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Catalytic Asymmetric Roskamp Reaction of α-Alkyl-α-diazoesters with Aromatic Aldehydes: Highly Enantioselective Synthesis of α-Alkyl-β-keto Esters

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The Roskamp reaction, which involves the interaction of alkyl diazoacetates with aldehydes in the presence of Lewis acids, is one of the most powerful and efficient methods for the synthesis of β-keto esters (R^2 = H, path a in Scheme 1).[1] Analogously, it could be extended to an asymmetric version involving α-alkyl-α-diazoesters, providing chiral α-alkyl-β-keto esters (R^2 = alkyl, Scheme 1). However, this strategy has received much less attention in the last two decades. There are two major reasons for this: (1) the reaction process can undergo three rearrangement pathways once the diazonium intermediate is generated, which makes it difficult to conduct chemoselectively (Scheme 1), and (2) in comparison with chiral α-alkyl-β-keto imides developed by Evans and co-workers,[2] chiral α-alkyl-β-keto esters may suffer racemization more easily via enolization. Maruoka and co-workers recently presented an intriguing chiral-auxiliary-based approach to the Roskamp reaction with α-alkyl-α-diazocarbonyl compounds.[3] As far as we know, no catalytic asymmetric example has been reported to date. Herein, we describe the first catalytic asymmetric Roskamp reaction using chiral *N*,*N*′-dioxide−scandium(III) complexes.[4]

Using our previously established chiral Lewis acid catalyst system,[4] we initially investigated the catalytic asymmetric Roskamp reaction of ethyl α-benzyl-α-diazoacetate (**1a**) with benzaldehyde (**2a**) promoted by metal complexes of the chiral *N*,*N*′-dioxide ligand **L1** (Table 1, entries 1−4). The reactions catalyzed by the $Y(OTf)_3$ and $La(OTf)_3$ complexes of **L1** were sluggish (Table 1, entries 1 and 2). The zinc complex of **L1** gave moderate enantioselectivity with poor reactivity (Table 1, entry 3). $Sc(OTf)_3$ was found to be a suitable Lewis acid,[5] providing the product **3a** in 95% yield and 78% ee (Table 1, entry 4 vs entries 1−3). Encouraged by this result, we next explored complexes of other *N*,*N*′-dioxide ligands with $Sc(OTf)_3$. As for the amino acid backbone, L-ramipril acid-derived *N*,*N*′-dioxide **L3** achieved higher enantioselectivity and yield (Table 1, entry 6 vs entries 4 and 5). Steric hindrance of the ligand plays a key role in promoting both the enantioselectivity and reactivity, and the highly sterically demanding ligand **L3** turned out to be the best one (Table 1, entries 6−9). To our delight, the reaction time was reduced to 2 h when 3 Å molecular sieves were used as an additive (Table 1, entry 10). Remarkably, when the catalyst loading was decreased to 0.05 mol %, the enantioselectivity was slightly enhanced to 95% ee without any loss of reactivity (Table 1, entry 11 vs 10). The catalyst loading could even be reduced to 0.01 mol %, giving the same enantioselectivity with a prolonged reaction time (Table 1, entry 12).

It is noteworthy that the possible byproducts that could be produced via R^3 migration (Scheme 1, path b)[3c,6] or epoxide formation (Scheme 1, path c)[7] were not detected in the current system. The product **3a** suffered racemization to some extent during the purification with silica gel column chromatography, but fortunately, the product and the catalyst could be easily isolated by flash filtration through a thin silica gel layer without racemization.[8]

Scheme 1

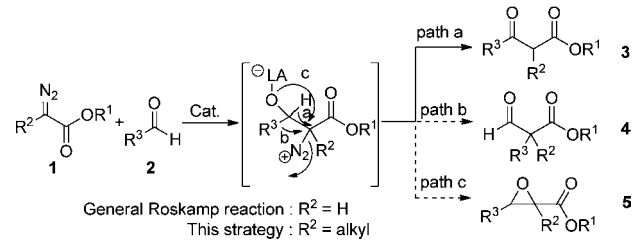
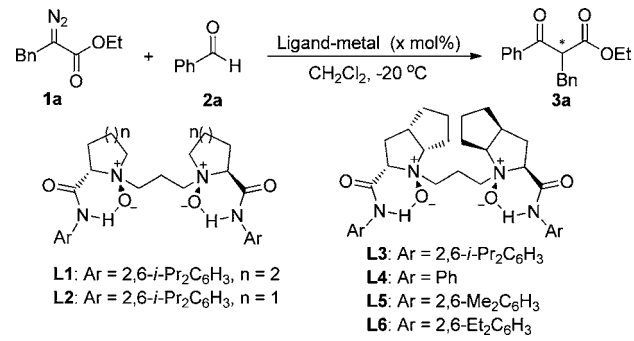


Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	metal	x (mol %)	time (h)	ee (%)[b]	yield (%)[c]
1	**L1**	$Y(OTf)_3$	5	29	−	trace
2	**L1**	$La(OTf)_3$	5	29	−	trace
3	**L1**	$Zn(OTf)_2$	5	29	55	8
4	**L1**	$Sc(OTf)_3$	5	7	78	95
5	**L2**	$Sc(OTf)_3$	5	7	75	90
6	**L3**	$Sc(OTf)_3$	5	7	94	97
7	**L4**	$Sc(OTf)_3$	5	29	40	10
8	**L5**	$Sc(OTf)_3$	5	28	78	82
9	**L6**	$Sc(OTf)_3$	5	28	80	81
10[d]	**L3**	$Sc(OTf)_3$	5	2	94	97
11[d,e,f]	**L3**	$Sc(OTf)_3$	0.05	2	95	97
12[d,e,g]	**L3**	$Sc(OTf)_3$	0.01	56	95	80

[a] Unless otherwise noted, reactions were carried out with **L**/$Sc(OTf)_3$ (1/1), 0.1 mmol of **1a**, and 0.1 mmol of **2a** in 0.5 mL of CH_2Cl_2 at −20 °C. [b] Determined by chiral HPLC after flash filtration as the isolation procedure. [c] Isolated yield after silica gel column chromatography. [d] Using 3 Å molecular sieves (10.0 mg) as an additive. [e] Reaction was carried out with **L3**/$Sc(OTf)_3$ (1/1.2), 1.0 mmol of **1a**, and 1.0 mmol of **2a**. [f] Using 0.2 mL of CH_2Cl_2. [g] Using 0.1 mL of CH_2Cl_2.

The substrate scope was investigated under the optimized conditions (Table 1, entry 11), as shown in Table 2. With 0.05 mol % catalyst, a series of α-alkyl-α-diazoesters reacted smoothly with benzaldehyde, delivering the corresponding products in

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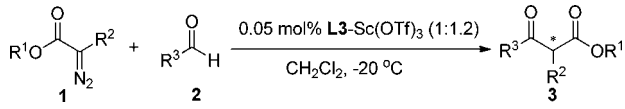
Table 2. Substrate Scope of the Catalytic Asymmetric Roskamp Reaction[a]

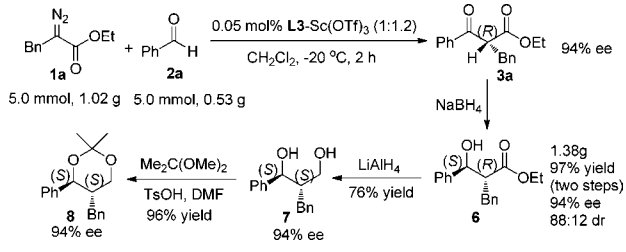


1 2 3

entry	R^1, R^2	R^3	3	ee (%)[b]	yield (%)[c,d]
1	Et, Bn	Ph	**3a**	95 (*R*)	97 (77)
2	Me, Bn	Ph	**3b**	96	99 (66)
3	*i*-Pr, Bn	Ph	**3c**	95	99 (84)
4	*t*-Bu, Bn	Ph	**3d**	92	95 (90)
5	Bn, Bn	Ph	**3e**	96	99 (66)
6	Bn, 	Ph	**3f**	98	90 (29)
7	Bn, allyl	Ph	**3g**	94	96 (40)
8	Bn, propargyl	Ph	**3h**	95	85 (73)
9	Bn, Me	Ph	**3i**	86	97 (53)
10	Bn, Et	Ph	**3j**	91	96 (70)
11	Me, Bn	2-$MeOC_6H_4$	**3k**	95	98 (62)
12	Me, Bn	3-$MeOC_6H_4$	**3l**	98	98 (79)
13	Me, Bn	4-$MeOC_6H_4$	**3m**	96	97 (92)
14	Me, Bn	3-$PhOC_6H_4$	**3n**	98	98 (70)
15	Me, Bn	3-ClC_6H_4	**3o**	97	96 (64)
16	Me, Bn	3-$NO_2C_6H_4$	**3p**	96	93 (45)
17	Me, Bn	4-PhC_6H_4	**3q**	97	94 (84)
18	Me, Bn	4-FC_6H_4	**3r**	94	96 (82)
19	Me, Bn	4-ClC_6H_4	**3s**	95	97 (79)
20	Me, Bn	4-BrC_6H_4	**3t**	95	99 (77)
21	Me, Bn	4-CNC_6H_4	**3u**	93	97 (40)
22	Me, Bn	3,4-$Cl_2C_6H_3$	**3v**	97	98 (70)
23	Bn, Bn	4-BrC_6H_4	**3w**	95	95 (85)
24	Me, Bn	2-naphthyl	**3x**	98	90 (84)
25	Me, Bn	2-thienyl	**3y**	87	99 (80)
26	Me, Bn	2-furyl	**3z**	90	92 (81)

[a] Reactions were carried out with 0.05 mol % **L3**/Sc(OTf)$_3$ (1/1.2), **1** (1.0 mmol), **2** (1.0 mmol), and 3 Å molecular sieves (10.0 mg) in 0.2 mL of CH_2Cl_2 at −20 °C for 0.5−24 h (for details, see the Supporting Information). [b] Determined by chiral HPLC after flash filtration as the isolation procedure. [c] Isolated yield after silica gel column chromatography. [d] The results in parentheses are the eroded ee values after silica gel column chromatography.

Scheme 2. Scaled-Up Version of the Roskamp Reaction and Transformations of the Product



excellent yields and ee values (Table 2, entries 1−10). Meanwhile, regardless of the electronic properties or steric hindrance of the substituents on the aromatic aldehydes, excellent yields and ee values were also obtained (Table 2, entries 11−23). Notably, condensed-ring and heteroaromatic aldehydes were tolerated under the current system (Table 2, entries 24−26). However, poor results were obtained for aliphatic and α,β-unsaturated aldehydes.

As expected, almost the same result was obtained when the model reaction was scaled up to the gram scale (Scheme 2). More significantly, **3a** was easily converted to the β-hydroxy ester in good diastereoselectivity and excellent yield without racemization. Furthermore, the pure major diastereomer **6** isolated by silica gel chromatography was reduced to the chiral 1,3-diol **7**, which is a useful building block in syntheses of both natural products and biological compounds.[9] The relative configuration of **7** was determined to be trans by conversion of the diol to cyclic acetonide **8** and comparison of its analytical data with the reported data.[10] The absolute configuration at the secondary alcohol stereocenter was determined to be *S* using Horeau's method by the reaction of **6** with racemic 2-phenylbutyryl chloride.[11] Thus, the absolute configuration of **3a** is *R*.

In summary, we have achieved the first catalytic enantioselective Roskamp reaction of α-alkyl-α-diazoesters with aromatic aldehydes. Remarkably, with 0.05 mol % chiral *N*,*N*′-dioxide−scandium(III) complex, the reaction was performed well over a series of substrates, giving the desired products chemoselectively in excellent yields (up to 99%) and enantioselectivities (up to 98% ee) under mild conditions. This protocol provides a promising method for the synthesis of chiral α-alkyl-β-keto esters and 1,3-diols. Further extension of the approach to ketones is underway.

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Supporting Information Available: Experimental details and analytical data (NMR, HPLC, and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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