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Stereocontrolled asymmetric synthesis*

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Abstract: Stereo differentiated asymmetric syntheses have been achieved by *S*-indoline derivations. Diels–Alder cycloadditions of *S*-indoline chiral acrylamides with cyclopentadiene proceed with high diastereofacial selectivity, giving either *endo-R* or *endo-S* products depending on Lewis acid and the structures of chiral dienophiles. Diastereo- and enantioselective pinacol coupling reactions of chiral α-ketoamides mediated by samarium diiodide afforded extremely high diastereoselectivities. Enantiopure (*S*,*S*)- or (*R*,*R*)-2,3-dialkyltartaric acid and derivatives can be synthesized for the first time depending on the structure of α-ketoamides.

Lewis acid-catalyzed addition of dienes to chiral acrylamides is a useful reaction because it provides one of the most effective methods for creating new chiral centers during the formation of six-membered rings [1]. Lewis acids have been used for chelate formation in Diels–Alder cyclizations to obtain high diastereofacial selectivities [1–5]. In general, the *S*-form of the chiral dienophile (auxiliary) exclusively affords the *endo-R* adduct over the *endo-S* one, and the *R* form exclusively gives the *S* adduct over the *endo*-R one. Issues associated with this absolute stereochemical control depending upon Lewis acids and the structures of dienophiles provide an important challenge in the area of practical Diels–Alder reaction designs.

In the hope of obtaining the opposite configuration of the *endo* adduct and understanding the mechanism, three different dienophiles **1**, **2**, and **3** were prepared and reacted with dienes in the presence of various Lewis acids. Here we describe the intriguing results obtained during development of Lewis acid-dependent stereocontrol toward both *endo-R* and *endo-S* configuration with high diastereofacial selectivity. In order to generalize the results, the requisite dienophiles **1–3** were synthesized from (*S*)-indoline-2-carboxylic acid [6]. They were purified, and their optical purities (>99.8% ee) were determined by high-performance liquid chromatography (HPLC) (Daicel chiral OD column, *i*-PrOH-*n*-hexane, 5:95). The preliminary studies involved reaction of **1–3** with **4** and **5**, as shown in Scheme 1.

Extremely high levels of asymmetric induction can be achieved in Diels–Alder cycloadditions of **1** or **3** with **4**; in contrast to other general disnophiles, **1** containing a carboxylate moiety reacts with **4** to give differently configures adducts depending on the Lewis acids employed; in the presence of $TiCl_4$, $Ti(OPr^i)_4$, or $SnCl_4$, **6a** was obtained as the major diastereomer (**6a**:**6b** = *endo-R*:*endo-S* = >99:1; entries 4–6 in Table 1), but with $AlEt_2Cl$, $ZnCl_3$, or $BF_3{\cdot}Et_2O$ the opposite configuration of **6b** was obtained (**6a**:**6b** = 1: >99; entries 1–3 in Table 1). In the case of **2**, the same trend of **7b** was observed, but in a less diastereoselective manner than for **1** (entries 16 and 17). In particular, **3** containing a diphenylsubstituted tertiary alcohol moiety affords exceptionally high diastereofacial selectivities (**8a**:**8b** = >99:1, yield = >90%; entries 7–15) regardless of the natures of the Lewis acid. The *endo* configurations were readily ascertained by iodolactonization of **6a–8a** with I_2 in dimethylformamide (DMF) [5b]. The *exo* compound cannot be lactonized under the same reaction conditions. The ratio of *endo-R* and *endo-S* was

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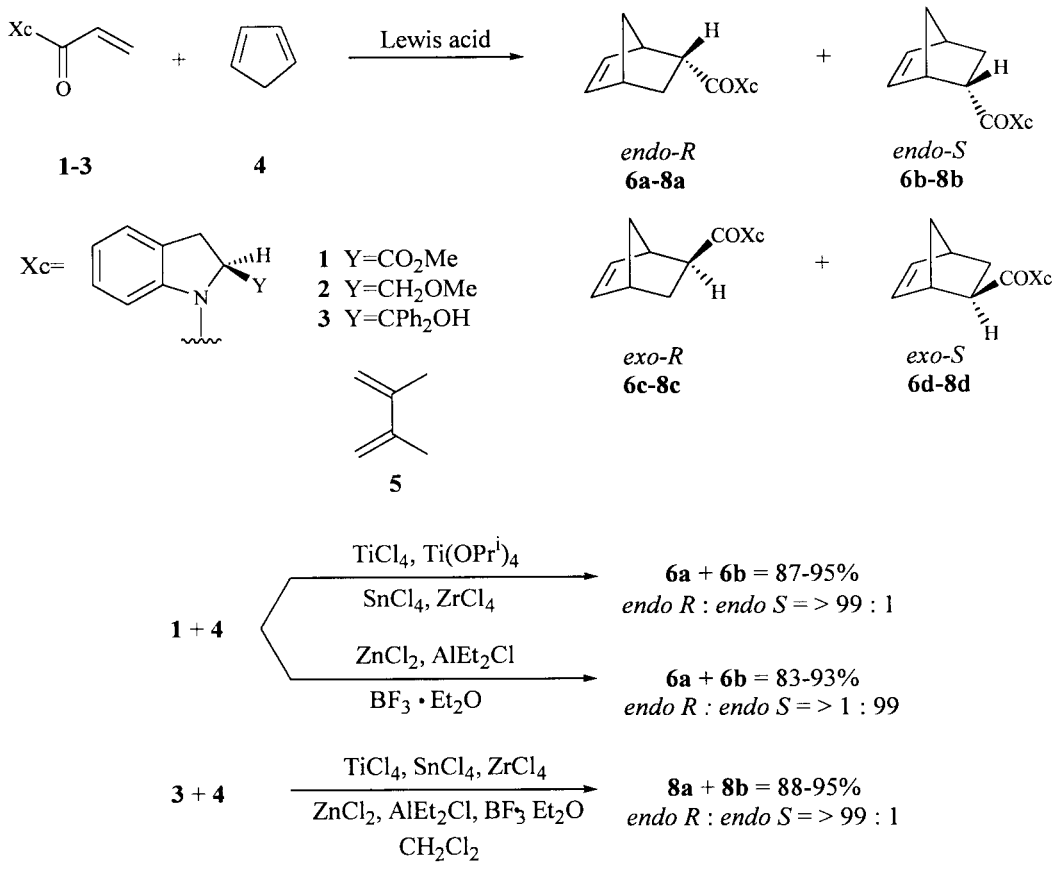
determined by HPLC with the crude **6a–8a** and **6b–8b** without purification. The absolute configuration of **6a**, **7b**, or **8a** was determined by reductive cleavage of **6a** to the known norborene-2-methanol and subsequent comparison of $[\alpha]_D$ values [7].



Scheme 1 Diels–Alder cyclizations of dienophiles with dienes in the presence of Lewis acids.

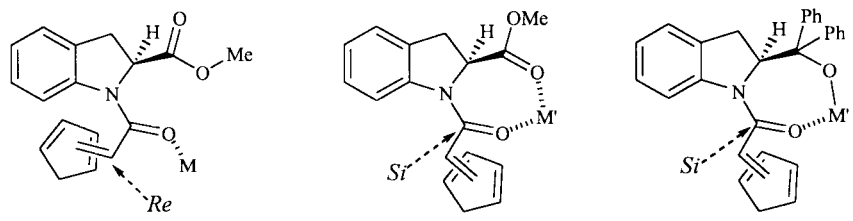
The differently configured adducts produced can be rationalized by the different intermediates formed between **1**–**3** and the metals of the Lewis acids. Compounds **1**–**3** react with **4** to favor formation of *endo-R* species **6a** or **8a** with $TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$, or $ZrCl_4$ probably via formation of seven-membered ring chelates with the acryloyl moiety of **10** or **11** having a *cisoid* conformation. Helmechen and coworkers reported the first evidence of formation of a seven-membered ring chelate complex. It is noteworthy that even in the absence of any Lewis acid, **3** reacts with **4** to give an excellent chemical yield (92%) and high stereofacial selectivity (*endo*:*exo* = >99:1, *endo-R*:*endo-S* = >99:1; entry 9 in Table 1) at 25 °C after a long reaction time (24 h). The results can be attributed to the hydrogen-bond *cisoid* conformation intermediate **11** where the hydrogen acts as a Lewis acid. On the other hand, **1** or **2** prefer *endo-S* formation **6b** or **7b** with $ZnCl_2$, $AlEtCl_2$, or $BF_3{\cdot}Et_2O$, with high diastereofacial selectivity probably resulting from intermediate **9**, as shown in Fig. 1. In contrast to Ti or Sn Lewis acids, relatively weaker Lewis acids such as Zn, Al, or B may not form a seven-membered ring complex, instead forming a weak coordination with the amide carbonyl group (**9**). In the case of Evans' model dienophile, an α,β-unsaturated *S*-oxazolidinone, the *endo-R* form was obtained and explained by for-

Table 1 Asymmetric Diels–Alder cycloaddition with **1** and **3**.

Entry	Dienophile	Lewis acid	T / °C	t / h	Yield (%)[a]	*endo* : *exo*[b]	*endo*[b] ds	Config.[c]
1	**1**	Et_2AlCl	-78	10	95	90 : 10	>99 : 1	*S*
2	**1**	$BF_3{\cdot}Et_2O$	-78	5	90	94 : 6	>99 : 1	*S*
3	**1**	$ZnCl_2$	25	12	90	83 : 17	99 : 1	*S*
4	**1**	$TiCl_4$	0	10	92	95 : 5	99 : 1	*R*
5	**1**	$Ti(OPr^i)_4$	25	12	87	72 : 28	94 : 6	*R*
6	**1**	$SnCl_4$	-78	5	92	95 : 5	91 : 9	*R*
7	**3**	-	25	48	92	>99 : 1	>99 : 1	*R*
8	**3**	Et_2AlCl	-40	10	95	>99 : 1	>99 : 1	*R*
9	**3**	$AlCl_3$	-40	8	88	>99 : 1	>99 : 1	*R*
10	**3**	$BF_3{\cdot}Et_2O$	-78	5	91	>99 : 1	>99 : 1	*R*
11	**3**	$ZnCl_2$	25	12	90	>99 : 1	>99 : 1	*R*
12	**3**	$TiCl_4$	25	7	90	>99 : 1	>99 : 1	*R*
13	**3**	$Ti(OPr^i)_4$	25	15	89	>99 : 1	>99 : 1	*R*
14	**3**	$SnCl_4$	-78	10	91	98 : 2	98 : 2	*R*
15	**3**	$ZrCl_4$	-40	5	93	>99 : 1	>99 : 1	*R*
16	**2**	$EtAlCl_2$	-78	7	83	88 : 12	86 : 14	*S*
17	**2**	$TiCl_4$	-78	12	75	85 : 15	97 : 3	*R*

[a]Isolated yield. [b]Determined by HPLC analysis (Chiral Column: Daicel OD). [c]Confirmed by $[\alpha]_D$ of iodolactone or norbornene-2-methanol.

mation of a six-membered ring intermediate with Et_2AlCl, which was clarified by a ^{13}C NMR study. However, in contrast to a significant chemical shift change [8a] in the **1**-$SnCl_4$ chelation complex **11**, ^{13}C NMR measurement of the **1**-Et_2AlCl mixture did not show significant changes in the chemical shifts for either of the amide or ester carbonyl peaks [8b], *which can be explained by a weak coordination* (**9**) between **1** and Et_2AlCl. Species **1** and **3** also reacted with less reactive acrylic diene **5** at 25 °C to result in the same trend: for **1** with $TiCl_4$ the ratio of *endo R*:*endo S* was 97:3, while with $EtAlCl_2$ the ratio was revered to 3:97, which is comparable to entry 1; for **3** with both $TiCl_4$ and Et_2AlCl, *endo R*:*endo S* = 97:3 and 94:6 respectively, which is comparable to entries **8** and **12**.



9 **10** **11**

M = Zn, Al, or B M' = Ti, Sn, Zr, or H

Fig. 1 Possible intermediates in Diels–Alder reactions.

In summary, asymmetric Diels–Alder cycloadditions of **1**, or **3** with **4** proceed with absolutely stereocontrolled diastereofacial selectivities in both *endo-S* and *endo-R* (up to >99% de) depending upon Lewis acids used and the structures of chiral dienophiles.

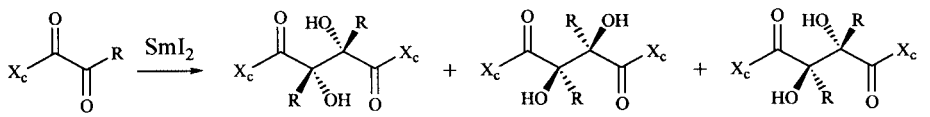
Multidentate and chiral C_2-symmetric ligands are well known to possess their ability to impart asymmetry to transition and main group elements [9]. C_2-symmetric diols are among the most frequent applied examples of such molecules, especially in the area of asymmetric catalysis. Most diol ligands have been derived from C_2-symmetric molecules that occur naturally in optically pure form (such as tartaric acid). However, the numbers of chiral precursors available from natural products are seriously limited.

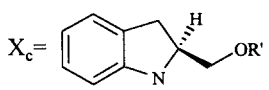
The pinacol coupling was first described long time ago [10], but this reaction is still a versatile tool for chemists. The intermolecular coupling of various aldehydes or ketones to the corresponding pinacols has been extensively studied. However, pinacols in an enantiopure form have not really been obtained using this type of coupling. Although the asymmetric dihydroxylation of olefins mediated by osmium tetroxide has become one of the most useful methods for the preparation of C_2-symmetric diols, asymmetric dihydroxylation of tetrasubstituted olefins are extremely rare and give low enantioselectivity.

SmI_2 has been utilized successfully as a one-electron donating agent for diverse organic reactions including intermolecular or intramolecular pinacol coupling reactions of aldehydes. However, the intermolecular coupling of ketones has afforded low diastereoselectivities.

Chiral 2,3-dialkyltartaric acids could be utilized for designing chiral catalysts or auxiliaries for use in various asymmetric reactions and as chiral intermediates in the synthesis of natural products. However, to our knowledge, the synthesis of enantiopure 2,3-disubstituted tartaric acid (a quaternary pinacol) has never been reported, although a chiral 2,3-dimethyltartaric acid was obtained by chiral resolution. A chiral tertiary pinacol can be obtained by using pinacol coupling of ketones by photolysis in a chiral solvent or by using a chiral auxiliary, however, the diastereoselectivities are low.

We describe the coupling of the chiral α-ketoamides **12** in the presence of SmI_2, hexamethylphosphoramide (HMPA), and *t*BuOH in tetrahydrofuran (THF) to give pinacol **13** with extremely high diastereoselectivity (>98% de in some case; Scheme 2). This is the first example of such high stereoselectivity for disubstituted tartaric acid derivatives in intermolecular pinacol coupling reactions of α-ketoamides.





12a: R= R'= Me
12b: R= Et, R'=Me
12c: R= Ph, R'= Me
12d: R= Me, R'= TBPS
12e: R= Et, R'= TBPS
12f: R= *n*Pr, R'= TBPS
12g: R= *n*Hex, R'= TBPS
12h: R= Ph, R'= TBPS
16a: R'= Me
16b: R'= TBPS

Scheme 2 Pinacol coupling reactions of **12a–h** in the presense of SmI_2, HMPA, and *t*BuOH. TBPS = *tert*-butyldiphenylsilyl, HMPA = hexamethylphosphomide.

Table 2 Pinacol coupling of **12a–h**[a]

Entry	Substrate	SmI_2 (eq.)	HMPA (eq.)	*t*BuOH (eq.)	Time (h)	Yield (%)	**13 : 14 : 15**[b]
1	**12a**	1.5	0	0	0.1	64	71:~0:29
2	**12a**	2.0	2	4	0.1	51	94:~0:6
3	**12a**	2.0	4	4	0.1	42	95:~0:5
4	**12a**	2.0	4	4	1	61	95:~0:5
5	**12a**	2.0	4	4	2	57	95:~0:5
6	**12a**	2.0	4	4	5	58	94:~0:6
7	**12b**	2.0	2	4	0.1	61	95:~0:5
8	**12b**	2.0	4	4	0.1	39	98:~0:2
9	**12c**	2.0	4	4	5	-[c]	-
10	**12d**	2.5	4	4	5	69	96:~0:4[d]
11	**12e**	2.5	0	0	5	87	95:~0:5
12	**12e**	3.0	4	4	5	87	95:~0:5[e]
13	**12e**	2.5	4	4	5	79	>99:~0:1
14	**12f**	2.5	4	4	5	67	>99:~0:1
15	**12g**	2.5	4	4	5	83	97:~0:3
16	**12h**	2.5	4	4	5	-[c]	-

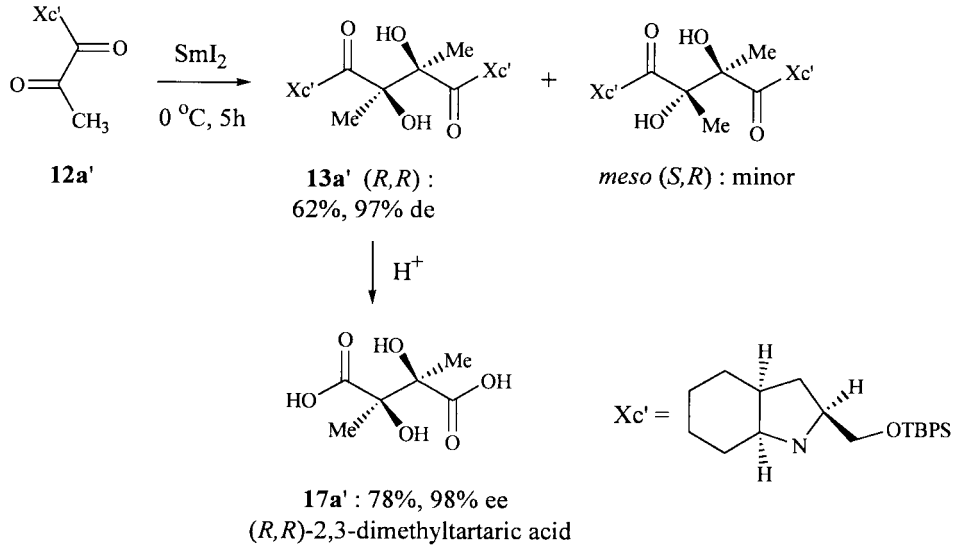
[a]Reactions carried out at -78 °C in THF. [b]Determined by HPLC analysis. [c]The reduction of α–carbonyl group to the secondary alcohols was the major reaction. [d]After recrystallization the ratio of 13:15 = >99:1. [e]Toluene was used as the solvent.

The results obtained are summarized in Table 2. The coupling of pyruvamide **12a** using SmI_2 in the absence of HMPA and *t*BuOH gave low stereoselectivity (**13**:**14**:**15** = 71:~0:29, entry 1). However, the coupling of **12a** in the presence of SmI_2, HMPA, and *t*BuOH occurred with high diastereoselectivity (**13**:**14**:**15** = 95:~0:5, entry 5). Moreover, the coupling of **12e** and **12f** resulted in extremely high diastereofacial selectivity (**13**:**14**:**15** = >99:~0:1, entries 13 and 14). HMPA is known to increase the reaction rate and stereoselectivity of SmI_2–mediated reactions, and *t*BuOH is often used as a proton source for these reactions. The pinacol coupling reaction can form three stereoisomers of (*S*,*S*), (*R*,*R*), and (*S*,*R* or *R*,*S*; *meso* form). The *meso* form (*S*,*R* and *R*,*S*) was easily confirmed by ^{13}C NMR spectroscopy; however, formation of (*R*,*R*)-pinacol could not be detected.

When the *tert*-butyldiphenylsilyl (TBPS) substituent was introduced to give the chiral auxiliary **16b**, the pinacol coupling reactions of **12d**–**1g** had a longer reaction time (5 h) and gave extremely high diastereoselectivities (**13**:**14**:**15** up to >99:~0:1, entries 10–15 in Table 2), probably due to the steric effect of the bulky TBPS moiety. The coupled product **2a** was readily hydrolyzed with 3M HCl in dioxane at 25 °C for 4 h to give (*S*,*S*)-2,3-dimethyltartaric acid (**17a**) (85% yield) together with recovered chiral auxiliary, (*S*)-2-methoxymethylindolione (90%) with no loss of chirality. (*S*,*S*)-2,3-Diethyltartaric acid was obtained by hydrolysis of **13b** and shows an opposite sign of specific rotation {$[\alpha]_D^{16}$ = –6.37 (c = 0.926, H_2O)} to that of (*S*,*S*)-2,3-dimethyltartaric acid {$[\alpha]_D^{16}$ = +13.1 (c = 0.598, H_2O), $[\alpha]_D^{20}$ +13.4 (c = 4.0, H_2O)}. As the specific rotation and the absolute configuration of (*S*,*S*)-2,3-diethyltartaric acid have not been reported previously, its absolute configuration was determined by comparing

the CD spectrum of *O,O*-dianisoyl-2,3-diethyltartaric anhydride with the previously known *O,O*-dianisoyl-2,3-dimethyltartaric anhydride. The absolute configuration of **13d** was also determined by X-ray analysis [11].

In chemical transformations, the synthesis of the individual enantiomers is generally achieved by using chiral sources. However, sometimes natural sources of one of the enantiomers may be limited. Thus, it is desirable and important to obtain both enantiomers by stereocontrolled reactions of prochiral compounds that utilize the same chiral source [6,12]. We have found that (2*S*,3a*S*,7a*S*)-N-pyruvoyl-2-(tert-butyldiphenylsilyloxy)octahydroindoline **12a'** (99.8% ee), affords the opposite configuration of **13a'** (R,R diol:97% de). The ratio of *R,R*:*S,S*:*meso* is 98.5:~0:1.5. The ratio was determined by chiral HPLC analysis with a Daicel OD column. The absolute configuration of **13a'** was determined by comparison of the measured optical rotation of (*S,S*)-2,3-dimethyltartaric acid (**17a'**) {$[\alpha]_D^{20}$ = –13.2 (c = 4.0, H_2O)}, obtained by hydrolysis of **13a'**, with the literature value (Scheme 3).



Scheme 3 Pinacol coupling reaction of compound **12a'** and subsequent hydrolysis to form **17a'**.

In conclusion, it has been demonstrated that diastereo- and enantioselective pinacol coupling reactions of chiral α-ketoamides mediated by SmI_2 afforded extremely high diastereoselectivities (>99% de in some cases). Enantiopure (*S,S*)- or (*R,R*)-2,3-dialkyltartaric acid derivatives can now be synthesized for the first time depending on the structure of α-ketoamides [13].

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