Lewis-acid catalysis of the asymmetric Diels–Alder reaction of dimenthyl fumarate and cyclopentadiene

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Received 4 March 2002; accepted 9 April 2002

Abstract—The effects of Lewis acid catalysts, solvent, catalyst loading, and temperature on the diastereomeric excess in the Diels–Alder reaction of (+)-dimenthyl fumarate and cyclopentadiene were investigated. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

In conjunction with a process development project focused on the design of a large scale synthesis strategy for the production of the adenosine A1 antagonist BG9719 (CVT-124)[1] we saw the need for large amounts of enantiomerically pure (2R,3R)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid (Fig. 1).
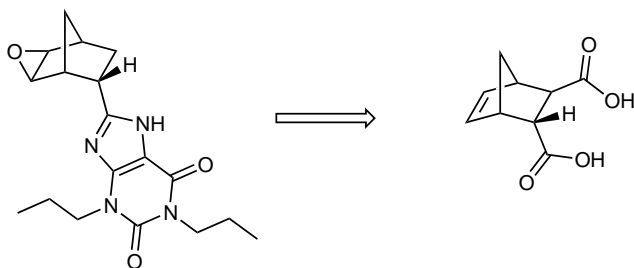
The physical and fiscal constraints of large-scale production of this intermediate via a chiral Diels–Alder reaction limited our synthetic options for this process. Thus, we turned our attention to inexpensive, recyclable chiral auxiliaries.[2] Menthol has served as an inexpensive chiral auxiliary in asymmetric Diels–Alder reactions.[3–10] For example, Yamamoto and co-workers

BG9719 (CVT-124)

Figure 1. Chiral building block for BG9719.

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demonstrated that menthol was an effective and readily available chiral auxiliary in the Et$_2$AlCl-catalyzed Diels–Alder reaction between fumarate and cyclopentadiene.[4] The Hamanaka group later added that the use of SnCl$_4$ as the Lewis acid catalyst also gave excellent stereoselectivity, although its use in the synthesis of a pharmaceutical precursor would be problematic.[5] We undertook an investigation of the asymmetric Diels–Alder reaction of dimenthyl fumarate and cyclopentadiene in an effort to develop reaction conditions more suitable for large-scale synthesis.

2. Results and discussion

Starting material preparation was quite straightforward. Fumaroyl chloride was heated to 50°C with (+)-menthol to form a melt. The reaction proceeded well without solvent and gave 85% yield of the (+)-dimenthyl fumarate after purification (Fig. 2).

The effects of Lewis acid catalysts, solvent, catalyst loading and temperature on the diastereomeric excess in the Diels–Alder reaction of (+)-dimenthyl fumarate and cyclopentadiene were investigated (Table 1). The asymmetric Diels–Alder reaction was initially examined under a standard set of conditions (1.1 equiv. of Lewis acid; toluene; 25°C, 2 h, Fig. 3). Poor diastereomeric excesses (<5%) were observed with BiCl$_3$, titanium isopropoxide, ZnCl$_2$, MgCl$_2$, and in the absence of a Lewis acid catalyst. Aluminum-based Lewis acids gave Diels–Alder adducts in moderate to good de (55–70%). Within the titanium series of catalysts, TiCl$_4$ and TiBr$_4$ gave the highest overall de values at 75 and 80%, respectively.
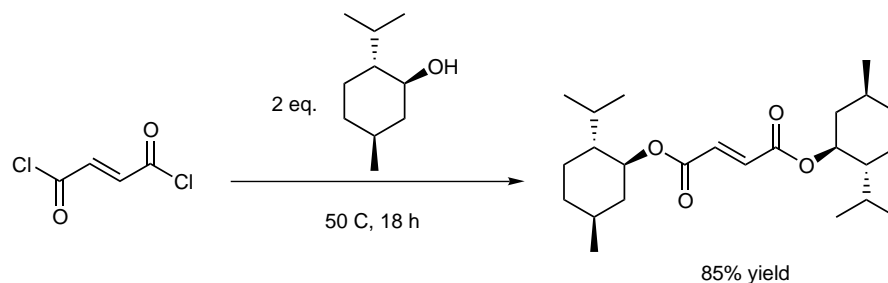
Figure 2. Double esterification of fumaroyl chloride.

Table 1. Influence of various Lewis acid catalysts on the asymmetric Diels–Alder reaction of dimenthyl fumarate and cyclopentadiene[a]

Lewis acid	% De[b]	% Conversion[c]
None	5	100
BiCl$_3$	4	100
ZnCl$_2$	5	100
FeBr$_3$	ND	<5
MgCl$_2$	5	100
Ti(OCH(CH$_3$)$_2$)$_4$	5[d]	100
TiCl$_2$(OCH(CH$_3$)$_2$)$_2$	27	100
TiF$_4$	44	<5
TiCl$_4$	75	100
TiBr$_4$	80	100
BF$_3$·Et$_2$O	53	<5
AlCl$_3$	55	100
Me$_2$AlCl	67	100
Et$_2$AlCl	69	100
EtAlCl$_2$	70	100
DAD[e]	66	100

[a] All reactions performed with 1.1 equiv. LA, 1.5 equiv. Cp, for 2 h in toluene at 25°C.
[b] Diastereomeric excesses determined by comparison of signals assigned to vinylic protons in ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] Prepared from 0.5 equiv. of titanium isopropoxide and 0.5 equiv. of TiCl$_4$.
[e] Prepared from 0.5 equiv. of AlMe$_3$ and 0.5 equiv. of BHT.

The influence of solvents upon the diastereomeric excess was dramatic. With TiCl$_4$ catalysis the de increased from 28% in benzotrifluoride to an optimum of 75% in toluene (Table 2).

In the series of aluminum-based Lewis acid catalysts, toluene again displayed the best performance except in the case of EtAlCl$_2$ which gave the Diels–Alder adduct

Table 2. The effects of solvent, catalyst amounts, and temperature on the TiCl$_4$-mediated reaction of dimenthyl fumarate and cyclopentadiene

Lewis acid[a]	% De[b]	Solvent
TiCl$_4$	28	Benzotrifluoride
TiCl$_4$	39	Diethyl ether
TiCl$_4$	52	Hexane
TiCl$_4$	75	Toluene
TiCl$_4$ (2.2 equiv.)	74	Toluene
TiCl$_4$ (−35°C)	78	Toluene

[a] Unless otherwise noted all reactions performed with 1.1 equiv. TiCl$_4$, 1.5 equiv. Cp, for 2 h at 25°C.
[b] Diastereomeric excesses determined by comparison of signals assigned to vinylic protons in ^{1}H NMR.

in 74% de (Table 3). Toluene, the solvent which gave the Diels–Alder adducts with the highest diastereomeric purity was the solvent of choice for the balance of the investigation.

Increases in the amount of Lewis acid catalyst from one equivalent to 2.2 equiv. gave mixed results with respect to de. With TiCl$_4$ and Me$_2$AlCl there was little effect on the stereoselectivity of the reaction with the addition of excess Lewis acid.

In the case of Et$_2$AlCl, however, an improvement from 69 to 77% de was observed. As with many chiral Diels–Alder reactions the stereoselectivity of the reaction was sensitive to reaction temperature. As the reaction temperature was decreased from room temperature to −35°C a modest increase in de was observed in the TiCl$_4$-mediated reaction. Greater increases in de were observed with the aluminum-based catalysts: Et$_2$AlCl and DAD. The catalyst loading and temperature effects with the aluminum-based Lewis acids parallel those reported by Yamamoto.[4]
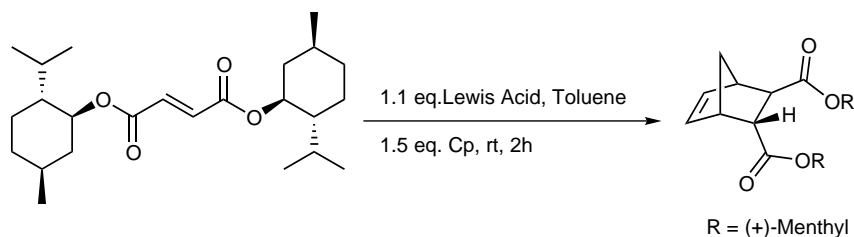

Figure 3. Lewis-acid catalyzed Diels–Alder reaction of (+)-dimenthyl fumarate.
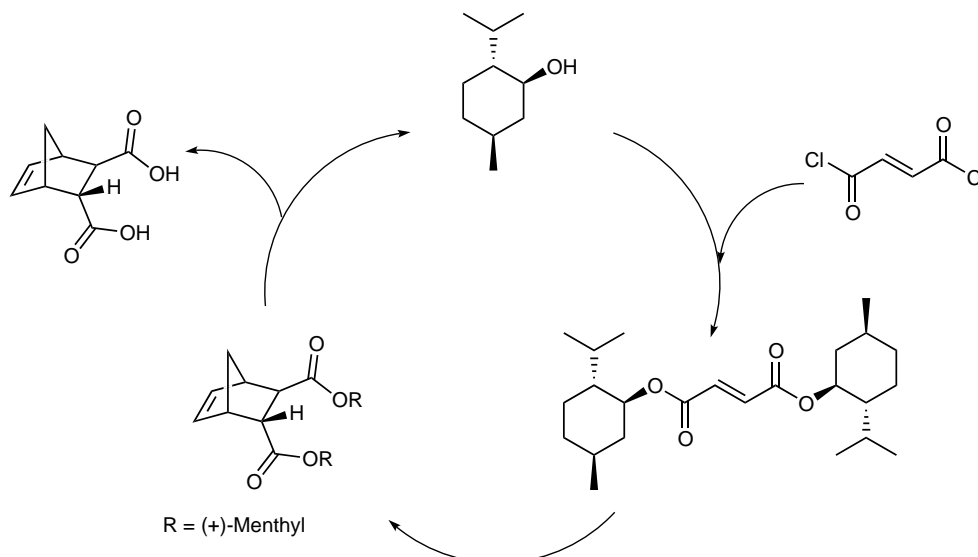
Figure 4. Recycling strategy for menthol auxiliary.

Table 3. The effects of solvent, catalyst amounts, and temperature on the aluminum-based Lewis acid-mediated reaction of dimenthyl fumarate and cyclopentadiene[a]

Lewis acid	% De[b]	Solvent
AlCl$_3$	10	MTBE
AlCl$_3$	28	Hexane
AlCl$_3$	55	Toluene
Me$_2$AlCl	67	Toluene
Me$_2$AlCl (2.2 equiv.)	68	Toluene
Et$_2$AlCl	38	Diethyl ether
Et$_2$AlCl	67	Hexane
Et$_2$AlCl	70	Benzotrifluoride
Et$_2$AlCl	69	Toluene
Et$_2$AlCl (2.2 equiv.)	77	Toluene
Et$_2$AlCl ($-35°$C)	83	Toluene
EtAlCl$_2$	37	Benzotrifluoride
EtAlCl$_2$	47	MTBE
EtAlCl$_2$	70	Toluene
EtAlCl$_2$	74	Hexane

[a] Unless otherwise noted all reactions performed with 1.1 equiv. LA, 1.5 equiv. Cp, for 2 h at 25°C.
[b] Diastereomeric excesses determined by comparison of signals assigned to vinylic protons in ^{1}H NMR.

In conclusion, we have investigated a wide range of Lewis-acid catalysts and reaction conditions for the asymmetric Diels–Alder reaction of dimenthyl fumarate and cyclopentadiene. The scalability of the room temperature reaction catalyzed by TiCl$_4$ in toluene and recovery of the menthol auxiliary fit into the recycling strategy detailed in Fig. 4 and will be the subject of further investigation.

3. Experimental

3.1. (+)-Dimenthyl fumarate

Fumaroyl chloride (23.75 g, 0.155 mol) and (+)-men-thol (48.53 g, 0.311 mol) were combined in a round-bottomed flask equipped with a stir bar and drying tube and brought to 50°C. The melt was stirred overnight (between 18 and 24 h). The reaction mixture was dissolved in EtOAc and the solution was washed with satd NaHCO$_3$, brine, dried with Na$_2$SO$_4$, and concentrated in vacuo. Flash chromatography (silica) (95:5 hexane:EtOAc) of the crude material yielded (+)-dimenthyl fumarate (52.00 g, 85%). ^{1}H NMR (CDCl$_3$, 270 MHz) δ (ppm) 6.83 (s, 1H), 5.80 (dt, 1H), 2.05 (m, 1H), 1.85 (dt, 1H), 1.70 (m, 2H), 1.60–1.40 (m, 2H), 1.15–1.00 (m, 2H), 0.95–0.85 (m, 7H), 0.80 (d, 3H).

3.2. Diels–Alder reaction sample procedure

Under nitrogen, a 1 M solution of TiCl$_4$ (2.55 mL) in toluene was added to a solution of (+)-dimenthyl fumarate (1.00 g, 2.55 mmol) in toluene (10 mL). The reddish solution was stirred for 15 min and then freshly distilled cyclopentadiene (0.315 mL, 3.82 mmol) was added dropwise. After 2 h, satd aqueous NaHCO$_3$ (5 mL) was added and the mixture was extracted with Et$_2$O (3×20 mL). The combined ether extracts were washed with satd brine, dried with Na$_2$SO$_4$, and concd in vacuo to yield the Diels–Alder adduct (1.14 g, 97%, 75% de). ^{1}H NMR (CDCl$_3$, 270 MHz) δ (ppm) 6.25 (dd, 1H), 6.05 (dd, 1H) 4.65 (m, 2H), 3.30 (s, 1H), 3.10 (s, 1H), 2.65 (d, 1H), 2.00–1.80 (m, 5H), 1.70–1.55 (m, 7H), 1.55–1.30 (m, 7H), 1.10–0.75 (m, 14H), 0.70 (dt, 6H).

3.3. Determination of diastereoselectivities

The diastereomeric excesses of the reaction products were determined using the method described by Kabalka et al.[10] The ratios of Diels–Alder adducts were calculated by comparison of the areas of the vinylic protons (6.5 ppm) in the ^{1}H NMR.

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