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Highly Stereoselective Hydroxy-Directed Diels−Alder Reaction

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The successful stereocontrol of the Diels−Alder reaction of semicyclic dienes possessing a secondary and tertiary allylic magnesium alkoxide alcohol functionality and activated dienophiles such as methyl acrylate, methacrolein, acrolein, and *N*-phenylmaleimide is described.

Introduction

The creation of multiple carbon−carbon bonds with regio- and stereoselectivity makes the Diels−Alder reaction a spearhead in the development of efficient syntheses of natural and nonnatural products.[1] The π-facial diastereoselectivity of the Diels−Alder reaction has been the subject of many synthetic and theoretical studies over the last 20 years.[2] Different theoretical models such as orbital interactions[3] and steric,[4] torsional,[5] and electronic effects[6] have been considered to explain the π-facial selectivity of perturbed dienes.

Independent research by Overman[7] and Frank[8] has shown that heteroatomic substitutions at the α-allylic position on semicyclic dienes can control the diastereoselectivity in [4+2] cycloaddition (eq 1, Scheme 1). Allylic ether substituents (R = CH₃, Si(alkyl)) are considered anti directors, thereby favoring the endo-anti product formation (dr > 25:1). When R = H, the endo-syn product
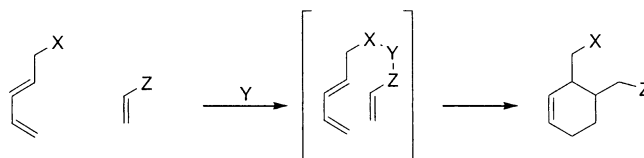

FIGURE 1. General mechanism for the tethered Diels−Alder reaction.

was isolated in 10−36% yield depending on the nature of the solvents used. Carreno et al. reported a similar ratio with a diene possessing an allylic alcohol at the β position (eq 2).[9]

Problems of regio- and π-facial selectivity are amplified when employing a nonsymmetrical dienophile such as methyl vinyl ketone.[10] To solve this problem of selectivity, our approach is based on using a temporary tether, thus transforming an intermolecular Diels−Alder reaction into an intramolecular process by linking the dienophile and the diene together (Figure 1).

Temporary metal tethers in cycloaddition reactions have been the subject of many studies.[11] Pioneer work of Tamao and Ito clearly demonstrated the usefulness of silicon as a disposable tether in Diels−Alder reactions.[12] Although the silyl acetal linkage of the diene and dienophile perfectly controls the regiochemistry, additional transformations are necessary to install and/or remove the anchor unit. Recently, other metal-based temporary tethers such as Mg,[13] Zn,[14] B,[15] and Al[13] have proven to be effective when using nonactivated dieno-

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(1) For review, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, 41, 1650.

(2) (a) Yadav V. K.; Senthil, G.; Babu, G.; Parvez, M.; Reid, J. L. *J. Org. Chem.* **2002**, *67*, 1109. (b) Letourneau, J. E.; Wellman, M. A.; Burnell, J. D. *J. Org. Chem.* **1997**, *62*, 7272. (c) Wellman, M. A.; Burry, L. C.; Letourneau, J. E.; Bridson, J. N.; Miller, D. O.; Burnell, J. D. *J. Org. Chem.* **1997**, *62*, 939. (d) Crisp, G. T.; Gebauer, M. G. *J. Org. Chem.* **1996**, *61*, 8425. (e) Gandolfi, R.; Amade, M. S.; Rastelli, A.; Bagatti, M.; Montanari, D. *Tetrahedron Lett.* **1996**, *37*, 517. (f) Fallis, A. G.; Lu, Y.-F. *Adv. Cycloaddit.* **1993**, *3*, 1 and references therein.

(3) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301.

(4) (a) Burnell, J. D.; Valenta, Z. *Can, J. Chem.* **1991**, *69*, 179. (b) Tsuji, T.; Ohkita, M.; Nishida, S. *J. Org. Chem.* **1991**, *56*, 997. (c) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (d) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (e) Corey, E. J.; Sarshar, S.; Lee, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 12089. (f) Xidos, J. D.; Poirier, R. A.; Pye, C. C.; Burnell, J. D. *J. Org. Chem.* **1998**, *63*, 105.

(5) (a) Houk, K. N.; Li, Y.; Evanseck, J. P. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682. (b) Coxon, J. M.; Froese, R. D. J.; Ganguly, B.; Marchand, A. P.; Morokuma, K. *Synlett* **1999**, 1681. (c) Brown, F. K.; Houk, K. N.; Burnell, J. D.; Valenta, Z. *J. Org. Chem.* **1987**, *52*, 3050. (d) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971.

(6) (a) Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, H. *J. Am. Chem. Soc.* **1995**, *117*, 5992. (b) Coxon, J. M.; Fong, S. T.; McDonald, D. Q.; Steel, P. J. *Tetrahedron Lett.* **1993**, *34*, 163. (c) Roush, W.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380. (d) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.

(7) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.

(8) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472.

(9) Carreno, M. C.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **1998**, *63*, 8320.

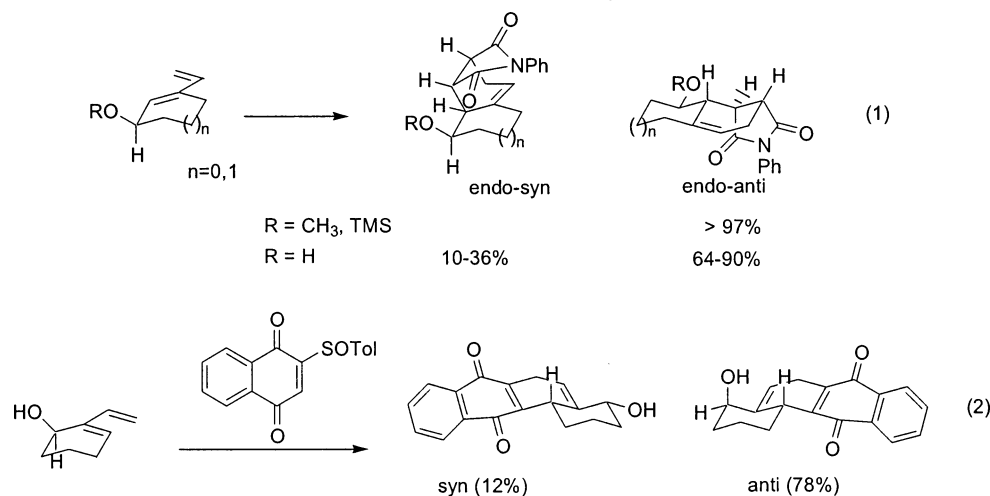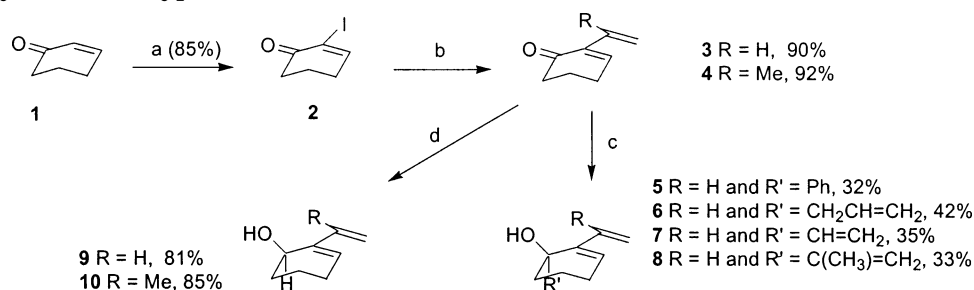(10) Kawamata, T.; Harimaya, K.; Iitaka, Y.; Inayama, S. *Chem. Pharm. Bull.* **1989**, *37*, 2307.

(11) For review, see: Shea, K. J.; Zandi, K. S.; Gauthier, D. R. *Tetrahedron* **1998**, *54*, 2289 and references therein.

(12) (a) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (b) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (c) Sieburth, S.; Fensterbamk, L. *J. Org. Chem.* **1992**, *57*, 5279.
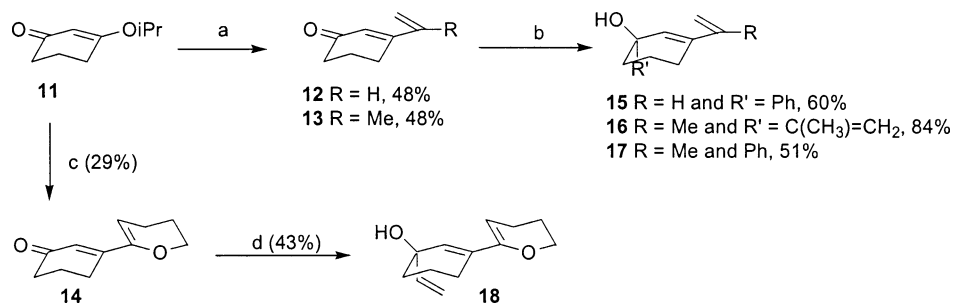
(13) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595.

(14) Olsson, R.; Bertozzi, F.; Fredj, T. *Org. Lett.* **2000**, *2*, 1283.

(15) (a) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450. (b) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, Z.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (c) Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254−1257. (d) Narasaka, K.; Shimada, K.; Osoda, N.; Iwasawa, N. *Synthesis* **1991**, 1171

SCHEME 1. Intermolecular Diels−Alder Reaction with Semicyclic Dienes

R = CH₃, TMS
R = H

$R = CH_3, TMS$
$R = H$

endo-syn
10-36%

> 97%
64-90%

(1)

syn (12%)   anti (78%)   (2)

SCHEME 2. Synthesis of Type I Dienes[a]

3 R = H, 90%
4 R = Me, 92%

5 R = H and R' = Ph, 32%
6 R = H and R' = CH₂CH=CH₂, 42%
7 R = H and R' = CH=CH₂, 35%
8 R = H and R' = C(CH₃)=CH₂, 33%

9 R = H, 81%
10 R = Me, 85%

[a] Reagents and conditions: (a) I₂, pyridine, Et₂O. (b) CH₂=CRMgBr, ZnBr₂, Pd(PPh₃)₄, THF−DMF. (c) R'MgBr, Et₂O, −78 °C. (d) NaBH₄, CeCl₃−7H₂O, MeOH.

SCHEME 3. Synthesis of Type II Dienes[a]

11

12 R = H, 48%
13 R = Me, 48%

15 R = H and R' = Ph, 60%
16 R = Me and R' = C(CH₃)=CH₂, 84%
17 R = Me and Ph, 51%

14   18

[a] Reagents and condtiions: (a) CH₂=CRMgBr, THF −78 °C. (b) R'MgBr, Et₂O, −78 °C. (c) DHP, *t*-Buli, THF, −78 to 0 °C. (d) CH₂=CHMgBr, THF, −78 °C.

philes. All of these reactions require harsh conditions and high temperatures to form the metal−alkoxide diene species and involve dienes possessing a primary alcohol. The use of Lewis acids in the control of the Diels−Alder reactions has also been well studied.[16] However, there is a conspicuous paucity of examples in the literature for their use with dienes possessing a tertiary alcohol. To address the issue of employing a metal-based temporary tether to control the diastereoselectivity of the Diels−Alder reaction, two types of semicyclic dienes were prepared.

Results and Discussion

The synthesis of the type I dienes began with α iodination of 2-cyclohexenone **1** to give iodoenone **2** in 85% yield (Scheme 2).[17] Palladium-catalyzed cross coupling under Negishi conditions[18] provided ketodienes **3**[2a] and **4**[19] in 90% and 92% yield, respectively. Subsequent Grignard addition with phenyl-, allyl-, or vinylmagnesium bromide afforded dienes **5**−**8** in modest yields. In the same vain, ketone dienes **3** and **4** were exposed to Luches' reduction condition to furnish the corresponding

(16) (a) Oppolzer, W. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapter 4.1.4, pp 339−345. (b) First example of Diels−Alder accelerated by Lewis acid: Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

(17) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.
(18) (a) Pour, M.; Ngishi, E. *Tetrahedron Lett.* **1996**, *37*, 4679. (b) Negeshi, E.; Owczarczyk, Z. R.; Swanson, D. *Tetrahedron Lett.* **1991**, *32*, 4453.
(19) Laredo, G. C.; Maldonada, L. A. *Heterocycles* **1987**, *25*, 179.

SCHEME 4. Temporary Tethered Diels−Alder Reaction
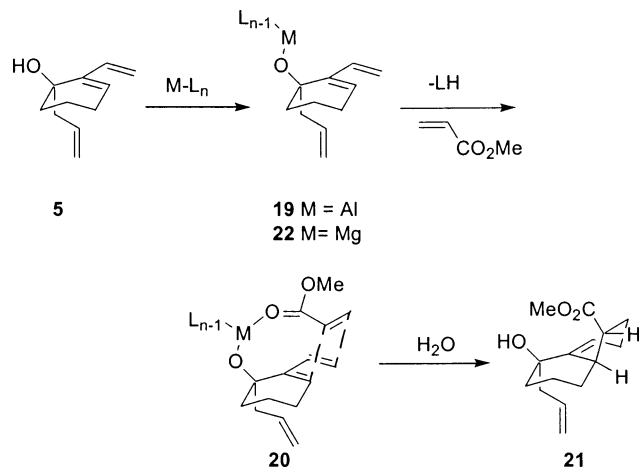
alcohols **9**[9] and **10**[20] in 81% and 85% yield, respectively. Due to their instability, these dienes were used within 2−3 h after a quick purification on silica gel doped with triethylamine.

The second set of dienes (type II) was synthesized as outlined in Scheme 3. This synthetic sequence started with isopropyl enol ether **11**, followed by addition of vinyl- and isopropenylmagnesium bromide and 6-lithio-3,4-dihydro-*2H*-pyrane to give and ketones **12**,[21] **13**, and **14**, respectively, in 29−48% yield. With use of the same conditions previously described, nucleophilic addition with vinyl-, isopropyl-, and phenylmagnesium bromide was performed on **12**, **13**, and **14** to afford the desired semicyclic dienes **15**−**18** in 43−84% yield. The documented success of aluminum-based Lewis acids in the Diels−Alder reaction influenced our decision to begin the investigation with AlMe₃, AlMeCl₂, and AlMe₂Cl. It was envisaged that an Al-alkoxide species **19** would be generated after mixing the Lewis acid with diene **5** (Scheme 4). Upon addition of methyl acrylate the complex **20** would be formed and then undergo a [4+2] cycloaddition with complete stereocontrol to give cycloadduct **21**.

The success we anticipated was not achieved. The aluminum-based Lewis acids under investigation all failed. In each case, a black, viscous substance was produced with the addition of the Lewis acid at −78 or −90 °C. Upon the addition of methyl acrylate, no cycloaddition products were isolated. The ¹H NMR of the crude mixture showed complete degradation of the diene. The instability of these dienes restricted the choice of Lewis acid and conditions in the development of this methodology. The futility of the Al Lewis acids meant that the tether would have to be made via other means.

We then turned our attention to the formation of a magnesium alkoxide tether. This type of tether has been used by Kanemasa and co-workers in the stereocontrol of metal-assisted 1,3-dipolar cycloaddition of an alkenoxymagnesium bromide and an electron-deficient dienophile.[22] Recently, Ward reported intramolecular Diels−Alder reactions by self-assembly of dienoxymagnesium bromide and methyl acrylate.[23]

TABLE 1. Hydroxy-Directed Diels−Alder with PhMgBr

Entry	Diene	Dienophile	Product	Yield[a] (dr > 25:1)[b]
1	**6**	CO₂Me	**21**	65%
2	**7**	CO₂Me	**23**	85%
3	**17**	CO₂Me	**24**	69%
4	**16**	CO₂Me	**25**	30%

[a] Yields were calculated after purification on silica gel. [b] dr values were determined by 300- and 500-MHz ¹H NMR of the crude reaction mixture.
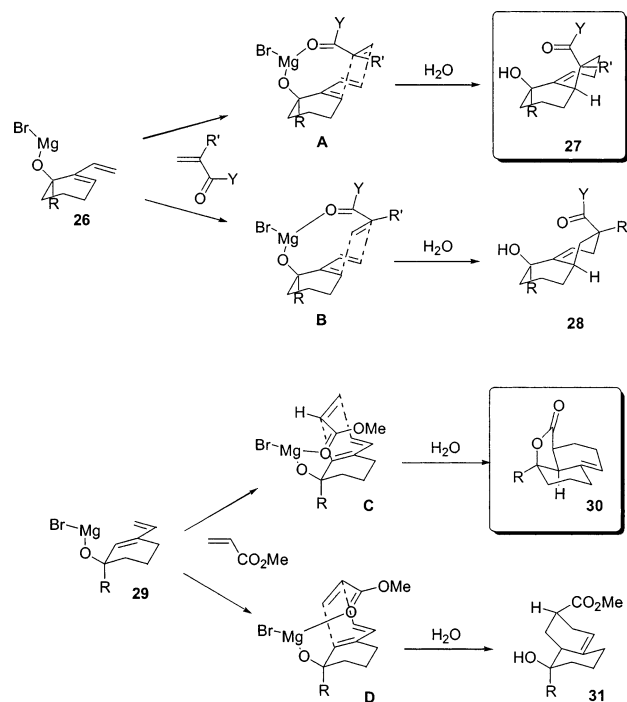
FIGURE 2. Proposed mechanism for the hydroxy-Diels−Alder reaction.

A solution of diene **6** in toluene was treated with 2 equiv of phenylmagnesium bromide (1.0 M in THF) at

(20) Werner, H.; Rouh, R. J. *J. Org. Chem.* **1985**, *50*, 618

(21) (a) Strekowski, L.; Kong. S.; Battiste, M. A. *J. Org. Chem.* **1988**, *53*, 901. (b) Hayakawa, K. S.; Ohsuti, S.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 947.

(22) (a) Kanemasa, S.; Okuda, K.; Yamamoto, H.; Kaga, S. *Tetrahedron Lett.* **1997**, *38*, 4095. (b) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324. (c) Kanemasa, S.; Nishiuchi, M. *Tetrahedron Lett.* **1993**, *34*, 4011.
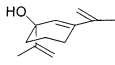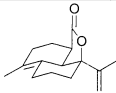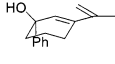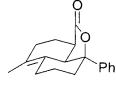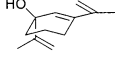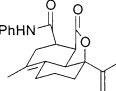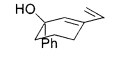
(23) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937.
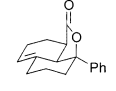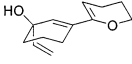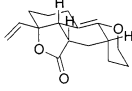
TABLE 2. Hydroxy Directed Diels–Alder Reaction with Dienes Type I

Entry	Diene	Dienophile	Base	Product	Yield[a]	dr[b]
1	**5**	CHO (methacrolein)	Et₃N	**32**	39%	> 25:1
2	**5**	CO₂Me (methyl acrylate)	Et₃N	**33**	66%	8:1
3	**5**	CO₂Me (methyl acrylate)	2,6-lutidine	**33**	89%	12:1
4	**5**	CHO (acrolein)	2,6-lutidine	**34**	73%	> 25:1
5	**7**	CO₂Me (methyl acrylate)	2,6-lutidine	**23**	73%	> 25:1
6	**7**	CHO (methacrolein)	Et₃N	**35**	74%	> 25:1
7	**8**	CHO (methacrolein)	Et₃N	**36**	71%	> 25:1
8	**9**	CO₂Me (methyl acrylate)	Et₃N	**37**	76%	> 25:1
9	**9**	CHO (acrolein)	Et₃N	**38**	82%	> 25:1
10	**9**	CHO (methacrolein)	Et₃N	**39**	78%	> 25:1
11	**10**	CO₂Me (methyl acrylate)	Et₃N	**40**	73%	> 25:1
12	**10**	CHO (acrolein)	Et₃N	**41**	68%	> 25:1
13	**10**	CHO (methacrolein)	Et₃N	**42**	66%	> 25:1

[a] Yields were calculated after purification on silica gel. [b] dr values were determined by 300- and 500-MHz ^{1}H NMR of the crude reaction mixture.

TABLE 3. Hydroxy-Directed Diels−Alder Reaction with Dienes Type II

Entry	Diene	Dienophile	Base	Product	Yield[a] (dr > 25:1)[b]
1	**16**	CO_2Me	Et_3N	**25**	57%
2	**17**	CO_2Me	Et_3N	**24**	58%
3	**16**	NPh	Et_3N	**44**	80%
4	**15**	CO_2Me	Et_3N	**43**	57%
5	**18**	CO_2Me	Et_3N	**45**	78%

[a] Yields were calculated after purification on silica gel. [b] dr values were determined by 300- and 500-MHz ^{1}H NMR of the crude reaction mixture.

−78 °C to form in situ the magnesium alkoxide **21** (Scheme 4). Three equivalents of methyl acrylate was added and the reaction mixture was slowly warmed to room temperature. After the mixture was stirred for 3 h, the desired cycloadduct **21** was isolated in 65% yield as the sole diastereomer. Application of this method to other dienes was performed and the results of the cycloaddition reactions are depicted in Table 1. The reaction gave yields ranging from 30% (entry 4) to 85% (entry 2). In all entries, the regio- and diastereoselectivity ratio was greater than 25:1 for both the type I (entries 1 and 2) and type II dienes (entries 3 and 4). The reaction proves to be tolerant for a variety of substituents at the tertiary alcohol.
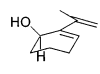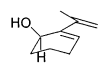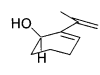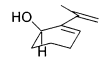
The high regio- and diastereoselectivity can be rationalized by the proposed transition state depicted in Figure 2. In the case of the type I dienes, the endo-facial approach of the dienophile is governed by the complexation of the magnesium alkoxide **26** with the dienophile carbonyl, i.e., syn to the tertiary alcohol (Figure 2). The endo approach of the dienophile can occur via two possible transition states **A** and **B**. In transition state **A**, an eight-membered-ring intermediate is formed whereas in transition state **B** a nine-membered-ring intermediate is formed. Transition state **A** is favored due to less strain when the dienophile approaches the diene. The exclusive formation of **27** over **28** is thus readily explained.
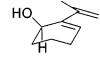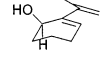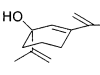
In the case where type II dienes such as **29** are used, the same analysis is applied. The dienophile can approach in two ways to give transition state intermediates

C or **D**. Cycloadduct **30** is formed via a seven-membered-ring transition state **C** whereas cycloadduct **31** would result from the more strained eight-membered-ring transition state **D**. Cycloadduct **31** was never observed in the crude reaction mixture. Although the results with PhMgBr were successful, they were not entirely satisfactory because of the irreproducibility of the reaction yields. It was discovered that the yield of the reaction was closely related to the quality and the concentration of the PhMgBr being used. In general, the use of a freshly prepared solution of PhMgBr (1−1.5 M in THF) gave good yields. However, as the Grignard reagent aged, the yields diminished. The inconsistency of the yields with PhMgBr necessitated an alternative means of forming the semicyclic diene magnesium alkoxide. Vedejs and collaborators reported the formation of magnesium alkoxides using $MgBr_2 \cdot Et_2O$ and Et_3N.[24] Applying this method to the tertiary alcohol **5**, we discovered that the sequence of addition of these reagents is imperative to the success of the reaction. The successful method involves addition of 4 equiv of Et_3N to a solution of $MgBr_2 \cdot Et_2O$ (2 equiv) in dichloromethane at room temperature. This mixture must be stirred until a pink color persists. The diene is then added and stirred for 20 min. Finally, the dienophile is added and the reaction is allowed to proceed with stirring. The results of the $MgBr_2 \cdot Et_2O$ mediated reaction are shown in Tables 2 and 3.

(24) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.

TABLE 4. Hydroxy-Diels−Alder Reaction with Other Lewis Acids

Entry	Diene	Lewis acid	Base	Product	Yield
1	**10**	MgCl$_2$	Et$_3$N	**42**	58%
2	**10**	MgI$_2$	Et$_3$N	**42**	35%
3	**10**	ZnBr$_2$	Et$_3$N	**42**	31%
4	**10**	VCl$_3$	Et$_3$N	Decomp.	---
5	**10**	PhBCl$_2$	Et$_3$N	Decomp.	---
6	**10**	Mg(OTf)$_2$	2,6-lutidine	S.M.	---
7	**16**	MgCl$_2$	Et$_3$N	**25**	65%

Excellent diastereoselectivity was observed in most cases. It was discovered, however, that a prolonged exposure to MgBr$_2$−OEt$_2$ and Et$_3$N resulted in epimerization at C5 of cycloadduct **33** (Table 2, entry 2). The aldehyde **34** also epimerized under MgBr$_2$−OEt$_2$ and Et$_3$N conditions (12 h) to give a mixture of α/β at C5 of 1:7. To circumvent this, triethylamine was replaced by 2,6-lutidine and the diastereoselectivity was improved to 12:1 (entry 3) and >25:1 (entry 4). As was the case with PhMgBr, the reactions with MgBr$_2$·Et$_2$O and triethylamine or 2,6-lutidine were highly regio- and diastereoselective. This method provided good and reproducible yields. The reaction maintained its tolerance to a variety of substituents on the tertiary alcohol and was shown to be successful with semicyclic dienes having a secondary allylic alcohol (Table 2, entries 8−13). To further demonstrate the scope of the reaction, acrolein (Table 2, entries 4, 9, and 12), methacrolein (Table 2, entries 1, 6, 7, 10, and 13), and *N*-phenylmaleimide (Table 3, entry 3) were used as dienophiles in addition to methyl acrylate. These dienophiles worked remarkably well with yields as high as 82%. The relative stereochemistry of cycloadducts **23** and **24** was established by X-ray crystallography, which supported, without ambiguity, the proposed mechanism and transition states depicted in Figure 2.[25]

We also investigated the effect of different halogens on the magnesium, as well as that of other metals, on the reaction. The results are summarized in Table 4. MgCl$_2$ gave similar yields to MgBr$_2$·OEt$_2$ (Table 4, entries 1 and 7) whereas MgI$_2$ provided a substantially lower yield (entry 2). Surprisingly, Mg(OTf)$_2$ did not lead to any cycloaddition products. Only starting material was recovered (entry 6). It was discovered that zinc bromide and triethylamine gave the desired product but the yield was considerably lower (entry 3). When semicyclic dienes of type I and type II were exposed to MgBr$_2$·OEt$_2$, MgCl$_2$, MgI$_2$, and ZnBr$_2$ and methyl acrylate in dichloromethane without triethylamine or 2, 6-lutidine, a complex mixture resulted from which it was not possible to isolate the desired cycloadducts. These experiments confirmed without ambiguity the crucial role of the Lewis bases for the formation of the corresponding magnesium alkoxide **26** and **29** as depicted in Figure 2.

Summary

The results presented in this study show the successful development of a method that controls the regio- and stereoselectivity of the Diels−Alder reaction with PhMgBr or MgBr$_2$·OEt$_2$ and triethylamine of semicyclic dienes possessing a secondary and tertiary allylic alcohol functionality in the α or β position and activated dienophiles

(25) **23** was reduced to the corresponding alcohol with DibalH in THF to provide crystalline material.

such as methyl acrylate, methacrolein, acrolein, and *N*-phenylmaleimide. In the case of the PhMgBr-controlled reactions, optimal results were obtained when a freshly prepared bottle of the Grignard reagent was used. The reactions with magnesium bromide diethyl etherate and triethylamine show an improvement in yields of the PhMgBr reactions. Various Lewis acids were examined, among which only $MgBr_2 \cdot OEt_2$, $MgCl_2$, MgI_2, and $ZnBr_2$ with the conjunct use of triethylamine or 2,6-lutidine proved to yield the expected Diels−Alder products in high regio- and diastereoselectivity. The simplicity and efficiency of this method has a tremendous potential in organic synthesis, and is presently being used in our laboratory in the total synthesis of natural products.

Experimental Section

All reactions were carried out under dry N_2 atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. THF and Et_2O were freshly distilled from sodium/benzophenone. Dichloromethane, triethylamine, and DMF were freshly distilled from CaH_2. $ZnBr_2$ was flame dried under vacuum (1 mmHg). $MgBr_2 \cdot OEt_2$ was prepared from Mg and dibromoethane in THF and stored in a glovebox ($O_2 < 1$ ppm and $H_2O < 1$ ppm). The other commercially available reagents were used directly, unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) analysis of aliquots, using aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out on 230−400 mesh silica gel 60. For purification of compounds containing tertiary alcohol functionality, the silica gel was doped with 2% Et_3N. TLC plates were viewed under UV light and stained with phosphomolybdic acid or *p*-anisaldehyde staining solutions. GC/MS used a cross linked 5% PH ME siloxane column (30 m × 0.25 mm, 0.25 μm film). ^1H and ^{13}C NMR spectra were recorded on a 300- or 500-MHz spectrometer. IR spectra were recorded on a FTIR spectrometer.

General Procedure for Diels−Alder Reactions: Method A. Phenylmagnesium bromide (1.2 equiv) was added, via syringe, to a 0.1 M solution of the diene (1 equiv) in toluene at 0 °C. The reaction was stirred for 15 min then cooled to −78 °C. After an additional 15 min of stirring, the dienophile (methyl acrylate) (1 equiv) was added via syringe. The temperature was slowly raised to room temperature and the reaction was monitored by TLC until complete. A solution of saturated aqueous NH_4Cl was then added, followed by extraction with ether (3×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was then purified by flash chromatography (10−20% EtOAc in hexanes) to provide the desired cycloadduct.

Method B. Triethylamine (4 equiv) was added to a mixture of $MgBr_2 \cdot OEt_2$ (2 equiv) in CH_2Cl_2 (2 M) and stirred until the initial pale yellow color turned slightly pink. At this time, a solution of the diene (1 equiv) in CH_2Cl_2 (0.5 M) was added via cannula. The reaction was stirred for 20 min, then the dienophile (2 equiv) was added, via syringe. The mixture was stirred and the reaction was monitored to completion by TLC. A solution of saturated aqueous NH_4Cl was then added, followed by extraction (3×) with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (10−20% EtOAc in hexanes) to provide the desired cycloadduct.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for compounds **2**−**18**, **21**−**25**, and **32**−**45** and copies of ^1H and ^{13}C NMR for all new compounds; ORTEP views of **23** reduced as an alcohol and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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