## Catalytic enantioselective 1,3-dipolar cycloadditions of alkyl diazoacetates with $\alpha$ , $\beta$ -disubstituted acroleins<sup>†</sup><sup>‡</sup>

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A catalytic route to highly functionalized chiral 2-pyrazolines by an asymmetric 1,3-dipolar cycloaddition reaction of ethyl diazoacetate with  $\alpha$ -substituted and  $\alpha$ , $\beta$ -disubstituted acroleins has been developed; in the presence of chiral (*S*)-oxazaborolidinium ion 1 as catalyst, the reaction proceeded with high to excellent enantioselectivities (up to 99% ee).

Cycloaddition reactions of diazoalkanes with olefinic dipolarophiles have received considerable interest because the resulting pyrazolines and pyrazoles can be converted into a variety of nitrogen-containing molecules.<sup>1–5</sup> Over the past decade, highly diastereoselective variants of these reactions using different chiral auxiliaries have been reported.<sup>2</sup> In comparison, catalytic asymmetric 1,3-dipolar cycloaddition reactions of diazoalkanes with olefins have not been well explored to date.

The Kanemasa group reported the first enantioselective, chiral Lewis acid-catalyzed cycloaddition of trimethylsilyldiazomethane to  $\beta$ -alkyl-substituted,  $\alpha$ , $\beta$ -unsaturated oxazolidinone imides as a bidentate dipolarophile.<sup>3</sup> The Maruoka group developed an enantioselective cycloaddition between diazoacetates and readily available  $\alpha$ -substituted acroleins in the presence of a chiral titanium BINOLate catalyst<sup>4</sup> and extended this methodology to a short synthesis of the alkaloid manzacidin A. Recently, the Sibi group reported similar cycloaddition reactions of diazoacetates to  $\alpha$ , $\beta$ -unsaturated pyrazolidinone imides using Mg<sup>2+</sup>-based Lewis acid catalysts.<sup>5</sup> However, it is important to note that in these reported 1,3-dipolar cycloadditions, the substrate scope was limited or fewer atom-economical bidentate dipolarophiles were used.

Given the limited substrate scope and low efficiency in enantioselective diazoacetate 1,3-dipolar cycloaddition, we evaluated the chiral oxazaborolidinium ions **1** as Lewis acid catalysts for these reactions (Scheme 1). Catalysts **1**, generated from the corresponding oxazaborolidines by protonation with trifluoromethanesulfonimide (triflimide), behave as powerful Lewis acids and have been proven to be effective catalysts for enantioselective Diels–Alder reactions,<sup>6</sup> cyanosilylations,<sup>7</sup> Michael reactions<sup>8</sup> and recently, three component coupling reactions.<sup>9</sup> In addition, there is much evidence for the formation of complexes between catalysts **1** and aldehydes.<sup>6c,7a,10</sup>

Initially, the 1,3-dipolar cycloaddition reaction between tert-butyl diazoacetate and methacrolein was examined in the presence of 20 mol% oxazaborolidinium ion 1a, activated by triflimide. When the reaction was carried out at -78 °C in toluene, the desired cycloadduct, optically active 2-pyrazoline, was formed in moderate yield and 82% ee. However, with dichloromethane as the solvent, the desired cycloadduct was obtained in an improved yield and enantioselectivity. Replacement of the tert-butyl group of diazoacetate by the sterically less hindered ethyl group under similar conditions produced the desired product in 81% yield and 90% ee (Table 1, entry 3). The same reaction with chiral catalyst 1a activated by triflic acid provided the desired product in a better yield (88%) but with reduced enantioselectivity (84% ee). We then investigated the effect of changing the catalyst boracycle substituent, and found that the best boron aryl substituent is phenyl (entries 5 and 6). Ar = 3,5-dimethylphenyl (mexyl) as the aryl substituent in 1c provided better enantioselectivity relative to Ar = phenyl in 1b, which is consistent with the results from previous studies (entry 6).

After determination of the most favorable parameters for 1,3-dipolar cycloadditions catalyzed by the cationic Lewis acids 1, the scope of this methodology was studied with various  $\alpha$ -substituted acroleins using 1b and 1c as catalysts. As shown in Table 2, excellent yields and enantioselectivities were obtained with 2-ethyl, 2-isopropyl and 2-cyclohexyl acroleins (Table 2, entries 2–5). In the case of 2-benzyl acrolein, the use of the mexyl-substituted catalyst 1c improved the ee of 3 to 91% (entry 7).

Attempts to expand the scope of the enantioselective 1,3-dipolar cycloaddition of ethyl diazoacetate with  $\alpha$ , $\beta$ -disubstituted acroleins are illustrated in Table 3. When



Scheme 1 Enantioselective 1,3-dipolar cycloaddition of diazoacetates with  $\alpha$ , $\beta$ -disubstituted acroleins.

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Table 1Enantioselective 1,3-dipolar cycloaddition between alkyldiazoacetate and methacrolein catalyzed by  $1^a$ 

$$N_2CHCO_2R + Me H \xrightarrow{O}_{CH_2CI_2, -78^\circ C} RO_2C \xrightarrow{N-NH}_{CH_2CI_2, -78^$$

| Entry | R    | Catalyst | t/h | Yield $(\%)^b$ | Ee $(\%)^c$ |
|-------|------|----------|-----|----------------|-------------|
| $1^d$ | t-Bu | 1a       | 5   | 55             | 82          |
| 2     | t-Bu | 1a       | 1   | 61             | 88          |
| 3     | Et   | 1a       | 2   | 81             | 90          |
| $4^e$ | Et   | 1a       | 2   | 88             | 84          |
| 5     | Et   | 1b       | 2   | 87             | 91          |
| 6     | Et   | 1c       | 2   | 86             | 95          |

<sup>*a*</sup> All reactions were performed with methacrolein and alkyl diazoacetates (1.5 equiv.) at -78 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by chiral HPLC analysis after reduction of the aldehyde. <sup>*d*</sup> Toluene was used instead of dichloromethane as a solvent. <sup>*e*</sup> TfOH was used instead of Tf<sub>2</sub>NH for the preparation of catalyst **1a**.

**Table 2** Enantioselective 1,3-dipolar cycloaddition between ethyl diazoacetate and  $\alpha$ -substituted acroleins catalyzed by **1b** and **1c**<sup>*a*</sup>

|                                       | R H . | cat. (20 mol%) |       |
|---------------------------------------|-------|----------------|-------|
| N <sub>2</sub> CHCO <sub>2</sub> Et + |       | CH₂CI₂, -78ºC  | 2 CHO |

| Entry | R                 | t/h | Catalyst | Yield $(\%)^b$ | Ee $(\%)^{c}$   |
|-------|-------------------|-----|----------|----------------|-----------------|
| 1     | Me                | 2   | 1c       | 86             | 95 <sup>d</sup> |
| 2     | Et                | 1   | 1b       | 91             | 91              |
| 3     | <i>i</i> -Pr      | 1   | 1b       | 97             | 92              |
| 4     | $C_{6}H_{11}$     | 1   | 1b       | 94             | 85              |
| 5     | $C_6H_{11}$       | 1   | 1c       | 94             | 92              |
| 6     | PhCH <sub>2</sub> | 0.5 | 1b       | 72             | 76              |
| 7     | PhCH <sub>2</sub> | 0.5 | 1c       | 72             | 91              |
|       |                   |     |          |                |                 |

<sup>*a*</sup> All reactions were performed with  $\alpha$ -substituted acrolein and ethyl diazoacetates (1.5 equiv.) at -78 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by chiral HPLC analysis. <sup>*d*</sup> The absolute configuration was assigned as (*R*)-enriched. For details see the ESI.

1-cyclohexenecarboxaldehyde was employed as the dipolarophile at -78 °C in dichloromethane, a 31% yield of bicyclic pyrazoline 4 was isolated with high enantioselectivity, along with  $\beta$ -keto ester 5 (35%)<sup>11</sup> (entry 1). Fortunately, the isolated yield of 4 could be improved by performing reaction at -93 °C using propionitrile as the solvent (entry 2). Under optimized conditions, 1,3-dipolar cycloadditions of 1-cyclopentene or 1-cycloheptene carboxaldehyde provided the desired bicyclic 2-pyrazolines in good yields and with high enantioselectivities (entries 3 and 4). Encouraged by the high enantioselectivity observed in the 1,3-dipolar cycloaddition of ethyl diazoacetate with cyclic  $\alpha,\beta$ -substituted enals, we applied the same catalytic conditions to acyclic  $\alpha$ -alkyl or aryl- $\beta$ -alkyl disubstituted acroleins. Remarkably, good results were obtained with the  $\alpha,\beta$ -dimethyl acrolein and  $\alpha$ -phenyl- $\beta$ -ethyl acrolein (entries 5 and 8). To the best of our knowledge, these are the first examples of a chiral Lewis acid-catalyzed 1,3-dipolar



Table 3 Enantioselective 1,3-dipolar cycloaddition between ethyl

diazoacetate and  $\alpha,\beta$ -disubstituted acroleins catalyzed by  $\mathbf{1b}^{a}$ 

| Entry | $\mathbf{R}^1,  \mathbf{R}^2$      | t/h | Yield $(\%)^b$ | Ee $(\%)^{c}$ |
|-------|------------------------------------|-----|----------------|---------------|
| $1^d$ | -(CH <sub>2</sub> ) <sub>4</sub> - | 1   | 31             | 92            |
| 2     | $-(CH_2)_4-$                       | 1   | 75             | 92            |
| 3     | -(CH <sub>2</sub> ) <sub>3</sub> - | 0.5 | 73             | 97            |
| 4     | -(CH <sub>2</sub> ) <sub>5</sub> - | 0.5 | 70             | 85            |
| 5     | Me, Me                             | 1   | 93             | 90            |
| 6     | Me, Et                             | 1   | 90             | 85            |
| 7     | Ph, Me                             | 1   | 70             | 92            |
| 8     | Ph, Et                             | 1   | 81             | 99            |

<sup>*a*</sup> Unless indicated, all reactions were performed with α,β-substituted acroleins and ethyl diazoacetates (1.5 equiv.) at -93 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by chiral HPLC analysis. <sup>*d*</sup> Reaction was performed at -78 °C with CH<sub>2</sub>Cl<sub>2</sub> as the solvent.

cycloaddition between a diazoacetate and  $\alpha$ , $\beta$ -disubstituted acroleins.



The observed stereochemistry in the asymmetric reaction using oxazaborolidinium ion catalysts 1 can be explained with the transition state model shown in Fig. 1. The coordination mode of the  $\alpha$ , $\beta$ -unsaturated aldehyde to 1 is the same as that previously proposed in enantioselective Diels-Alder and cyanosilylation reactions. This organized formyl C-H···O hydrogen-bonded complex can reduce the LUMO energy of the  $\alpha$ ,  $\beta$ -unsaturated aldehyde. As shown in Fig. 1, the formyl carbon is situated above the bulky phenyl group, which effectively screens the rear face of the acrolein from attack by ethyl diazoacetate. Thus, the endo mode of addition of the 1,3-dipole from the front face of the acrolein is favorable and leads to the (4S,5R)-pyrazoline as the major enantiomer. Due to the greater screening ability of the mexyl group, catalyst 1c provided higher ee compared to catalyst 1b (Table 2, entries 4-7).



Fig. 1 Transition state model for the asymmetric 1,3-dipolar cycloaddition reaction between ethyl diazoacetate and  $\alpha$ , $\beta$ -disubstituted acroleins.

In summary, we have developed a highly enantioselective, catalytic reaction between ethyl diazoacetate and  $\alpha$ -substituted or  $\alpha$ , $\beta$ -disubstituted acroleins, producing highly functionalized chiral (5*R*)-pyrazolines in good yields with high enantioselectivities. The absolute configuration of the products could be predicted by the transition state model in Fig. 1. We believe that these results will be useful in the synthesis of various optically active pyrazolines. Further optimization of this catalytic asymmetric reaction and extension of the reaction scope, as well as synthetic applications are in progress.

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