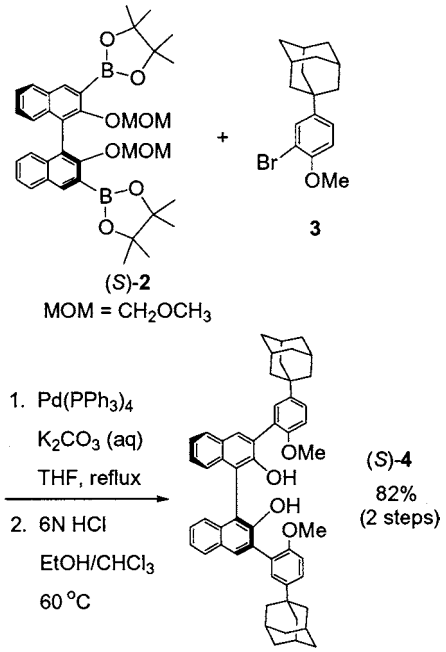


BINOL

The optically active 1,1′-binaphthyl compound containing bulky 3,3′-aryl substituents, (*S*)-**4**, was synthesized according to Scheme 1.[9] The Suzuki coupling[10] of (*S*)-**2** with an aryl

Scheme 1. Synthesis of the Novel 1,1′-Binaphthyl Compound (*S*)-**4**



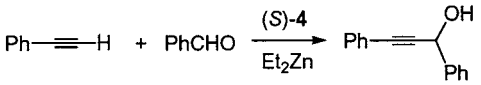
(*S*)-**2**
MOM = CH_2OCH_3

3

bromide containing an adamantanyl substituent (**3**) followed by hydrolysis gave (*S*)-**4** in 82% yield.[11] The ^1H NMR spectrum of this compound shows its C_2 symmetry with a singlet observed at δ 3.81 for the two methyl groups. This also demonstrates that no diastereomeric isomers arose from the bulky adamantanyl-substituted 3,3′-aryl groups unlike what we observed in the analogous 3,3′-naphthyl compounds.[12] That is, the rotation barrier for the 3,3′-aryl groups around the aryl−aryl single bonds of (*S*)-**4** is still very small. The specific optical rotation ($[\alpha]_D$) of (*S*)-**4** is −94.1 (*c* 0.6, CH_2Cl_2).

We studied the application of (*S*)-**4** in the reaction of phenylacetylene with benzaldehyde in the presence of diethylzinc (Scheme 2). We found that this reaction was

Scheme 2. Reaction of Phenylacetylene with Benzaldehyde in the Presence of (*S*)-**4** and Diethylzinc



strongly influenced by the solvent. Very low enantioselectivity was observed in toluene (22% ee, entry 1) and methylene chloride (13% ee, entry 2). However, there was a dramatic enhancement in enantioselectivity when THF was used as the solvent (84% ee, entry 3). Decreasing the reaction temperature from room temperature to 0 °C led to increased ee but it reduced both the reaction rate and yield (entry 4). Increasing the amount of the ligand from 10 to 20 mol % gave a lower ee of 76% (entry 5). This could be attributed to a concentration effect. When the amount of diethylzinc was increased from 2 to 4 equiv, the reaction proceeded faster but more side product resulted from the diethylzinc addition to benzaldehyde (entries 6, 7).

Table 1. Reaction of Phenylacetylene with Benzaldehyde Catalyzed by (*S*)-**4** in the Presence of Diethylzinc

entry	Et_2Zn (equiv)	(*S*)-**4** (mol %)	solvent	temp	time (h)	ee (%)	yield (%)
1	2.0	10	toluene	rt	5	22	
2	2.0	10	CH_2Cl_2	rt	5	13	
3	2.0	10	THF	rt	18	84	75
4	2.0	10	THF	0 °C	36	88	42
5	2.0	20	THF	rt	16	76	
6	4.0	10	THF	rt	9	83	57
7	4.0	10	THF	0 °C	36	92	48

Following is a description of the experimental procedure used in entry 3 of Table 1. Under nitrogen, to a solution of (*S*)-**4** (19 mg, 10 mol %) in THF (3 mL, dried with activated alumina) in a 10 mL Schlenk flask was added diethylzinc (53.0 μL, 0.5 mmol, 2.0 equiv). After the mixture was stirred at room temperature for 1 h, phenylacetylene (42.0 μL, 0.38 mmol, 1.5 equiv) was added and the stirring continued for an additional 1 h. Benzaldehyde (25.5 μL, 0.25 mmol) was then added, and the reaction mixture was stirred for 18 h.

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(11) Characterization of (*S*)-**4**: $[\alpha]_D = -94.1$ (*c* 0.6, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 1.73−1.83 (m, 12H), 1.97 (d, J = 2.4 Hz, 12H), 2.11 (s, br, 6H), 3.81 (s, 6H), 5.95 (s, br, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.28−7.41 (m, 8H), 7.51 (d, J = 2.4 Hz, 2H), 7.89−7.94 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.20, 35.97, 37.00, 43.61, 56.32, 111.15, 115.57, 123.88, 125.18, 125.94, 126.69, 128.42, 129.36, 129.46, 131.39, 133.65, 144.76, 150.62, 154.56. APCI-MS *m/z*: 749.6 (100, M + 1 − H_2O). HRMS (FAB) calcd for $C_{54}H_{54}O_4$ (M^+): 766.4022; found: 766.4038.

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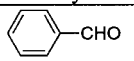
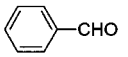
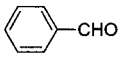
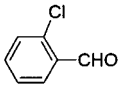
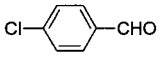
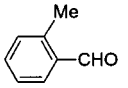
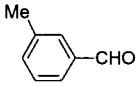
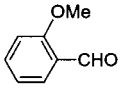
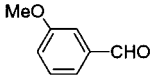
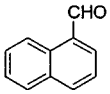
Table 2. Reaction of Phenylacetylene with Aromatic Aldehydes in the Presence of (*S*)-**4** and Diethylzinc[a]

entry	aldehyde	isolated yield (%)	ee (%)[b]
1		75	84
2[c]		42	88
3[c,d]		48	92
4		74	94
5		75	85
6		72	84
7		63	84
8		64	91
9		71	85
10[c]		45	80

[a] Reactions were carried out with 10 mol % (*S*)-**4**, 2.0 equiv of Et_2Zn, and 1.5 equiv of phenylacetylene in THF at room temperature unless otherwise noted. [b] Determined by HPLC analysis on a Chiralcel OD column. [c] Temp = 0 °C. [d] Et_2Zn (4.0 equiv) was used.

The reaction was then quenched with 1 N HCl, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography of the residue on silica gel using hexane/ethyl acetate as eluent gave the product 1,2-diphenyl-prop-2-yn-1-ol (39 mg) in 75% yield. The configuration of the product was *S* as determined by comparing its optical rotation with the literature data.[8c]

The above procedure was applied to the reaction of phenylacetylene with a variety of aromatic aldehydes catalyzed by (*S*)-**4** in the presence of diethylzinc. As the results summarized in Table 2 show, enantioselectivities ranging from 80 to 94% ee were achieved for the reaction of phenylacetylene with aromatic aldehydes containing electron-donating or electron-withdrawing substituents at the *o*-, *m*-, or *p*-positions.

In summary, we have demonstrated that a novel 1,1′-binaphthyl compound containing bulky 3,3′-aryl substituents is a good enantioselective catalyst for the reaction of phenylacetylene with various aromatic aldehydes under very mild conditions. Unlike the previously reported 1,1′-binaphthyl catalysts, this new compound does not need the use of $Ti(O^iPr)_4$. In addition, it also does not require a separated step to prepare the alkynylzinc reagent. This has greatly simplified the experimental procedure for this reaction.

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