Asymmetric Synthesis

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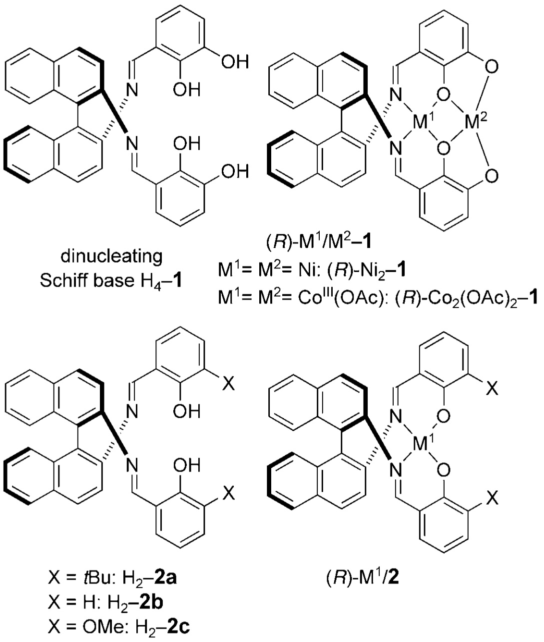
A Stable Homodinuclear Biscobalt(III)–Schiff Base Complex for Catalytic Asymmetric 1,4-Addition Reactions of β-Keto Esters to Alkynones**

Zhihua Chen, Makoto Furutachi, Yuko Kato, Shigeki Matsunaga, and Masakatsu Shibasaki**

Bifunctional cooperative asymmetric catalysis is currently a popular research topic in organic synthesis. Various bifunctional metal and organocatalysts have been reported during the last decade.[1] As part of our ongoing research into this issue, we recently reported the utility of cooperative bimetallic complexes of the Schiff base **1** (Scheme 1),[2–5] the catalytic properties of which differed from those of well-established monometallic salen complexes.[6] Combined complexes of Cu/Sm,[2] Pd/La,[3] and Ni/Ni[4] were utilized for enantioselective 1,2-addition reactions, such as nitro-Mannich[2,4] and nitroaldol reactions.[3] Herein, we report studies on the further expansion of the scope of bimetallic Schiff base catalysis to 1,4-addition reactions with electron-deficient alkynes. In contrast to 1,4-addition reactions to electron-deficient alkenes,[7] catalytic enantioselective α-alkenylation reactions by addition to electron-deficient alkynes are rare.[8] The utility of products with a C=C double bond that can be further functionalized makes the development of catalytic asymmetric 1,4-addition reactions to alkynes highly desirable. Jørgensen[8a] and Maruoka[8b] reported enantioselective 1,4-addition reactions of 1,3-diketones to alkynones and α-cyanoacetates to an alkynoate moiety. However, the asymmetric 1,4-addition of β-keto esters to alkynones has not been reported to date. A new homodinuclear complex $Co^{III}_2(OAc)_2$–**1** (Scheme 1) was suitable for the 1,4-addition of β-keto esters to alkynones. Reactions performed with 2.5–0.25 mol % catalyst loading at ambient temperature afforded products with high enantioselectivity (up to 99 % *ee*).

To find a suitable metal combination for the 1,4-addition reaction of β-keto ester **4**, we selected alkynone **3a** as a model substrate. The catalyst screening results are summarized in Table 1. A Ni_2–**1** complex (Scheme 1),[4] which was suitable for 1,2-addition to imines, gave moderate enantioselectivity (entry 3, 32 % *ee*), while rare-earth-metal complexes gave poor enantioselectivity (Table 1, entries 1 and 2). Among other metals screened (Table 1, entries 4–6), the $Co^{III}_2(OAc)_2$–**1** complex[9] gave product **5aa** in 52 % *ee* (entry 6). By changing the ester moiety of the β-keto ester to a *tert*-butyl group (Table 1, entry 7, **4b**) and the solvent to *i*Pr_2O (entry 8), the enantioselectivity improved to 97 % *ee*, albeit in a modest *E*/*Z* ratio. It is noteworthy that the reaction proceeded without difficulty even under solvent-free conditions at room temperature, to give product **5ab** in 97 % *ee* after 1 h (entry 9). In Table 1, entries 8 and 9, high enantioselectivity was observed both for the *E* isomer and *Z* isomer. Because the absolute configurations of the *E* isomer and the *Z* isomer were the same, we investigated a one-pot sequential asymmetric 1,4-addition/isomerization process to obtain the product **5ab** in both a high *E*/*Z* ratio and with high enantioselectivity. As shown in Table 1, entry 10, the first 1,4-addition proceeded smoothly with 2.5 mol % catalyst under solvent-free conditions within 4 h. Ph_2MeP (30 mol %) was added to the reaction mixture for isomerization after completion of the 1,4-addition reaction, to predominantly afford the *E* adduct **5ab** in greater than 95 % yield (calculated from the ^{1}H NMR spectrum) and with 96 % *ee*.



Scheme 1. Structures of dinucleating Schiff base H_4–**1**, salen ligands **2a**–**2c**, and di- and mononuclear Schiff base complexes.

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[*] Z. Chen, M. Furutachi, Y. Kato, Dr. S. Matsunaga,
Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp
Homepage: http://www.f.u-tokyo.ac.jp/~kanai/e_index.html

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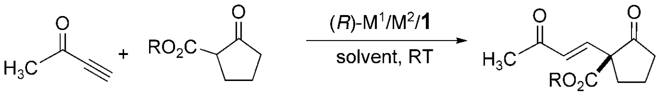
Table 1: Optimization of catalytic asymmetric 1,4-addition of β-keto ester **4** to alkynone **3a** using complexes of dinuclear Schiff base **1**.



3a **4** (1.1 equiv) **5**
R = Me: **4a**; R = *t*Bu: **4b**

Entry	R, **4**	M¹	M²	Solvent	Isomerization	Cat. [mol %]	*t* [h]	*E*:*Z*[a]	Yield [%][a]	*ee* [%]
1	Me, **4a**	Cu	Sm(O*i*Pr)	THF	–	5	12	1:1	76	1[b]
2	Me, **4a**	Pd	La(O*i*Pr)	THF	–	5	12	1:1	47	14[b]
3	Me, **4a**	Ni	Ni	THF	–	5	12	3:1	95	32[b]
4	Me, **4a**	Zn	Zn	THF	–	5	12	n.d.	trace	n.d.
5	Me, **4a**	Cu	Cu	THF	–	5	12	n.d.	0	n.d.
6	Me, **4a**	Co(OAc)	Co(OAc)	THF	–	5	12	3:1	> 95	52[b]
7	*t*Bu, **4b**	Co(OAc)	Co(OAc)	THF	–	5	12	2:1	> 95	92[b]/89[c]
8	*t*Bu, **4b**	Co(OAc)	Co(OAc)	*i*Pr$_2$O	–	5	12	3:1	> 95	97[b]/97[c]
9	*t*Bu, **4b**	Co(OAc)	Co(OAc)	neat	–	5	1	3:1	> 95	97[b]/97[c]
10	*t*Bu, **4b**	Co(OAc)	Co(OAc)	neat	+ (Ph$_2$MeP)[d]	2.5	4	> 30:1	> 95	96[b]

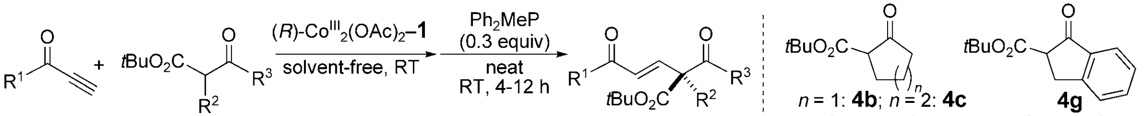
[a] Yield and *E*/*Z* ratio were determined from the ^{1}H NMR spectrum of the crude mixture. [b] Enantioselectivity of the *E* isomer. [c] Enantioselectivity of the *Z* isomer. [d] After the 1,4-addition, Ph$_2$MeP (0.3 equiv) was added to the reaction mixture, which was then stirred for an additional 12 h at RT for isomerization under solvent-free conditions.

The substrate scope of the one-pot sequential 1,4-addition/isomerization process is summarized in Table 2. Because the bimetallic Co$_2$(OAc)$_2$–**1** catalyst was stable towards air and moisture, the catalyst that was stored in air at room temperature for more than six months was used for the procedures outlined in Table 2 without loss of reactivity and enantioselectivity. In addition, the first 1,4-addition reaction was successfully performed in air without solvent in all entries.[10] Both alkyl–alkynyl ketones **3a** and **3b** (Table 2, entries 1 and 2) and aryl–alkynyl ketones **3c**–**3f** (entries 3–6) gave predominantly *E* adducts in high enantioselectivity (98–95 % *ee*) under the optimized reaction conditions. Both cyclic and acyclic β-keto esters **4c**–**4g** were applicable to afford products in 99–91 % *ee* (Table 2, entries 7–11). The catalyst loading could be successfully reduced to 0.25 mol %, while maintaining high enantioselectivity and reactivity (entry 12, 97 % *ee*, 85 % yield, 4 h).

A preliminary investigation revealed that the bimetallic Co$_2$(OAc)$_2$–**1** catalyst was also applicable to an electron-deficient alkene.[7c] As shown in Table 3, the reaction of nitroalkene **6** with β-keto ester **4a** was successfully performed with 2.5 mol % catalyst in air and without solvent; high diastereoselectivity and enantioselectivity were achieved at room temperature (Table 3, entry 1, dr ≥ 30:1, 98 % *ee*). Catalyst loading was successfully reduced to 0.2–0.1 mol % at high concentrations (THF, 20 M, Table 3, entries 2 and 3), while maintaining high enantioselectivity. Pure **7a** was isolated in 87 % yield and 99 % *ee* only by recrystallization and without purification by column chromatography (Table 3, entry 2).

The results of the control experiments in Table 4 implied that two Co metal centers are essential for high enantioselectivity and reactivity. The use of several different monometallic Co^{III}(OAc)–salen complexes **2a**–**2c** (Scheme 1) resulted in poor yields and enantioselectivities of the products, which confirms the importance of the outer Co metal

Table 2: One-pot sequential catalytic asymmetric 1,4-addition/isomerization process with β-keto esters **4b**–**4g** and alkynones **3a**–**3f** using Co$_2$(OAc)$_2$–**1**.[a]

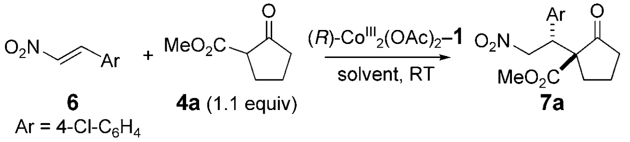


3 **4b**-**4g** (1.1 equiv) **5**
n = 1: **4b**; *n* = 2: **4c** **4g**
4d: R^2 = Me, R^3 = Me; **4e**: R^2 = Et, R^3 = Me
4f: R^2 = PhCH$_2$–, R^3 = Me

Entry	R¹	**3**	**4**	Cat. [mol %]	*t* [h]	**5**	*E*/*Z*[b]	Yield[c] [%]	*ee*[d] [%]
1	Me	**3a**	**4b**	2.5	4	**5ab**	> 30:1	92	96
2	cyclohexyl	**3b**	**4b**	2.5	4	**5bb**	> 30:1	92	95
3	Ph	**3c**	**4b**	2.5	4	**5cb**	> 30:1	93	95
4	4-ClC$_6$H$_4$	**3d**	**4b**	2.5	4	**5db**	> 30:1	91	96
5	4-MeOC$_6$H$_4$	**3e**	**4b**	2.5	4	**5eb**	> 30:1	93	98
6	3-thienyl	**3f**	**4b**	2.5	4	**5fb**	> 30:1	96	95
7	Ph	**3c**	**4c**	2.5	4	**5cc**	> 30:1	95	91
8	Ph	**3c**	**4d**	2.5	9	**5cd**	> 30:1	83	96
9	Ph	**3c**	**4e**	2.5	9	**5ce**	> 30:1	94	99
10	Me	**3a**	**4f**	2.5	9	**5af**	> 30:1	75	97
11	Me	**3a**	**4g**	2.5	9	**5ag**	> 30:1	92	96
12	Me	**3a**	**4b**	0.25	4	**5ab**	> 30:1	85	97

[a] 1,4-Addition reactions were performed under solvent-free conditions at room temperature (24–28 °C) in air with 1.1 equiv of **4**. After the indicated time for the 1,4-addition, Ph$_2$MeP (0.3 equiv) was added to the reaction mixture, which was stirred for 4–12 h at RT under Ar. The absolute configuration of **5cb** was determined by comparing the sign of the optical rotation with the data reported in Ref. [8d]. [b] The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product after purification by column chromatography. [d] Enantioselectivity of the *E* isomer.

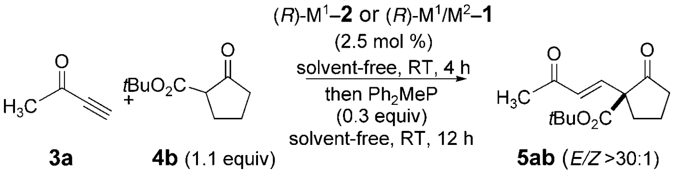
Table 3: Catalytic asymmetric 1,4-addition of β-keto ester **4a** to nitroalkene **6** using $Co_2(OAc)_2$–**1**.[a]



Entry	Cat. [mol %]	Solvent	*t* [h]	d.r.[b]	Yield [%]	*ee* [%]
1	2.5	neat	6	>30:1	94[c]	98
2	0.2	THF (20 M)	24	>30:1	87[d]	99
3	0.1	THF (20 M)	48	16:1	98[c]	95

[a] 1,4-Addition reactions were performed under solvent-free conditions at room temperature (24–28 °C) in air with 1.1 equiv of **4a**. [b] The d.r. value was determined by ^{1}H NMR analysis. [c] Yield of isolated product after purification by column chromatography. [d] **7a** was obtained in pure form by recrystallization of the crude product without purification by column chromatography.

Table 4: Control experiments using mononuclear complexes $Co^{III}(OAc)$–salen **2a**–**2c** and heterodinuclear complex **1**.[a]



Entry	Schiff base	M^1	M^2	Yield [%]	*ee* [%]
1	**2a**	Co(OAc)	none	0	n.d.
2	**2b**	Co(OAc)	none	56	36
3	**2c**	Co(OAc)	none	0	n.d.
4	**1**	Cu	Co(OAc)	66	10
5	**1**	Pd	Co(OAc)	67	8

[a] 1,4-Addition reactions were performed under solvent-free conditions at room temperature (24–28 °C) with 1.1 equiv of **4b**. After 4 h for 1,4-addition, Ph_2MeP (0.3 equiv) was added to the reaction mixture, which was then stirred for 12 h at RT.

center (Table 4, entries 1–3). In addition, heterobimetallic Cu/Co(OAc)–**1** (entry 4) and Pd/Co(OAc)–**1** (entry 5) complexes showed moderate reactivity and poor enantioselectivity, which suggests the importance of inner Co metal center for good enantioselectivity. We believe that cooperative functions of two Co metal centers are important;[11,12] further mechanistic studies to clarify the functions of two Co metal centers are underway.

In summary, we have developed a stable homodinuclear $Co_2(OAc)_2$–Schiff base complex that expands the scope of bimetallic cooperative Schiff base catalysis. The complex Co_2–**1** was suitable for the 1,4-addition of β-keto esters to alkynones and a nitroalkene. The reactions proceeded in high yields and with high enantioselectivities at room temperature under highly concentrated conditions (neat–20 M) using 0.1–2.5 mol % catalyst loading without air or moisture sensitivity.[10] Further mechanistic studies[12] as well as full details on the substrate scope and limitations of electron-deficient alkenes will be reported in due course.

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[9] $Co^{III}_2(OAc)_2$–**1** was synthesized from $Co^{II}(OAc)_2$ and Schiff base H_4–**1** in EtOH at reflux in air. The structure was assigned to be $Co^{III}_2(OAc)_2$–**1**·2 H_2O based on elemental analysis results.

[10] If necessary, the reactions reported in this manuscript can also be performed in $i\mathrm{Pr}_2O$ (reactions in Table 2), and THF under dry Ar (reactions in Table 3), to give products in comparable yields and stereoselectivities.

[11] For intermolecular cooperative mechanism of monometallic Co–salen complexes, see Ref. [6c] and references therein.

[12] Preliminary mechanistic studies showed a linear relationship between the enantiomeric excess of $Co_2(OAc)_2$–**1** catalyst and product **5ab**. An initial rate kinetic study using nitroalkene **6** and β-keto ester **3a** showed first-order dependency on the bimetallic $Co_2(OAc)_2$–**1** catalyst.