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Asymmetric synthesis by stereocontrol*

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Abstract: Diels–Alder cycloadditions of *S*-indoline chiral acrylamides with cyclopentadiene in the presence of Lewis acids 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. Furthermore, it was demonstrated that α,β-unsaturated amides coupled with SmI_2 to dimerized products containing two chiral carbons which were first obtained as the adjacent chiral carbons.

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.

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 dienophiles, **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), but with $AlEt_2Cl$, $ZnCl_3$, or $BF_3{\cdot}Et_2O$, the opposite configuration of **6b** was obtained (**6a**:**6b** = 1:>99). In the case of **2**, the same trend of **7b** was observed, but in a less diastereoselective manner than for **1**. In particular, **3** containing a diphenyl-substituted tertiary alcohol moiety affords exceptionally high diastereofacial selectivities (**8a**:**8b** = >99:1, yield = >90%) regardless of the natures of the Lewis acid. The *endo* configurations were readily ascertained by iodolactonization of **6a**–**8a** with I_2 in DMF [5b]. The ratio of *endo-R* and *endo-S* was 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].

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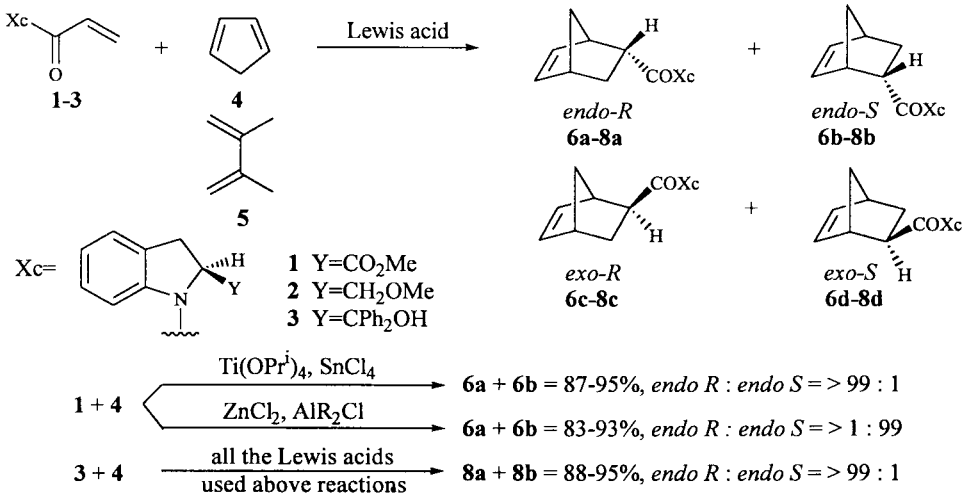


Scheme 1

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 (Fig. 1). 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. 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 reversed to 3:97, for **3** with both $TiCl_4$ and Et_2AlCl, *endo-R*:*endo-S* = 97:3 and 94:6 respectively.

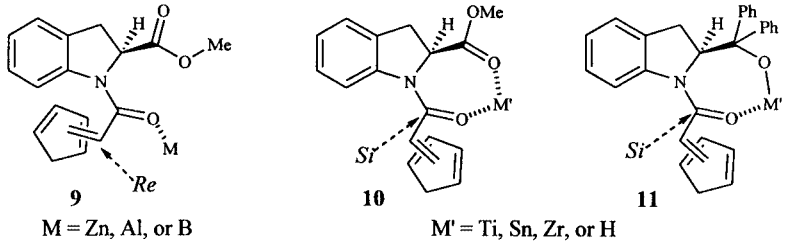
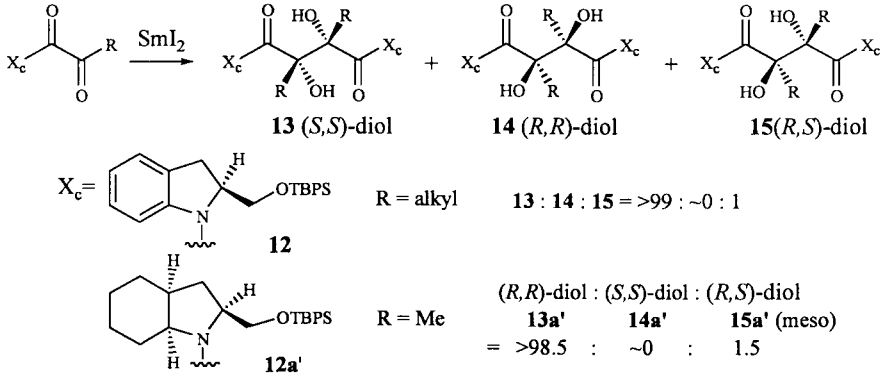


Fig. 1 Possible intermediates in Diels–Alder reactions.

The pinacol coupling was first described a long time ago [8], 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.

We describe the coupling of the chiral α-ketoamides **12** in the presence of SmI_2, 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.

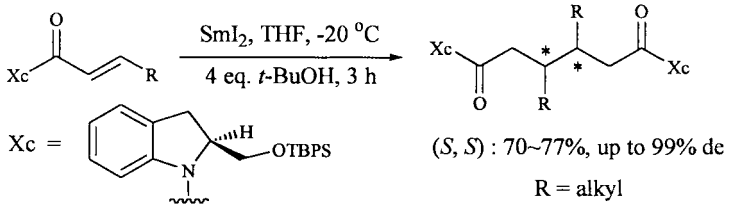


Scheme 2 Pinacol coupling reacitons of **12** and **12a′** in the presence of SmI_2, HMPA, and *t*BuOH.

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 [6,9]. 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.

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 [10].

In connection with the pinacol coupling reaction, α,β-unsaturated amides have been found to react with SmI_2 to form dimerized products containing two chiral carbons which are first obtained as the adjacent chiral hydrocarbons (Scheme 3).



Scheme 3 Dimerizations of α,β-unsaturated amides in the presence of SmI_2.

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