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DIASTEREOSELECTIVE DIELS-ALDER REACTIONS BETWEEN SUBSTITUTED 1,3-BUTADIENES AND N-α-METHYLBENZYLMALEIMIDE

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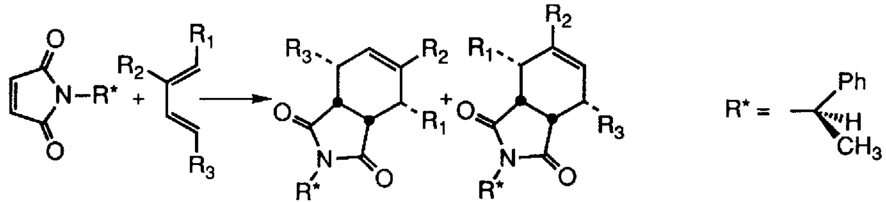
Summary The $TiCl_4$ catalyzed reaction between 2-*t*-butyl-1,3-butadiene and N-α-methylbenzylmaleimide at -65°C affords diastereomeric Diels-Alder adducts in a 15 1 ratio The structure of the major adduct was determined by x-ray

As part of our studies concerning the synthesis of optically active alkaloids, we required a simple synthetic route to various stereochemically pure and optically homogeneous substituted pyrrolidines Of the several possible solutions considered, the Diels-Alder reaction between unsymmetrical dienes and N-chirally substituted maleimides seemed particularly attractive Reported here are the results of our preliminary studies of the reactions between various 1,3-butadienes and N-α-methylbenzylmaleimide which show that excellent selectivity can be achieved in some cases (Scheme 1)[1]

Maleimides are powerful dienophiles, reacting readily with a variety of dienes through a normal *endo* cycloaddition process In spite of intense recent interest in asymmetric Diels-Alder reactions,[2] there appear to be no reports of reactions involving chiral (R*) N-substituted maleimides[3] Because the resident chirality in such dienophiles is relatively remote from the reacting centers, one might suspect that asymmetric induction in such reactions would be inefficient The expected *endo* nature of the reaction, however, gives some cause for optimism, particularly with dienes substituted at the 2-position (see Scheme 2)

Scheme 1



1 **2-9** **10** **11**

To test this idea, racemic N-α-methylbenzylmaleimide (**1**) was prepared in two steps (55% yield) from maleic anhydride and d,l-α-methylbenzylamine by initial formation of the maleamic acid followed by cyclization with hot acetic anhydride[4,5] Initial cycloaddition results with several dienes were not particularly encouraging (Table 1) For instance, reaction of maleimide **1** with 5 equivalents of isoprene (**2**) in CH_2Cl_2 at 25° for 24 hours resulted in the smooth formation of the diastereoisomeric Diels-Alder adducts **10** and **11** (entry 1) Unfortunately, the ratio of these two products, as determined from integration of the vinylic methyl absorptions in the 300 MHz ^1H NMR spectrum (δ 1 56 & δ 1 68) of the crude product, was only 3 2 This ratio was confirmed by integration of several resonances in the ^{13}C spectrum, *eg* , the aromatic carbons at δ 120 2 and δ 120 5 in the major and minor isomers, respectively A similar experiment with *trans*-piperylene (**3**) afforded the two adducts in a ratio of 1 2 1 (entry 2) while substitution at both the 1 and 2 position as in 1-vinylcyclohexene (**4**)[6a] afforded the two products in a ratio of 3 2 (entry 3) Although 2-phenylbutadiene[6b] exhibited disappointing diastereoselectivity (1 1 1) (entry 4), incorporating a larger group as in 2-*t*-butylbutadiene (**6**)[6c,d] improved the product ratio to 2 5 1 (entry 5) The product ratios from a series of three oxygenated dienes (**7**, **8**, and **9**) ranged from 3 2 (entries 6 & 7) to 1 1 (entry 8)

TABLE 1 Uncatalyzed Reactions Between N-α-Methylbenzylmaleimide (**1**) and Substituted Butadienes (**2** - **9**)

entry	diene	R_1	R_2	R_3	Conditions[a]	Ratio
1	**2**	H	Me	H	CH_2Cl_2/25°/24h	3 2
2	**3**	Me	H	H	CH_2Cl_2/25°/24h	1 2 1
3	**4**	-$(CH_2)_4$-		H	CH_2Cl_2/25°/48h	3 2
4	**5**	H	Ph	H	CH_2Cl_2/25°/24h	1 1 1
5	**6**	H	t-Bu	H	CH_2Cl_2/25°/48h	2 5 1
6	**7**	H	OMe	OTMS	CH_2Cl_2/25°/24h	3 2
7	**8**	H	OTMS	H	CH_2Cl_2/25°/140h	3 2
8	**9**	OMe	H	H	CH_2Cl_2/25°/36h	1 1

[a] Footnote 7

It was possible to improve the diastereoselectivity for some of the hydrocarbon dienes (**2**, **3**, **4**, & **6**) by carrying out the reactions in the presence of various Lewis acids (Table 2) Although only marginal improvements were noted for dienes **2**, **3**, and **4** (entries 1 - 3), significant enhancements were observed for the reactions with 2-*t*-butylbutadiene (**6**) in the presence of either $TiCl_4$ or $EtAlCl_2$ (0 8 equivalents) (entries 4 & 7) The 15 1 ratios were determined by analytical hplc and integration of the *t*-butyl resonances in the crude product mixture (δ 0 76 & δ 0 87) These results were particularly gratifying since the Diels-Alder reactions could be routinely carried out on multigram scale (10 grams of **1**) to yield a solid product which after recrystalization from hexane afforded a 64% yield of pure cycloadduct, mp 87-89°C

Several comments about the Lewis acid-catalyzed reactions with diene **6** are in order First, several Lewis acids ($BF_3 \bullet Et_2O$, $ClTi(OiPr)_3$, Et_2AlCl) were ineffective in promoting Diels-Alder reaction with maleimide **1**, leading either to no observable reaction at -65°C or to diene polymerization Partial reaction was observed with $SnCl_4$ at -65°C (entry 8), although diene polymerization was still competitive In general, it was found that Lewis acid catalysis was only successful when pre-complexation of **1** with the Lewis acid in CH_2Cl_2 at -65°C led to a yellow colored solution It was also found that 0 8 equivalents of Lewis acid, either $TiCl_4$ or $EtAlCl_2$, was optimal since less catalyst gave a lower ratio (entry 5, 0 4 equivalents) while more catalyst led to diene decomposition (entry 6, 1 2 equivalents) Finally, toluene appears to be a less effective solvent than methylene chloride (entry 9 *vs* entry 4)

TABLE 2 Lewis Acid Catalyzed Reactions Between Maleimide 1 and Several Butadienes

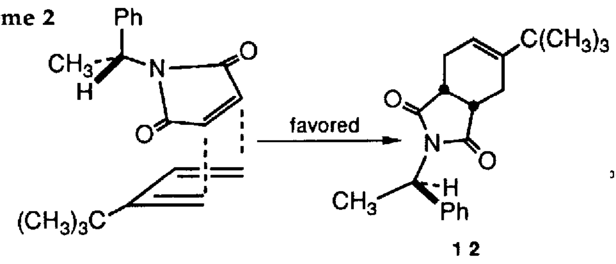
entry	diene	Conditions[a]	Catalyst	Ratio
1	2	CH_2Cl_2/-65°/24h	$TiCl_4$ (0 8eq)	2 1
2	3	CH_2Cl_2/-65°/24h	$EtAlCl_2$ (0 8eq)	3 2[b]
3	4	CH_2Cl_2/-65°/24h	$EtAlCl_2$ (0 8 eq)	2 1[b]
4	6	CH_2Cl_2/-65°/36h	$TiCl_4$ (0 8 eq)	15 1
5	6	CH_2Cl_2/-65°/72h	$TiCl_4$ (0 4 eq)	6 1
6	6	CH_2Cl_2/-65°/36h	$TiCl_4$ (1 2 eq)	15 1[b]
7	6	CH_2Cl_2/-65°/36h	$EtAlCl_2$ (0 8 eq)	15 1
8	6	CH_2Cl_2/-65°/36h	$SnCl_4$ (0 8 eq)	5 1[b]
9	6	$PhCH_3$/-65°/48h	$TiCl_4$ (0 8 eq)	9 1

[a] Footnote 8 [b] Footnote 9

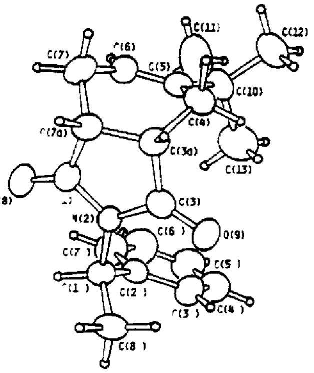
Knowledge of the absolute sense of the chiral induction in the cycloaddition reaction is important for future applications Making the assumption that, in the expected *endo* transition state,[10] the bulky phenyl ring of the α-methylbenzyl group is directed away from the reacting diene, the transition state indicated below should be favored because of the smaller interaction between the diene substituent and maleimide chiral auxiliary (*t*-butyl/H *vs* *t*-butyl/Me) This model, which would favor the formation of product **12** from R-α-methylbenzylmaleimide and 2-*t*-butylbutadiene (**6**), would also account for the reduced stereoselectivities encountered in the cycloadditions with 1-substituted dienes, since a substituent at this position is relatively remote from the chiral auxiliary Verification of the stereochemical outcome of the reaction was obtained through X-ray crystallographic analysis[11] of the major product **12** from the reaction between maleimide **1** and diene **6** These results were entirely consistent with the transition state picture presented below The greater selectivities observed in the Lewis acid catalyzed reactions of **1** appear to be more a consequence of the lower reaction temperatures which were possible in the catalyzed reactions than the enhanced preference for *endo* approach which has been documented for some Lewis acid-catalyzed Diels-Alder reactions [12]

In conclusion, N-α-methylbenzyl maleimide reacts smoothly with a variety of substituted butadienes to give diastereomeric ratios ranging from 1 1 to 15 1, depending on the nature of the diene substituent, Lewis acid catalyst, and reaction solvent and temperature As such, a variety of optically active substituted pyrrolidines is now readily available [13] A survey of the Diels-Alder reactions of other N-substituted chiral maleimides is currently in progress

Scheme 2



12



References and Notes

1 (a) Partial financial assistance from the Duke University Research Council is acknowledged with appreciation (b) A portion of this work was presented at the 197th meeting of the American Chemical Society, April 9 - 14, 1989, Dallas, Texas; ORGN 30

2 For leading references on asymmetric Diels-Alder reactions see (a) L A Paquette, in *Asymmetric Synthesis*, Vol 3, J D Morrison, Ed , Academic Press New York 1984, pp 455-483 (b) W Oppolzer, *Ang Chem, Int Ed Eng* , **23**, 876 (1984) (c) D A Evans, K T Chapman, J Bisaha, *J Am Chem Soc* , **110**, 1238 (1988), and references cited therein (d) W Carruthers, "Cycloaddition Reactions in Organic Synthesis," Pergamon Press, New York, 1990, pp 61-72

3 Several related chiral 1,2,4-triazoline-3,5-diones have been prepared and employed as dienophiles in Diels-Alder reactions (a) L A Paquette and R F Doehner, *J Org Chem* , **45**, 5105 (1980) (b) L A Paquette, Y Hanzawa, G J Hefferon, and J F Blount, *ibid* , **47**, 265 (1982)

4 General procedure N E Searle, U S Pat 2,444,536 **(1948)**, *Chem Abst* , **1948**, *42*, 7340

5 Optically maleimide **1** has been previously prepared by several groups It has not, apparently, been employed as a reagent for asymmetric synthesis (a) T Oishi and M Fujimoto, *J Polymer Sci , Polymer Chem Ed* , **22**, 2789 (1984) (b) T Doiuchi, and H Yamaguchi, *European Polymer J* , **20**, 831 (1984) (c) V M Rangnekar, S R Lokhande, R P Bhamari, and B G Khadse, *Ind J Chem* , **22**, 1070 (1983) (d) V M Rangnekar, R P Bhamari, and B G Khadse, *Ind J Pharm Sci* , **46**, 196 (1984)

6 (a) A Kergomard, J C Tartivat, and J P Vuillerme, *Bull Soc Chim Fr* , 297 (1975) (b) H J Backer, and J R van der Bij,*Rec Trav Chim* , **62**, 561 (1943) (c) C S Marvel, and R G Woolford, *J Org Chem* , **23**, 1658 (1968) (d) H J Backer, and J Strating, *Rec Trav Chim* , **53**, 525 (1934) (e) D Craig, J J Shipman, and R B Fowler, *J Am Chem Soc* , **83**, 2885 (1961)

7 The survey cycloadditions reported in Table 1 were all performed on 50 mg (0 25 mmol) of maleimide **1** and 2 5 mmol (10 eq) diene in 5 mL CH_2Cl_2 The times listed are those required for complete consumption of **1** After removal of the solvent and excess diene, yields of crude products were in the 90 - 100% range

8 The Lewis acid catalyzed cycloadditions from Table 2 were performed on the same scale (50 mg) by first pre-complexing a CH_2Cl_2 solution of **1** with the indicated Lewis acid at -65° before adding the diene (5 eq) Unless otherwise indicated, the reactions were continued to completion for the indicated time, with crude yields after removal of catalyst and excess diene being 70- 95%

9 This reaction was terminated before all of **1** was consumed because of competitive Lewis acid-catalyzed polymerization of the diene

10 See, for example, H Kwart, and I Burchuk, *J Am Chem Soc* , **74**, 3094 (1972)

11 Details of the crystal structure analysis of **12** will be provided in the full account of this work, but are available at this time on request

12 K N Houk and R W Strozier, *J Am Chem Soc* , **95**, 4094 (1973) In a control experiment, an uncatalyzed reaction maintained at -65° for six months went to approximately 25% completion to give the two cycloadducts in a ~20/1 ratio

13 Diels-Alder reaction of R (1), $[\alpha]_D^{20}$ +57 9°, with diene **6** afforded a 90% yield of optically active **12**, mp 85-87°, $[\alpha]_D^{20}$ +47° (c=16 mg/mL, THF) Treatment of **12** with $LiAlH_4$ in ether at room temperature for two hours afforded, after workup, the corresponding isoindole in 90% yield, $[\alpha]_D^{20}$ +47 5° (c=32 mg/mL, THF) All compounds gave satisfactory elemental analyses and exhibited consistent spectral data (IR, ^1H NMR, ^{13}C NMR)

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