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Evaluation of Enantiopure *N*-(Ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol for Catalytic Asymmetric Addition of Organozinc Reagents to Aldehydes

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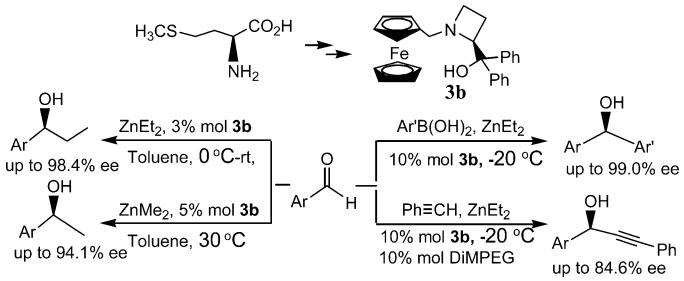

A facile and practical approach to preparation of enantiopure *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)-methanol was developed from cheap and easily available L-(+)-methionine. Synthetic highlights include the three-step, one-pot construction of the chiral azetidine ring and the development of an improved one-step procedure for the synthesis of the key intermediate L-2-amino-4-bromobutanoic acid. Enantiopure *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol was evaluated for catalytic asymmetric addition of organozinc reagents to aldehydes. The asymmetric ethylation, methylation, arylation, and alkynylation of aldehydes achieved enantioselectivity of up to 98.4%, 94.1%, 99.0%, and 84.6% ee, respectively, in the presence of a catalytic amount of chiral *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol. Our results demonstrated further that the four-membered heterocycle-based backbone was a good potential chiral unit for the catalytic asymmetric induction reaction, and the hindrance of the bulky ferrocenyl group, compared to a phenyl group, played an important role in the enantioselectivities. A possible transition for the catalytic asymmetric addition has been proposed on the basis of the crystal structure of the chiral ligand **3b** including two HOAc molecules and previous studies.

Introduction

The carbon−carbon bond-forming reaction is one of the most useful operations for the construction of complex natural and unnatural organic molecules. Addition of organometallic reagents to carbonyl compounds is among the most fundamental reaction for this purpose, and its enantioselective transformation, producing a C−C bond and a chiral alcohol center simultaneously, is particularly important. Among various organometallic compounds, organozinc reagents such as diethylzinc, diphenylzinc, and alkynylzinc serve as excellent nucleophiles in the presence of chiral ligands because of their good tolerance of various functionalities, including esters, amides, nitro groups, and nitriles. Moreover, this variation of organozinc species allows for high synthetic versatility. Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol producing an addition product with moderate enantioselectivity (49% ee) in 1984,[1] the asymmetric addition of these reagents to prochiral carbonyl compounds has been studied extensively, and various chiral ligands have been synthesized to induce asymmetry in

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(2) Reviews on enantioselective organozinc additions to aldehydes: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (d) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92. (e) Walsh, P. *Acc. Chem. Res*. **2003**, *36*, 739. (f) Li, Z.-B.; Pu, L. *Tetrahedron* **2003**, *59*, 9873. (g) Zhu, H.-J.; Jiang, J.-X.; Ren, J.; Yan, Y.-M.; Pittman, C. U. *Curr. Org. Synth.* **2005**, *2*, 547. (h) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127.

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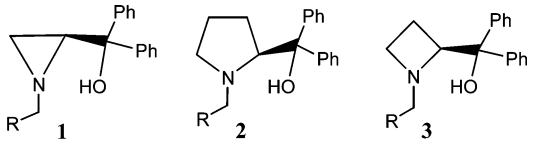
this reaction, including amino alcohols (*N*,*O*-ligands), diols (*O*,*O*-ligands), diamines (*N*,*N*-ligands), and so on.[2] However, to the best of our knowledge, there is no report on a general ligand for asymmetric addition of various organozinc reagents to the prochiral aldehydes with high enantioselectivities, probably due to differences of reactivity of organozinc species (methylzinc < ethylzinc < phenylzinc < alkynylzinc). The development of new chiral ligands plays a key role for overcoming this limitation, because subtle changes in conformational, steric, and/or electronic properties of the chiral ligands can often result in dramatic variation of the enantioselectivity and reactivity.

In recent years,[3−7] we have been exploring the use of chiral ferrocene-based ligands in catalytic asymmetric synthesis because of their planar chirality, rigid bulkiness, ease of derivatization, and stability. Chiral copper complexes of *N*,*P*-ferrocenyl ligands with central and planar chirality as efficient catalyst have been applied to the enantioselective addition of diethylzinc to the *N*-diphenylphosphinoylimines,[3] and the application for highly enantioselective 1,4-conjugate addition of diethylzinc to chalcones has also been demonstrated.[4] Chiral ferrocenylamidophosphine ligand for copper-catalyzed asymmetric addition of diethylzinc to imines has been evaluated,[5] and it is only one example that can afford highly enantioselective addition of diethylzinc to the C═N bond of the different types of imines such as *N*-sulfonylimines and *N*-phosphinoylimines.

A series of chiral ferrocenylaziridino alcohols have been synthesized and applied to catalytic asymmetric addition of diethylzinc to aldehydes, and in the best case, enantioselectivities of up to 99% ee were obtained.[6] Evaluation of chiral ferrocenylpyrrolidino alcohols for catalytic asymmetric addition of diethylzinc to aldehydes has been reported.[7] Moreover, in our previous investigation,[6c,d] we discovered that the replacement of the phenyl group on the nitrogen atom of three-membered heterocycle-based skeleton with a ferrocenyl unit led to a dramatic increase in the enantioselectivity from 49% ee to 92.7% ee when used as the catalyst in the addition of diethylzinc to benzaldehyde in the presence of 5 mol % of chiral ligands **1b** (Figure 1). Similar phenomena were also observed in the presence of 5 mol % of chiral ligands **2b** (Figure 1). More interestingly, four-membered heterocycle containing a β-amino alcohol moiety as a chiral ligand for catalytic asymmetric addition of diethylzinc to benzaldehyde afforded the best enantioselectivity when R was a phenyl group (Figure 1). In order to examine the generality of these findings or observations, we decided to synthesize enantiopure *N*-(ferrocenylmethyl)-azetidin-2-yl(diphenyl)methanol **3b** (Figure 1, R = Fc) and evaluated its application in catalytic asymmetric addition of organozinc reagents to aldehydes.



R = Ph **1a**: 49% ee[8] **2a**: 64.6% ee[9] **3a**: 88% ee[10]

R = Fc **1b**: 92.7% ee[6c, d] **2b**: 90.8% ee[7] **3b**: ?% ee

FIGURE 1. Structure of some chiral nitrogen heterocycles containing a β-amino alcohol moiety.

Among chiral nitrogen heterocycle, azetidines seem to be the least well studied to date, in terms of both synthetic methods and applications. This is also the case for chiral 2-substituted azetidines, as compared with the corresponding aziridines and pyrrolidines. The main reason for the lack of progress may be the difficult access to those strained heterocycles from acyclic derivatives, especially in enantiomerically pure form. The alternative method for the synthesis of the targeted molecule is to carry out one-step alkylation of enantiomeric pure (*S*)-azetidine-2-carbxylic acid,[11] but the (*S*)-azetidine-2-carboxylic acid is commercially available in milligram quantities only and is very expensive. Therefore, it seems highly desirable to find a simple, efficient, economical protocol for asymmetric construction of the chiral four-membered ring from cheap and easily available compounds.

More recently, we have reported in a preliminary communication the facile and practical approach to preparation of enantiopure *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol from commercially available L-2-amino-4-bromobutanoic acid and its application in catalytic asymmetric ethylation and arylation of arylaldehydes.[12] In this paper, we present the extension of this study, including (1) starting from much cheaper L-(+)-methionine (in our eyes, L-2-amino-4-bromobutanoic acid is very expensive)[13] to prepare and purify enantiopure *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol. (2) Highly enantioselective addition of various organozinc reagents such as dimethylzinc, diethylzinc, diphenylzinc, and alkynylzinc to aldehydes was assessed. (3) A possible transition state for the organic species addition reaction is proposed.

Results and Discussion

Synthesis of Chiral Ligand. The preparation of azetidino alcohol **3b** is shown in Scheme 1. Starting from the source of chirality L-(+)-methionine, the synthetic route consists of eight steps but only requires four "pots". The L-homoserine **5** was prepared readily on a large-scale from L-methionine **4** through

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(4) Liu, L.-T.; Wang, M.-C.; Zhao, W.-X.; Zhou, Y.-L.; Wang, X.-D. *Tetrahedron: Asymmetry* **2006**, *17*, 136.
(5) (a) Wang, M.-C.; Xu, C.-L.; Zou, Y.-X.; Liu, H.-M.; Wang, D.-K. *Tetrahedron Lett.* **2005**, *46*, 5413. (b) Wang, M.-C.; Xu, C.-L.; Cheng, F.; Ding, X. *Tetrahedron* **2006**, *62*, 12220.
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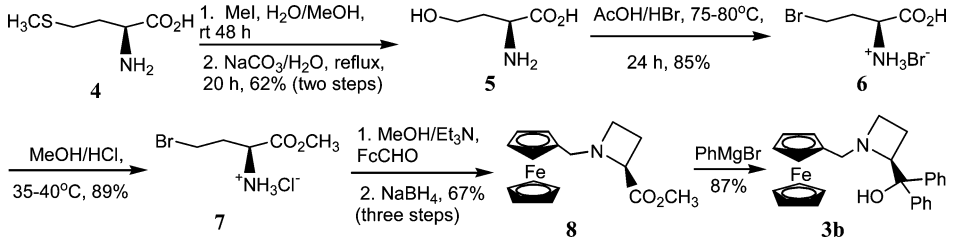
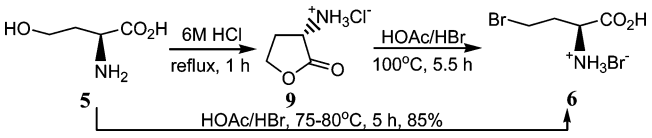
(12) Wang, M.-C.; Wang, X.-D.; Ding, X.; Jing, T.-T. *Synlett* **2006**, 3443.
(13) L-2-Amino-4-bromobutanoic acid hydrobromide is commercially available in 1 g quantities only, 1 g = 916 RMB; L-(+)-methionine, 1 kg = 3380 RMB (1 g = 3.38 RMB). Prices were taken from Aldrich, 2007−2008.

SCHEME 1. Synthesis of Chiral Compound 3b



SCHEME 2. Synthesis of Chiral Compound 6



S-methylation with methyl iodide followed by hydrolysis according to literature procedure.[14]

L-2-Amino-4-bromobutanoic acid **6**, the key intermediate in this synthesis, was obtained in two steps by ring opening of (*S*)-homoserine lactone hydrochloride **9**, which was prepared from L-homoserine **5** using the method reported by Koch (Scheme 2).[14a] To shorten synthetic route, we developed an improved and convenient one-step procedure for the direct conversion of L-homoserine **5** into L-2-amino-4-bromobutanoic acid **6** in the presence of AcOH saturated with HBr in 85% yield.

The treatment of **6** with methanol saturated with dry HCl afforded methyl L-2-amino-4-bromobutanoate **7** in 89% yield.[15]

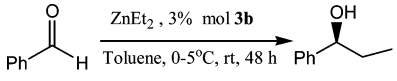
Construction of the four-membered ring heterocycle from acyclic compound is a key step in this synthesis. We developed a simple three-step, one-pot protocol for the efficient conversion of methyl L-2-amino-4-bromobutanoate **7** to methyl (*S*)-*N*-(ferrocenylmethyl)azetidine-2-carboxylate **8** involving condensation, reduction, and cyclization.[12] Ferrocenecarboxaldehyde was first condensed with compound **7** in MeOH in the presence of Et_3N and then reduced by $NaBH_4$, to give the desired methyl (*S*)-*N*-(ferrocenylmethyl)azetidine-2-carboxylate **8**, which was cyclized in situ. The treatment of **8** with PhMgBr afforded the corresponding chiral ferrocenyl *β*-amino alcohol **3b** (87%). The single-crystal growth of **3b** was performed in a mixture of hexane/ethyl acetate/acetic acid (2:1:0.3) at room temperature, and orange red crystals containing two AcOH molecules were obtained.

The *N*-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol **3b** containing two AcOH molecules was further characterized by X-ray diffraction.[16] The X-ray structure analysis revealed that the *N*-ferrocenylmethyl group on the nitrogen atom of the heterocycle is positioned anti to the diphenylhydroxymethyl group on the heterocycle (see Supporting Information). The four-membered N1, C12, C13, C14 ring moiety is almost a planar structure, with the sum of the four bond angles being 357.5°.

TABLE 1. Properties of Hydrogen Bonds for Compound 3b Including Two HOAc Molecules (Å and deg)

D−H···A	*d*(D−H)	*d*(H···A)	*d*(D···A)	∠(D−H···A)
O(5)−H···O(3)	0.82	1.83	2.643(6)	168.2
O(1)−H···O(2)	0.87(6)	1.88(6)	2.734(5)	171(5)
N(1)−H···O(3)	0.89(5)	1.88(5)	2.731(4)	159(4)

SCHEME 3. Asymmetric Addition of Diethylzinc to Benzaldehyde



The subtle distortion of the four-membered ring unit showed that an azetidine ring was a slightly more flexible framework than an aziridine ring. The N(1)−C(12)−C(13), C(12)−C(13)−C(14), N(1)−C(14)−C(13), C(12)−N(1)−C(14) bond angles are 90.3°, 88.7°, 88.8°, and 89.7°, respectively. The nitrogen atom in the azetidine ring has a trigonal-pyramidal structure with 315.4° for the sum of the three bond angles [C(12)−N(1)−C(14), 89.7°; C(12)−N(1)−C(11), 113.4°; C(11)−N(1)−C(14), 113.3°]. H^+ is at the apex of the trigonal-pyramidal structure. The single-crystal structure is formed by the intermolecular hydrogen bonds between compound **3b** and HOAc, and properties of the hydrogen bonds are summarized in Table 1.

Asymmetric Addition of Diethylzinc to Benzaldehyde. Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% ee) in 1984,[1] the asymmetric addition of diethylzinc to aldehydes has been studied extensively, and products with excellent enantiomeric excesses have been achieved with all types of substrates.[2a−c,g] Due to the adequate reactivity of diethylzinc (vs dimethylzinc and diphenylzinc) and the sensitivity of the reaction to changes in the ligand structure, the enantioselective reaction of diethylzinc with benzaldehyde has also become a classical test to examine whether or not the designed chiral ligands induce high enantioselectivities. In order to examine the catalytic behavior of the chiral ligand **3b**, the asymmetric addition of diethylzinc to benzaldehyde has been investigated in toluene in 0−20 °C in the presence of 3% ligand **3b** (Scheme 3). The reactions using **3b** as catalyst afforded 1-phenylpropanol (*S*-configuration) in excellent yields (97%) with outstanding enantiomeric excesses (98.4% ee).

Recently, Zwanenburg et al. reported the same type of chiral ligand **3a** (R = Ph) for the addition of diethylzinc to benzaldehyde with good enantioselectivities (88% ee) in the presence of 20 mol % **3a**.[10] A comparison of our results (98.4% ee, 3 mol % **3b**) with those (88% ee, 20 mol % **3a**) of Zwanenburg et al. demonstrates that the replacement of the phenyl group on the nitrogen atom of the azetidine-based skeleton by a ferrocenyl

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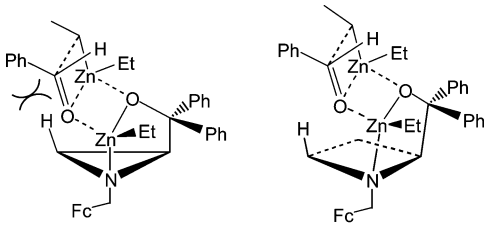
(16) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-648759. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, CAMBRIDGE CB2 1EZ, UK [fax: (+44) 1223−336-033; e-mail: deposit@ccdc.cam.ac.uk], or see the Supporting Information.



10 **11**

FIGURE 2. Possible transition states.

unit leads to a remarkable improvement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde. These results also suggest that the hindrance of the ferrocenyl group, compared to a phenyl group, plays an important role in the enantioselectivities. The outstanding enantioselectivity of the chiral ligand **3b**, as compared with **3a** (R = Ph), gives further support to the generality of the advantage of the replacement of the phenyl group on the nitrogen atom of a heterocycle-based skeleton by a ferrocenyl unit.

Compared with the same type of chiral three-membered heterocycle-based ligand, (2*S*)-1-(ferrocenylmethyl)aziridin-2-yl(diphenyl)methanol **1b** (Figure 1, R = Fc, 92.7% ee)[6c,d] and five-membered heterocycle-based (ferrocenylmethyl)pyrrolidin-2-yl(diphenyl)methanol **2b** (Figure 1, R = Fc, 90.8% ee)[7] and (2*S*)-1-(ferrocenylmethyl)azetidin-2-yl(diphenyl)methanol **3b** afforded the best asymmetric induction (98.4% ee). Similar phenomena were also observed in the three-,[8] four-,[10] or five-membered[9] heterocycle-based *β*-amino alcohols with a *N*-substituted benzyl unit (Figure 1, R = Ph). Shi and co-workers gave also the similar results for the asymmetric addition of diethylzinc to arylaldehydes in the chiral C_2-symmetric disubstituted backbone of three-, four-, or five-membered rings.[17]

The X-ray structures of the noncomplexed ligands did not provide direct information about the structure of the catalytically active metal complex, but they did help with the understanding of the reaction mechanism and the effect of free ligands on reaction enantioselectivity. A comparison of the three-membered heterocycle-based structure **1b**[6c] with the four-membered structure **3b** (see Supporting Information) showed that they exhibit certain similarities with respect to rigidity, configuration, and conformation. The *S* absolute configuration of addition product for the asymmetric addition of diethylzinc to benzaldehyde, the same as the addition of diethylzinc to benzaldehyde catalyzed by **1b**,[6c,d] was noted. On the basis of this observation and a great number of previous theoretical studies on the mechanism of this reaction[18] combined with our previous results,[6a] we proposed a possible transition state, **11** (Figure 2), which was similar to **10**,[6a] for the asymmetric addition of diethylzinc to benzaldehyde catalyzed by **3b**. In the transition state **11**, the *se* face of benzaldehyde was attacked by nucleophile, affording the corresponding addition product with the *S* absolute configuration.

As was mentioned above, for the same type of chiral ligands, four-membered heterocycle-based ligands afforded higher enantioselectivity than three-membered heterocycle-based ligands in the asymmetric addition of diethylzinc to benzaldehyde. The only difference between them was the ring area of the aziridine and azetidine ring. Three-membered heterocycle-based ligands possess a slightly more rigid ring backbone and more sterical congestion than four-membered heterocycle-based ligands, because the aziridine ring has the smaller ring area. The totally rigid and sterically congested transition state **10** led to the presence of the nonbonded repulsion between the phenyl ring of benzaldehyde and the hydrogen atom on the aziridine ring,[6a] which was responsible for the slightly lower enantioselectivity compared to the azetidine case. Instead, in transition state **11**, the nonbonded repulsion between the phenyl ring of benzaldehyde and the hydrogen atom on the aziridine ring was avoided due to the slightly less rigid (subtle distortion of azetidine ring architecture) and less sterically congested (a great increase in the area of azetidine ring) ring.

Asymmetric Addition of Dimethylzinc to Aldehydes. Encouraged by the above result, we focused our attention on the asymmetric addition of dimethylzinc to aldehydes. Due to the lower reactivity of dimethylzinc than diethylzinc,[19] asymmetric addition of dimethylzinc to aldehydes has attracted much less attention than the corresponding diethylzinc addition. However, in recent years, the enantioselective addition of dimethylzinc to aldehydes has received special attention in the presence of catalytic amounts of chiral ligands,[20] because the asymmetric addition of dimethylzinc to aldehydes allows the synthesis of the chiral 1-hydroxyethyl moiety that is widespread in the structure of natural products and drug compounds.[21] In addition, the corresponding addition products are also useful chiral intermediates for the preparation of chiral ligands for enantioselective synthesis.[22] The lack of reactivity of dimethylzinc combined with the importance of addition products in synthesis prompted us to examine the catalytic efficiency of the chiral ligand **3b** in the asymmetric addition of dimethylzinc to aldehydes.

At the outset of our study, we examined a reaction of dimethylzinc with benzaldehyde under the same conditions as diethylzinc addition. In the presence of 3 mol % **3b**, there was

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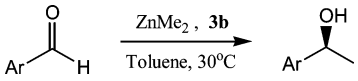
TABLE 2. Asymmetric Addition of Dimethylzinc to Aldehyde Catalyzed by 3b[a]



entry	Ar	3b (mol %)	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]	config[d]
1	C_6H_5	3	0	72	trace		*S*
2	C_6H_5	3	30	48	83	80.2	*S*
3	C_6H_5	5	30	48	90	84.8	*S*
4	C_6H_5	10	30	48	90	85.0	*S*
5	C_6H_5	5	10	120	79	74.2	*S*
6	*p*-MeC_6H_4	5	30	48	97	92.3	*S*
7	*m*-MeC_6H_4	5	30	48	95	84.3	
8	*o*-MeC_6H_4	5	30	48	93	73.6	*S*
9	*p*-$MeOC_6H_4$	5	30	48	97	93.6	*S*
10	*m*-$MeOC_6H_4$	5	30	48	99	90.5	*S*
11	*o*-$MeOC_6H_4$	5	30	48	93	82.3	*S*
12	*m*-$PhOC_6H_4$	5	30	48	99	93.0	*S*
13	*p*-$Me_2NC_6H_4$	5	30	48	82	89.1	*S*
14	*o*-ClC_6H_4	5	30	48	98	80.2	*S*
15	*m*-ClC_6H_4	5	30	48	95	90.2	*S*
16	*p*-ClC_6H_4	5	30	48	94	77.8	*S*
17	*m*-BrC_6H_4	5	30	48	93	90.5	*S*
18	*p*-BrC_6H_4	5	30	48	97	91.5	*S*
19	3,4-$OCH_2OC_6H_3$	5	30	48	97	94.1	*S*
20	ferrocenyl	5	30	48	81	93.8	*S*
21	$PhCH_2CH_2CHO$	5	30	48	64	71.6	*S*

[a] The mol ratio of Me_2Zn:aldehyde was 2:1. [b] Isolated yields. [c] Determined by HPLC using chiral columns: Chiralcel OD or OB, respectively. In all cases, the product chromatograms were compared against a known racemic mixture. [d] Absolute configuration assigned by comparison with known elution order from Chiralcel OD or OB columns according to the literature and considering the similarity in the stereochemical reaction pathway (Figure 3).

almost no reaction after 72 h at 0 °C. At room temperature (30 °C), the reaction afforded the desired addition product in 83% yield with 80.2% ee. Increasing the amount of ligand from 3 to 5 mol % led to a further improvement in catalytic activity and reaction enantioselectivity (Table 2, entry 3 vs 2), and further addition of 10 mol % ligand did not benefit the enantioselectivity and the yield of the products (Table 2, entries 4 vs 3). Thus, 5 mol % chiral ligand and 30 °C were selected as the best reaction conditions in toluene.

The asymmetric addition of dimethylzinc to a variety of aldehydes was next examined under the best reaction conditions, and the results are presented in Table 2 (entries 6−21). As can be seen from Table 2, good to excellent enantioselectivities could be achieved for various aromatic aldehydes, including ortho-, para-, and meta-substituted benzaldehydes (Table 2, entries 6−18), heliotropin (Table 2, entry 19), and ferrocenecarboxaldehyde (Table 2, entry 20). The presence of electron-donating or electron-withdrawing substituents on the aromatic ring is also compatible with these reaction conditions, but the electronic effects of substituents on the reaction enantioselectivity were observed. For example, aromatic aldehydes with electron-donating group were methylated with higher enantioselectivities than with electron-withdrawing group. *o*-Methyl- and *o*-methoxy-substituted benzaldehydes afforded lower enantioselectivities than other meta- and para-substituted benzaldehydes with donating group, probably due to steric effects of the ortho substituents. The chiral ligand **3b** was also tested with aliphatic aldehyde. It was found that this catalyst gave also good enantioselectivity for the addition of dimethylzinc to 3-phenylpropionaldehyde (Table 1, entry 19). These results are comparable with the best literature values hitherto reported for the asymmetric addition of dimethylzinc to aldehydes.

Asymmetric Aryl Transfer to Aldehydes. Recently, the enantioselective arylation of aldehydes has received special attention in the presence of catalytic amounts of chiral ligands, because the arylation products of this reaction are chiral diarylmethanols,[23,24] some of which are key intermediates for the preparation of pharmacologically and biologically important compounds.[25] In this context, the asymmetric arylation of aldehydes using arylboronic acids as aryl resources,[24] in comparison with Ph_2Zn or Ph_2Zn-Et_2Zn as aryl resources,[23] becomes an attractive method for the preparation of diarylmethanols in high enantioselectivity. This new protocol allows the easy preparation of several substituted arylzinc reagents and therefore the synthesis of a wide range of substituted chiral diarylmethanols. In addition, phenylboronic acids offer a cheaper alternative to the expensive diphenyl zinc, and the background reaction[23b] generated by use of Ph_2Zn itself as aryl resource is avoided. More interestingly, another feature of this methodology is that both enantiomers of a given diarylmethanol can be easily prepared in excellent yields and high enantiomeric excesses with the same catalyst, just by the appropriate choice of both reaction partners: arylboronic acid and aldehyde. Unfortunately, ligands that effectively catalyze the asymmetric arylation of aldehydes using arylboronic acids as aryl resource with high ee values are relatively rare. In order to examine the catalytic efficiency of chiral ligand **3b**, the asymmetric aryl transfer to aldehydes was tested.

The asymmetric phenylation of 4-tolualdehyde was tested (Table 3, entries 1−5). The phenylzinc reagent was prepared in situ by heating a mixture of diethylzinc and phenylboronic

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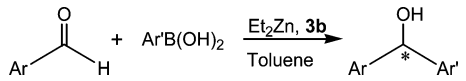
TABLE 3. Asymmetric Arylation of Arylaldehydes Catalyzed by 3b[a]



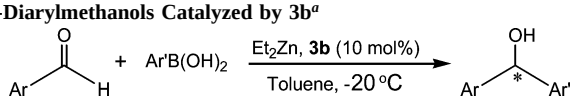
entry	Ar	Ar′	**1** (mol %)	temp (°C)	yield (%)[b]	ee (%)[c]	config[d]
1	*p*-MeC_6H_4	C_6H_5	10	0	96	89.0	*S*
2	*p*-MeC_6H_4	C_6H_5	10	−20	95	92.0	*S*
3	*p*-MeC_6H_4	C_6H_5	10	−40	71	88.5	*S*
4	*p*-MeC_6H_4	C_6H_5	5	−20	88	84.0	*S*
5	*p*-MeC_6H_4	C_6H_5	15	−20	96	92.1	*S*
6	*o*-$MeOC_6H_4$	C_6H_5	10	−20	86	83.9	*S*
7	*m*-$MeOC_6H_4$	C_6H_5	10	−20	99	87.1	*S*
8	*p*-$MeOC_6H_4$	C_6H_5	10	−20	95	83.3	*S*
9	*m*-$PhOC_6H_4$	C_6H_5	10	−20	94	93.9	*S*
10	*o*-ClC_6H_4	C_6H_5	10	−20	94	83.4	*S*
11	*m*-ClC_6H_4	C_6H_5	10	−20	98	90.8	*S*
12	*p*-ClC_6H_4	C_6H_5	10	−20	80	83.1	*S*
13	*m*-BrC_6H_4	C_6H_5	10	−20	97	85.7	*S*
14	*o*-$CF_3C_6H_4$	C_6H_5	10	−20	92	91.1	*S*
15	3,4-$OCH_2OC_6H_3$	C_6H_5	10	−20	99	88.2	*S*
16	ferrocenyl	C_6H_5	10	−20	84	95.5	*S*
17	C_6H_5	*o*-MeC_6H_4	10	−20	88	95.7	*R*
18	C_6H_5	2-Naph	10	−20	79	70.0	*R*

[a] The mol ratio of Ar′$B(OH)_2$:Et_2Zn:aldehyde was 1:3:1. [b] Isolated yields. [c] Determined by HPLC using chiral columns: Chiralcel OD or OB or Chiralpak AD, respectively. In all cases, the product chromatograms were compared against a known racemic mixture. [d] Absolute configuration assigned by comparison with known elution order from Chiralcel OD or OB or Chiralpak AD columns according to the literature and considering the similarity in the stereochemical reaction pathway (Figure 3).

acid in hexanes to 60 °C for 12 h. We first investigated the effect of reaction temperature on enantioselectivity in the presence of 10 mol % of the chiral ligand **3b**. Decreasing the reaction temperature from 0 °C to −20 °C led to an increase in the enatioselectivity from 89.0% to 92.0% (Table 3, entries 1 and 2). We attempted to decrease the reaction temperature further in order to have better enantioselectivity, but a big decrease in both yield and enantioselectivity was observed when the reaction was performed at −40 °C (Table 3, entry 3). Then, we examined the effects of the chiral ligand loading on enantioselectivity. Lowering the ligand amount from 10% to 5% led to a decrease in both yield and enantioselectivity at −20 °C (Table 3, entry 4 vs 1). Increasing the ligand loading from 10% to 15% did not result in an improvement of yield and enantioselectivity (Table 3, entries 2 and 5). These reaction conditions were tested on other arylaldehydes in the presence of the ligand **3b** (Table 3, entries 6−16). As can be seen from Table 1, good to excellent enantioselectivities could be achieved for various aromatic aldehydes containing ortho-, para-, and meta-substituents on the benzene ring. The presence of electron-donating or electron-withdrawing substituents on the aromatic ring also furnished the corresponding products in good to outstanding levels of enantioselectivity. The best asymmetric induction (as high as 95.5% ee) was found by using a ferrocenyl aldehyde as the substrate (Table 3, entry 16).

In order to examine if different aryl groups could be transferred to benzaldehyde with the same level of enantioselectivity, the aryl transfer reaction of some substituted phenylboronic acids with benzaldehyde was investigated (Table 3, entries 17 and 18). (*R*)-*o*-Methylphenylphenylmethanol with excellent enantioselectivity of up to 95.7% ee was obtained when *o*-methylphenylboronic acid was used as the aryl transfer reagent (Table 3, entry 17). The asymmetric naphthalenyl transfer to benzaldehyde gave the lower enantioselectivity (70.9% ee), probably because of the steric effects of a bulky naphthalenyl group.

TABLE 4. Enantioselective Preparation of (*R*)- and (*S*)-Diarylmethanols Catalyzed by 3b[a]



entry	Ar	Ar′	yield (%)[b]	ee (%)[c]	config[d]
1	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	92	91.4	*R*
2	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	91	93.3	*S*
3	*p*-MeC_6H_4	*p*-ClC_6H_4	95	95.1	*R*
4	*p*-ClC_6H_4	*p*-MeC_6H_4	93	95.3	*S*
5	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	89	93.8	*R*
6	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	94	94.6	*S*
7	*p*-MeC_6H_4	*o*-MeC_6H_4	92	82.3	*R*
8	*o*-MeC_6H_4	*p*-MeC_6H_4	95	96.2	*S*
9	*p*-$MeOC_6H_4$	*o*-MeC_6H_4	97	81.7	*R*
10	*o*-MeC_6H_4	*p*-$MeOC_6H_4$	93	>99.0	*S*
11	*p*-ClC_6H_4	*o*-MeC_6H_4	84	59.2	*R*
12	*o*-MeC_6H_4	*p*-ClC_6H_4	92	95.0	*S*

[a] The mole ratio Ar′$B(OH)_2$:Et_2Zn:aldehyde was 1:3:1. [b] Isolated yields. [c] Determined by HPLC using chiral columns: Chiralcel OD or OB or Chiralpak AD, respectively. In all cases, the product chromatograms were compared against a known racemic mixture. [d] Absolute configuration assigned by considering the similarity in the stereochemical reaction pathway (Figure 3).

Noteworthy is the fact that both *R* and *S* enantiomers of a given product can be readily prepared in high yields with excellent enantioselectivivities in the presence of the identical catalyst, only by the reverse combination of both reaction partners (arylboronic acid and aromatic aldehydes). But the so far assessed substrate scope seems to be rather limited. Usually, phenyl transfer to aromatic aldehydes (substituted benzaldehydes) or aryl transfer to benzaldehyde has been investigated, affording aryl*phenyl*methanols. To the best of our knowledge, only one example has been just reported about the synthesis of diarylmethanols with two differently substituted aryl groups by organozinc reagents.[26]

In order to examine the applicability of the approach to more functionalized diarylmethanols, a series of reverse combinations of the reaction of arylaldehydes with arylboronic acid were tested, and the results are summarized in Table 4. As seen in Table 4, just by the appropriate choice of both reaction partners, in most cases, both the enantiomers of a given diarylmethanol can be easily obtained in excellent yields with high to outstanding enantioselectivivities by means of the same catalyst **3b** (Table 4, entries 1−12). Probably due to the steric effects of the ortho substituent and the withdrawing-electronic effect of the substrate, the reaction of *o*-methylphenylboronic acid with *p*-chlorobenzaldehyde afforded the corresponding product with a moderate ee value (Table 4, entry 11).

Asymmetric Addition of Alkynylzinc to Arylaldehydes. The asymmetric addition of alkynylzinc to aldehydes is particularly useful, because the resulting chiral secondary propargylic alcohols are important precursors to many organic molecules, including natural products and pharmaceutical

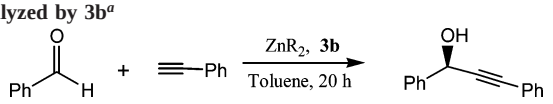
(26) Schmidt, F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703.

compounds.[27] In addition, the acetylene and hydroxyl functions of the propargylic alcohol products can be used to construct very diverse molecular structures. In the past few years,[28] great progresses have been made on asymmetric alknylzinc additions to aldehydes in the presence of either stoichiometric or catalytic quantities of chiral ligands including *N*-methylephedrine,[29] BINOL and its derivatives,[30] β-hydroxy amides,[31] and other amino alcohol compounds.[32] The above results of highly enantioselective methylation, ethylation, and arylation of aldehydes inspired us to test the asymmetric addition of alkynylzinc to aldehydes in the presence of (2*S*)-1-(ferrocenylmethyl)-azetidin-2-yl(diphenyl)methanol **3b** in order to achieve highly enantiopure propargylic alcohols.

In an initial screening, asymmetric addition of alkynylzinc to benzaldehyde was tested in order to explore optimal reaction conditions (Table 5, entries 1−12). The alkynylzinc reagent was formed in situ by deprotonation of phenylacetylene with dialkylzinc at room temperature. In the presence of catalytic amounts of chiral ligand **3b** (10 mol %), asymmetric addition of alkynylzinc to benzaldehyde afforded the corresponding propargylic alcohol in good yield with 56.8% ee at −10 °C. Recently, Dahmen reported that the additive DiMPEG [dimethoxypoly(ethylene glycol)] could improve the enantioselectivity of the reaction. To our delight, addition of 2.5 mol % DiMPEG 2000 to the catalytic system led to an increase in the enantioselectivity from 56.8 to 70.4% ee. Upon further increasing the additive amounts to 5 and 10 mol %, the enantioselectivity rose to 74.4 and 84.6% ee. However, a decrease in chemical yield and enantioselectivity was observed when additive loading was 15 mol %. We also investigated the effect of reaction temperature on enantioselectivity in the presence of 10 mol % of the chiral ligand **3b** and 10 mol % DiMPEG 2000. The highest ee (84.6%) was observed when the reaction was carried out at −10 °C.

Under the optimized reaction condition (Table 5, entry 4), we examined the scope of the reaction using a variety of aromatic aldehyde substrates, and the results are summarized in Table 6. In all cases, chiral ligand **3b** proved to be effective, and the corresponding propargylic alcohols were produced in good yields (82−91%) and high enantioselectivities (70.8−84.6%). Chiral ligand **3b** is comparable to the existing amino alcohol ligands for alkynyl addition using a terminal alkyne and

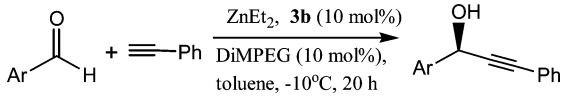
TABLE 5. Asymmetric Addition of Alkynylzinc to Benzaldehyde Catalyzed by 3b[a]



entry	ZnR_2	DiMPEG (mol %)	**3b** (mol %)	temp (°C)	yield (%)[b]	ee (%)[c]	config[d]
1	Et_2Zn	0	10	−10	83	56.8	*R*
2	Et_2Zn	2.5	10	−10	81	70.4	*R*
3	Et_2Zn	5	10	−10	86	74.5	*R*
4	Et_2Zn	10	10	−10	81	84.6	*R*
5	Et_2Zn	15	10	−10	82	80.8	*R*
6	Et_2Zn	10	10	−20	79	77.4	*R*
7	Et_2Zn	10	10	15	92	65.5	*R*
8	Et_2Zn	10	10	0	89	74.8	*R*
9	Et_2Zn	10	10	−40	20	33.2	*R*
10	Et_2Zn	10	5	−10	79	78.4	*R*
11	Et_2Zn	10	20	−10	87	80.5	*R*
12	Me_2Zn	10	10	−20	97	61.2	*R*

[a] The mol ratio of phenylacetylene:Et_2Zn:benzaldehyde was 2:2:1. [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD column. The product chromatograms were compared against a known racemic mixture. [d] Absolute configuration assigned by known elution order from a Chiralcel OD column according to the literature.[32f]

TABLE 6. Asymmetric Addition of Alkynylzinc to Arylaldehydes Catalyzed by 3b[a]



entry	Ar	yield (%)[b]	ee (%)[c]	config[d]
1	C_6H_4	81	84.6	*R*
2	*o*-$MeOC_6H_4$	89	74.5	*R*
3	*m*-$MeOC_6H_4$	88	77.3	*R*
4	*p*-$MeOC_6H_4$	82	76.3	*R*
5	*m*-$PhOC_6H_4$	90	84.3	*R*
6	*p*-MeC_6H_4	87	77.3	*R*
7	*o*-ClC_6H_4	82	75.2	*R*
8	*m*-ClC_6H_4	88	75.4	*R*
9	*p*-ClC_6H_4	91	74.1	*R*
10	3,4-$OCH_2OC_6H_3$	85	70.8	*R*

[a] The mole ratio of phenylacetylene:Et_2Zn:benzaldehyde was 2:2:1. [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD column. In all cases, the product chromatograms were compared against a known racemic mixture. [d] Absolute configuration assigned by known elution order from a Chiralcel OD column according to the literature and considering the similarity in the stereochemical reaction pathway (Figure 3).[32f]

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diethylzinc in the presence of chiral ligands,[32] although the maximum asymmetric induction obtained was 84.3% ee.

Conclusions

We described in this paper a facile and practical approach to asymmetric preparation of the enantiopure *N*-(ferrocenylmethyl)-azetidin-2-yl(diphenyl)methanol from cheap and easily available L-(+)-methionine. In the key cyclization step, the three-step, one-pot protocol for construction of the chiral azetidine ring was developed. The enantioselective addition of organozinc reagents to aldehydes was investigated in the presence of a catalytic amount of the enantiopure *N*-(ferrocenylmethyl)-azetidin-2-yl(diphenyl)methanol **3b**. The asymmetric ethylation, methylation, arylation, and alkynylation of aldehydes achieved enantioselectivity of up to 98.4%, 94.1%, 99.0%, and 84.6% ee, respectively. The results showed that the chiral ligand **3b** was a general catalyst for asymmetric addition of various organozinc reagents such as methylzinc, ethylzinc, phenylzinc, and alkynylzinc to the prochiral aldehydes with high enantioselectivities. In addition, we demonstrated further that the four-membered heterocycle-based backbone was a good potential chiral unit for the catalytic asymmetric induction reaction, and the hindrance of the bulky ferrocenyl group, compared to a phenyl group, played an important role in the enantioselective addition reactions. A possible transition state for the catalytic asymmetric addition has been proposed on the basis of the crystal structure of the chiral ligand **3b** including two HOAc molecules and previous studies. Further applications of the chiral compound **3b** for asymmetric synthesis are under investigation in our laboratory.

Experimental Section

Synthesis of L-Homoserine 5. L-(+)-Methionine **4** (75 g, 0.5 mol) was suspended in H_2O/MeOH (1400 mL/200 mL), and methyl iodide (75 mL, 1.21 mol) was added. The resulting two-phase system was stirred vigorously for 48 h. The volume of the solvent was then reduced to one-third by evaporation, and simultaneously excess methyl iodide was removed. Water was added to a total volume of 1000 mL, and $NaHCO_3$ (42 g, 0.5 mol) was added. This solution was refluxed for 15 h and cooled, and the solvent was evaporated under reduced pressure to yield thick syrup. This residue was dissolved in a minimum quantity of water (140 mL), with heating. Addition of acetone (270 mL) followed by ethanol (3000 mL) caused immediate precipitation of L-homoserine **5** as a white solid (37 g, 62%). Mp 202−203 °C (dec) [lit.[33] mp 203 °C (dec)]. $[\alpha]_D^{20} = 8.2$ (*c* 3.08, H_2O) [lit.[33] $[\alpha]_D^{26} = 8.0$ (*c* 5, H_2O)]. ^{1}H NMR (400 MHz, D_2O): δ 1.79−1.87 (m, 1H), 1.92−2.01 (m, 1H), 3.54−3.58 (m, 2H), 3.66 (dd, $J = 4.8$ Hz, $J = 7.4$ Hz, 1H).

Synthesis of L-2-Amino-4-bromobutanoic Acid Hydrobromide 6. L-Homoserine **5** (1.6 g, 13.3 mmol) and AcOH (36 mL, saturated with HBr) were placed in an autoclave, which was immersed in an oil bath, and then the temperature was raised to 75−80 °C. After stirring for 5 h, the temperature was gradually lowered to room temperature overnight. The precipitate was collected by suction filtration on a Büchner funnel and was washed with Et_2O. Recrystallization of the product from $C_2H_5OH-Et_2O$ afforded L-2-amino-4-bromobutanoic acid hydrobromide **6** (3.1 g, 85%). Mp 187−188 °C [lit.[14] mp 188−190 °C]. $[\alpha]_D^{20} = +11.8$ (*c* 0.21, DMF) [lit.[14] $[\alpha]_D = +11.8$ (*c* 0.20, DMF)]. ^{1}H NMR (400 MHz, DMSO): δ 2.22−2.41 (m, 2H), 3.59−3.71 (m, 2H), 4.00 (d, $J = 5.6$ Hz, 1H), 8.33 (s, 3 H), 8.57 (s, 1H).

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Synthesis of Methyl L-2-Amino-4-bromobutanoate hydrochloride 7. l-2-Amino-4-bromobutanoic acid hydrobromide **6** (4.2 g, 15.6 mmol) was suspended in methanol (120 mL), dry HCl was passed through for 2 h at such a rate that the temperature of the reaction mixture was maintained at 35−40 °C. The solution was evaporated to dryness, the residue was dissolved in methanol, and the solution was again evaporated to dryness; the same procedure was repeated once more, the residual oil was dried in vacuo over sodium hydroxide, and the resulting crystals were triturated with ether, collected, and washed with ether. Recrystallization of the product from $C_2H_5OH-Et_2O$ gave methyl L-2-amino-4-bromobutanoate hydrochloride **7** (3.3 g, 89%). Mp 100.3−102.1 °C [lit.[15] mp 98−99 °C]. $[\alpha]_D^{20} = +29.1$ (*c* 0.83, CH_3OH).

Synthesis of Methyl (*S*)-*N*-(Ferrocenylmethyl)azetidine-2-carboxylate 8. Methyl l-2-amino-4-bromobutanoate hydrochloride **7** (2.4 g, 10.3 mmol) was dissolved in 14 mL of anhydrous methanol and cooled to 0 °C. Triethylamine (1.7 mL, 11.9 mmol) was added, and the reaction was stirred for 10 min. Ferrocenecarboxaldehyde (2.2 g, 10.3 mmol) was added, the reaction mixture was stirred for 5 h, and the reaction was monitored by TLC. Sodium borohydride (0.4 g) was added portionwise to the reaction mixture over a period of 1 h. After stirring for 24 h, methanol was evaporated under the reduced pressure at 40 °C. The resulting residue was carefully neutralized with 3% HCl to pH = 7−8 and extracted three times with 3 × 20 mL portions of EtOAc. The combined ether extract was washed with brine, dried over Na_2SO_4, and evaporated under the reduced pressure. The resulting residue was purified by preparative TLC with petroleum (60−90 °C)/EtOAc (3:1) as developing solvent to give **8** in 67% yield (2.2 g). $[\alpha]_D^{20}$ −97 (*c* 0.84, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09−2.16 (m, 1H), 2.27−2.36 (m, 1H), 2.92−2.98 (m, 1H), 3.26 (t, $J = 6.8$ Hz, 1H), 3.48, 3.54 (dd, $J = 12.8$ Hz, each 1H), 3.66 (s, 3H), 3.70 (d, $J = 8.4$ Hz, 1H), 4.11 (s, 7H), 4.14 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 49.7, 51.8, 56.4, 63.3, 68.15, 68.18, 68.4, 69.5, 69.6, 81.7, 173.0. IR (KBr pellet): 3092, 3007, 2950, 2842, 1742, 1436, 1400, 1340, 1229, 1201, 1104, 1037, 1001, 819. HRMS (ESI): calcd for $C_{16}H_{19}FeNO_2$ M^+ 313.0765, found 313.0767; $(M + Na)^+$ 336.0663, found 336.0655.

Synthesis of *N*-(Ferrocenylmethyl)azetidin-2-yl(diphenyl)-methanol 3b. A Grignard reagent was prepared in the usual way from 68 mg (2.8 mmol) of magnesium and methyl iodide (0.18 mL, 2.8 mmol) in Et_2O (6 mL). The solution was cooled to 0 °C before addition of a solution of **8** (114 mg, 0.36 mmol) in Et_2O (2 mL). The reaction mixture was stirred for 3 h at 0 °C and then was heated to reflux for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4, and after filtration the solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC with hexane/EtOAc (3:1) as developing solvent to give **3b** (97 mg, 85%). Mp 122.7−123.9 °C. $[\alpha]_D^{20}$ −27.2 (*c* 0.36, $CHCl_3$). $[\alpha]_D^{20}$ −27.2 (*c* 0.32, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87−2.09 (m, 1H), 1.92−2.03 (m, 1H), 2.81, 2.87 (dd, $J = 13.2$ Hz, each 1H), 2.89−2.93 (m, 1H), 3.18 (t, $J = 6.0$ Hz, 1H), 3.83−4.05 (m, 9H), 4.27 (t, $J = 7.2$ Hz, 1H), 5.20 (s, 1H), 7.18−7.61 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.42, 49.44, 55.2, 67.6, 68.0, 68.4, 69.2, 70.9, 75.7, 82.9, 128.2, 126.0, 126.6, 126.7, 128.0, 128.2, 144.1, 147.2. IR (KBr pellet): 3418, 3086, 3030, 2963, 2926, 2841, 1632, 1600, 1490, 1447, 1383, 1319, 1232, 1163, 1038, 1105, 996, 814, 748, 701. MS (ESI): calcd for $C_{27}H_{27}FeNO$ $(M + H)^+$ 438, found 438. HRMS (ESI): calcd for $C_{27}H_{27}FeNO$ $(M + H)^+$ 438.1520, found 438.1521.

X-ray Crystallographic Study. An orange red crystal of approximate dimensions 0.20 × 0.18 × 0.17 mm was mounted on a glass fiber. Crystallographic data for **3b** containing two HOAc molecules were measured on a Rigaku RAXIS-IV imaging plate area detector. The data were collected at 291(2) K using graphite-

monochromated Mo Kα ($\lambda = 0.710\,73$ Å), $1.71° < \theta < 25.50°$. The structures were solved by a direct method and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package. Crystal data for **3b** containing two HOAc molecules: triclinic P_1, $a = 7.4950$ [15] Å, $\alpha = 97.02$ [3]°, $b = 8.1766$[16] Å, $\beta = 98.63$ [3]°, $c = 12.237$[2] Å, $\gamma = 109.63$[3]°, $V = 686.3(2)$ Å^3, formula unit $C_{31}H_{35}FeNO_5$ with $Z = 1$, $D_{calcd} = 1.349$ g cm^{-3}, $F(000) = 294$, μ(Mo Kα) $= 0.590$ mm^{-1}. Full-matrix least-squares refinement on F^2 based on 2381 independent reflections ($R_{int} = 0.0000$) converged with 352 parameters. Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0341$, $wR_2 = 0.0797$; R indices (all data): $R_1 = 0.0381$, $wR_2 = 0.0824$; GoF $= 1.015$.

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Supporting Information Available: HPLC analysis details for asymmetric methylation, arylation, and alkynylation of aldehydes, copies of the ^{1}H spectra of compounds **5**, **6**, copies of the ^{1}H and ^{13}C NMR spectra of compounds **8** and **3b**, and X-ray data of compound **3b** containing two HOAc molecules in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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