JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

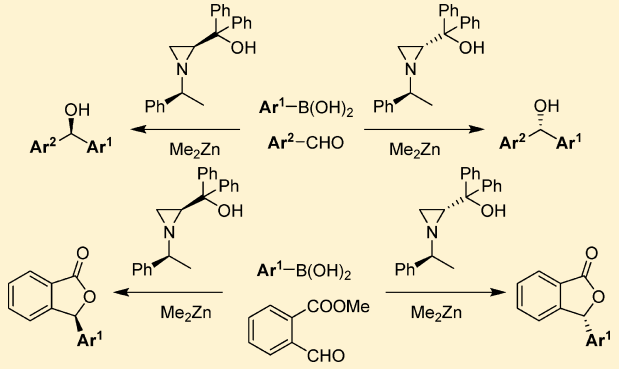
Diastereomeric Aziridine Carbinol Catalyzed Enantioselective Arylation Reaction: Toward the Asymmetric Synthesis of Both Enantiomers of Chiral 3-Aryl Phthalide

Xixi Song, Yuan-Zhao Hua, Jing-Guo Shi, Ping-Ping Sun, Min-Can Wang,* and Junbiao Chang*

The College of Chemistry and Molecular Engineering, Zhengzhou University, No. 75 Daxue Road, Zhengzhou, Henan Province 450052, P. R. China

Supporting Information

ABSTRACT: The diastereomeric aziridine carbinols are applied, respectively, as efficient chiral ligand in the catalysis of asymmetric arylation and sequential arylation-lactonization cascade. The two diastereomers, which are facilely synthesized from the same chiral source, function as pseudo enantiomers in arylation of aromatic aldehydes providing the different enantiomers of the diarylmethanols with almost the same excellent enantioselectivities. The arylation method is also carried out in tandem with lactonization process to afford a concise synthetic approach to both enantiomers of optically active 3-aryl phthalide.



INTRODUCTION

The catalytic enantioselective addition of arylzinc species to aromatic aldehydes in the presence of chiral ligand is one of the powerful asymmetric arylation methods, which produces biologically and pharmacologically valuable diarylmethanols.[1] As early as in 2002, Bolm and co-workers introduced an important arylation protocol for the catalyzed synthesis of optically active diarylmethanols with excellent enantioselectivities.[2] The reactive arylalkylzinc species, which was the real arylating agent, was generated from arylboronic acid and dialkylzinc reagent via the boron to zinc transmetalation. Since various commercially available and readily prepared arylboronic acids could be used as aryl source, the scope of transferable aryl groups has been extensively broadened. Following the early pioneering work, the arylation protocol is well studied, and many efficient chiral ligands have been developed.[3] However, compared to the intensive practical application of the protocol, the strategy for asymmetric synthesis of each enantiomer of the arylation product has not been fully developed.[4]

Traditionally, in order to prepare each enantiomer of diarylmethanol, all two enantiomers of a chiral ligand are usually required for asymmetric catalysis (Scheme 1, eq 1). One enantiomer (e.g., **1a** in eq 1, Scheme 1) can often be synthesized from natural chiral sources, such as L-amino acids, which are available in only one absolute configuration, but the other enantiomer (e.g., **1b** in eq 1, Scheme 1) may be not equally accessible. To overcome the limitation, a strategy based on the swapping of aryl groups has been developed (Scheme 1, eq 2).[1,5] Each enantiomer of diarylmethanol can be selectively accessed by using the same enantiomer of chiral ligand (e.g., **1a** in eq 2, Scheme 1), just by interchanging the aryl groups of arylboronic acid and aldehyde ($\mathbf{Ar^1}$ and $\mathbf{Ar^2}$ in eq 2, Scheme 1). However, the aryl moiety bearing strong electronic withdrawing group, such as ester or amide, is not suitable for swapping, because of the insufficient nucleophilicity. Additionally, the applicability of the strategy in complicated synthetic process, such as a tandem sequence, is also limited by the requirement of two different sets of reactants.

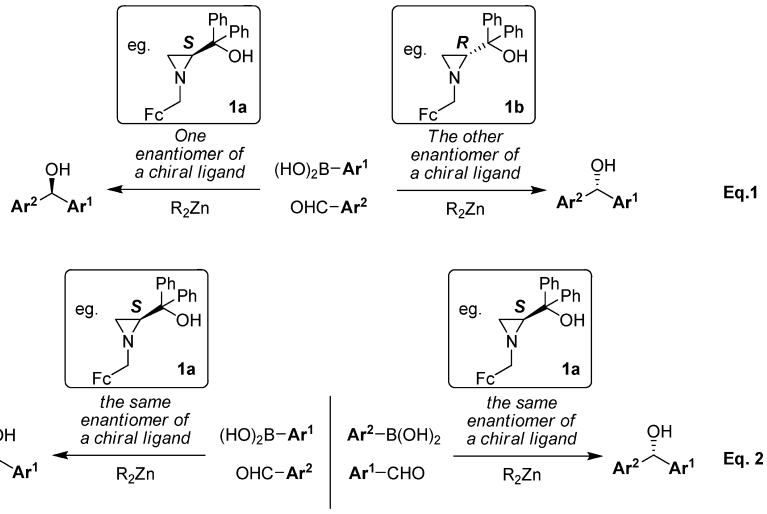
Recently in our research group, a pair of diastereomeric aziridine carbinols (Scheme 2, **3a** and **3b**) was facilely synthesized in two steps from the same starting materials, with (*S*)-α-methylbenzyl amine **2** as the only chiral source.[6] The two ligands share the same chiral *N*-(*S*)-phenylethyl moiety, but bear the β-amino alcohol backbones of the opposite absolute configurations. Each diastereomer catalyzed asymmetric alkylation of various aldehydes, and afforded opposite enantiomers of alkylation products in almost identical excellent enantioselectivities. To broaden the applicability of the pseudo enantiomeric ligand pair, we directly apply them in the asymmetric arylation of aromatic aldehyde by using the boron to zinc transmetalation protocol, and each enantiomer of diarylmethanol is produced from the same set of reactants (Scheme 2, eq 1).

In another aspect, the 3-functionalized phthalides are widely distributed in a large population of natural products, and possess broad physiological and biological activities, which

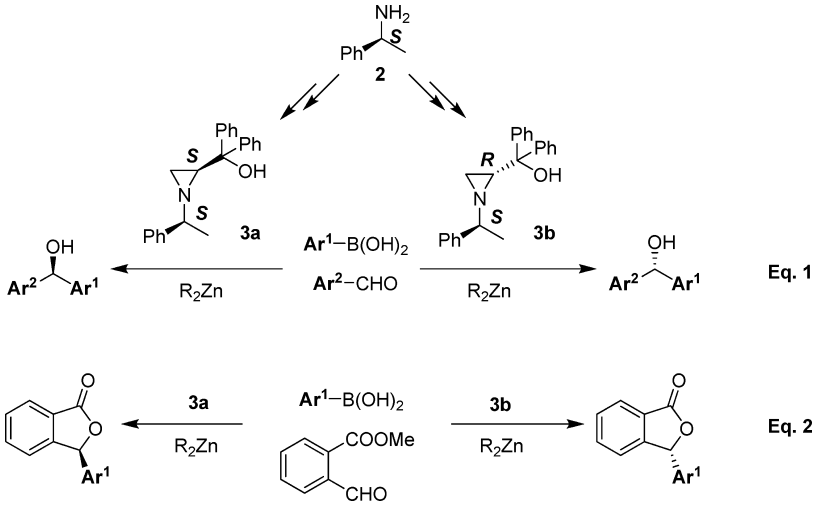
Received: April 8, 2014
Published: June 9, 2014

dx.doi.org/10.1021/jo500796w | J. Org. Chem. 2014, 79, 6087–6093

Scheme 1. Previous Strategies for the Construction of Both Enantiomers of Diarylmethanol



Scheme 2. Access to Each Enantiomer of Diarylmethanol and Its Derivative by Using Diastereomeric Aziridine Carbinol as Chiral Ligand



render them important structural motifs for natural product syntheses and pharmaceutical elaborations.[7] Although various catalytic strategies have been developed for the asymmetric synthesis of chiral phthalides, most of these methods require expensive transition-metals as well as laboriously accessible chiral ligands, some of them do not give satisfactory stereoselectivity, and neither of them could facilely construct each enantiomer of the chiral framework.[8] In this context, considering the readily availability of cheap organozinc reagents, arylboronic acids and our diastereomeric aziridine carbinol ligands, we develop the asymmetric tandem approach to construct each enantiomer of chiral 3-aryl phthalide by using the Bolm's arylation protocol (Scheme 2, eq 2).

RESULTS AND DISCUSSION

Consideration of Diastereomeric Ligands. During the development of suitable chiral ligands for the Bolm's asymmetric arylation, it is found that most of the effective ligands share the bidentate backbone with two different heteroatoms as donors, and the successful catalytic results have been acquired predominantly by using β-amino alcohol as chiral backbone.[5a,b] Despite efforts in developing novel ligand framework, few studies have focused on the behavior of different diastereomeric β-amino alcohols in the asymmetric arylation.[5b,i]

Recently, the two diastereomeric triphenylprolinols (Figure 1, **5a** and **5b**) were synthesized by Correia and Lüdtke and co-

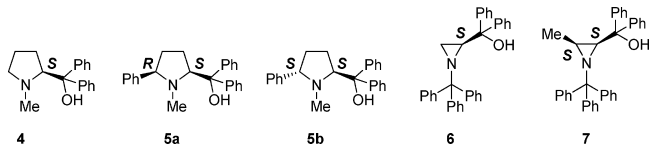


Figure 1. Examples of β-amino alcohol ligands for asymmetric arylation.

workers, and were used as effective chiral ligands in the asymmetric arylation of aldehydes.[5b] Because the diarylprolinol ligand **4** and the two diastereomeric analogues (Figure 1, **5a** and **5b**), respectively, afforded chiral diarylmethanol product in the same absolute configuration and comparable enantioselectivity, it is assumed that the chiral center outside the β-amino alcohol backbone does not provide decisive contribution to stereoselective induction. Besides the five-membered frame-

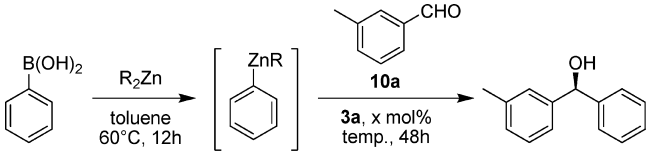
dx.doi.org/10.1021/jo500796w | J. Org. Chem. 2014, 79, 6087–6093

work, aziridine-2-methanol analogues (Figure 1, **6** and **7**) were also examined in the Bolm's arylation reaction by Braga and Wessjohann and co-workers.[5i] However, compared to ligand **6**, which gave excellent enantioselectivity, the ligand **7** with an extra methyl substituent on the aziridine ring produced a poor stereoselectivity of 17% ee.

On the basis of these examples, we speculated that an extra chiral center outside the enantiopure aziridine ring might not interfere with stereoselective induction in asymmetric catalysis. As for the diastereomeric aziridine carbinols (Scheme 2, **3a** and **3b**), the *N*-(*S*)-phenylethyl moiety originated from the chiral source (*S*)-α-methylbenzyl amine **2** and served as a chiral auxiliary during the preparation of diastereomers.[6] In this context, we proposed that the *N*-(*S*)-phenylethyl moiety should simply function as a steric hindrance group, and make little decisive contribution to the stereoselective induction in the catalysis of asymmetric arylation reaction. As a result, the diastereomers (**3a** and **3b** in Scheme 2) would behave as pseudo enantiomers (such as **1a** and **1b** in Scheme 1).

Optimization of Reaction Conditions. Initially, the optimization of reaction conditions was carried out, and one diastereomer of aziridine carbinols was directly used in the template reaction (Table 1). On the basis of the boron to zinc transmetalation protocol, phenylboronic acid **8a** was treated with diethylzinc in toluene at 60 °C. After the phenylalkylzinc species **9a** was prepared, the chiral ligand **3a** and 3-methylbenzaldehyde **10a** were added into the reaction mixture. When the arylation process was carried out at 20 °C, the (*S*)-phenyl(*m*-tolyl)methanol **11a-S** was obtained as desired product in only 22% yield and 43% ee (Table 1, entry 1). In Bolm's classical protocol, the 3-fold excess of dialkylzinc reagent comparing with arylboronic acid was usually used.[2,3,5] After optimization, it was found that the increase of the usage of diethylzinc to nearly 5-fold excess would give improved results in both yield and enantioselectivity (Table 1, entry 2). If the reaction temperature was decreased to 0 °C, the diarylmethanol was afforded in 78% yield without sacrifice of stereoselectivity (Table 1, entry 3). Further lowering the temperature to −20 °C decreased the reaction yield to 27% (Table 1, entry 4). Additionally, when the catalyst loading was decreased to 5 mol %, the yield was brought down to 50% (Table 1, entry 5). The increase of catalyst loading to 20 mol % could significantly boost the reaction yield to 83% and the enantioselectivity to 80% ee (Table 1, entry 6). To our delight, when the organozinc reagent was changed from diethylzinc to dimethylzinc, the enantiomeric excess increased to 96% (Table 1, entry 7). With dimethylzinc as the selected reagent, reaction temperature and catalyst loading were screened again (data not shown in Table 1), and the optimal conditions remained the same as of diethylzinc.

Table 1. Optimization of Reaction Conditions of the Catalytic Asymmetric Arylation of 3-Methylbenzaldehyde[a]



entry	R	**3a** (mol %)	temp. (°C)	yield (%)	ee (%)[b]
1[c]	Et	10	20	22	43
2	Et	10	20	26	48
3	Et	10	0	78	49
4	Et	10	−20	27	51
5	Et	5	0	50	66
6	Et	20	0	83	80
7	Me	20	0	76	96

[a]Reaction conditions: The mixture of phenylboronic acid **8a** (0.5 mmol) and dialkylzinc (2.4 mmol) was heated at 60 °C for 12 h, and substrate **10a** (0.25 mmol) together with chiral ligand **3a** (mol % relative to **10a**) were added to the reaction mixture and stirred for 2 days at designated temperature. [b]The ee value was determined by HPLC using Chiralcel OD column, and the absolute configuration of **11a-S** was assigned as *S* by correlation to literature data.[9] [c]The 3-fold excess of dialkylzinc (1.5 mmol) comparing with **8a** was used.

Scope of Asymmetric Arylation Reaction. Encouraged by the results obtained in the template reaction, substrate scope was further expanded to test the generality of the method (Table 2). Under the optimal reaction conditions, when another diastereomer **3b** was used as chiral ligand, the (*R*)-phenyl(*m*-tolyl)methanol **11a-R**, which is the opposite enantiomer of **11a-S**, was afforded in 72% yield and 98% ee (Table 2, entry 2). It was found that the arylation reactions of various aromatic aldehydes were complete after 2 days with good to high yields (72−96%) and moderate to excellent enantioselectivities (80−98% ee), irrespective of the position and electronic nature of the substituents on the phenyl ring (Table 2). Meanwhile, various substituted arylboronic acids were also well-tolerated in the catalytic system (Table 2, entries 11−18).

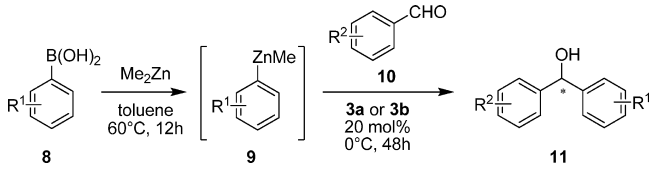
In most of these cases, each enantiomer of a chiral diarylmethanol was produced in similar good yield and almost identical excellent enantioselectivity of more than 90% ee. Each diastereomeric aziridine carbinol ligand demonstrated almost the same ability in enantioselective induction. On the basis of our previous conformational analysis of the ligands, we proposed that the ligand **3a** should control the addition of arylmethylzinc species to the *Si*-face of the prochiral aromatic aldehydes, and the ligand **3b** should control the addition to the *Re*-face.[6]

Design of Cascade Process. Considering that the organozinc reagents possess the appropriate balance between nucleophilicity and basicity, and the high functional-group tolerance, we envision that the diastereomeric aziridine carbinol catalyzed arylation can be carried out in conjunction with lactonization to stereoselectively produce each enantiomer of chiral 3-aryl phthalide (Scheme 3). The bifunctional substrate, methyl 2-formylbenzoate **12**, was chosen for the sequential processes. As shown in the proposed mechanism, the reactive arylalkylzinc species is *in situ* generated by using the boron to zinc transmetalation. After the enantioselective aryl transfer to the electronic deficient aldehyde **12**, the resulting diarylmethoxy alkyl zinc intermediate **13** would proceed with intramolecular cyclization to generate 3-aryl phthalide **14**. The similar strategies based on addition−lactonization cascade have been reported by using different catalytic systems.[8b,c] Comparing with those works, our method would provide a more practical approach from the following aspects: (i) the use of a cheap transition metal, (ii) a broad range of transferable aryl group, and (iii) the accessibility to each enantiomer of chiral 3-aryl phthalide product.

Scope of Asymmetric Arylation−Lactonization Cascade. On the basis of the above proposition, the methyl 2-formylbenzoate **12** was directly applied into the well-developed

dx.doi.org/10.1021/jo500796w | J. Org. Chem. 2014, 79, 6087−6093

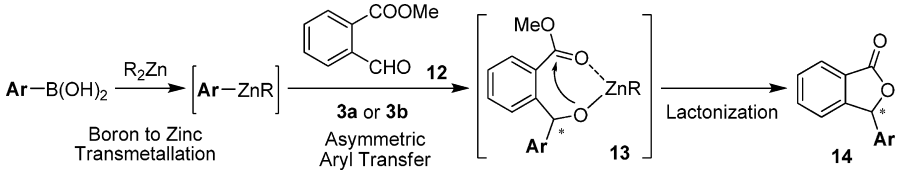
Table 2. Catalytic Asymmetric Arylation of Aromatic Aldehydes with Arylboronic Acid by Using Diastereomeric Aziridine Carbinol as Chiral Ligand[a]



entry	R^1	R^2	ligand	11	yield (%)	ee (%)[b]	configuration[c]
1	H	3-Me	**3a**	**11a-S**	76	96	*S*
2	H	3-Me	**3b**	**11a-R**	72	98	*R*
3	H	2-Me	**3a**	**11b-S**	79	80	*S*
4	H	2-Me	**3b**	**11b-R**	86	96	*R*
5	H	4-MeO	**3a**	**11c-S**	84	96	*S*
6	H	4-MeO	**3b**	**11c-R**	78	98	*R*
7	H	2-Br	**3a**	**11d-S**	87	97	*S*
8	H	2-Br	**3b**	**11d-R**	90	97	*R*
9	H	4-Cl	**3a**	**11e-S**	88	96	*S*
10	H	4-Cl	**3b**	**11e-R**	90	96	*R*
11	4-Me	4-Cl	**3a**	**11f-S**	94	96	*S*
12	4-Me	4-Cl	**3b**	**11f-R**	96	97	*R*
13	4-Me	2-MeO	**3a**	**11g-R**	90	94	*R*
14	4-Me	2-MeO	**3b**	**11g-S**	95	96	*S*
15	4-MeO	H	**3a**	**11c-R**	84	97	*R*
16	4-MeO	H	**3b**	**11c-S**	83	98	*S*
17	4-MeO	4-Cl	**3a**	**11h-S**	89	97	*S*
18	4-MeO	4-Cl	**3b**	**11h-R**	94	89	*R*

[a]Reaction conditions: The mixture of arylboronic acid **8** (0.5 mmol) and dimethylzinc (2.4 mmol) was heated at 60 °C for 12 h, and substrate **10** (0.25 mmol) together with chiral ligand **3a** or **3b** (mol % relative to **10**) were added to the reaction mixture and stirred for 2 days at 0 °C. [b]Determined by chiral HPLC. [c]The absolute configuration of **11** was assigned by correlation to literature data.[5,9,10]

Scheme 3. Proposed Reaction Mechanism for the Asymmetric Arylation−Lactonization Cascade



arylation conditions without further optimization, and each enantiomer of chiral 3-aryl phthalide **14** was efficiently produced in enantiomerically enriched form (Table 3). Various substituted arylboronic acids were inspected in the cascade process to broaden the substrate scope. Good yields were obtained, and enantioselectivities of opposite enantiomers were nearly identical in most cases (Table 3, entries 1 vs 2, 3 vs 4, etc.).

The pattern of enantioselectivities implied a strong electronic dependency. The phenylboronic acid (Table 3, entries 11 and 12) and substituted arylboronic acids bearing electronic donating groups (Table 3, entries 1−10) gave moderate to excellent enantioselectivities ranging from 77% to 97% ee. And the arylboronic acids bearing weak electronic withdrawing groups (Table 3, entries 13−18) provided poor to mediocre enantioselectivities from 7% to 56% ee. Comparing with the strong electronic effect, the steric hindrance effect was weak. As for the same substituent, such as methyl, methoxyl, or chlorine, on arylboronic acid, different substituted positions gave similar enantioselective outcomes (Table 3, entries 1, 3 and 5, etc.).

CONCLUSION

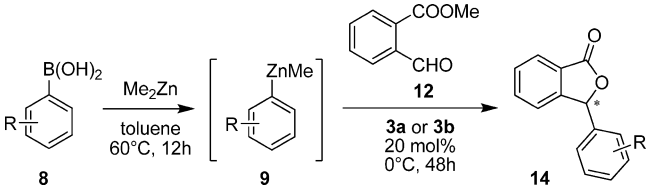
In summary, we reported the application of the diastereomeric aziridine carbinol in the catalytic asymmetric arylation reaction and the sequential arylation−lactonization cascade. The two diastereomeric ligands, which were facilely synthesized from the same chiral source, functioned as pseudo enantiomers in the asymmetric arylation of aromatic aldehydes, and each enantiomer of chiral diarylmethanol product was furnished in almost identical excellent enantioselectivity. The diastereomer catalyzed arylation method was directly applied to the arylation−lactonization process to develop a concise synthetic approach to both enantiomers of optically active 3-aryl phthalides. The usefulness of the diastereomeric aziridine carbinol ligands in asymmetric catalysis was broadened.

EXPERIMENTAL SECTION

General Methods. NMR spectra (^{1}H and ^{13}C) were performed on a commercial spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using solution in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in Hz; the ^{13}C NMR was proton-decoupled carbon NMR ($^{13}C\{^1H\}$ NMR). TLC was performed on dry silica gel plates developed with petroleum ether (60−90 °C) and ethyl acetate (EtOAc). The diastereomeric aziridine carbinol ligands (**3a** and **3b**)[6]

dx.doi.org/10.1021/jo500796w | J. Org. Chem. 2014, 79, 6087−6093

Table 3. Catalytic Asymmetric Synthesis of Both Enantiomers of 3-Aryl Phthalides by Using Diastereomeric Aziridine Carbinols[a]



entry	R	ligand	14	yield (%)	ee (%)[b]	configuration[c]
1	4-Me	**3a**	**14a-S**	93	96	*S*
2	4-Me	**3b**	**14a-R**	96	93	*R*
3	3-Me	**3a**	**14b-S**	88	91	*S*
4	3-Me	**3b**	**14b-R**	93	84	*R*
5	2-Me	**3a**	**14c-S**	93	94	*S*
6	2-Me	**3b**	**14c-R**	95	92	*R*
7	4-MeO	**3a**	**14d-S**	93	86	*S*
8	4-MeO	**3b**	**14d-R**	80	77	*R*
9	3-MeO	**3a**	**14e-S**	85	89	*S*
10	3-MeO	**3b**	**14e-R**	98	84	*R*
11	H	**3a**	**14f-S**	94	97	*S*
12	H	**3b**	**14f-R**	92	91	*R*
13	4-Cl	**3a**	**14g-S**	85	44	*S*
14	4-Cl	**3b**	**14g-R**	87	7	*R*
15	3-Cl	**3a**	**14h-S**	85	33	*S*
16	3-Cl	**3b**	**14h-R**	79	56	*R*
17	2-Cl	**3a**	**14i-R**	75	21	*R*
18	2-Cl	**3b**	**14i-S**	69	14	*S*

[a]Reaction conditions: The mixture of arylboronic acid **8** (0.5 mmol) and dimethylzinc (2.4 mmol) was heated at 60 °C for 12 h, and substrate **12** (0.25 mmol) together with chiral ligand **3a** or **3b** (mol % relative to **12**) were added to the reaction mixture and stirred for 2 days at 0 °C. [b]Determined by chiral HPLC. [c]The absolute configuration of **14** was assigned by correlation to literature data and considering the similarity in the stereochemical reaction pathway.[8,11]

and the substrate **12** were synthesized according to reported procedures. All other reagents were commercially available and used as received.

General Procedure for the Asymmetric Syntheses of Chiral Diarylmethanols 11 and 3-Aryl Phthalides 14. The mixture of 0.5 mmol arylboronic acid **8** and 2.4 mmol dimethylzinc (1.2 M in hexane) was stirred in 1.5 mL of anhydrous toluene at 60 °C for 12 h. After the reaction vessel was cooled to room temperature of 25 °C, 20 mol % chiral ligand **3a** or **3b** was added, and the reaction mixture was stirred at room temperature for 15 min. After the mixture was cooled to 0 °C, 0.25 mmol benzaldehyde substrate **10** or **12** was added into the reaction flask. After stirring for 2 days at 0 °C, the reaction mixture was quenched by 10 mL of saturated NH_4Cl aqueous solution and was extracted with 20 mL of diethyl ether three times. The combined organic phase was washed by brine, and was dried with anhydrous Na_2SO_4. The solvent was evaporated, and the crude residue was purified by column chromatography (petroleum ether/EtOAc). Absolute configurations of products **11** and **14** were assigned by correlation to literature data and considering the similarity in the stereochemical reaction pathway.[5,8−12]

(*S*)-Phenyl(*m*-tolyl)methanol (11a-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 76% yield (37.3 mg) and 96% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 100/2, flow rate = 1.0 mL/min, λ = 216 nm): $t_R(S)$ = 22.0 min, $t_R(R)$ = 32.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.30 (m, 4H), 7.27−7.14 (m, 4H), 7.07 (d, J = 7.3 Hz, 1H), 5.78 (s, 1H), 2.32 (s, 3H), 2.27 (br, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 144.0, 138.4, 128.7, 128.6, 127.7, 127.4, 126.7, 123.8, 76.5, 21.7 ppm.

(*S*)-Phenyl(*o*-tolyl)methanol (11b-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 79% yield (39.2 mg) and 80% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 100/2, flow rate = 0.5 mL/min, λ = 216 nm): $t_R(S)$ = 69.1 min, $t_R(R)$ = 63.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.48 (m, 2H), 7.34−7.28 (m, 4H), 7.26−7.17 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 5.96 (s, 1H), 2.31 (br, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 141.6, 135.6, 130.7, 128.7, 127.8, 127.7, 127.3, 126.5, 126.3, 73.6, 19.6 ppm.

(*S*)-(4-Methoxyphenyl)(phenyl)methanol (11c-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 84% yield (45.0 mg) and 96% ee. HPLC (Chiralcel AD, hexane/*i*-PrOH = 100/2, flow rate = 0.5 mL/min, λ = 216 nm): $t_R(S)$ = 102.7 min, $t_R(R)$ = 94.3 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.28 (m, 4H), 7.25−7.22 (m, 3H), 6.83 (d, J = 8.7 Hz, 2H), 5.74 (s, 1H), 3.75 (s, 1H), 2.42 (br, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 144.2, 136.4, 128.6, 128.1, 127.5, 126.6, 114.0, 75.9, 55.4 ppm.

(*S*)-(2-Bromophenyl)(phenyl)methanol (11d-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 87% yield (57.2 mg) and 97% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min, λ = 216 nm): $t_R(S)$ = 45.6 min, $t_R(R)$ = 29.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56−7.50 (m, 2H), 7.38−7.22 (m, 6H), 7.24−7.09 (m, 1H), 6.14 (s, 1H), 2.58 (br, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 142.3, 133.0, 129.3, 128.6, 127.9, 127.8, 127.2, 123.0, 74.9 ppm.

(*S*)-(4-Chlorophenyl)(phenyl)methanol (11e-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 88% yield (48.1 mg) and 96% ee. HPLC (Chiralcel OB, hexane/*i*-PrOH = 90/10, flow rate =1.0 mL/min, λ = 216 nm): $t_R(S)$ = 21.6 min, $t_R(R)$ = 14.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.29 (m, 4H), 7.27−7.26 (m, 5H), 5.74 (s, 1H), 2.50 (br, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 142.4, 133.4, 128.8, 128.7, 128.1, 128.0, 126.7, 75.7 ppm.

(*S*)-(4-Chlorophenyl)(*p*-tolyl)methanol (11f-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 94% yield (54.7 mg) and 96% ee. HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 216 nm): $t_R(S)$ = 72.6 min, $t_R(R)$ = 65.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28−7.27 (m, 4H), 7.20−7.11 (m, 4H), 5.72 (s, 1H), 2.37 (br, 1H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 140.8, 137.8, 133.3, 129.5, 128.7, 128.0, 126.7, 75.6, 21.3 ppm.

(*R*)-(2-Methoxyphenyl)(*p*-tolyl)methanol (11g-R). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 90% yield (51.4 mg) and 94% ee. HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min, λ = 216 nm): $t_R(S)$ = 41.6 min, $t_R(R)$ = 37.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27−7.22 (m, 4H), 7.11 (d, J = 8 Hz, 2H), 6.95−6.86 (m, 2H), 6.02 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 140.4, 136.8, 132.1, 128.7, 127.8, 126.6, 120.9, 110.8, 72.1, 55.5, 21.2 ppm.

(S)-(4-Chlorophenyl)(4-methoxyphenyl)methanol (11h-S). Purified by column chromatography (petroleum ether/EtOAc = 9:1) to give the product in 89% yield (55.3 mg) and 97% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 100/2, flow rate = 0.5 mL/min, λ = 216 nm): $t_R(S)$ = 94.1 min, $t_R(R)$ = 103.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26−7.20 (m, 6H), 6.82 (d, J = 8.5 Hz, 2H), 5.74 (s, 1H), 3.75 (s, 3H), 2.11 (br, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 142.4, 135.8, 133.1, 128.5, 127.9, 127.8, 114.0, 75.2, 55.3 ppm.

(*S*)-3-*p*-Tolylisobenzofuran-1(3*H*)-one (14a-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 93% yield (52.1 mg) and 96% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 5.82 min, $t_R(R)$ = 6.92 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.5 Hz, 1H), 7.64−7.51 (m, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.18−7.12 (m, 4H), 6.36 (s, 1H), 2.33 (s, 3H) ppm. ^{13}C NMR (100

dx.doi.org/10.1021/jo500796w | J. Org. Chem. 2014, 79, 6087−6093

MHz, $CDCl_3$): δ = 170.7, 149.9, 139.4, 134.4, 133.5, 129.7, 129.4, 127.1, 125.7, 125.6, 123.0, 82.8, 21.3 ppm.

(*S*)-3-*m*-Tolylisobenzofuran-1(3*H*)-one (14b-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 88% yield (49.3 mg) and 93% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 5.82 min, $t_R(R)$ = 7.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.5 Hz, 1H), 7.66−7.52 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.28−7.16 (m, 2H), 7.08−7.06 (m, 2H), 6.36 (s, 1H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 150.0, 139.0, 136.5, 134.5, 130.2, 129.4, 129.0, 127.6, 125.7, 124.2, 123.0, 83.0, 21.5 ppm.

(*S*)-3-*o*-Tolylisobenzofuran-1(3*H*)-one (14c-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 93% yield (52.1 mg) and 94% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 7.03 min, $t_R(R)$ = 9.01 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1H), 7.68−7.54 (m, 2H), 7.34−7.10 (m, 4H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.67 (s, 1H), 2.48 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 149.3, 137.1, 134.2, 134.1, 131.1, 129.3, 129.0, 127.2, 126.4, 125.6, 123.0, 80.5, 19.3 ppm.

(*S*)-3-(4-Methoxyphenyl)isobenzofuran-1(3*H*)-one (14d-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 93% yield (55.9 mg) and 86% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 9.31 min, $t_R(R)$ = 11.37 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1H), 7.67−7.53 (m, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.32−6.88 (m, 4H), 6.37 (s, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 160.6, 150.0, 134.4, 129.5, 129.0, 128.5, 126.1, 125.8, 123.1, 114.6, 82.9, 55.5 ppm.

(*S*)-3-(3-Methoxyphenyl)isobenzofuran-1(3*H*)-one (14e-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 85% yield (51.1 mg) and 89% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 8.73 min, $t_R(R)$ = 13.20 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.5 Hz, 1H), 7.66−7.53 (m, 2H), 7.36−7.27 (m, 2H), 6.91−6.79 (m, 2H), 6.37 (s, 1H), 3.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 160.2, 149.8, 138.1, 134.5, 130.2, 130.1, 129.6, 125.8, 123.0, 119.3, 114.8, 112.6, 82.7, 55.5 ppm.

(*S*)-3-Phenylisobenzofuran-1(3*H*)-one (14f-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 94% yield (49.4 mg) and 97% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 6.83 min, $t_R(R)$ = 8.63 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.5 Hz, 1H), 7.65−7.52 (m, 2H), 7.37−7.25 (m, 6H), 6.39 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 149.8, 136.5, 134.5, 129.5, 129.4, 129.1, 127.0, 125.7, 123.0, 82.8, 29.8 ppm.

(*S*)-3-(4-Chlorophenyl)isobenzofuran-1(3*H*)-one (14g-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 85% yield (52.0 mg) and 44% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 7.13 min, $t_R(R)$ = 8.04 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1H), 7.69−7.55 (m, 2H), 7.37−7.21 (m, 5H), 6.38 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 135.5, 135.2, 134.7, 129.8, 129.4, 128.6, 128.3, 126.0, 125.7, 123.0, 82.0 ppm.

(*S*)-3-(3-Chlorophenyl)isobenzofuran-1(3*H*)-one (14h-S). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 85% yield (52.0 mg) and 33% ee. HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(S)$ = 7.73 min, $t_R(R)$ = 8.25 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1H), 7.69−7.55 (m, 2H), 7.36−7.32 (m, 3H), 7.19 (d, *J* = 6.5 Hz, 1H), 6.37 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 149.2, 138.6, 135.1, 134.7, 130.5, 129.8, 127.1, 126.0, 125.5, 125.2, 123.0, 81.8 ppm.

(*R*)-3-(2-Chlorophenyl)isobenzofuran-1(3*H*)-one (14i-R). Purified by column chromatography (petroleum ether/EtOAc = 4:1) to give the product in 75% yield (45.9 mg) and 21% ee. HPLC (Chiralcel OD, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_R(R)$ = 7.23 min, $t_R(S)$ = 8.20 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1H), 7.66−7.47 (m, 4H), 7.32−7.20 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.95 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 149.7, 134.8, 134.7, 133.1, 130.4, 130.3, 129.7, 127.8, 127.7, 126.0, 125.6, 123.1, 79.3 ppm.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The ^{1}H and ^{13}C NMR spectra of diastereomeric aziridine carbinols **3a** and **3b**, diarylmethanols **11**, methyl 2-formylbenzoate **12**, and 3-aryl phthalides **14**; chiral HPLC spectra of chiral diarylmethanols **11**, and chiral 3-aryl phthalides **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wangmincan@zzu.edu.cn.

*E-mail: changjunbiao@zzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (NSFC: 81330075, 21272216 and 21302173) and the China Postdoctoral Science Foundation (2013M541984). We express our gratitude to Professor Wei Wang (University of New Mexico), Professor Gregory Cook (North Dakota State University) and Dr. Narayanaganesh Balasubramanian (North Dakota State University) for editing and giving comments on this manuscript.

■ REFERENCES

(1) For selective reviews on the catalytic asymmetric addition of arylzinc species, see: (a) Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139−208. (b) Lemire, A.; Côté, A.; Janes, M. K.; Charette, A. B. *Aldrichimica Acta* **2009**, *42*, 71−83. (c) Paixão, M. W.; Braga, A. L.; Lüdtke, D. S. *J. Braz. Chem. Soc.* **2008**, *19*, 813−830. (d) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454−470. (e) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (f) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308. (g) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188. (h) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.

(2) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851.

(3) For selected recent examples on the asymmetric addition to aldehydes by using boron-zinc transmetalation, see: (a) Kumar, R.; Kawasaki, H.; Harada, T. *Org. Lett.* **2013**, *15*, 4198−4201. (b) Wouters, A. D.; Ludtke, D. S. *Org. Lett.* **2012**, *14*, 3962−3965. (c) Bedford, R. B.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Nunn, J.; Okopie, R. A.; Sankey, R. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 5435−5438. (d) Hatano, M.; Gouzu, R.; Mizuno, T.; Abe, H.; Yamada, T.; Ishihara, K. *Catal. Sci. Technol.* **2011**, *1*, 1149−1158. (e) Wang, S.; Onaran, M. B.; Seto, C. T. *Org. Lett.* **2010**, *12*, 2690−2693. (f) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483−12493. (g) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericas, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098−1101.

(4) For selective reviews on the asymmetric preparation of both enantiomers, see: (a) Bartok, M. *Chem. Rev.* **2010**, *110*, 1663−1705. (b) Hayashi, M.; Tanaka, T. *Synthesis* **2008**, *2008*, 3361−3376. (c) Mallat, T.; Orglmeister, E.; Baiker, A. *Chem. Rev.* **2007**, *107*, 4863−4890. (d) Bartok, M. *Curr. Org. Chem.* **2006**, *10*, 1533−1567. (e) Sibi, M.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719−755. (f) Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955−962.

(5) For selected recent examples, see: (a) Schwab, R. S.; Soares, L. C.; Dornelles, L.; Rodrigues, O. E. D.; Paixão, M. W.; Godoi, M.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, *2010*, 3574−3578. (b) Moro, A. V.; Tiekink, E. R. T.; Zukerman-Schpector, J.; Lüdtke, D. S.; Correia, C. R. D. *Eur. J. Org. Chem.* **2010**, *2010*, 3696−3703. (c) Liu, C.; Guo,

Z. L.; Weng, J.; Lu, G.; Chan, A. S. *Chirality* **2010**, *22*, 159−164. (d) Godoi, M.; Alberto, E. E.; Paixão, M. W.; Soares, L. A.; Schneider, P. H.; Braga, A. L. *Tetrahedron* **2010**, *66*, 1341−1345. (e) Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 415−419. (f) Wang, M.-C.; Wang, X.-D.; Ding, X.; Liu, Z.-K. *Tetrahedron* **2008**, *64*, 2559−2564. (g) Ruan, J.; Lu, G.; Xu, L.; Li, Y.-M.; Chan, A. S. C. *Adv. Synth. Catal.* **2008**, *350*, 76−84. (h) Jin, M. J.; Sarkar, S. M.; Lee, D. H.; Qiu, H. *Org. Lett.* **2008**, *10*, 1235−1237. (i) Braga, A. L.; Paixao, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879−2882.

(6) Wang, M.-C.; Wang, Y.-H.; Li, G.-W.; Sun, P.-P.; Tian, J.-X.; Lu, H.-J. *Tetrahedron: Asymmetry* **2011**, *22*, 761−768.

(7) For recent selected reviews on synthesis and biological applications of phthalides, see: (a) Mo Jun Xiong, B. S. P.; Zhong Hui Li, B. S. P. *Curr. Org. Chem.* **2007**, *11*, 833−844. (b) Beck, J.; Chou, S. *J. Nat. Prod.* **2007**, *70*, 891−900. (c) Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. *Studies in Natural Products Chemistry*; Attaur, R., Ed.; Elsevier: Oxford, U.K., 2005; Vol. *32*, Part L, pp 611−669.

(8) For recent examples on asymmetric synthesis of 3-functionalized phthalides, see: (a) Fujioka, M.; Morimoto, T.; Tsumagari, T.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K. *J. Org. Chem.* **2012**, *77*, 2911−2923. (b) Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368−374. (c) Xing, C. H.; Liao, Y. X.; He, P.; Hu, Q. S. *Chem. Commun.* **2010**, *46*, 3010−3012. (d) Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6026−6027. (e) Phan, D. H.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608−15609. (f) Chang, H. T.; Jeganmohan, M.; Cheng, C. H. *Chem.—Eur. J.* **2007**, *13*, 4356−4363.

(9) (a) Glynn, D.; Shannon, J.; Woodward, S. *Chem.—Eur. J.* **2010**, *16*, 1053−1060. (b) Uenishi, A.; Nakagawa, Y.; Osumi, H.; Harada, T. *Chem.—Eur. J.* **2013**, *19*, 4896−4905.

(10) Sato, I.; Toyota, Y.; Asakura, N. *Eur. J. Org. Chem.* **2007**, 2608−2610.

(11) Zhang, Z.-B.; Lu, Y.-Q.; Duan, X.-F. *Synthesis* **2011**, 3435−3438.

(12) For the pioneering work of ligand 6, see: Lawrence, C. F.; Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Synlett* **1999**, 1571−1572.