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Diastereo- and enantioselective hydrodimerization of β-monosubstituted acrylic acid amides induced by chiral samarium(II) complexes

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Abstract

The chiral samarium(II) complex prepared from SmI_2, (*R*)-BINOL, and an achiral tertiary amine promoted the reductive homo-coupling reaction of β-monosubstituted acrylic acid amides to give the corresponding 3,4-*trans*-disubstituted adipamides with high enantioselectivities (up to 85% ee).

Although remarkable progress has been made in the field of asymmetric synthesis, the stereocontrol of radical reactions, especially intermolecular ones, still remain one of the most difficult problems in modern organic synthesis. Recently, some successful trials have been made in the field of free radicals.[1] However, the chiralities are, in most cases, involved in the substrates or reagents[2] (so-called substrate- or reagent-control) and the reactions which proceed under catalyst-control or ligand-control have not been extensively developed.[3] Different from free radicals, conjugated ketyl radicals generated from α,β-unsaturated amides, by treating them with a one-electron transfer reagent such as SmI_2, have anion parts, and therefore, it would be possible to kinetically differentiate the enantiotopic face of the ketyl radicals for the subsequent reaction with the aid of their counter cations coordinated with appropriate chiral ligands as illustrated in Fig. 1. We now report the ligand-controlled enantioselective hydrodimerization of acrylamide derivatives which proceed through the formation of the conjugated ketyl radicals (Scheme 1).[4]

The reaction was carried out as follows: To a cold solution of (*R*)-BINOL and an amine in THF was added a THF solution of SmI_2 at −78°C and the mixture was stirred for 0.5 h at the same temperature, and then *N,N*-dibenzylcrotonamide **1a** was added. As shown in Table 1, the chiral complexes having the molar ratio of SmI_2:(*R*)-BINOL:amine=1:2:4 afforded the product **2a** (Scheme 2) with higher enantioselectivities than the corresponding 1:1:2 complexes (cf. entries 1 versus 2, and 3 versus 4).[5,6] No *meso* isomer was produced as previously reported.[7]

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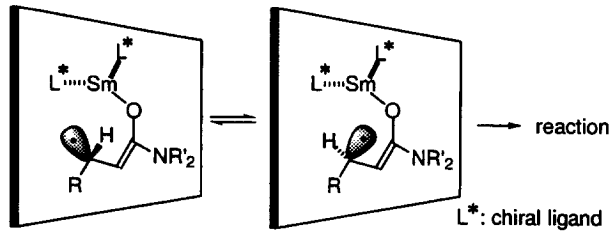
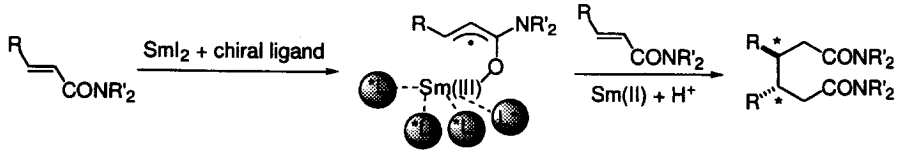


Figure 1. Kinetic discrimination of the enantiotopic face of conjugated ketyl radicals by chiral ligands

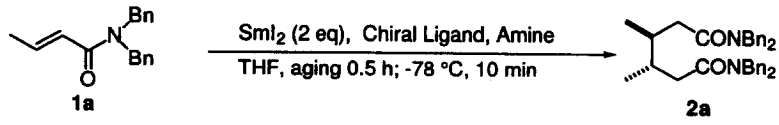


Scheme 1.

Table 1
Effect of molar ratios and amines on the enantioselectivity of the hydrodimerization of **1a**

Entry	Chiral Ligand (eq)	Amine (eq)	Product (**2a**)	
			Yield (%)	ee (%)[a]
1[b]	(*R*)-BINOL (2)	*i*-Pr_2NEt (4)	34	55 (+)
2	(*R*)-BINOL (4)	*i*-Pr_2NEt (8)	20	69 (+)
3[b]	(*R*)-BINOL (2)	TMEDA (4)	38	33 (+)
4	(*R*)-BINOL (4)	TMEDA (8)	29	71 (+)
5	(*R*)-BINOL (4)	Et_3N (8)	6	60 (+)
6	(*R*)-BINOL (4)	(-)-sparteine (8)	14	50 (+)
7	(*S*)-BINOL (4)	(-)-sparteine (8)	32	61 (-)
8	(*R*)-BINOL (4)	*N*-methylpiperidine (8)	35	67 (+)
9	(*R*)-BINOL (4)	2,2,6,6-tetramethylpiperidine (8)	34	66 (+)
10	(*R*)-BINOL (4)	*cis*-1,2,6-trimethylpiperidine (8)	20	44 (+)

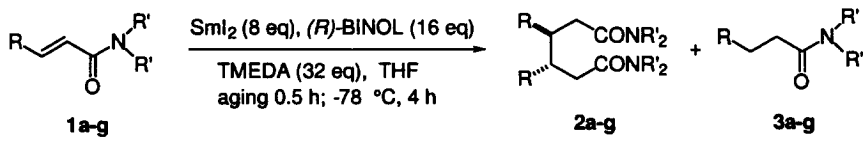
a) Determined by HPLC using Chiral PAK AD. The sign of the optical rotation is shown in parenthesis. b) Reaction time: 4 h.



Scheme 2.

A variety of amines as a component of the chiral samarium complexes were also examined for the reaction of **1a**.[8] As can be seen from Table 1, the use of diisopropylethylamine (entry 2), TMEDA (entry 4), *N*-methylpiperidine (entry 8) and 2,2,6,6-tetramethylpiperidine (entry 9) afforded relatively high ees. When (−)-sparteine was used in combination with (*R*)-BINOL or (*S*)-BINOL, where a matching or mismatching effect can be anticipated, a small difference was observed in the product's ee indicating that (*S*)-BINOL/(−)-sparteine is a matching pair (entry 6 versus 7). In order to clarify the scope and limitation of the present method, the reactions of other substrates were examined. The reactions of **1a–1g** were

carried out by using SmI_2 (8 equiv.),[9] (*R*)-BINOL (16 equiv.), and TMEDA (32 equiv.) in THF at –78°C for 4 h (Scheme 3) and the results are summarized in Table 2. As expected, high enantioselectivities (up to 85% ee) were obtained when primary alkyl-substituted acrylic amides **1a–1d** were used as substrates. As the β-substituent becomes bulky, the yield of the coupling product decreased (entries 1–4), and in the case of **1e** (R=*i*-Pr) and **1f** (R=*t*-Bu), only the saturated amides **3e** and **3f** were almost quantitatively produced. The reaction of *N,N*-diphenylcrotonamide (**1g**) afforded the coupling product **2g** as a mixture of diastereomers (entry 7). The high reactivity of **1g**, and hence the high concentration of the conjugated ketyl radical intermediate, might be responsible for the formation of the *meso* isomer. It is also interesting to note that the sense of enantioselection is reversed (entry 1 versus 7).



Scheme 3.

Table 2
Effect of the substituents of substrates on the enantioselectivity

Entry	Substrate		Product / Yield (%)		2a-g	
	R	R'	2a-g	3a-g	*dl* : *meso*	ee (%)[a]
1	Me	Bn (**1a**)	70	20	*dl* only	71 (+)
2	Et	Bn (**1b**)	45	42	*dl* only	82 (+)
3	*n*-Pr	Bn (**1c**)	35	46	*dl* only	82 (+)
4	$BnCH_2$	Bn (**1d**)	20	52	*dl* only	85 (+)[b]
5	*i*-Pr	Bn (**1e**)	—	95	—	—
6	*t*-Bu	Bn (**1f**)	—	99	—	—
7	Me	Ph (**1g**)	55	44	63:37	44 (-)

a) Determined by HPLC using Chiral PAK AD unless otherwise noted. The sign of the optical rotation is shown in parenthesis. b) Determined by HPLC using Chiral PAK OT(+).

A possible nine-membered chelate transition state which leads to the enantioselective C–C bond formation is shown in Fig. 2, in which the conjugated ketyl radical and the ligated crotonamide are arranged in a *cis*-relationship on the chiral coordination sphere of samarium.

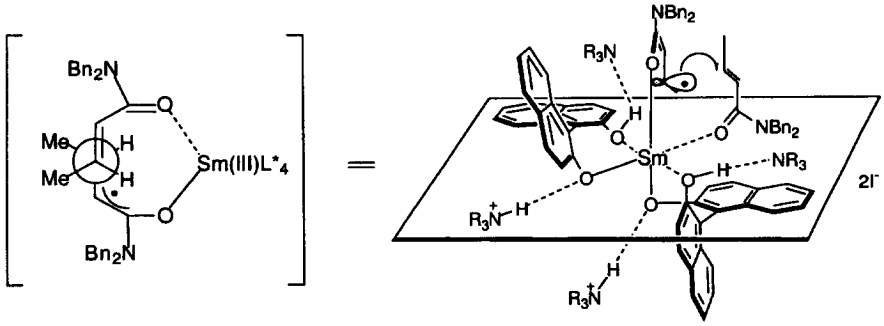


Figure 2. A possible transition state for the enantioselective hydrodimerization of crotonamide **1a**

In conclusion, the use of 2 equiv. of enantiopure BINOL in combination with achiral tertiary amines for the SmI_2-promoted reductive homo-coupling reaction of β-substituted acrylic acid amides brought about a high degree of asymmetric inductions (up to 85% ee). This is the first successful example of the completely diastereoselective and highly enantioselective C–C bond formation which proceeds through conjugated radical intermediates. Although the chemical yields are not always high, the method would be useful for the preparation of optically active 3,4-*trans*-disubstituted adipic acid derivatives, because they can be obtained in one step with high ees and the chiral source (BINOL) can be quantitatively recovered in an enantiopure state by aqueous alkaline extraction.

Acknowledgements

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4. A part of this work was presented at the 16th Meeting of the Rare Earth Society of Japan, Osaka, May, 1999.
5. Other BINOL derivatives such as 3,3′-diphenyl-BINOL, 6,6′-diphenyl-BINOL, and H_8-BINOL gave less satisfactory results. Also, the use of dilithium binaphthoxide (4 equiv.) in the presence of *t*-butanol in place of the BINOL–amine system afforded **2a** with low ee (6%).
6. $Ln(OTf)_3$:BINOL:amine=1:1:2 system has successfully been used for the asymmetric Diels–Alder reaction: Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.
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8. No reaction took place at −78°C in the absence of amines.
9. As the chiral samarium complex gradually decomposed even at −78°C, an excess amount of the reagent was used.