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A Homodinuclear Mn(III)$_2$−Schiff Base Complex for Catalytic Asymmetric 1,4-Additions of Oxindoles to Nitroalkenes

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Oxindoles bearing a quaternary carbon stereocenter at the 3-position are ubiquitous in nature and utilized as building blocks for alkaloid synthesis[1a,b] as well as development of potential therapeutic agents.[1c] Among them, oxindoles with β-amino functionality are among the most attractive and valuable synthetic targets. Catalytic enantioselective approaches for such a structural motif, such as the Heck reaction,[2a] allylic alkylation,[2b,c] aldol reactions of oxindoles with β-amino moieties,[2d] and cyanoamidation,[2e] have been reported over the past decade.[2,3] Further development to increase the structural diversity of β-aminooxindoles, however, is highly desirable. Catalytic asymmetric 1,4-addition of 3-substituted oxindoles to nitroalkenes provides an alternative straightforward access to β-aminooxindoles with vicinal quaternary/tertiary stereocenters. Despite recent progress on organo- and metal-catalyzed asymmetric 1,4-additions of various nucleophiles to nitroalkenes,[4] there are no examples using oxindoles as nucleophiles. Herein, we report a new homodinuclear Mn$_2$−Schiff base **1** complex (Figure 1) for catalytic asymmetric 1,4-additions of 3-substituted oxindoles to nitroalkenes, giving products in up to 96% ee and >30:1 dr.

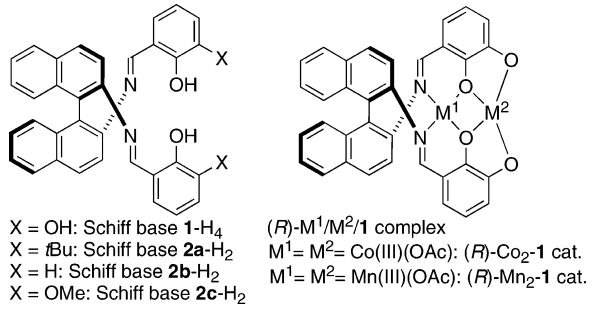
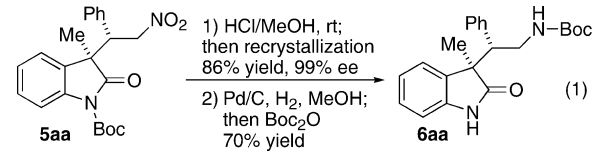


Figure 1. Structures of dinucleating Schiff base **1**-H$_4$, salens **2**-H$_2$, and bimetallic Schiff base **1** complexes.

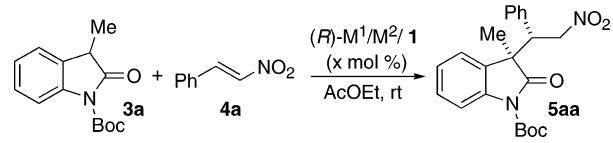
As a part of our ongoing research on bimetallic Schiff base catalysis,[5,6] we recently developed a homodinuclear Co(III)$_2$−Schiff base **1** complex for catalytic asymmetric 1,4-additions of β-keto esters to nitroalkenes.[5d] Therefore, we began optimization studies using Co$_2$−**1** for reactions of *N*-Boc oxindole **3a** and nitroalkene **4a** (Table 1). Initial trials with Co$_2$−**1**, however, resulted in poor enantio- and diastereoselectivity (7% ee, dr = 2:1; entry 1).[7] To find a suitable catalyst for the reaction of oxindole **3a**, we screened other metals (entries 2−6), and a new homodinuclear Mn(III)$_2$−Schiff base **1** complex[8] gave the best reactivity, diastereoselectivity, and enantioselectivity (97% ee, dr > 30:1; entry 6). Furthermore, the catalyst loading was successfully reduced to 2.5 mol % under concentrated conditions (1.0 M), giving **5aa** in 99% isolated yield, 95% ee, and 22:1 diastereoselectivity (entry 7).

The substrate scope of the reaction is summarized in Table 2.[7] The Mn$_2$−**1** complex (2.5 mol %) promoted the 1,4-additions of oxindole **3a** to various nitrostyrene derivatives **4b**−**f** with either an electron-donating or electron-withdrawing substituent on the aromatic ring, giving the products in high enantioselectivity (94−96% ee; entries 2−6).[9] The diastereoselectivity depended on the substituent and decreased with an ortho substituent on the aromatic ring (entry 6). β-Heteroaryl nitroalkenes **4g** and **4h** also showed good selectivity (90−91% ee; entries 7−8). With β-alkyl nitroalkenes, the reactivity decreased; thus, we utilized β-alkenyl-substituted nitroalkenes **4i** and **4j** as the synthetic equivalent of β-alkyl nitroalkenes in entries 9 and 10. The reactions of **4i** and **4j** were run with 5 mol % Mn$_2$−**1** complex and selectively gave 1,4-adducts in 93−87% ee. Oxindole **3b** with a Bn substituent at the 3-position also gave the product **5ba** in high enantioselectivity (95% ee; entry 11). 5-Methoxyoxindole **3c** and 5-fluorooxindole **3d** were applicable as well (entries 12 and 13). The catalyst loading was further decreased to 1 mol %, giving **5aa** in 99% yield and 92% ee (entry 14). Because Mn$_2$−**1** was bench-stable, reactions using β-aryl and β-heteroaryl nitroalkenes were successfully performed under open-air conditions without regard to oxygen and moisture exposure (entries 1−8, 11−14). The product **5aa** was readily transformed into β-aminooxindole **6aa**, as shown in eq 1.



To gain preliminary insight into the dinuclear Mn catalysis, we performed several control experiments (Table 3). Use of the monometallic Mn−salen **2a**−**c** complexes resulted in modest reactivity and/or selectivity (entries 1−3), suggesting the importance of the outer Mn center for the present reaction. Heterobimetallic Cu/Mn−**1** and Pd/Mn−**1** complexes showed good reactivity but

Table 1. Screening of Bimetallic M^1/M^2−Schiff Base **1** Complexes for 1,4-Addition of Oxindole **3a** to Nitroalkene **4a**[a]

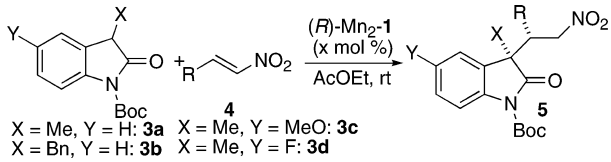


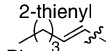
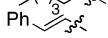
entry	M^1	M^2	*x*	time (h)	dr[b]	% yield[b]	% ee
1	CoOAc	CoOAc	10	33	2:1	33	7
2	Ni	Ni	10	33	2:1	96	57
3	Cu	Cu	10	33	5:1	46	3
4	Pd	Pd	10	33	2:1	21	0
5	Zn	Zn	10	72	7:1	90	0
6[c]	MnOAc	MnOAc	10	33	>30:1	98	97
7[d]	MnOAc	MnOAc	2.5	24	22:1	99[e]	95

[a] The reaction was performed in AcOEt at room temperature (20−25 °C) with 2 equiv of **3a**. [b] Yield and dr were determined by ^{1}H NMR analysis of the crude mixture. [c] Performed in 0.2 M AcOEt. [d] Performed in 1.0 M AcOEt. [e] Isolated yield after purification by column chromatography.

10.1021/ja903566u CCC: $40.75

Table 2. Catalytic Asymmetric 1,4-Additions of Oxindoles **3** to Nitroalkenes **4** Using the $Mn_2(OAc)_2$−Schiff Base **1** Complex[a]

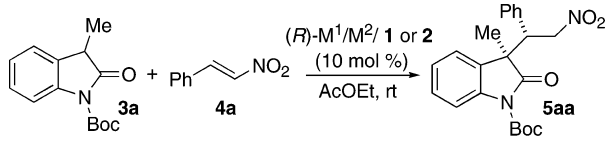


entry	3	R	4	cat. (x mol %)	time (h)	5	dr[b]	% yield[c]	% ee
1	**3a**	Ph	**4a**	2.5	24	**5aa**	22:1	99	95
2	**3a**	4-MeO-C_6H_4	**4b**	2.5	24	**5ab**	14:1	87	95
3	**3a**	4-Cl-C_6H_4	**4c**	2.5	24	**5ac**	>30:1	90	96
4	**3a**	4-Br-C_6H_4	**4d**	2.5	24	**5ad**	>30:1	92	96
5	**3a**	3-Br-C_6H_4	**4e**	2.5	24	**5ae**	20:1	93	94
6	**3a**	2-Br-C_6H_4	**4f**	2.5	24	**5af**	5:1	99	95
7	**3a**	2-furyl	**4g**	2.5	24	**5ag**	13:1	92	91
8	**3a**	2-thienyl	**4h**	2.5	24	**5ah**	14:1	99	90
9[d]	**3a**		**4i**	5	22	**5ai**	11:1	83	93
10[d]	**3a**		**4j**	5	24	**5aj**	13:1	85	87
11	**3b**	Ph	**4a**	2.5	24	**5ba**	6:1	90	95
12	**3c**	Ph	**4a**	2.5	24	**5ca**	>30:1	89	92
13	**3d**	Ph	**4a**	2.5	24	**5da**	11:1	99	85
14	**3a**	Ph	**4a**	1	24	**5aa**	20:1	99	92

[a] The reaction was performed in 1.0 M AcOEt at room temperature (20−25 °C) under an open-air atmosphere with 2 equiv of **3**, unless otherwise noted. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield after purification by column chromatography. [d] Performed under Ar.

resulted in poor diastereo- and enantioselectivity (entries 4 and 5). These results indicated that two Mn metal centers are essential for high stereoselectivity and reactivity. Thus, we speculate that cooperative functions of two Mn metal centers are important for the present reaction.[10] Further mechanistic studies to clarify the precise role of two Mn metal centers are ongoing.

Table 3. Control Experiments Using Mononuclear Mn(III)(OAc)−Salen **2a**−**c** and Heterodinuclear Schiff Base **1** Complexes



entry	M^1	M^2	ligand	time (h)	dr	% yield	% ee
1	MnOAc	none	**2a**	33	1.5:1	69	0
2	MnOAc	none	**2b**	33	4:1	65	44
3	MnOAc	none	**2c**	33	4:1	18	5
4	Cu	MnOAc	**1**	24	2:1	81	6
5	Pd	MnOAc	**1**	24	2:1	95	18[a]

[a] The major product was *ent*-**5aa**.

In summary, we have developed a homodinuclear $Mn_2(OAc)_2$−Schiff base **1** complex as a new entry into bimetallic Schiff base catalysis. Mn_2−**1** was suitable for 1,4-additions of 3-substituted oxindoles to β-aryl, β-heteroaryl, and β-alkenyl nitroalkenes. Reactions using 1−5 mol % of Mn_2−**1** proceeded at room temperature to give products in 99−83% yield, 96−85% ee, and >30:1−5:1 dr. Further studies to expand the electrophile scope are ongoing.[11,12]

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Supporting Information Available: Experimental procedures, spectral data for new compounds, determination of relative and absolute configurations, and a CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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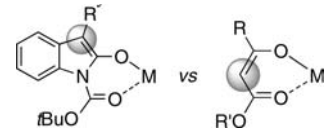
(7) We speculate that the Co_2−**1** complex optimized for β-keto esters was not suitable for *N*-Boc oxindole **3** because the reacting position of the enolate derived from **3** is different from that of enolates from β-keto esters. The Mn_2−**1** complex in this work is suitable for oxindole **3** but gave only modest selectivity for β-keto esters. No reaction proceeded with *N*-Bn oxindole or nonprotected oxindole. 3-Ph-*N*-Boc oxindole gave poor enantioselectivity.

(8) $Mn(III)_2(OAc)_2$−**1** was synthesized from $Mn(II)(OAc)_2$ and Schiff base

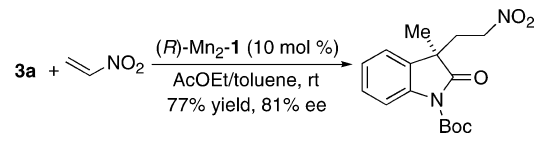


1-H_4 in refluxing EtOH under air. The structure was assigned as $Mn(III)_2(OAc)_2$−**1** on the basis of IR and elemental analysis.

(9) The absolute and relative configurations of **5af** were determined by single-crystal X-ray analysis after removal of the Boc group.

(10) Kinetic studies of the related Co_2−**1** catalyst in asymmetric 1,4-additions of β-keto esters suggested the intramolecular cooperative mechanism (see ref 5d). For the intermolecular bifunctional mechanism of monometallic salen complexes, see: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421, and references therein.

(11) Preliminary trials with nitroethylene at room temperature gave the product in 81% ee (not optimized), while use of β,β-disubstituted nitroalkenes resulted in no reaction.



(12) During revisions of this manuscript, Barbas and co-workers reported elegant organocatalytic asymmetric 1,4-additions of oxindoles to nitroalkenes. See: Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* [Online early access]. DOI: 10.1021/ja903520c. Published Online: June 5, 2009.

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