ORGANIC LETTERS

2002
Vol. 4, No. 26
4619−4621

Intramolecular Diels–Alder Reactions of Ester-Tethered 1,7,9-Decatrienoates: Bis[chloro(methyl)aluminum]trifluoromethanesulfonamide as a Catalyst

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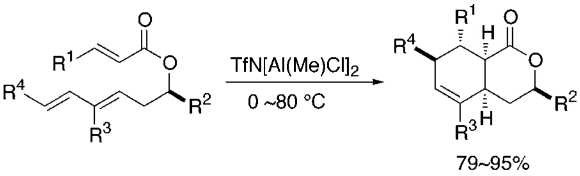
Received September 26, 2002

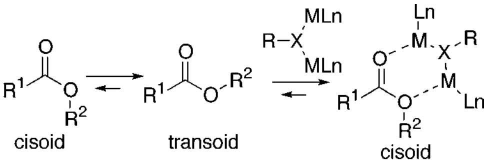
ABSTRACT



The intramolecular Diels–Alder reaction of 1,7,9-decatrienoate derivative with an ester tether is efficiently catalyzed by the bidentate Lewis acid, bis-aluminated trifluoromethanesulfonamide.

The intramolecular Diels−Alder (IMDA) reaction is a powerful method for the stereocontrolled construction of functionalized cyclohexene frameworks.[2,3] In IMDA reactions, the nature of the tether linking the diene and dienophile strongly influences the reactivity of the substrate and the structure of the transition state, and thus the stereochemical outcome. Incorporation of an ester linkage in the tether often has a deleterious effect on the reaction. Even under the conditions necessary to force a reaction, cyclized products are obtained in low yields.[2−4] Moreover, in some cases the reaction fails to yield any cyclized products.[4] Such reduced reactivity of ester-tethered substrates, in particular 1,6,8-nona- and 1,7,9-decatrienoate systems, has been attributed to a preference for transoid ester geometry due primarily to dipole repulsion between carbonyl and ethereal oxygen atoms and the high energy rotational barrier to the cisoid form in which the diene and dienophile are in close proximity and as such are required for a reaction to proceed (Scheme 1).[5−7]

Scheme 1



Consequently, poor overlap of the nonbonding electrons of the ethereal oxygen and carbonyl group in the transition state is considered to be the major factor responsible for this low reactivity.[8] Lewis acid-mediated reaction, often effective for intermolecular versions, does not always work well in the

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[2] For reviews on IMDA reactions, see: (a) Roush, W. R. In *Advances in cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 91−146. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, pp 513−550. (c) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984; Vol. 32, pp 1−374. (d) Weinreb, S. W. *Acc. Chem. Res.* **1985**, *18*, 16.

[3] For references of natural product syntheses, see: (a) Fallis, A. G. *Acc. Chem. Rev.* **1999**, *32*, 464−474. (b) Suzuki, Y.; Murata, T.; Takao, K.; Tadano, K. *J. Synth. Org. Chem.* **2002**, *60*, 679−689.

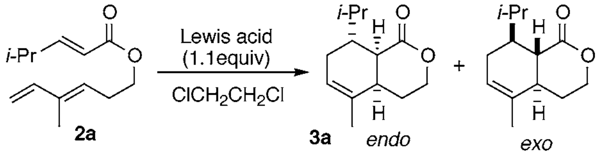
[4] (a) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789−1792. (b) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170−5180.

10.1021/ol026963f CCC: $22.00

IMDA reaction of the ester-tethered substrates.[5d,9] In this paper, we report that the bidentate Lewis acid **1** derived from trifluoromethanesulfonamide ($TfNH_2$, 1 mol) and dimethylaluminum chloride (Me_2AlCl, 2 mol) efficiently promotes the IMDA reaction of the ester-tethered decatriene system **2**.

We presumed that if both oxygen atoms of the ester group could simultaneously coordinate to a bidentate Lewis acid (possibly in equilibrium with other complexes such as a doubly coordinated carbonyl oxygen atom), the cisoid geometry of the ester would be encouraged and the dienophile would be more strongly activated than with a monodentate Lewis acid (Scheme 1).[10] We screened Lewis acids having a general formula Met-X-Met (Met = Al, B, Ti, Zn; X = NSO_2R, O) using 3,5-hexadienyl acrylate derivative **2a** as a model substrate. The thermal IMDA reaction of **2a** was recently reported to give the cycloadduct **3a** in 79% yield (endo/exo = 5), upon heating at 150 °C for 10 days[8a] or in 43% yield after 20 h at 200 °C,[11] respectively (entries 7 and 8; Table 1). With this substrate, monodentate Lewis acids ($TiCl_4$, $MeAlCl_2$, etc.) were not effective.[8a] However, in the presence of 1.1 equiv of $TfN[Al(Me)Cl]_2$ (**1**)[12] generated in situ by mixing $TfNH_2$ (1 mol) and Me_2AlCl (2 mol) in 1,2-dichloroethane at 0 °C (Scheme 2), the IMDA reaction of **2a** proceeded at 80 °C within 3 h to give **3a** in 83% yield with high endo-selectivity (endo/exo = 11) (Table 1, entry 2). As shown in Table 1, with $TfN(AlMe_2)_2$, a longer reaction time was required for complete conversion (10 h, entry 1), while with $TfN(AlCl_2)_2$ the reaction proceeded rapidly to provide **3a** in much reduced yield (run 3). When $PhSO_2N[Al(Me)Cl]_2$ was used, 4-methyl-3,5-hexadienol was liberated (ca 15% based on **2a**; entry 4). Finally, $(Me_2Al)_2O$ and $(Me_2AlO)_2SO_2$ catalyzed the conversion of **2a** to **3a** at slower rates (entries 5 and 6). Thus, of the Lewis acids examined, we found $TfN[Al(Me)Cl]_2$ (**1**) to be the most effective catalyst for the conversion of **2a** to **3a**.

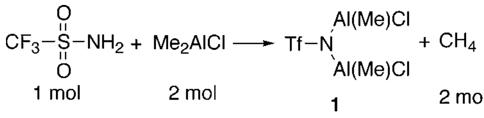
Table 1. Effect of Lewis Acid on the IMDA Reaction of **2a**



entry	Lewis acid	temp/°C	time/h	yield/%[a]	endo/exo
1	$TfN(AlMe_2)_2$	80	10	75	12
2	$TfN[Al(Me)Cl]_2$	80	3	83	11
3	$TfN(AlCl_2)_2$	80	1	45	10
4[b]	$PhSO_2N[Al(Me)Cl]_2$	80	10	74	10
5[c]	$(Me_2Al)_2O$	80	9	24	10
6[d]	$(Me_2AlO)_2SO_2$	80	10	41	13
7[e]	none	150	240	79	5
8[f]	none	200	20	43	

[a] Isolated yield. [b] 4-Methyl-3,5-hexadienol was isolated in 15% yield. [c] Recovery of **2a**, 50%. [d] Recovery of **2a**, 48%. [e] Reference 8a. [f] Reference 11.

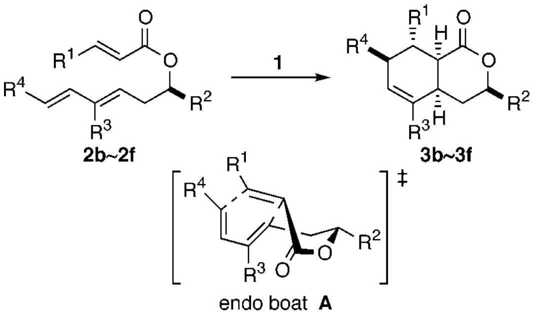
Scheme 2



$CF_3SO_2NH_2 + Me_2AlCl \longrightarrow TfN[Al(Me)Cl]_2 + CH_4$

The results of the IMDA reactions of substituted 3,5-hexadienyl enoate derivatives **2b−f** are shown in Table 2. With 1 equiv of **1** the IMDA reaction of the acrylates **2b−e**

Table 2. $TfN[Al(Me)Cl]_2$-Catalyzed IMDA Reaction of 3,5-Hexadienyl Enoate Derivatives[a]



2b $R^{1,3,4}$=H, R^2=Me
2c R^{1-4}=H
2d $R^{1,2,4}$=H, R^3=Me
2e R^{1-3}=H, R^4=Et
2f R^1=Ph, R^{2-4}=H

entry	2	solvent	temp/°C	time/h	3	yield/%[b]
1	**2b**	CH_2Cl_2	rt	1	**3b**	91
2	**2b**	toluene	0	2	**3b**	85
3[c]	**2b**	$ClCH_2CH_2Cl$	50	7	**3b**	79
4	**2c**	CH_2Cl_2	rt	1	**3c**	88
5	**2c**	toluene	0	2	**3c**	90
6[c]	**2c**	$ClCH_2CH_2Cl$	50	6	**3c**	85
7	**2d**	CH_2Cl_2	rt	1	**3d**	91
8	**2d**	toluene	0	2	**3d**	95
9[c]	**2d**	$ClCH_2CH_2Cl$	50	1	**3d**	81
10	**2e**	$ClCH_2CH_2Cl$	rt	2	**3e**	82
11	**2f**	$ClCH_2CH_2Cl$	80	5	**3f**	78

[a] 1.1 equiv of $TfN[Al(Me)Cl]_2$ was used unless otherwise stated. [b] Isolated yield. [c] 30 mol % of **1** was used.

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(6) Polar solvent effect on the IMDA reaction of ester-tethered substrates: (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469−5470. (b) Jung, M. E. *Synlett* **1990**, *4*, 186−190. See also intramolecular radical addition of allyl α-iodoalkanoates in water: Yoshimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omote, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041−11047.

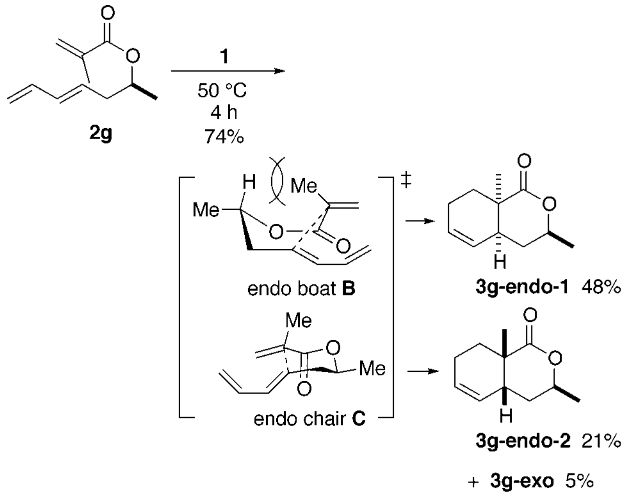
(7) Efficient IMDA reactions employing hydroxamate tethers have been reported. Ichikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S.; Kobayashi, H. *J. Am. Chem. Soc.* **2001**, *123*, 4607−4608.

(8) (a) Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett.* **2000**, *2*, 1835−1837. For theoretical discussions of the transition states in the IMDA reaction of 1,3,9-decatrienoates, see: (b) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938−1940. (c) See also ref 4a.

proceeded within a short period (1−2 h) below room temperature to give the cycloadducts **3b−e** in good yields. Even a catalytic amount of **1** (30 mol %) at 50 °C in 1,2-dichloroethane affected the IMDA reaction in a synthetically useful manner (entries 3, 6, and 9). In all cases shown in Table 2, cis-fused IMDA adducts **3b−f** were obtained as a single isomer with the illustrated relative configuration.[13] The observed diastereoselectivity, in particular the relative configuration between the Me group and the ring-junction in **3b**, indicates that the reaction proceeds via endo-boatlike transition state **A**. This conformational preference is in accord with previous results in 1,3,9-decatrienone studies[2a] and fully consistent with the favorable geometric influence of the bidentate Lewis acid on ester tether. [8]

In the presence of **1** (1.1 equiv), the IMDA reaction of methacrylate derivative **2g**[14] proceeded at 50 °C to give an isomeric mixture of the cycloadducts **3g** in 74% yield (endo/exo = 14) (Scheme 3). The cis-fused cycloadducts thus obtained consist of two isomers in a ratio of 2.3:1. The major isomer, **3g-*endo*-1**, is derived via endo-boatlike transition state **B**, in which α-methyl substituent has a psuedo-flagpole interaction with the hydrogen attached on the ether carbon. Endo-chairlike transition state **C** competitively participates leading to the formation of the minor isomer **3g-*endo*-2**.[8b]

Scheme 3



To gain a qualitative understanding of the activation of ester-tethered substrates by Lewis acids such as **1**, we have carried out NMR studies using methyl crotonate. The ^{13}C NMR spectrum (100 MHz) of a mixture of methyl crotonate and $TfN(AlMe_2)_2$ in $CDCl_3$ at room temperature shows the original signal of the β-carbon (δ 144.7) shifted to a lower field (δ 155.8; $\Delta\delta$ = 11.1 ppm). The chemical shift difference of the ester methyl group also shifted to a lower field ($\Delta\delta$ = 4.2 ppm). However, $TfN[Al(Me)Cl]_2$ complex exhibited greater corresponding shifts ($\Delta\delta$ = 15.1 and $\Delta\delta$ = 6.2 ppm). These differences in chemical shift caused by the complexation with **1** support a significant electronic activation of the double bond of the enoate moiety.[15]

In conclusion, we have shown that the IMDA reaction of 1,7,9-decatrienoate derivatives with an ester tether is efficiently catalyzed by the bidentate Lewis acid, bis-aluminated trifluoromethanesulfonamide **1**. Further studies on the structure of the bidentate complexes, scope in IMDA reactions, and application to the synthesis of natural products are under way.

Supporting Information Available: Experimental procedure for **2** and **3** and their characterization data, and structure determination of **3b** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For examples of significant activation of the carbonyl group by a bidentate Lewis acid, see: (a) Hanawa, H.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 5365−5368. (b) Hanawa, H.; Maekawa, N.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 8379−8382.

(11) Kim, P.; Hantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett.* **2000**, *2*, 1831−1834.

(12) Reaction of sulfonamide ($TfNH_2$, $PhSO_2NH_2$; 1 mol) and methylaluminum reagent (2 mol) readily liberates 2 mol of gas suggesting the formation of bis-aluminated sulfonamide. Although the exact structure of each bis-aluminated sulfonamide is not clear from their NMR spectra, in this text we have tentatively formulated it as *N*,*N*-bis-aluminated structure $RSO_2N(AlLn_2)_2$. It has been reported that bis(trimethylsilyl)trifluoromethanesulfonamide exists as a mixture of *N*,*N*- and *N*,*O*-bis-silylated forms in solution, see: Jonas, S.; Westerhausen, M.; Simchen, G. *J. Organomet. Chem.* **1997**, *548*, 131−137.

(13) Thermal IMDA reaction of **2c** (210 °C, 5 h) was reported to give the cycloadduct (42% yield) as a mixture of stereoisomers. See ref 4b.

(14) To the best of our knowledge, no successful example of the IMDA reaction of 1,3,9-decatriene systems tethered by an α-substituted ester moiety such as a methacrylate **2g** has been reported.

(15) The ^{1}H NMR (400 MHz) of $TfN[Al(Me)Cl]_2$ complex at room temperature showed broadened signals indicating the existence of plural complex forms in relatively slow equilibrium, which, at −50 °C, turned to sharp signals of a mixture of three sets of complexes in a ratio of 3:2:1.