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Catalytic Asymmetric Synthesis of 3-Aminooxindoles: Enantiofacial Selectivity Switch in Bimetallic vs Monometallic Schiff Base Catalysis

Shinsuke Mouri, Zhihua Chen, Harunobu Mitsunuma, Makoto Furutachi, Shigeki Matsunaga,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received October 19, 2009; E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position constitute a common structural motif in natural products and biologically active compounds.[1] Among them, oxindoles with heteroatoms at the stereogenic center are useful in medicinal chemistry.[2] Various methods for catalytic asymmetric synthesis of 3-fluorooxindoles[3] and 3-hydroxyoxindoles,[4] as well as their applications to the synthesis of pharmaceuticals, have been reported. Several diastereoselective approaches have been developed for synthesizing chiral 3-aminooxindoles using chiral auxiliaries.[5] Catalytic asymmetric methods for 3-aminooxindoles, such as Pd-catalyzed asymmetric α-arylation, however, are rare.[6] Because 3-aminooxindoles are useful units found in therapeutic agents, such as AG-041R, a gastrin/CCK-B receptor agonist,[2a] and SSR-149415 for the treatment of anxiety and depression,[2b,c] further development of a catalytic asymmetric method to expand the structural diversity of available chiral 3-aminooxindoles is highly desirable. Catalytic asymmetric benzylic amination of oxindoles provides straightforward access to 3-aminooxindoles. Despite the recent progress in catalytic asymmetric α-amination of various carbonyl donors,[7] the use of oxindoles was only recently reported by Liu, Chen, and co-workers.[8] Although they achieved the first catalytic asymmetric amination of oxindoles, the method remains to be improved for the synthesis of biologically active compounds. For example, (a) 10 mol % catalyst was required for good reactivity, and (b) the key N−N bond cleavage of amination adducts was not reported, possibly because di-isopropyl azodicarboxylate was essential for high enantioselectivity.[9] Synthetically more useful di-*tert*-butyl azodicarboxylate gave only modest enantioselectivity, and (c) only 3-benzyl-type substituted oxindoles afforded greater than 90% ee. Herein, we report our efforts to address these issues. Amination of 3-substituted oxindoles with di-*tert*-butyl azodicarboxylate was promoted by 1−2 mol % of a dinuclear Ni_2−Schiff base **1** complex (Figure 1), giving products in up to 99% ee and 99% yield. Transformation of the products, including the formal synthesis of AG-041R and the synthesis of an oxindole with a spiro-β-lactam unit, was also demonstrated.

As a part of our ongoing research on bimetallic Schiff base catalysis,[10−12] we recently developed a homodinuclear Mn_2−Schiff base **1** complex for the catalytic asymmetric 1,4-addition of 3-substituted-oxindoles to nitroalkenes.[11] Therefore, we began our optimization studies using Mn_2−**1** for reactions of *N*-Boc oxindole **3a** and azodicarboxylate **4a** (Table 1). Initial trials with Mn_2−**1**, however, resulted in only modest enantioselectivity (entry 1, 79% ee). To determine a suitable catalyst for the reaction of oxindole **3a**, we screened other metals (entries 2−6), and a homodinuclear Ni_2−**1** complex[10c] gave the best reactivity and enantioselectivity (entry 6, 97% ee). Toluene was the best solvent among those screened, and **5aa** was obtained in 99% ee (entry 8). Catalyst loading was successfully reduced to 1 mol % at 50 °C, giving **5aa** in 99% yield and 96% ee after 12 h (entry 9). Furthermore, the

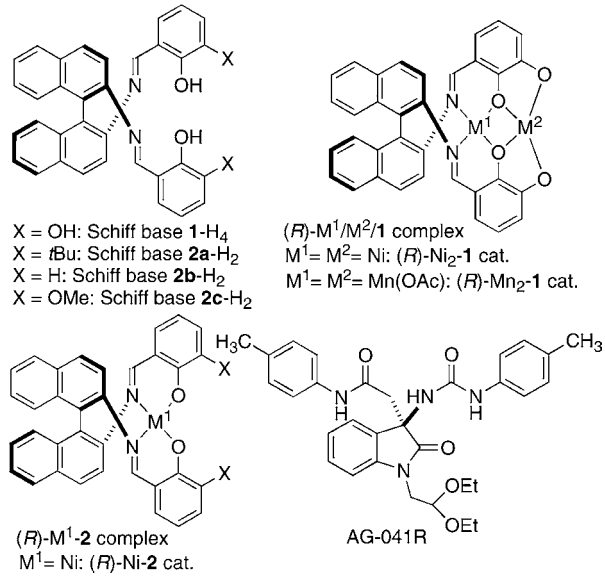
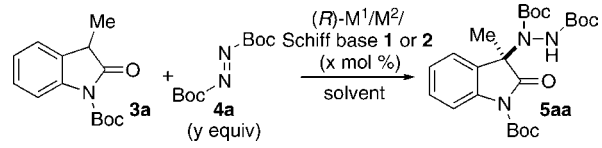


Figure 1. Structures of dinucleating Schiff base (*R*)-**1**−H_4, bimetallic Schiff base (*R*)-**1** complexes, Schiff base (*R*)-**2**−H_2, monometallic Schiff base (*R*)-**2** complexes, and AG-041R.

Table 1. Optimization of Reaction Conditions



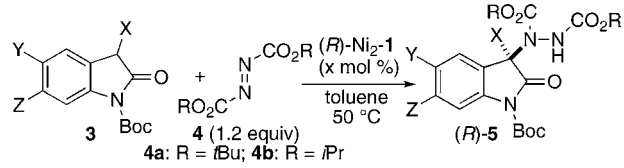
entry	M^1	M^2	Schiff base	*x*	solvent	*y*	temp (°C)	time (h)	% yield[a]	% ee
1	Mn-OAc	Mn-OAc	**1**	10	AcOEt	2.0	rt	18	95	79
2	Co-OAc	Co-OAc	**1**	10	AcOEt	2.0	rt	18	99	69
3	Cu	Cu	**1**	10	AcOEt	2.0	rt	18	68	14
4	Pd	Pd	**1**	10	AcOEt	2.0	rt	18	80	1
5	Zn	Zn	**1**	10	AcOEt	2.0	rt	18	78	5
6	Ni	Ni	**1**	10	AcOEt	2.0	rt	12	99	97
7	Ni	Ni	**1**	10	THF	2.0	rt	12	99	51
8	Ni	Ni	**1**	10	toluene	2.0	rt	12	99	99
9	Ni	Ni	**1**	1	toluene	2.0	50	12	99	96
10	Ni	Ni	**1**	1	toluene	1.2	50	18	99[b]	99
11	Ni	none	**2a**	1	toluene	1.2	50	12	99	13
12	Ni	none	**2b**	1	toluene	1.2	50	18	97	93[c]
13	Ni	none	**2c**	1	toluene	1.2	50	18	99[b]	94[c]
14	Pd	Ni	**1**	10	toluene	2.0	rt	12	99	15
15	Cu	Ni	**1**	10	toluene	2.0	rt	12	82	11[c]
16	Ni	none	**1**	1	toluene	1.2	50	18	42	55

[a] Determined by ^{1}H NMR analysis of crude mixture. [b] Isolated yield after purification by column chromatography. [c] *ent*-**5aa** was obtained as major isomer.

amount of **4a** was also successfully reduced to 1.2 equiv while maintaining good reactivity and enantioselectivity (entry 10, 99% isolated yield, 99% ee). To check the utility of the bimetallic Ni complex, control experiments were performed in entries 11−16.[13] In entries 11−13, monometallic Ni-salen **2a**, **2b**, and **2c** complexes (Figure 1) prepared from a same chiral source [(*R*)-1,1′-binaphthyl-2,2′-diamine] were used. The Ni-salen **2a** complex with *tert*-Bu substituents resulted in poor enantioselectivity (entry 11, 13% ee). Sterically less hindered monometallic (*R*)-Ni−**2b** and (*R*)-Ni−**2c** complexes smoothly promoted the reaction, and an unexpected reversal of enantiofacial selectivity was observed in comparison with bimetallic (*R*)-Ni_2−**1** (entry 10 vs entries 12−13).[14] The enantioselectivity was, however, slightly lower than bimetallic (*R*)-Ni_2−**1** [entry 10, (*R*)-**5aa**, 99% ee vs entries 12−13, (*S*)-**5aa**, 93−94% ee]. On the other hand, heterobimetallic Pd/Ni/**1** and Cu/Ni/**1** complexes required 10 mol % catalyst loading for good reactivity and gave **5aa** in poor enantioselectivity (entries 14−15). With a Ni/**1** = 1:1 complex, enantioselectivity was modest (entry 16). Therefore, The use of freshly prepared dinuclear (*R*)-Ni_2−**1** is recommended for high *R*-selectivity, because a mononuclear (*R*)-Ni−**1** catalyst derived from partial decomposition of (*R*)-Ni_2−**1** would lead to lower enantioselectivity.

The substrate scope of the reaction under optimized reaction conditions with (*R*)-Ni_2−**1** is summarized in Table 2.[15] The amination of various 3-substituted oxindoles **3** with **4a** was promoted by 1 mol % of the Ni_2−**1** complex at 50 °C. 3-Methyl, allyl, (*E*)-cinnamyl, and benzyl substituted oxindoles **3a**−**3d** gave products in 99−91% ee (entries 1−4). 5- or 6-Substituted oxindoles were also applicable. 5-MeO-, 5-F-, 5-Cl-, and 6-Cl-oxindoles **3e**−**3h** and **3l** gave products in 99−94% ee (entries 5−8, 13). It is noteworthy that ester and nitrile groups were also compatible, and products **5ia**−**5ja** were obtained in 96−87% ee (entries 9−10). Moreover, not only di-*tert*-butyl azodicarboxylate **4a** but also di-isopropyl azodicarboxylate **4b** gave high enantioselectivity using 2 mol % of the Ni_2−**1** complex in THF (entries 11−12, 95−91% ee).

Table 2. (*R*)-Selective Catalytic Asymmetric Amination of Oxindoles **3** with Homobimetallic (*R*)-Ni_2−**1** Complex[a]

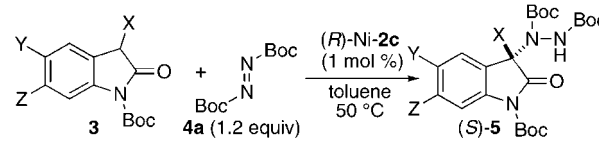


entry	X	Y	Z	**3**	**4**	cat. (*x* mol %)	**5**	time (h)	% yield[b]	% *ee*
1	Me	H	H	**3a**	**4a**	1	**5aa**	18	99	99
2	allyl	H	H	**3b**	**4a**	1	**5ba**	18	99	97
3[d]	(*E*)-cinnamyl	H	H	**3c**	**4a**	1	**5ca**	18	86	91
4[d]	Bn	H	H	**3d**	**4a**	1	**5da**	18	93	99
5	Me	MeO	H	**3e**	**4a**	1	**5ea**	18	91	94
6[d]	Me	F	H	**3f**	**4a**	1	**5fa**	18	95	96
7	allyl	F	H	**3g**	**4a**	1	**5ga**	18	90	98
8[d]	allyl	Cl	H	**3h**	**4a**	1	**5ha**	18	93	95
9	-CH_2CO_2Me	H	H	**3i**	**4a**	1	**5ia**	18	98	96
10	-CH_2CN	H	H	**3j**	**4a**	1	**5ja**	18	89	87
11[c]	Me	H	H	**3a**	**4b**	2	**5ab**	18	94	95
12[c,d]	Me	Br	H	**3k**	**4b**	2	**5kb**	18	92	91
13	Bn	H	Cl	**3l**	**4a**	1	**5la**	18	98	99

[a] Reaction was performed in toluene (0.1 M) at 50 °C under Ar atmosphere with 1.2 equiv of **4** unless otherwise noted. [b] Isolated yield after purification by column chromatography. [c] Reaction was run in THF (0.1 M). Toluene gave less satisfactory enantioselectivity in entries 11−12. [d] (*S*)-Ni_2-**1** was used, and (*S*)-**5** was obtained in major.

The substrate scope of the mononuclear (*R*)-Ni−**2c** catalyst is summarized in Table 3. In all entries, the reversal of enantioselectivity was observed, and (*R*)-Ni−**2c** gave products (*S*)-**5** in moderate to high enantioselectivity (80−98% ee). In entries 1−2, 4, and 6−10, enantioselectivity was lower than that with bimetallic (*R*)-Ni_2−**1**, while monometallic (*R*)-Ni−**2c** showed superior enantioselectivity for **3c** and **3e** (entries 3 and 5). We assume that the observed enantiofacial selectivity switch[14] in Tables 2 and 3 would be caused by a difference in the position of a Ni-enolate intermediate. With bimetallic (*R*)-Ni_2−**1**, a sterically less hindered Ni-aryloxide in the outer O_2O_2 cavity would function as a Brønsted base to generate the Ni-enolate in the outer cavity, while a Ni-aryloxide in the N_2O_2 cavity should generate the Ni-enolate in the case of monometallic (*R*)-Ni−**2c**. Because heterobimetallic Pd/Ni/**1** and Cu/Ni/**1** complexes gave poor enantioselectivity (Table 1, entries 14−15), the Ni metal center in the N_2O_2 inner cavity of bimetallic (*R*)-Ni_2−**1** is also important for high *R*-selectivity observed in Table 2, possibly as a Lewis acid to control the orientation of azodicarboxylates **4** from the sterically hindered inner cavity.

Table 3. (*S*)-Selective Catalytic Asymmetric Amination of Oxindoles **3** with Monometallic (*R*)-Ni-**2c** Complex[a]



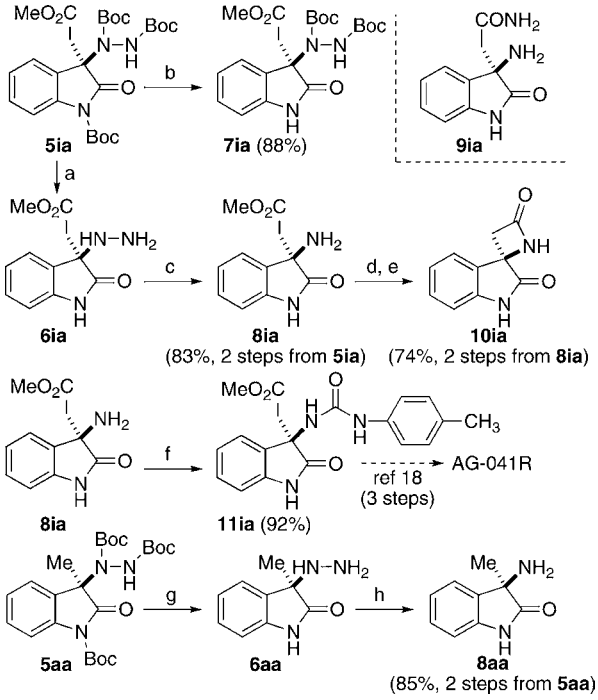
entry	X	Y	Z	**3**	cat. (*x* mol %)	**5**	time (h)	% yield[b]	% *ee*
1	Me	H	H	**3a**	1	**5aa**	18	99	94
2	allyl	H	H	**3b**	1	**5ba**	18	94	80
3	(*E*)-cinnamyl	H	H	**3c**	1	**5ca**	18	95	92
4	Bn	H	H	**3d**	1	**5da**	18	93	93
5	Me	MeO	H	**3e**	1	**5ea**	18	96	98
6	Me	F	H	**3f**	1	**5fa**	18	91	87
7	allyl	F	H	**3g**	1	**5ga**	18	93	92
8	allyl	Cl	H	**3h**	1	**5ha**	18	94	87
9	-CH_2CO_2Me	H	H	**3i**	1	**5ia**	18	96	91
10	Bn	H	Cl	**3l**	1	**5la**	18	91	85

[a] Reaction was performed in toluene (0.1 M) at 50 °C under Ar atmosphere with 1.2 equiv of **4**. [b] Isolated yield after purification by column chromatography.

To demonstrate the synthetic utility of the products, we investigated product transformations (Scheme 1). Three Boc moieties in **5ia** were successfully removed with 3 M HCl in 1,4-dioxane/MeOH at room temperature to afford **6ia**. On the other hand, selective removal of *N*-Boc in the oxindole unit was also achieved with TFA, giving **7ia** in 88% yield. For the N−N bond cleavage in **6ia**, Rh/C under H_2 atmosphere produced the best results to give **8ia** in 83% yield (two steps from **5ia**). Other catalysts, such as Pd/C and Raney Ni, gave a much less satisfactory yield of **8ia** due to the competitive formation of amide **9ia** and other byproducts. Among the 3-aminooxindoles, 3-aminooxindole with a spiro-β-lactam unit constitutes an important class of compounds that is utilized for synthetic studies of chartelline alkaloids.[16] After hydrolysis of the methyl ester in **8ia**, we examined spiro-β-lactam formation. Although it was previously reported that spiro-β-lactam formation of unprotected oxindole resulted in a poor yield under several conventional conditions, such as BOP-Cl,[16c] treatment with MsCl and $NaHCO_3$ in CH_3CN at 80 °C[17] gave spiro-β-lactam **10ia** in 74% yield (two steps from **8ia**). By treating with isocyanate, **8ia** was also readily converted into **11ia** (92% yield), which is a known key intermediate for AG-041R synthesis.[18] Removal of the Boc groups in **5aa** and the N−N bond cleavage within **6aa** also proceeded smoothly under the similar procedure, giving 3-aminooxindole **8aa** in 85% yield (in two steps). For the N−N bond cleavage

of **6aa**, the use of Rh/C rather than Pd/C or Raney Ni was essential to suppress undesirable deamination via the C−N bond cleavage at the benzylic position.

Scheme 1. Transformation of Amination Adducts **5**[a]



[a] Reagents and conditions: (a) 3 M HCl, 1,4-dioxane/MeOH, rt, 2 h; (b) TFA, CH_2Cl_2, rt, 15 min, 88% yield; (c) Rh/C, H_2 (1 atm), MeOH, rt, 6 h, 83% yield in two steps from **5ia**; (d) 2 M *aq.* NaOH, MeOH, rt, 2 h; (e) MsCl, $NaHCO_3$, CH_3CN, 80 °C, 18 h, 74% yield in two steps from **8ia**; (f) *p*-tolyl isocyanate, MeCN, rt, 2 h, 92% yield; (g) 4 M HCl, 1,4-dioxane, rt, 2 h; (h) Rh/C, H_2 (1 atm), MeOH, rt, 5 h, 85% yield in two steps from **5aa**.

In summary, we developed a highly enantioselective catalytic asymmetric access to 3-aminooxindoles with a tetrasubstituted carbon stereocenter. A homodinuclear Ni_2−Schiff base **1** complex was suitable for catalytic asymmetric amination of 3-substituted oxindoles with azodicarboxylates. Reactions using 1−2 mol % of (*R*)-Ni_2−**1** proceeded at 50 °C to give (*R*)-products in 99−89% yield and 99−87% ee. Reversal of enantiofacial selectivity was observed between bimetallic and monometallic Schiff base complexes, and monometallic (*R*)-Ni−Schiff base **2c** gave (*S*)-products in 98−80% ee. Transformation of the products into an optically active oxindole with a spiro-β-lactam unit and a known key intermediate for AG-041R synthesis was also demonstrated. Further studies to clarify the precise role of two Ni metal centers as well as the origin of enantio-switching are ongoing.

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

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