

# Enantioselective Synthesis of *syn*- $\alpha$ -Aryl- $\beta$ -hydroxy Weinreb Amides: Catalytic Asymmetric Roskamp Reaction of $\alpha$ -Aryl Diazo Weinreb Amides

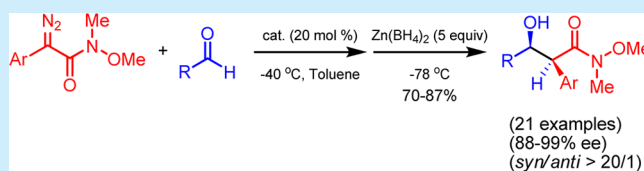
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**S** Supporting Information

**ABSTRACT:** A convenient one-pot procedure to synthesize a variety of highly optically active *syn*- $\alpha$ -aryl- $\beta$ -hydroxy Weinreb amides using an asymmetric Roskamp/reduction strategy is described. An oxazaborolidinium ion catalyzed asymmetric Roskamp reaction of  $\alpha$ -aryl diazo Weinreb amides with aldehydes produced  $\alpha$ -phenyl- $\beta$ -keto Weinreb amides, which were in situ reduced with zinc borohydride to give *syn*- $\alpha$ -aryl- $\beta$ -hydroxy Weinreb amides in good yields (up to 87%) with high enantioselectivities (up to 99% ee) and *syn* stereoselectivities (>20:1).

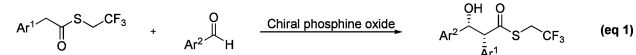


Enantioenriched  $\alpha$ -alkyl- $\beta$ -hydroxy carbonyl compounds are versatile synthetic intermediates for the synthesis of natural products and pharmaceutical agents. Because of their utility, the development of synthetic methods to prepare such compounds has been the subject of intense research. Among numerous methods, the asymmetric aldol reaction<sup>1</sup> is generally regarded as one of the most efficient tools for their synthesis. In particular, since the mid-1990s, various methods for directed aldol reactions have been developed to produce chiral  $\alpha$ -alkyl- $\beta$ -hydroxy carbonyl compounds using various chiral auxiliaries and catalysts.<sup>1,2</sup> However, compared to  $\alpha$ -alkyl carbonyl compounds, enantioselective syntheses of the corresponding  $\alpha$ -aryl- $\beta$ -hydroxy carbonyl compounds<sup>3</sup> have rarely been reported, and to the best of our knowledge, only two catalytic enantioselective methods have been reported. The Benaglia group developed a chiral phosphine oxide catalyzed aldol reaction using thioesters and aldehydes (Scheme 1, eq 1).<sup>3g</sup> In a complementary approach, the Davies group reported an asymmetric intermolecular C–H functionalization by a chiral dirhodium catalyst, which after TBS deprotection provided *syn*-aldol products with high enantioselectivities (Scheme 1, eq 2).<sup>3h,i</sup> However, limited substrate scope and low yields have necessitated the development of new catalytic enantioselective methods.

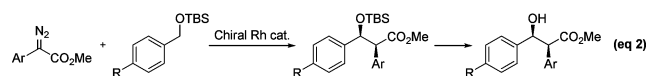
Recently, Lewis acid catalyzed enantioselective Roskamp reactions using  $\alpha$ -alkyl diazoesters were reported by both the Feng laboratory<sup>4a</sup> and our group.<sup>4b</sup> In this type of reaction, formal asymmetric C–H insertion into an aldehyde bond provided  $\alpha$ -alkyl- $\beta$ -ketoesters in high yields and with excellent enantioselectivities. Strategically, we envisioned that subsequent stereoselective reduction of the Roskamp product,  $\alpha$ -aryl- $\beta$ -keto carbonyl compounds **1**, would generate chiral *syn*- $\alpha$ -aryl- $\beta$ -hydroxy carbonyl compounds **2** in a one-pot manner (Scheme 1, eq 3). We describe here a new method for the synthesis of

## Scheme 1. Catalytic Asymmetric Methods To Prepare Chiral *syn*- $\alpha$ -Aryl- $\beta$ -hydroxy Carbonyl Compounds

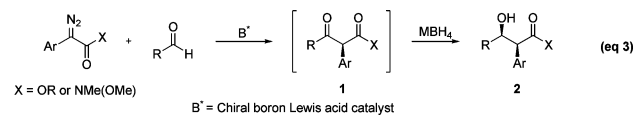
### Organocatalytic direct aldol reaction of thioesters



### C–H functionalization by rhodium catalyst



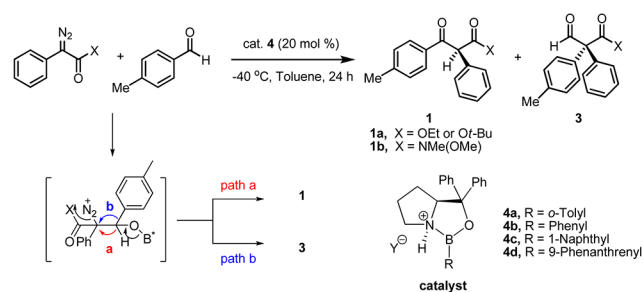
### Roskamp reaction and reduction (this work)



highly optically active *syn*- $\alpha$ -aryl- $\beta$ -hydroxy carbonyl compounds, which can be regarded as an alternative to the catalytic asymmetric aldol reaction.

Initially, asymmetric Roskamp reactions between ethyl or *tert*-butyl  $\alpha$ -phenyl diazoesters and *p*-tolualdehyde were examined to find optimized conditions for the synthesis of  $\alpha$ -aryl- $\beta$ -ketoesters **1a** (Table 1, entries 1 and 2). However, when the reaction was carried out at  $-40$  °C in the presence of 20 mol % oxazaborolidinium ion **4a**<sup>5</sup> activated by triflic imide, the desired  $\alpha$ -phenyl- $\beta$ -ketoester **1a** was formed as a minor product in  $\sim$ 20% yield via 1,2-hydride shift (path a), and the major *p*-tolyl migration product **3a** was isolated in  $\sim$ 60% yield (Table 1, path b).<sup>4c,d</sup>

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**Table 1. Optimization of the Asymmetric Roskamp Reaction of  $\alpha$ -Phenyl Diazo Weinreb Amides with *p*-Tolualdehyde<sup>a</sup>**


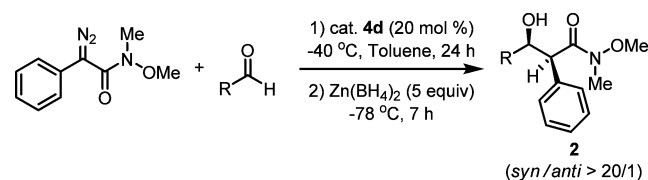
| entry | cat. | X                       | Y                 | 1/3 <sup>b</sup> | yield <sup>c</sup> (%) | ee <sup>d</sup> (%) |
|-------|------|-------------------------|-------------------|------------------|------------------------|---------------------|
| 1     | 4a   | OEt                     | Tf <sub>2</sub> N | 1:3              | 22                     | <sup>e</sup>        |
| 2     | 4a   | <i>o</i> - <i>t</i> -Bu | Tf <sub>2</sub> N | 1:3              | 20                     | <sup>e</sup>        |
| 3     | 4a   | NMe(OMe)                | Tf <sub>2</sub> N | >20:1            | 47                     | 80                  |
| 4     | 4a   | NMe(OMe)                | TfO               | >20:1            | 51                     | 82                  |
| 5     | 4b   | NMe(OMe)                | TfO               | >20:1            | 92                     | 89                  |
| 6     | 4c   | NMe(OMe)                | TfO               | >20:1            | 87                     | 91                  |
| 7     | 4d   | NMe(OMe)                | TfO               | >20:1            | 90                     | 91                  |

<sup>a</sup>The reaction of diazo compounds (0.18 mmol) with *p*-tolualdehyde (0.21 mmol) was performed in the presence of **4** (20 mol %) in 0.5 mL of toluene at  $-40$  °C. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis of the crude product. <sup>c</sup>Isolated yield of **1**. <sup>d</sup>The ee of **1** was determined by chiral HPLC. <sup>e</sup>The ee was not determined.

We next considered changing the ester group of the  $\alpha$ -phenyl diazoester to alternative groups such as thioesters or amides.<sup>6</sup> Since the *N*-methoxy-*N*-methylamide (Weinreb amide) group has many advantages in terms of facile transformation to ketones or aldehydes,<sup>7a</sup> we applied the  $\alpha$ -phenyl diazo Weinreb amide<sup>7b</sup> to these catalytic conditions.

Gratifyingly, replacement of the ester group of the diazo compound with the Weinreb amide group afforded  $\alpha$ -phenyl- $\beta$ -keto Weinreb amide **1b** as the major product in 47% yield and 80% ee with an excellent 1/3 ratio (>20:1) (Table 1, entry 3). Due to the presence of an acidic proton in **1b**, chromatography had to be carried out at  $-78$  °C to avoid erosion of the ee value.<sup>4b</sup> The enantioselectivity of the product increased slightly in the presence of the catalyst activated by triflic acid (Table 1, entry 4). We then investigated the effect of changing the boracycle catalyst substituents and found that the best boron aryl substituent was the 9-phenanthrenyl group (Table 1, entries 5–7). The reaction with catalyst **4d** in toluene provided optically active  $\alpha$ -phenyl- $\beta$ -keto Weinreb amide **1b** in 90% yield and 91% ee (Table 1, entry 7). As far as we know, this is the first example of catalytic asymmetric Roskamp reaction with  $\alpha$ -aryl diazo carbonyl compound.

With optimized conditions for the synthesis of  $\alpha$ -phenyl- $\beta$ -keto Weinreb amide **1b** in hand, we investigated diastereoselective reduction conditions for the synthesis of *syn*- $\alpha$ -phenyl- $\beta$ -hydroxy Weinreb amide **2ba**. Due to difficulty in the isolation of **1b** without loss of optical purity at rt, direct reduction of the ketone of **1b** in a one-pot manner was applied to the preparation of **2ba**. As reducing reagent, zinc borohydride<sup>8</sup> appeared to be superior to lithium borohydride or sodium borohydride in terms of *syn* stereoselectivity. When zinc borohydride was added at  $-78$  °C to **1b** prepared in situ by the optimized conditions in Table 1, *syn*- $\alpha$ -phenyl- $\beta$ -hydroxyamide **2ba** was isolated in 85% yield and 91% ee with an excellent *syn/anti* ratio (>20:1) (Table 2, entry 1).

**Table 2. Asymmetric Roskamp/Reduction Reaction of  $\alpha$ -Phenyl Diazo Weinreb Amides with Aldehydes<sup>a</sup>**


| entry          | 2   | R   | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|----------------|-----|---|------------------------|---------------------|
| 1              | 2ba | 4-MeC <sub>6</sub> H <sub>4</sub>               | 85                     | 91                  |
| 2              | 2ca | C <sub>6</sub> H <sub>5</sub>                   | 87                     | 89                  |
| 3 <sup>d</sup> | 2da | 4-MeOC <sub>6</sub> H <sub>4</sub>              | 75                     | 99                  |
| 4              | 2ea | 4-BrC <sub>6</sub> H <sub>4</sub>               | 80                     | 93                  |
| 5              | 2fa | 4-ClC <sub>6</sub> H <sub>4</sub>               | 82                     | 94                  |
| 6              | 2ga | 4-FC <sub>6</sub> H <sub>4</sub>                | 84                     | 92                  |
| 7              | 2ha | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | 79                     | 90                  |
| 8              | 2ia | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 74                     | 91                  |
| 9              | 2ja | 4-CNC <sub>6</sub> H <sub>4</sub>               | 80                     | 90                  |
| 10             | 2ka | 2-MeC <sub>6</sub> H <sub>4</sub>               | 72                     | 94                  |
| 11             | 2la | 2-FC <sub>6</sub> H <sub>4</sub>                | 83                     | 99                  |
| 12             | 2ma | 2-BrC <sub>6</sub> H <sub>4</sub>               | 81                     | 93                  |
| 13             | 2na | 1-Naph  | 70                     | 98                  |
| 14             | 2oa | 2-Naph  | 72                     | 89                  |
| 15             | 2pa | Et  | 78                     | 63                  |
| 16             | 2qa | <i>n</i> -Pen                                   | 83                     | 55                  |

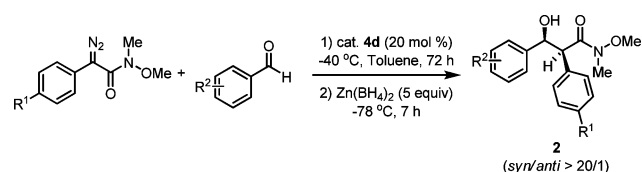
<sup>a</sup>The reaction of diazo Weinreb amides (0.18 mmol) with aryl aldehyde (0.21 mmol) was performed in the presence of **4d** (20 mol %) in toluene (0.5 mL) at  $-40$  °C, and Zn(BH<sub>4</sub>)<sub>2</sub> in ether was added at  $-78$  °C. <sup>b</sup>Isolated yield of **2**. <sup>c</sup>The ee of **2** was determined by chiral HPLC. <sup>d</sup>The reaction was performed at  $-40$  °C for 96 h.

With optimized one-pot reaction conditions in hand, we evaluated this methodology with a range of aldehydes. Regardless of the electronic properties of substituents on the aromatic aldehyde, the corresponding products **2** were obtained in good yields, high enantioselectivities, and excellent *syn*-stereoselectivities (Table 2, entries 1–14). While *ortho*-substituted benzaldehydes were not good substrates for the chiral oxazaborolidinium catalyst **4** in general,<sup>4b,5c</sup> one-pot reactions furnished the products **2ka**, **2la**, and **2ma** in good yields with excellent enantioselectivities (Table 2, entries 10–12). By contrast, this protocol with aliphatic aldehydes provided the corresponding products **2** with moderate enantioselectivities (Table 2, entries 15 and 16).

Encouraged by the good results illustrated in Table 2, we applied this catalytic methodology to a variety of diazo-Weinreb amides. For *para*-substituted phenyl diazo Weinreb amides, substitution with electron-withdrawing groups, such as *p*-Br or *p*-CF<sub>3</sub>, provided high yields and enantioselectivities regardless of the electronic properties of substituents on the aromatic aldehyde (Table 3, entries 1–7). However, substitution with electron-donating groups, such as *p*-Me, gave *syn*- $\alpha$ -*p*-tolyl- $\beta$ -hydroxy Weinreb amides **2** with lower enantioselectivities (Table 3, entries 8 and 9).

Further chemical transformations of the optically active  $\alpha$ -aryl- $\beta$ -hydroxy Weinreb amides are illustrated in Scheme 2. Grignard reaction of **2ca** with methylmagnesium chloride<sup>9</sup> led to the  $\alpha$ -aryl- $\beta$ -hydroxy ketone **5** in 84% yield without the need to protect the chiral alcohol (Scheme 2). Spectral data for the purified **5** were in good accordance with literature data confirming the *syn*-stereochemistry of **2**.<sup>10</sup> In addition, TBS protection of **2db** followed by DIBAL-H reduction provided

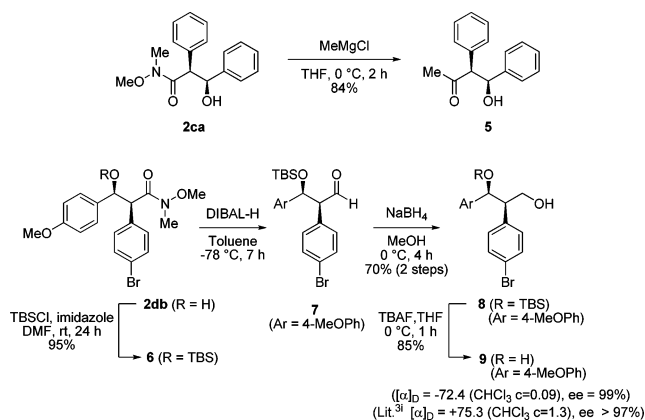
**Table 3. Asymmetric Roskamp/Reduction Reaction of  $\alpha$ -Aryl Diazo Weinreb Amides with Aryl Aldehydes<sup>a</sup>**



| entry          | 2   | R <sup>1</sup>  | R <sup>2</sup> | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|----------------|-----|-----------------|----------------|------------------------|---------------------|
| 1              | 2bb | CF <sub>3</sub> | 4-Me           | 80                     | 93                  |
| 2              | 2eb | CF <sub>3</sub> | 4-Br           | 81                     | 95                  |
| 3              | 2jb | CF <sub>3</sub> | 4-CN           | 80                     | 93                  |
| 4              | 2bc | Br              | 4-Me           | 87                     | 88                  |
| 5              | 2ec | Br              | 4-Br           | 74                     | 92                  |
| 6              | 2jc | Br              | 4-CN           | 82                     | 94                  |
| 7 <sup>d</sup> | 2db | Br              | 4-OMe          | 73                     | 99                  |
| 8 <sup>e</sup> | 2bd | Me              | 4-Me           | 74                     | 82                  |
| 9 <sup>e</sup> | 2ed | Me              | 4-Br           | 76                     | 72                  |

<sup>a</sup>The reaction of diazo Weinreb amide (0.18 mmol) with aldehyde (0.21 mmol) was performed in the presence of **4d** (20 mol %) in toluene (1.0 mL) at  $-40\text{ }^{\circ}\text{C}$ , and  $\text{Zn}(\text{BH}_4)_2$  in ether was added at  $-78\text{ }^{\circ}\text{C}$ . <sup>b</sup>Isolated yield of **2**. <sup>c</sup>The ee of **2** was determined by chiral HPLC. <sup>d</sup>The Roskamp reaction was performed at  $-40\text{ }^{\circ}\text{C}$  for 120 h. <sup>e</sup>The Roskamp reaction was performed at  $-40\text{ }^{\circ}\text{C}$  for 24 h.

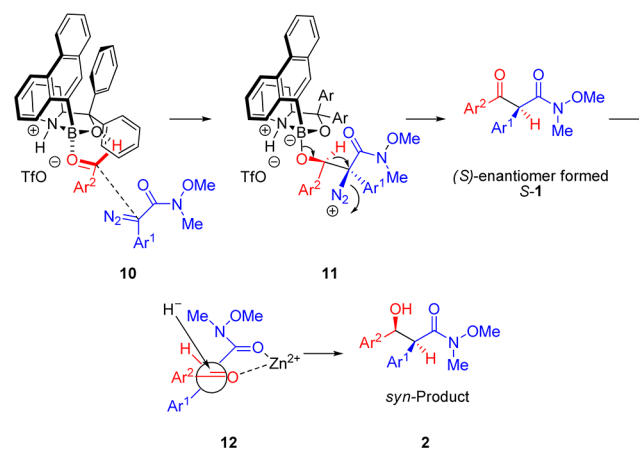
**Scheme 2. Transformations of Weinreb Amides **2** to Ketone, Aldehyde, and 1,3-Diol**



the corresponding aldehyde **7**,<sup>11</sup> which was reduced to alcohol **8** in 70% yield for the two steps. Finally, 1,3-diol **9** was prepared by deprotection of the TBS group with TBAF. Comparison of the optical rotation data of **9** confirmed the absolute (2*S*,3*S*) stereochemistry of **2**.<sup>3h,i</sup>

The observed stereochemistry for the asymmetric Roskamp reaction of the  $\alpha$ -aryl diazo Weinreb amide using oxazaborolidinium ion catalyst **4d** can be rationalized on the basis of the transition-state model shown in **Scheme 3**. The mode of coordination of aryl aldehyde to **4d** is the same as has been previously observed in enantioselective cyanosilylation,<sup>12</sup> Roskamp reaction of diazoesters,<sup>4b</sup> and formal C–C insertion reactions.<sup>4c</sup> In the pre-transition-state assembly **10**, shown in **Scheme 3**, the aldehyde group is situated above the phenyl group, which effectively shields the *re* face (back) from attack by the  $\alpha$ -aryl diazo Weinreb amide. Meanwhile, an apparent  $\pi$ – $\pi$  interaction between the aryl ring of the aldehyde with the diazo Weinreb amide aryl group holds the two aryl rings together.<sup>13</sup> Thus, nucleophilic addition of the diazo Weinreb amide from the *si* face (front) of the aldehyde is facilitated,

**Scheme 3. Transition-State Model for the Asymmetric Roskamp Reaction of  $\alpha$ -Aryl Diazo Weinreb Amides with Ar-CHO Catalyzed by **4d** and the Reduction Mechanism with Zinc Borohydride**



leading to intermediate **11**. Chemoselective hydride migration with loss of nitrogen provides the  $\alpha$ -aryl- $\beta$ -keto Weinreb amide *S*-1 as the major enantiomer, which is then reduced to form the *syn* (2*S*, 3*S*)- $\alpha$ -aryl- $\beta$ -hydroxy Weinreb amide **2**. The 3*S* stereochemistry of **2** can be explained by the chelation-controlled model **12** with  $\text{Zn}(\text{BH}_4)_2$ .<sup>4b,14</sup>

In summary, we have disclosed an oxazaborolidinium ion catalyzed asymmetric synthesis of *syn*- $\alpha$ -aryl- $\beta$ -hydroxy Weinreb amides from various aldehydes and  $\alpha$ -aryl diazo Weinreb amides that provides high enantioselectivities and excellent diastereoselectivities. The present method may be considered a new strategic reaction that is an alternative to the catalytic asymmetric aldol reaction. The absolute configuration of the reaction product was the same as that predicted by the transition state model in **Scheme 3**. Additional applications of this catalytic asymmetric transformation and extension of the substrate scope are in progress.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02268.

Experimental procedures and full analytical data (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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