Asymmetric Diels–Alder Reactions of TMHD-acrylate using $TiCl_4 \cdot (Ar_nHg)_m$ Complexed Lewis Acids

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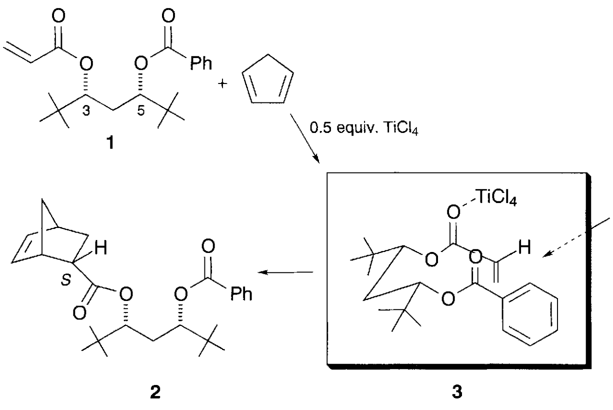
Diels–Alder reaction of (3*R*,5*S*)-5-benzoyloxy-2,2,6,6-tetramethyl-3-heptyl acrylate (TMHD-acrylate) **1** with cyclopentadiene in the presence of $TiCl_4 \cdot (Ar_nHg)_m$ complexed Lewis acids gives (1*R*,4*R*,6*R*)-2-norbornene-6-carboxylate derivative **4** predominantly, whereas the reaction in the presence of $TiCl_4$ alone affords its enantiomer **2** preferentially.

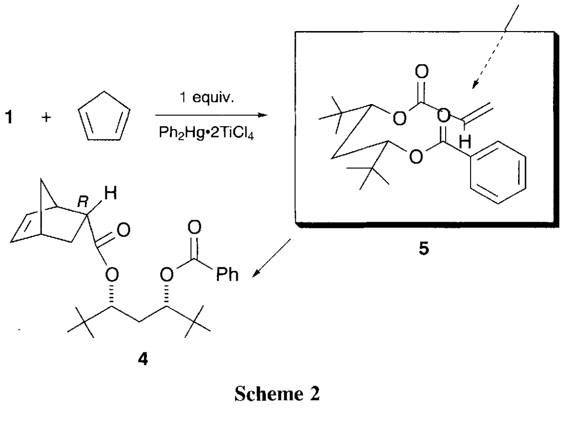
Most asymmetric Diels–Alder reactions of α,β-unsaturated esters bearing chiral auxiliaries have been carried out in the presence of Lewis acids or related additives, and thus have afforded the products, with high diastereoselectivities, which are expected from the reaction proceeding *via* the *s-trans* conformation of the enoates.[1] In certain enoates[2] and enamides,[3] the Lewis acid mediated reaction proceeds through the *s-cis* conformation primarily because of the result of the bidentate chelated geometry of the Lewis acid–ester (or amide) complexes. In fact, the Diels–Alder reaction of (3*R*,5*S*)-3-benzoyloxy-2,2,6,6-tetramethyl-5-heptyl acrylate (TMHD-acrylate) **1** with cyclopentadiene in the presence of 0.5 equiv. $TiCl_4$ gave adduct **2** with high diastereoselectivity in high chemical yield, which would arise from reaction *via* the *s-trans* geometry **3** of the enoate (Scheme 1).[4] We report here that the Diels–Alder reaction of **1** with cyclopentadiene in the presence of 1 equiv. $Ph_2Hg \cdot 2TiCl_4$ or 1 equiv. $\frac{1}{3}$(orthophenylenemercury)·$2TiCl_4$ gives the adduct **4** with high diastereoselectivity in high yield, which is expected to be produced *via* the *s-cis* arrangement **5** of the enoate (Scheme 2).

The results are summarized in Table 1. The reaction proceeded at room temperature with assistance of a Lewis acid to give **2** predominantly (entry 1). The absolute stereochemistry and ratio of the *exo*-diastereoisomers (minor product) were not determined. The reaction at −30 °C mediated by 1 equiv. $BF_3 \cdot OEt_2$ also gave **2** with higher diastereoselectivity (entry 2). With excess amounts of $BF_3 \cdot OEt_2$ (*e.g.* equiv.), the addition reaction was accompanied by dimerization of cyclopentadiene, giving the adducts in lower yield (entry 3). The use of 1 equiv. $TiCl_4$ resulted in dimerization of cyclopentadiene and no addition products were obtained (entry 4), but in the case of 0.5 equiv. $TiCl_4$, **2** was produced with significantly high diastereoselectivity in high chemical yield (entry 5). These results are in good agreement with the previous observation[4] and with the well-accepted mechanisation for Lewis acid mediated Diels–Alder reactions; Lewis acid complexation of enoates dramatically stabilizes the *s-trans* conformation relative to the *s-cis*[1] and thus the reaction proceeds predominantly through the *s-trans* geometry **3**; although the use of a Lewis acid enhances the diastereoselectivity and the reaction speed, it causes the competitive dimerization of cyclopentadiene and therefore catalytic amounts of a Lewis acid are generally utilized.

Very interestingly, the use of 1 equiv. $Ph_2Hg \cdot 2TiCl_4$ as a Lewis acid afforded **4** predominalty (entry 6). Furthermore, no dimerization of cyclopentadiene took place in spite of the use of excess $TiCl_4$ (2 equiv.). To a hexane solution of Ph_2Hg (1 equiv.) at −78 °C was added a 1.0 mol dm^{-3} CH_2Cl_2 solution of $TiCl_4$ (2 equiv.) and the mixture was stirred for 10 min at this temperature. The mixture was heterogeneous at this stage. A hexane solution of **1** (1 equiv.) and a hexane solution of cyclopentadiene (10 equiv.) were added, and the mixture was stirred at −30 °C for 10 h. In entries 7 and 8, **2** was produced predominantly, although $Ph_2Hg \cdot nTiCl_4$ (n = 1, 2) were used as Lewis acids. The difference between entry 6 and entries 7, 8 is the amount of $TiCl_4$; 2 equiv. $TiCl_4$ was utilized in entry 6 and 1 equiv. $TiCl_4$ in entries 7 and 8. No dimerization took place in entries 7 and 8 (*cf.* entry 4).



Scheme 1



Scheme 2

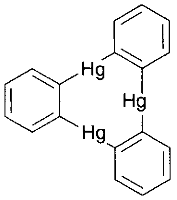
Table 1 Diels–Alder reaction between TMHD-acrylate **1** and cyclopentadiene[a]

Entry	Lewis acid (equiv.)	Isolated yield (%)[b]	*endo* : *exo*	Ratio of *endo* adduct **2**:**4**
1	None[c]	92	79:21	69:31
2	$BF_3 \cdot OEt_2$ (1.0)	84	90:10	75:25
3	$BF_3 \cdot OEt_2$ (3.0)	61	98:2	55:45
4	$TiCl_4$ (1.0)	—[d]	—	—
5	$TiCl_4$ (0.5)	96	90:10	81:19
6	$Ph_2Hg \cdot 2TiCl_4$ (1.0)	96	66:34	13:37
7	$Ph_2Hg \cdot 2TiCl_4$ (0.5)	99	83:17	69:31
8	$Ph_2Hg \cdot TiCl_4$ (1.0)	96	79:21	68:32
9	$\frac{1}{3}(ArHg)_3 \cdot 2TiCl_4$ (1.0)	97	78:22	8:92
10	$\frac{1}{3}(ArHg)_3 \cdot 2TiCl_4$ (1.0)	77	71:29	21:79

[a] All reactions were carried out with excess cyclopentadiene (*ca.* 3 equiv.) at −30 °C under nitrogen atmosphere, except where otherwise indicated. In entries 1–5 and 10, CH_2Cl_2 was used as solvent. In entries 6–9 CH_2Cl_2–hexane (1 : 1) was used as solvent. The product ratios were determined by HPLC. [b] Combined yield of *endo* and *exo* adducts. [c] The reaction was performed at room temp. [d] Dimerization of cyclopentadiene took place.

Furthermore, we used orthophenylene mercury[5] **6**, abbreviated to $(ArHg)_3$, instead of Ph_2Hg. Here again, the use of 2 equiv. $TiCl_4$ gave **4** with high diastereoselectivity (entry 9). The solvent effect upon diastereoselectivity and chemical yield was investigated in the $(ArHg)_3{\cdot}TiCl_4$ system (entries 9, 10). The use of hexane afforded high chemical yield and high diastereoselectivity (entry 9), although the diastereoselectivity decreased in the case of CH_2Cl_2 (entry 10). Here again, no dimerization took place in spite of the use of excess $TiCl_4$. Accordingly, it is concluded that the $(Ar_nHg)_m{\cdot}TiCl_4$ complexed Lewis acids direct the conformation of **1** to an *s-cis* form **5**, and dimerization of cyclopentadiene is alleviated in the complexed system compared with the presence of $TiCl_4$ alone.

Previously, we developed a $TiCl_4{\cdot}AsPh_3$ complexed Lewis acid which prevented dimerization of cyclopentadiene in certain Diels–Alder reactions.[6] The reaction of **1** with cyclopentadiene (3 equiv.) in CH_2Cl_2–hexane in the presence of 1 equiv. $TiCl_4{\cdot}AsPh_3$ gave a 73 : 27 mixture of **2** : **4** (*endo* : *exo* = 88 : 12). With 3 equiv. $TiCl_4{\cdot}AsPh_3$, the ratio of **2** : **4** became 38 : 62 (*endo* : *exo* = 72 : 28). These results and the observations made in Table 1 strongly suggested that the use of excess $TiCl_4$ would change the transition state geometry of **1** from the *s-trans* **3** to *s-cis* **5**. The use of excess $TiCl_4$ without being accompanied with dimerization is possible only by using the complexed $TiCl_4$ system. Since $(Ar_nHg)_m$ compounds are not Lewis bases, a mechanism for alleviating dimerization is presumably different from the mechanism in the case of $TiCl_4{\cdot}XPh_4XPh_3$ (X = As, Sb, P).[7] We assume that a rapid equilibrium between (arylmercury + $TiCl_4$) and the arylmercury·$TiCl_4$ complex may be the key to these interesting observations. It is presumed that the *s-cis* conformation is stabilized by the coordination of excess $TiCl_4$ to an ester oxygen of acrylate.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In order to obtain support for this speculation, we carried out the reaction of **1** with cyclopentadiene in the presence of $EtAlC_2$ which did not cause dimerization of cyclopentadiene under the reaction conditions. The use of 1 equiv. $EtAlCl_2$ at −30 °C in CH_2Cl_2–*n*-hexane (1 : 1) gave a 48 : 52 mixture of **2** : **4** in 75% yield (*endo* : *exo* = 91 : 9), whereas the the use of 3 equiv. $EtAlCl_2$ afforded a 12 : 88 mixture of **2** : **4** in 82% yield (*endo* : *exo*) = 91 : 9). The use of 4 equiv. $EtAlCl_4$ gave a similar high diastereoselectivity. Accordingly, it is clear that excess amounts of $TiCl_4$ (or $EtAlCl_2$) change the transition state geometry of **1** from **3** to **5**.

Received, 7th March 1995; Com. 5/01387I

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