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Direct catalytic asymmetric aldol reaction of β -keto esters with formaldehyde promoted by a dinuclear Ni₂-Schiff base complex[†]‡

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A homodinuclear Ni₂-Schiff base 1 complex (0.1–1 mol%) promoted the direct catalytic asymmetric aldol reaction of β -keto esters with formaldehyde, giving hydroxymethylated adducts in 94–66% ee.

The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesizing chiral β-hydroxy carbonyl compounds.^{1,2} To date, many chiral metal and organocatalysts have been developed for reactions of various donors with aldehydes.² The use of formaldehyde as a useful C1 unit in direct catalytic asymmetric aldol reactions, however, has been relatively limited, 3-5 possibly due to its high reactivity. Highly enantioselective chiral catalysts for indirect aldol reactions of formaldehyde with preformed silyl enolates have been developed,⁶ but for direct aldol reactions, there remains room for improvement in catalyst loading, catalyst reactivity, formaldehyde amount, and substrate scope. Herein, we report a homodinuclear Ni₂-Schiff base 1 complex-catalyzed direct asymmetric aldol reaction of β -keto esters with formaldehyde. Ni₂-1 (0.1–1 mol%; Fig. 1) gave the hydroxymethylated products in 66-94% ee.

Aqueous formaldehyde solution (*i.e.*, formalin) is the most convenient source of formaldehyde. A moisture-tolerant chiral catalyst is required to realize the direct catalytic asymmetric



Fig. 1 Structures of dinucleating Schiff base 1 and homodinuclear M_2 -Schiff base 1 complexes.

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‡ Electronic supplementary information (ESI) available: General experimental information, spectral data of new compounds, and copies of NMR spectral data. See DOI: 10.1039/b912380f

aldol reaction with formalin. As a part of our ongoing studies of bifunctional Lewis acid/Brønsted base catalysis,⁷ we recently reported the utility of dinuclear Schiff base complexes.⁸⁻¹² Homodinuclear transition metal-Schiff base 1 complexes⁸⁻¹⁰ are bench-stable and can be used without regard to their exposure to air and moisture. Thus, we expected that the bimetallic Schiff base complexes would be suitable for a direct aldol reaction with formalin. Initial optimization studies using β -keto ester 2a and formalin are summarized in Table 1. Among the homodinuclear Schiff base complexes screened, the Ni₂-1 catalyst⁸ gave promising results. The reaction of β-keto ester 2a with 1.2 equiv. of formalin in *i*-Pr₂O at 40 °C completed within 0.5 h, giving product 3a in 81% yield and 77% ee (entry 1). The reaction also proceeded smoothly in other solvents, but enantioselectivity was less satisfactory (entries 2–7). Other metal complexes, such as Co,⁹ Mn,¹⁰ Zn, and Pd, gave much less satisfactory enantioselectivity (entries 8-11, 1-30% ee). In entry 12, enantioselectivity decreased when the reaction time was prolonged (12 h, 63% ee). The results of entries 1 and 12 suggested that an undesirable retro-aldol reaction would proceed under the reaction conditions, resulting in lower enantiomeric excess after 12 h than after 0.5 h. In addition, the reaction proceeded at 40 °C, even in the absence of catalysts in *i*-Pr₂O (0.2 M), giving product 3a in 43% yield after 0.5 h (entry 13). To suppress the undesirable

 Table 1 Optimization of reaction conditions^a



Entry	М	x	Solvent	Conc./M	Time/h	% Yield	% ee
1	Ni	10	<i>i</i> Pr ₂ O	0.2	0.5	81	77
2	Ni	10	THF	0.2	0.5	87	65
3	Ni	10	Et ₂ O	0.2	0.5	87	60
4	Ni	10	EtOH	0.2	0.5	90	2
5	Ni	10	AcOEt	0.2	0.5	89	19
6	Ni	10	CH_2Cl_2	0.2	0.5	82	37
7	Ni	10	Toluene	0.2	0.5	84	20
8	Co(OAc)	10	<i>i</i> Pr ₂ O	0.2	1	82	22
9	Mn(OAc)	10	<i>i</i> Pr ₂ O	0.2	1	75	30
10	Zn	10	<i>i</i> Pr ₂ O	0.2	1	70	9
11	Pd	10	<i>i</i> Pr ₂ O	0.2	1	61	1
12	Ni	10	<i>i</i> Pr ₂ O	0.2	12	78	63
13	None	0	<i>i</i> Pr ₂ O	0.2	0.5	43	
14	Ni	0.1	<i>i</i> Pr ₂ O	0.02	1	94	93

^{*a*} Formalin (37% in water) was used in all entries. 1.2 equiv. of formalin were used in entries 1–13, while 1.1 equiv. were used in entry 14.

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Entry	2	Ni ₂ -1 (x mol%)	HCHO (y equiv.)	Time/h	% Yield ^b	% ee ^c
1	CO ₂ t-Bu	0.1	1.1	1	94	93
2	CO ₂ t-Bu	1	1.1	12	91	85
3	CO ₂ t-Bu	0.1	1.1	12	81	66
4	O CO ₂ t-Bu Me 2d	0.1	1.1	28	79	81
5	CO_2t -Bu Et 2e	1	10	48	32	79
6 ^{<i>d</i>}	$CO_2 t$ -Bu Et 2e	0.1	5	20	79	89
7	O CO ₂ t-Bu Bn 2f	1	3	120	43	75
8 ^{<i>d</i>}	O CO ₂ t-Bu Bn 2f	0.1	5	72	84	90
9	Ph CO ₂ <i>t</i> -Bu Me 2g	1	1.1	120	40	89
10 ^{<i>d</i>}	$CO_2 t$ -Bu	0.1	5	120	22	94

^{*a*} Formalin (37% in water) was used in entries 1–5, 7 and 9. ^{*b*} Isolated yield after purification by silica gel column chromatography. ^{*c*} Determined by HPLC analysis. ^{*d*} Paraformaldehyde (HCHO)_n was used.

racemic pathway, we performed the reaction under diluted conditions (0.02 M) to keep the formaldehyde concentration low. Furthermore, we performed the reaction with reduced catalyst loading (0.1 mol%) to avoid the undesirable retroaldol reaction and to obtain the aldol adduct under kinetic control. The reaction proceeded smoothly even with 0.1 mol% of Ni₂-1, giving the product in 94% yield and 93% ee after 1 h (entry 14).¹³

The substrate scope of the reaction is summarized in Table 2. Because the reactivity of β -keto esters 2 depends on

the structure, the reaction conditions, such as catalyst loading, reaction time, and the amount of formalin required, were optimized for each β-keto ester to achieve the highest enantioselectivity under kinetic control. The best results for each substrate are summarized in Table 2. The reactivity of β-keto ester 2b with a six-membered ring was lower than that of β -keto ester 2a, and product 3b was obtained in 91% yield and 85% ee with 1 mol% catalyst after 12 h (entry 2). With the seven-membered ring β -keto ester 2c, the reaction proceeded smoothly with 0.1 mol% catalyst, but enantioselectivity was modest (entry 3, 66% ee). Ni₂-1 was also applicable to acyclic β -keto esters 2d-2g. The reaction of 2d with a methyl substituent gave product 3d in 79% yield and 81% ee using 0.1 mol% catalyst after 28 h (entry 4). β-Keto esters 2e and 2f with bulkier substituents, however, were much less reactive, giving products in only 32-43% yield after 48-120 h (entries 5 and 7). For 2e and 2f, the use of paraformaldehyde instead of formalin effectively improved both yield and enantioselectivity. The reaction with 5 equiv. of paraformaldehyde proceeded well and products 3e and 3f were obtained in good yield and enantioselectivity using 0.1 mol% catalyst (entry 6, 79% yield, 89% ee; entry 8, 84% yield, 90% ee). With phenyl ketone 2g, good enantioselectivity was obtained (entries 9-10, 89-94% ee); however, it was difficult to improve the reactivity, even with paraformaldehyde.

In summary, we developed a homodinuclear Ni₂-Schiff base-catalyzed enantioselective hydroxymethylation of β -keto esters. The reaction proceeded with 0.1–1 mol% catalyst, and hydroxymethylated products were obtained in 66–94% ee and 22–94% yield (TON = up to 940). Further trials to expand the nucleophile scope are ongoing.

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