Asymmetric Synthesis

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Enantioselective Synthesis of α-Alkyl-β-ketoesters: Asymmetric Roskamp Reaction Catalyzed by an Oxazaborolidinium Ion**

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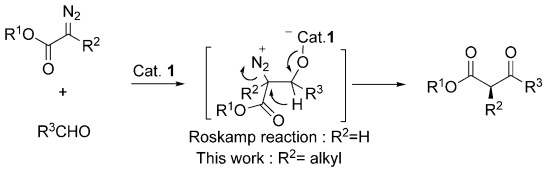
The Roskamp reaction,[1] a Lewis acid catalyzed reaction of alkyl diazoesters with aldehydes, is a powerful and useful synthetic method to construct β-keto carbonyl compounds, which have been utilized in the synthesis of natural products[2] (Scheme 1). An asymmetric variant of this transformation was previously effected using the chiral-auxiliary-based



Scheme 1. Asymmetric Roskamp reaction.

approach with a camphorsultam-derived diazocarbonyl compound.[3a] To the best of our knowledge, only a single successful example of an enantioselective Lewis acid catalyzed Roskamp reaction of α-alkyl-α-diazoesters with aromatic aldehydes using chiral *N,N′*-dioxide-scandium(III) complexes was recently reported.[3b] However, this methodology could not be applied to aliphatic aldehydes. In this context, we were interested in the possibility of developing a catalytic, asymmetric Roskamp reaction with broad applicability. Herein we report such an asymmetric transformation using the oxazaborolidinium ion Lewis acid catalysts **1** (Figure 1), one of which was recently found to effectively catalyze the enantioselective cyclopropanation of α-substituted acroleins with diazoacetates.[4a]

Catalysts **1** (Figure 1), which are generated from the corresponding oxazaborolidine by protonation with triflic acid or triflic imide, are powerful Lewis acids which have been demonstrated to be effective catalysts for various enantioselective carbon–carbon bond-forming reactions.[4] In addition, much evidence exists to support the formation of a complex between catalysts **1** and aldehydes.[4e] We have applied these oxazaborolidinium catalysts to the asymmetric Roskamp reaction of aliphatic aldehydes and α-alkyl-α-diazoesters.

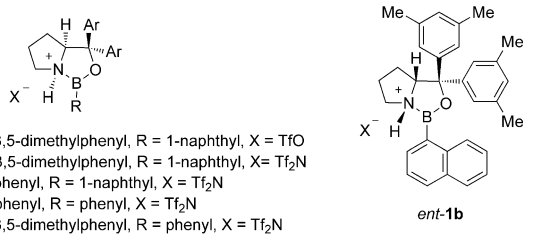
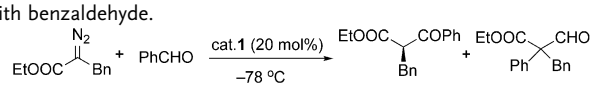


Figure 1. Catalysts screened for the enantioselective synthesis of α-alkyl-β-ketoesters. Tf = trifluoromethanesulfonyl.

Initially, the asymmetric Roskamp reaction between α-benzyl diazoester and benzaldehyde was examined in the presence of 20 mol% of the oxazaborolidinium ion **1a**, which was prepared by activation of its precursor with triflic acid (Table 1, entry 1). When the reaction was carried out at −78 °C in dichloromethane, the desired optically active α-alkyl-β-ketoester was formed in 82% yield and 87% *ee* with concomitant formation of **3**, the phenyl migration product (migration of R^3 instead of hydride; Scheme 1).[5] Product **2** was isolated by silica gel chromatography at −78 °C without erosion of the *ee* value.[3b]

Table 1: Optimization of the Roskamp reaction of α-benzyl diazoester with benzaldehyde.



Entry	Solvent	Cat.	*t* [h]	**2**/**3**[a]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	**1a**	1	90:10	82	87[d]
2	CH_2Cl_2	**1b**	1	89:11	80	90
3	CH_2Cl_2	**1c**	1.5	82:18	77	82
4	propionitrile	**1c**	1	67:33	60	79
5	toluene	**1c**	1.5	91:9	87	88
6	toluene	**1d**	1	93:7	90	92
7	toluene	**1e**	2	94:6	92	95

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **2**. [c] The *ee* value of **2** was determined by chiral HPLC. [d] The absolute configuration *R* was assigned to the major product. For details see the Supporting Information.

The same reaction performed with chiral catalyst **1b**, which was prepared by activation of its precursor with triflic imide, afforded an improved *ee* value despite slight decreases

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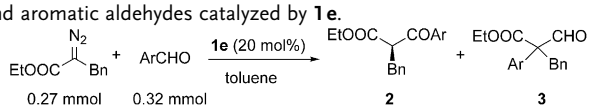
in chemoselectivity and yield (Table 1, entry 2). Next, we investigated the effect of solvent with catalyst **1c**, and found that toluene gave the best chemoselectivity, enantioselectivity, and yield (entries 3–5). Additional studies focused on changes in the structure of the catalyst. Reaction in toluene with the catalyst modified by substitution of the 1-naphthyl group on boron with a less hindered phenyl group (**1d**) provided the product with improved yield and *ee* value (entry 6). Reintroduction of the more hindered 3,5-dimethylphenyl groups into the catalyst led to the optimized reaction conditions. The reaction with catalyst **1e** in toluene at −78 °C provided the optically active α-alkyl-β-ketoester in 92 % yield and 95 % *ee* with a 94:6 chemoselectivity (entry 7).

With optimized reaction conditions for the asymmetric Roskamp reaction in hand, we evaluated this methodology with a range of substituted benzaldehydes. Regardless of the electronic properties of the substituents on the aromatic aldehyde, the reactions proceeded in a highly chemoselective manner, and the corresponding products were obtained in high yields and excellent enantioselectivities (Table 2,

Table 2: Asymmetric Roskamp reaction between α-benzyl diazoester and aromatic aldehydes catalyzed by **1e**.

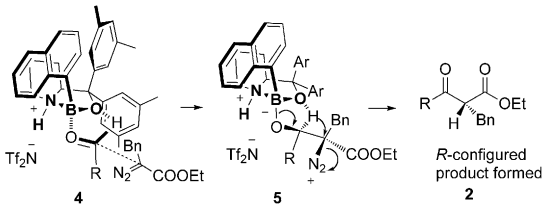


Entry	Ar	*T* [°C]	*t* [h]	**2**/**3**[a]	Yield [%][b]	*ee* [%][c]
1	Ph	−78	2	94:6	92	95
2	4-MeC_6H_4	−78	2	90:10	87	95
3	4-OMeC_6H_4	−55	1	92:8	85	91
4	4-BrC_6H_4	−78	1	94:6	91	94
5	4-$CF_3C_6H_4$	−95	1	89:11	82	96
6	3-OMe	−78	2	90:10	83	95
7	2-OMe	−55	5	76:24	69	80

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **2**. [c] The *ee* value of **2** was determined by HPLC using a chiral stationary phase after silica gel chromatography at −78 °C.

entries 2–6). However, *ortho*-anisaldehyde gave the desired α-benzyl-β-ketoester with lower enantioselectivity (entry 7). We believe the bulky 2-methoxy group of *ortho*-anisaldehyde significantly reduces the degree of complexation with the catalyst in the pretransition-state assembly (Scheme 2), thus leading to the observed lower enantioselectivity and yield.

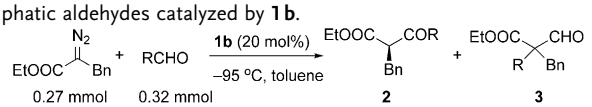
To further investigate the substrate scope of the present catalytic system, we performed the catalytic asymmetric Roskamp reaction with α-benzyl diazoester and a range of



Scheme 2. Transition-state model for asymmetric Roskamp reaction of α-benzyl diazoester and propionaldehyde catalyzed by **1b**.

aliphatic aldehydes. However, the best chiral catalyst, **1e**, for aromatic aldehydes was not the optimal catalyst for aliphatic substrates. The catalyst **1b**, bearing the more bulky naphthyl group on boron, was found to be more suitable for generating higher enantioselectivity (Table 3, entries 1 and 2).

Table 3: Asymmetric Roskamp reaction between α-benzyl diazoester and aliphatic aldehydes catalyzed by **1b**.



Entry	R	*t* [h]	**2**/**3**[a]	Yield [%][b]	*ee* [%][c]
1[d]	Et	0.5	79:21	73	87
2[e]	Et	0.5	82:18	76	97
3	Et	1.5	89:11	85	98[f]
4	Hex	1.5	92:8	90	98
5	*i*Pr	3	91:9	87	97
6	Cy	3	91:9	89	96
7	$CH_3O_2C(CH_2)_2$	3	94:6	92	97

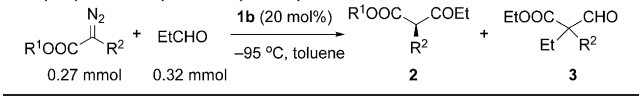
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **2**. [c] The *ee* value of **2** was determined by HPLC using a chiral stationary phase. [d] The reaction was performed at −78 °C catalyzed by **1e**. [e] The reaction was performed at −78 °C. [f] The absolute configuration *R* was assigned to the major product. For details see the Supporting Information. Cy = cyclohexyl.

As shown in Table 3, propionaldehyde, long-chain heptaldehyde, as well as more sterically hindered isopropyl and cyclohexyl carboxaldehydes successfully reacted with α-benzyl diazoester to provide the corresponding α-benzyl-β-ketoesters in high yields and excellent enantioselectivities (entries 3–6). This catalytic system was also applied to the functionalized aldehyde methyl 4-oxobutanoate to afford the α-benzyl-β-keto diester in 92 % yield with excellent chemo- and enantioselectivity (entry 7). To the best of our knowledge, these are the first examples of chiral Lewis acid catalyzed asymmetric Roskamp reactions with aliphatic aldehydes.

Encouraged by the good results exhibited in Table 3, we applied this catalytic Roskamp methodology to reactions of various α-alkyl diazoesters and propionaldehyde. As summarized in Table 4, the reactions produced the corresponding α-alkyl-β-ketoesters in high yields and chemoselectivities with excellent enantioselectivities (entries 1–7 and 9–11). While more sterically hindered R^1 groups gave enhanced selectivity for **2**, high product enantioselectivities were consistently observed (entries 1–4, and 12). Conversely, sterically hindered R^2 substituents, such as an isopropyl group, caused significant reductions in the ratio of **2**/**3**, as well as the product enantioselectivity (entry 8). Use of *ent*-**1b** as the catalyst (Figure 1) was found to effectively provide (*S*)-α-methyl-β-ketoester (*ent*-**2**) in 92 % yield and 97 % *ee* (entry 12).

The observed product stereochemistry from the asymmetric Roskamp reaction with the oxazaborolidinium ion catalyst **1b** could be rationalized based on the transition-state model shown in Scheme 2. The mode of coordination of propionaldehyde to **1b** is the same as has previously been shown to operate in enantioselective cyanosilylation,[4f] 1,3-dipolar cycloaddition,[4b] and cyclopropanation reactions.[4a] In

Table 4: Asymmetric Roskamp reaction of various α-alkyl diazoesters and propionaldehyde catalyzed by **1b**.

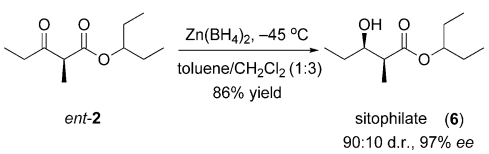


Entry	R^1	R^2	*t* [h]	**2**/**3**[a]	Yield [%][b]	*ee* [%][c]
1	Me	Bn	1	76:24	70	96
2	Et	Bn	1.5	89:11	85	98
3	*t*Bu	Bn	3	93:7	91	97
4	Bn	Bn	2	93:7	92	95
5	Bn	Me	0.5	92:8	89	94
6	Bn	allyl	3	89:11	86	93
7	Bn	Et	3	89:11	85	85
8[d]	Bn	*i*Pr	12	71:29	69	45
9	Et	Me	1	96:4	94	95
10[e]	Et	propargyl	2	96:4	83	86
11	Et	Et	1	88:12	85	95
12	3-pentyl	Me	1	93:7	92	97[f]

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **2**. [c] The *ee* value of **2** was determined by HPLC or GC using a chiral stationary phase. [d] The reaction was performed at −55 °C. [e] The *ee* value of the corresponding product decreased during isolation by silica gel chromatography at −78 °C. [f] Catalyst *ent*-**1b** was used. The *ee* value was determined by chiral HPLC after reduction with $Zn(BH_4)_2$ and *p*-methoxy benzoylation. The absolute configuration of *ent*-**2** was assigned as the *S* enantiomer. For details see the Supporting Information.

the pretransition-state assembly **4** (Scheme 2), the aldehyde is situated above the 3,5-dimethylphenyl group, which effectively shields the Re face (back) from attack by the diazoester. Because of a dipole–dipole interaction between the two carbonyl groups, the diazoester approaches the aldehyde group for nucleophilic addition with the ester group situated away from the aldehyde group. In addition, as a result of steric interactions, the large benzyl group is situated away from the aldehyde alkyl group. Thus, nucleophilic addition of the diazoester to the Si face (front) of the aldehyde, as shown in **4**, is facilitated and leads to the intermediate **5**. Chemoselective hydride transfer with loss of nitrogen provides the (*R*)-α-benzyl β-ketoester as the major enantiomer. Because of the greater screening ability of a 3,5-dimethylphenyl group, the catalyst **1e** provided a 3% higher *ee* value than catalyst **1d** (Table 1, entries 6 and 7).

Synthetic utility of the present reaction was further demonstrated by the synthesis of sitophilate (**6**; (2*S*,3*R*)-1-ethylpropyl 3-hydroxy-2-methylpentanoate; Scheme 3), the aggregation pheromone of the granary weevil *Sitophilus granarius*, a major cosmopolitan pest of stored cereal grains.[6] Purified (*S*)-α-methyl-β-ketoester (*ent*-**2**; Table 4, entry 12), which was generated using the current catalytic system was reduced with $Zn(BH_4)_2$[7] to afford **6** in good diastereoselectivity and high yield without racemization[8] (Scheme 3). Spectral data for the purified major diastereomer of **6** isolated after silica gel chromatography were in accord with literature data.[6] Comparison of the optical rotation data confirmed the absolute (2*S*,3*R*) stereochemistry [measured: $[\alpha]_D^{20} = -3.5$ ($CHCl_3$, c 1.0; Ref. [6]: $[\alpha]_D^{25} = -3.1$ ($CHCl_3$, $c = 1.7$)].



Scheme 3. Synthesis of the natural pheromone sitophilate.

In summary, we have developed a novel, catalytic asymmetric Roskamp reaction of α-alkyl diazoesters with both aromatic and aliphatic aldehydes, thereby producing α-alkyl-β-ketoesters in high yields and excellent enantioselectivities. The absolute configuration of the major reaction product was the same as that predicted by the transition-state model in Scheme 2. This methodology was successfully applied to a concise two-step synthesis of sitophilate. Additional applications of this catalytic asymmetric transformation and extension of the substrate scope are in progress.

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[8] Direct reduction without isolation of *ent*-**2** provided **6** in 80% yield and 97% *ee* (see the Supporting Information).

