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Activation of Functional Arylzincs Prepared from Aryl Iodides and Highly Enantioselective Addition to Aldehydes

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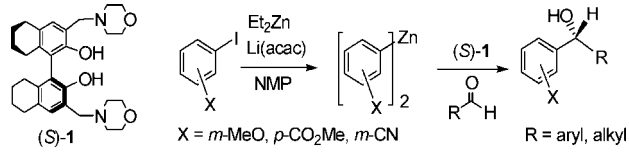
ABSTRACT

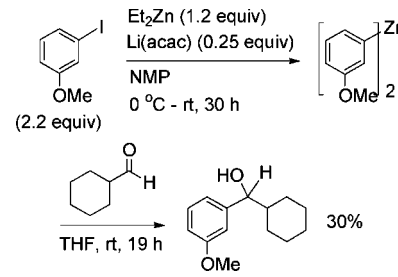


An easily available chiral ligand (*S*)-1 is found to activate the nucleophilic reaction of the arylzincs prepared in situ from the reaction of aryl iodides with Et_2Zn. Both high yields and high enantioselectivity (up to >99% ee) for the reaction of these arylzincs with a variety of aldehydes are obtained. The mild reaction conditions and the good functional group tolerance make this catalytic asymmetric process synthetically useful.

Addition of organozinc reagents to aldehydes to synthesize secondary alcohols has become a useful method because of the high functional group tolerance of the organozinc reagents. Many highly enantioselective catalysts have been developed for the asymmetric alkylzinc addition to aldehydes.[1] For the arylzinc additions, most of the reports are on the use of diphenylzinc because only this diarylzinc reagent is commercially available.[2] Bolm[3] and Dahmen[4] reported the use of the preprepared arylboronic acids and arylboranes in combination with Et_2Zn to generate various arylzincs for the catalytic asymmetric addition to aldehydes. Walsh prepared diarylzincs from the reaction of aryl bromides with ^{n}BuLi at low temperature and conducted the subsequent enantioselective addition to aldehydes.[5] Since the preparation of arylzincs in this method uses an alkyllithium, it could potentially limit the type of functional groups on the resulting diarylzincs.

Recently, Knochel reported a preparation of diarylzincs from the reaction of aryliodides with a dialkylzinc under very mild conditions.[6] The use of a dialkylzinc in this method instead of an alkyllithium allows the preparation of a great variety of functional arylzinc reagents. We tested the reaction of aldehydes with a few functional arylzincs prepared in situ with this method but only observed very low yields of the alcohol products. Scheme 1 shows the reaction of *m*-iodoanisole with Et_2Zn under Knochel's conditions, which presumably produced a diarylzinc complex.[6] When this arylzinc was treated with cyclohexanecarboxaldehyde at

Scheme 1. Preparation of a Substituted Arylzinc and Its Addition to an Aldehyde



(1) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
(2) (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470. (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445. (c) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222–4223. (d) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295–1296.
(3) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851.
(4) Dahmen, S.; Lormann, M. *Org. Lett.* **2005**, *7*, 4597–4600.
(5) Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175–4178.

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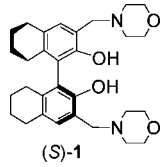
room temperature, the corresponding alcohol was isolated in only 30% yield after 19 h. Thus, these arylzincs have quite low nucleophilicity under the reaction conditions and need to be activated for addition to aldehydes.

Herein, we report our discovery of a catalytic process that can not only activate the arylzincs prepared in situ from the reaction of aryl iodides with Et_2Zn for the nucleophilic addition to aldehydes but can also provide excellent enantioselectivity.

Previously, we found that the chiral 1,1′-binaphthyl compound (*S*)-**1**, prepared in one step from (*S*)-H_8BINOL (5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol), was highly enantioselective for the reaction of diphenylzinc with aldehydes.[7] This compound was tested for the reaction of the functional arylzincs with aldehydes. We were delighted to find that in the presence of 10 mol % of (*S*)-**1**, the arylzinc generated in situ from *m*-iodoanisole reacts with cyclohexanecarboxaldehyde to give the desired secondary alcohol not only in greatly increased yield (94%) but also with very high enantioselectivity (>99% ee). Thus, (*S*)-**1** not only activates the nucleophilic arylzinc addition to the aldehyde but also has excellent stereocontrol.

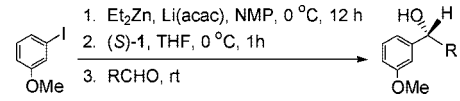


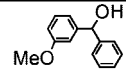
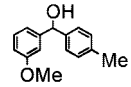
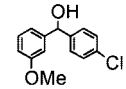
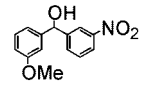
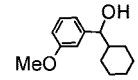
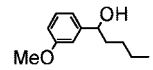
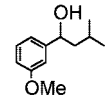
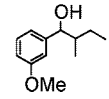
(*S*)-**1**

Table 1 summarizes the reaction of the in situ prepared (3-MeO-C_6H_4)$_2$Zn with various aldehydes catalyzed by (*S*)-**1**. In the presence of 10 mol % of (*S*)-**1**, the arylzinc additions to aromatic and aliphatic aldehydes are activated. Without (*S*)-**1**, the reactions are much slower with very low yields of the alcohol products. For example, almost no product was obtained for the arylzinc addition to *m*-nitrobenzaldehyde in the *absence* of (*S*)-**1** (entry 4). However, using (*S*)-**1** led to 93% yield of the desired diarylcarbinol. In addition, high enantioselectivity (83−>99% ee) was achieved for the arylzinc addition to both aromatic and aliphatic aldehydes. In entry 8, the addition to a chiral aldehyde generated both diastereomers in 1:1 ratio, each with over 99% ee.

Following is the general procedure used for the reactions shown in Table 1. Under nitrogen, to a 10 mL round-bottom flask (flame dried under vacuum) were added sequentially Li(acac) (24 mg, 0.23 mmol, 0.25 equiv), 3-iodoanisole (238 μL, 2.0 mmoL, 2.2 equiv), and NMP (1.5 mL). This mixture was cooled to 0 °C, and Et_2Zn (115 μL, 1.1 mmoL, 1.2 equiv) was added dropwise. The mixture was stirred at 0 °C for 12 h to which a solution of (*S*)-**1** (45 mg, 0.091 mmoL, 10 mol %) in THF (5 mL) was then transferred. This was stirred at 0 °C for 1 h and then warmed to room temperature. An aldehyde (0.91 mmoL) was added, and the reaction was monitored by TLC. Upon completion of the reaction, ammonium chloride (saturated aqueous) was added to quench the reaction. CH_2Cl_2 was used to extract the mixture three times. The organic fractions were dried over Na_2SO_4 and concentrated, and the residue was purified by flash column

Table 1. Addition of the Arylzinc Generated from *m*-Iodoanisole to Aldehydes in the Presence of (*S*)-**1**



entry	product	t (h)[a]	yield (%)	ee (%)	yield without (*S*)-**1**
1		7	93	91	56
2		11	95	91	43
3		10	85	90	41
4		8	93	83	trace
5		16	93	>99	30
6		14	85	96	10
7		16	85	93	17
8		10	90[b]	>99; 99	25

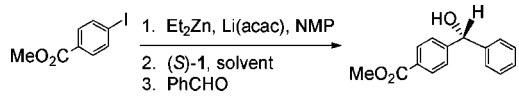
[a] Third step. [b] The combined yield of both diastereomers.

chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (0−12% ethyl acetate) to give the alcohol product as either an oil or solid in 85 to 95% yield. The ee's were 83−>99% determined by using HPLC: Chiralcel OD-H column (solvent: hexanes/2-propanol). The absolute configuration for (*m*-methoxyphenyl)phenylcarbinol generated from (*S*)-**1** was determined to be *R* by comparing its optical rotation with that reported in the literature.[8]

Using a procedure similar to that described above, we conducted the reaction of benzaldehyde with the arylzinc generated in situ from methyl *p*-iodobenzoate and Et_2Zn. As shown in entry 1 of Table 2, this gave only low yield (47%) and ee (67%) of the corresponding diarylcarbinol product. Increasing the time for the arylzinc formation step at room temperature increased the yield to 63% and the ee to 71% (entry 2). Using Ph_2Zn or Et_2Zn to prepare the zinc complex of (*S*)-**1** as the catalyst increased the yield but decreased the ee (entries 3,4). Increasing the amount of (*S*)-**1** to 20 mol % did not improve the enantioselectivity (entry 5). Changing the solvent in the second step from THF to toluene or Et_2O

(6) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017–1021.
(7) Qin, Y.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 273–277.
(8) Kosaka, M.; Sugito, T.; Kasai, Y.; Kuwahara, S.; Watanabe, M.; Harada, N.; Job, G. E.; Shvet, A.; Pirkle, W. H. *Chirality* **2003**, *15*, 324–328.

Table 2. Conditions for the Reaction of Methyl *p*-Iodobenzoate with Benzaldehyde in the Presence of Et_2Zn and (*S*)-**1**[a,b]



entry	reaction time first step (h)	(*S*)-**1** (mol %)	solvent second step (mL)	reaction temp second step (°C)	reaction temp third step (°C)	reaction time third step (h)	isolated yield (%)	ee (%)
1[c]	12	10	THF (5)	rt	rt	27	47	67
2[d]	12	10	THF (5)	rt	rt	27	63	71
3[e]	18	10	THF (5)	rt	rt	22	75	54
4[f]	16	10	THF (5)	rt	rt	27	90	52
5	18.5	20	THF (5)	0	rt	17.5	86	65
6[g]	21	10	toluene (5)	0	rt	23	quant.	45
7	21	10	Et_2O (5)	0	rt	23	80	55
8	18.5	10	CH_2Cl_2 (5)	0	rt	16	88	79
9	12	10	CH_2Cl_2 (10)	0	rt	9	93	84
10	17	20	CH_2Cl_2 (5)	0	rt	9	99	84
11	**18**	**20**	**CH_2Cl_2 (20)**	**0**	**0**	**17**	**97**	**94**

[a] Unless otherwise indicated, the following conditions were employed: 2.0 mmol of methyl *p*-iodobenzoate (2.2 equiv), 0.24 mmol of Li(acac) (0.25 equiv), 1.1 mmol of Et_2Zn (1.2 equiv), NMP (1.5 mL), and 0.91 mmol of benzaldehyde. Preparation of the arylzinc in the first step was conducted at 0 °C. Upon addition of a solution of (*S*)-**1** to the arylzinc solution, the reaction mixture was stirred for 1 h prior to addition of benzaldehyde. [b] ee's were measured on Chiralpak HPLC AD column (2% IPA:98% hexanes, 1 mL/min). [c] Arylzinc was prepared at 0 °C for 6 h and then at rt for 6 h. [d] Arylzinc was prepared at 0 °C for 0.5 h and then at rt for 11.5 h. [e] (*S*)-**1** was mixed with Ph_2Zn (2.0 equiv versus the ligand) at rt for 1 h and then combined with benzaldehyde before addition to the arylzinc solution. [f] (*S*)-**1** was mixed with Et_2Zn (2.0 equiv versus the ligand) at rt for 1 h and then combined with benzaldehyde before addition to the arylzinc solution. [g] 3.2 equiv of aryl iodide was used.

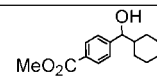
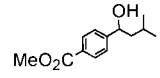
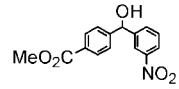
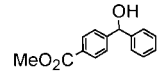
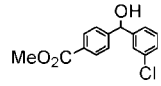
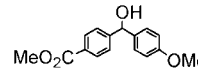
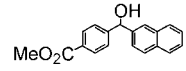
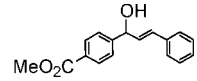
decreased the ee (entries 6 and 7). Using CH_2Cl_2 as the solvent in the second step significantly improved both the yield and ee (entry 8). Increasing the amount of CH_2Cl_2 further improved the enantioselectivity (entry 9). Finally, by using 20 mol % of (*S*)-**1** in CH_2Cl_2 at 0 °C, up to 97% yield and 94% ee were obtained for this reaction (entry 11).

The optimized conditions of entry 11 in Table 2 are applied to the reaction of various aldehydes with the arylzinc generated in situ from methyl *p*-iodobenzoate and Et_2Zn, and the results are summarized in Table 3. High yield and enantioselectivity are observed for a variety of aliphatic, aromatic, and α,β-unsaturated aldehydes. Using (*S*)-**1** has greatly activated the arylzinc addition with high stereocontrol. For example, without (*S*)-**1**, there is little addition of the arylzinc generated from methyl *p*-iodobenzoate to cyclohexanecarboxaldehyde (4% yield). In the presence of 20 mol % of (*S*)-**1**, the desired product was isolated in 86% yield and 96% ee (entry 1).

We also studied the reaction of benzaldehyde with the arylzinc generated from *m*-iodobenzonitrile in the presence of (*S*)-**1**. Table 4 summarizes the conditions for this reaction. It was found that THF was a better solvent than others such as CH_2Cl_2, toluene, and Et_2O (entries 1−11). The optimized conditions involved the use of 40 mol % of (*S*)-**1** and THF at 0 °C, which gave the product in 87% yield and 84% ee (entry 14).

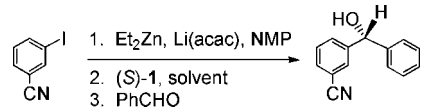
The conditions in entry 14 of Table 4 are applied to the reactions of several aldehydes with the arylzinc generated in situ from *m*-iodobenzonitrile and Et_2Zn. As shown in Table 5, good yields and enantioselectivity are observed for the addition to several aromatic and aliphatic aldehydes.

Table 3. Addition of the Arylzinc Generated from Methyl *p*-Iodobenzoate to Aldehydes in the Presence of (*S*)-**1**[a]

entry	product	t (h)[b]	yield (%)	ee (%)	yield without (*S*)-**1**
1		16	86	96	4
2		15	91	94	28
3		13	84	92	37
4		17	97	94	
5		15	93	88	
6		15	52	89	
7		15	89	92	
8		20	90	87	

[a] Conditions: 2.0 mmol of methyl *p*-iodobenzoate (2.2 equiv), 0.23 mmol of Li(acac) (0.25 equiv), 1.1 mmol of Et_2Zn (1.2 equiv), NMP (1.5 mL), (*S*)-**1** (20 mol %), and 0.91 mmol of aldehyde. Preparation of the arylzinc in the first step was conducted at 0 °C for 18 h. Upon addition of a CH_2Cl_2 (20 mL) solution of (*S*)-**1** to the arylzinc solution (second step), the reaction mixture was stirred at 0 °C for 1 h prior to addition of aldehyde (third step). [b] Third step.

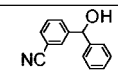
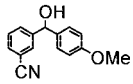
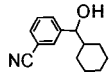
Table 4. Conditions for the Reaction of *m*-Iodobenzonitrile with Benzaldehyde in the Presence of Et_2Zn and (*S*)-**1**[a,b]



entry	*m*-iodobenzonitrile (equiv vs PhCHO)	(S)-**1** (mol%)	solvent second step (mL)	reaction temp second step (°C)	reaction temp third step (°C)	reaction time third step (h)	isolated yield (%)	ee (%)
1[c]	2.2	10	THF (5)	0	rt	30	77	66
2[c,d]	2.2	10	CH_2Cl_2 (5)	0	rt	20	93	35
3	2.2	10	CH_2Cl_2 (5)	0	rt	20	87	52
4	2.2	10	toluene (5)	0	rt	20	80	25
5[e]	2.2	10	Et_2O (5)	0	rt	20	80	42
6	2.2	20	THF (20)	0	rt	24	61	77
7	2.6[j]	20	CH_2Cl_2 (10)	0	0	22	65	52
8	2.6[j]	20	THF (10)	0	0	22	27	38
9[f]	2.2	20	THF (20)	rt	rt	24	70	71
10[f]	2.2	20	CH_2Cl_2 (20)	rt	rt	24	40	73
11[f,g]	3.2[k]	20	toluene (20)	rt	rt	36	70	17
12	2.2	20	THF (20)	0	11−13	44	50	79
13[h]	3.2[k]	40	THF (25)	rt	0	36	60	88
14[i]	**3.2**[k]	**40**	**THF (25)**	**rt**	**0**	**48**	**87**	**84**

[a] Unless otherwise indicated, the following conditions were employed: Li(acac) (0.25 equiv), Et_2Zn (1.2 equiv), NMP (1.5 mL), and 0.91 mmol of benzaldehyde. Arylzinc preparation proceeded at 0 °C for 18 h. A solution of (*S*)-**1** was added to the arylzinc solution and stirred for 1 h before the addition of benzaldehyde. [b] ee's were measured on a Chiralpak HPLC AD column (solvent: 2-propanol/hexanes). [c] Arylzinc was prepared at 0 °C for 17 h. [d] 1.1 mmol of *m*-iodobenzonitrile and 0.5 mmol of benzaldehyde were used. [e] (*S*)-**1** was sonicated in Et_2O for 45 m. [f] (*S*)-**1** was mixed with Ph_2Zn (2 equiv versus the ligand) at rt for 1 h and then combined with benzaldehyde before addition to the arylzinc solution. [g] Arylzinc was prepared at 0 °C for 12 h. [h] Arylzinc was prepared at 0 °C for 14 h and then at rt for 4 h. [i] Arylzinc was prepared at 0 °C for 2 h and then at rt for 34 h. [j] Li(acac) (0.31 equiv) and Et_2Zn (1.4 equiv). [k] Li(acac) (0.38 equiv) and Et_2Zn (1.8 equiv),

Table 5. Addition of the Arylzinc Generated from *m*-Iodobenzonitrile to Aldehydes in the Presence of (*S*)-**1**[a]

entry	product	t (h)[b]	yield (%)	ee (%)
1		48	87	84
2		48	74	79
3		48	82	91
4		48	77	>98

[a] Conditions: Li(acac) (0.38 equiv), Et_2Zn (1.8 equiv), NMP (1.5 mL), and 0.91 mmol of aldehyde. Arylzinc preparation proceeded at 0 °C for 2 h and rt for 34 h (first step). A THF (25 mL) solution of (*S*)-**1** (40 mol %) was added to the arylzinc solution (second step) and stirred at rt for 1 h. It was then cooled to 0 °C for the addition of aldehyde (third step). [b] Third step.

In summary, we have discovered that an easily available chiral ligand (*S*)-**1** can activate the nucleophilic reaction of the arylzincs prepared in situ from aryliodides and Et_2Zn. Both high yields and high enantioselectivity for the reaction of the arylzincs with a variety of aldehydes are obtained. The mild reaction conditions and the good functional group tolerance make this method synthetically useful. We are currently working on modifying the structure of the catalyst in order to further improve this catalytic asymmetric reaction.

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Supporting Information Available: Synthesis, characterization and ee determination of the chiral alcohol products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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