ORGANIC LETTERS

2000
Vol. 2, No. 9
1283−1286

Temporary in Situ Aluminum and Zinc Tethering in Diels–Alder Reactions

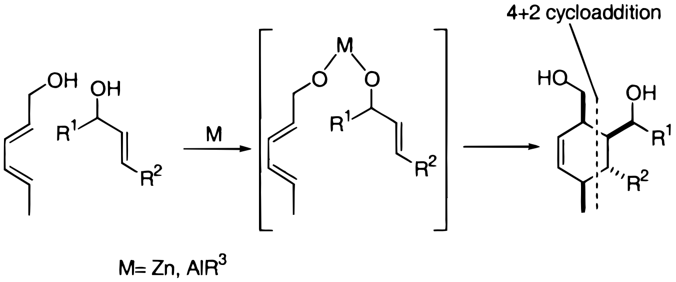
Fabio Bertozzi,[†] **Roger Olsson,***[,‡] **and Torbjörn Frejd**

Organic Chemistry 1, Department of Chemistry, Lund University, P.O. Box 124,
S-22100 Lund, Sweden, and Synthetic Chemistry, ACADIA Pharmaceuticals A/S,
Fabriksparken 58, DK-2600 Glostrup, Denmark

roger@acadia-pharm.com

Received February 25, 2000

ABSTRACT



Temporary tethering using aluminum or zinc in Diels–Alder reactions made possible the use of otherwise "noncompatible" combinations of dienes and dienophiles, resulting in the one-step formation of substituted cyclohexene 1,2-bis-methanols. Excellent regioselectivity and also significant stereoselectivity were obtained.

Transforming an intermolecular reaction into an intramolecular one, by connecting the reactants through a temporary linkage, is an efficient way to control the stereochemical outcome and to enhance the reactivity of the reaction. Temporary tethering requires easy introduction of a readily available linker and its facile cleavage after the reaction. In most of the reports concerning tethering in various types of reactions (cycloaddition, radical cyclization, nucleophilic delivery, and hydrosilylation), silicon derivatives have been used as linkers between the different reactants.[1] Silicon-tethered cycloadditions have been studied extensively, especially the intramolecular Diels−Alder (IMDA) reaction.[2] Although the IMDA reaction itself using the O−Si−O linker usually gives good to high yields, the formation of the unsymmetrical silyl acetals is quite complicated, drastically lowering the overall yield.[3] Another drawback of using the O−Si−O linker is that additional synthetic operations are required to introduce and/or remove the tether. A recent publication by Batey et al.[4] used C−B−O linking of alkenylboranes.

Phenylboronic acid has been used in several cases as an O−B−O linker for IMDA reactions.[5] During our work with alkylative endo opening of pyranosides using organometallic reagents (alkylaluminum, alkyltitanium, and alkylzinc reagents),[6] we envisaged that in cases in which the alkenols act as reaction partners the tethering could occur through

---

[†] Present address: Dip. di Chimica Bioorganica Università degli Studi di Pisa, Via Bonanno 33, 56126 Pisa, Italy.

[‡] ACADIA Pharmaceuticals A/S.

(1) For reviews, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. (c) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289.

(2) (a) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc*. **1992**, *114*, 7578. (b) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem*. **1992**, *57*, 5279. (c) Sieburth, S. M.; Lang, J. *J. Org. Chem*. **1999**, *64*, 1780.

(3) (a) Craig, D.; Reader, J. C. *Tetrahedron Lett*. **1990**, *31*, 6585. (b) Craig, D.; Reader, J. C. *Tetrahedron Lett*. **1992**, *33*, 4073. (c) Craig, D.; Reader, J. C. *Tetrahedron Lett*. **1992**, *33*, 6165.

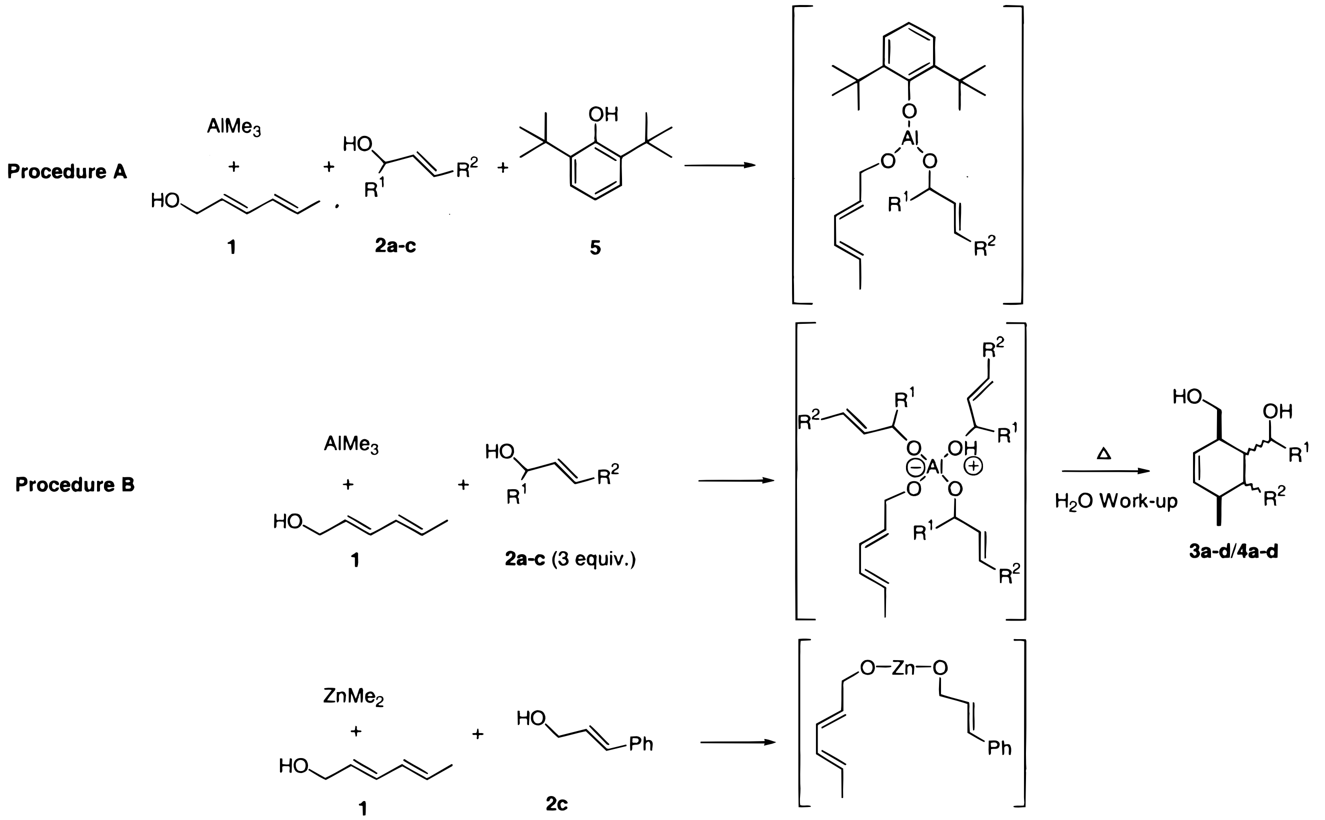
(4) Batey, R. A.; Thadani, A. V.; Lough A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.

(5) (a) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171. (b) Shimada, S.; Kazuhiko, O.; Naraska, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254. (c) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

(6) Olsson, R.; Berg, U.; Frejd, T. *Tetrahedron* **1998**, *54*, 3935.

10.1021/ol0057232 CCC: $19.00

Scheme 1



O−Al−O and O−Zn−O linkers by using simple commercial reagents (AlMe$_3$ and Et$_2$Zn, respectively), a tethering strategy to our knowledge not previously explored. However, Stork et al.[7] have reported one example using aluminum as a linker. A C−Al−O alanate was generated by addition of a Grignard reagent to Et$_2$AlCl followed by the addition of lithium alkoxide.

The objective of this work was to develop a general one-step procedure using aluminum or zinc as the linker atom and to apply this procedure to the Diels−Alder reaction. It is particularly interesting to force otherwise unreactive diene−dienophile partners to undergo the IMDA reaction. To obtain a general tethering procedure, it seemed important to generate a reacting species devoid of other byproducts (i.e., salts) that could interfere with the reaction later on. Consecutive addition of two different functionalized alcohols, the diene and the dienophile, respectively, to AlMe$_3$ or ZnMe$_2$ should in addition to the tethered species only generate gaseous methane. The aluminum or zinc tether would subsequently easily be cleaved off in the aqueous workup.

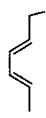
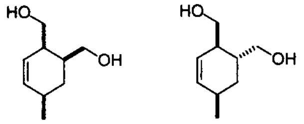
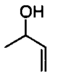
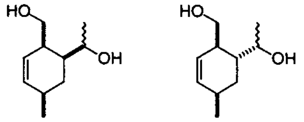
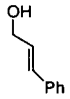
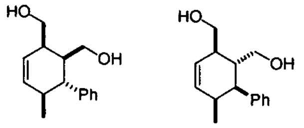
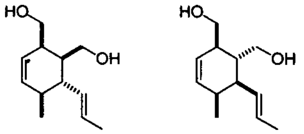
The experimental procedure was as follows: the tethered species were generated in situ simply by consecutive addition of diene, dienophile, and, in some aluminum cases, a third alcohol to a solution of AlMe$_3$ or ZnMe$_2$ in toluene at room temperature. A vigorous formation of methane indicated the formation of the aluminum or zinc alcoholates. After the gas evolution deceased, the reaction tube was sealed and the cycloaddition was performed at 160 °C for 60 h (Scheme 1).[8] The commercially available sorbic alcohol (**1**) and the unactivated allylic alcohols **2a**−**c** were used as diene and unactivated dienophiles, respectively (Table 1). Hydrolytic workup of the resulting metal alkoxide mixture liberated the reaction products, which were isolated by column chromatography. Two procedures were applied. In procedure A, 1 equiv of diene **1** and 1 equiv of dienophile **1** or **2a**−**c** were used, and in the aluminum cases a third nonreacting 2,6-di-*tert*-butylphenol (**5**) was used with the idea of replacing the remaining methyl group (Scheme 1). In procedure B, 1 equiv of diene **1** and 3 equiv of dienophile **1** or **2a**−**c** were used (Scheme 1). Procedure B gave in most cases better yields than procedure A but resulted in slightly lower diastereomeric ratios (Table 1). An exception to this trend was entry 3 where procedure A gave a higher yield compared to procedure B. A speculative explanation could be that dienophile **2c** used in entry 3 is larger than the other dienophiles used (**2a**, **2b**, and **1**). Thus, bringing together 3 equiv of dienophile **2c** and 1 equiv of diene **1** into a tethered complex in procedure B may exert a more unfavorable crowding for the outcome of the reaction compared to procedure A where the total number

---

(7) Chan, T. Y.; Stork, G. *J. Am. Chem. Soc.* **1995**, *117*, 6595.

(8) The tethered complexes shown in brackets are hypothetical complexes based on the stoichiometries of ligands versus aluminum. Other coordination patterns are reported. For synthetic utility of the hypercoordination of aluminum, see: Maruoka, K.; Ooi, T. *Chem, Eur. J.* **1999**, *5*, 829.

Table 1. Results of $AlMe_3$- and $ZnMe_2$-Tethered Diels–Alder Reactions

entry	diene	dienophile	products[a]
1	 **1**	 **2a**	 **3a** **4a**
		Procedure A	**3a/4a** 4:1, 52%
		Procedure B	**3a/4a** 3:1, 66%
2	**1**	 **2b**	 **3b** **4b**
		Procedure A	**3b/4b** 0%
		Procedure B	**3b/4b** 1:1, 49%
3	**1**	 **2c** :	 **3c** **4c**
		Procedure A	**3c/4c** 4:1, 70%
		Procedure B	**3c/4c** 2:1, 21%
		Using $ZnMe_2$	**3c/4c** 3:2, 27%
4	**1**	**1**	 **3d** **4d**
		Procedure A	**3d/4d** 3:1, 60%
		Procedure B	**3d/4d** 2:1, 77%

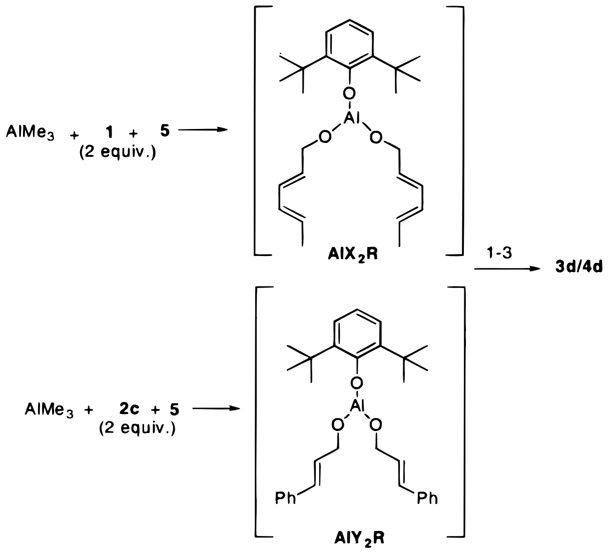
[a] The structures of the various cycloadducts were established by ^1H and ^{13}C NMR, COSY, NOESY, and HETCOR measurements.

of ligands in the tethered complex is smaller. The crowding effect in procedure B compared to procedure A does not seem to be pronounced when a smaller dienophile (i.e., **2a**, **2b**, or **1**) is used. Using zinc as a linker atom optimally gave the same complete regioselectivity as with aluminum, but with both a lower yield and diastereoselectivity (Scheme 1, Table 1, entry 3).

As expected, the cycloaddition reaction of these "non-compatible" dienes and dienophiles did not take place without the tethering. This together with the complete regioselectivity makes this simple procedure very attractive. As is evident from the product ratios of diols **3** and **4** (Table 1), the complete regioselectivity and diastereoselectivity indicate a reaction path via a tethered intermediate. The preferred formation of cycloadduct **3**, with cis stereochemistry between the hydroxymethyl groups tethered in the reaction, is in accordance with the results from the corresponding O–Si–O and the all-carbon tethered IMDA reactions.[9] Using diene **1** also as a dienophile resulted in a mixture of only two diastereomers, **3d** and **4d** (Table 1, entry 4). In contrast, the cyclodimerization of sorbic acid (the acid corresponding to **1**) gave eight different isomers in 8–20% yields.[10]

A drawback in both procedures A and B when **2a**–**c** were used as dienophiles was the formation of cyclodimerization products **3d** and **4d** from diene **1** (10–15% in procedure A and 5–10% in procedure B). To try to clarify if this dimerization reaction depended on a rapid ligand exchange or alternatively an intermolecular reaction or both, the following experiment was performed. Two different aluminum species were preformed in two separate reaction vessels. In the first, 1 equiv of $AlMe_3$ was reacted with 2 equiv of diene **1**, and in the second 1 equiv of $AlMe_3$ was reacted with 2 equiv of dienophile **2c**, which we assume cannot react with itself. In both cases 1 equiv of a third alcohol, **5**, was added. Thereafter the two preformed aluminum alcoholates were mixed and exposed to the reaction conditions mentioned (Scheme 2). Only the dimerization products resulting from the self-cycloaddition of **1**, i.e., **3d** and **4d**, were detected. This result indicated that neither a rapid ligand exchange nor an intermolecular reaction path was likely. Thus, the cyclodimerization of **1** most likely originates from the unselective alcoholate formation in the first reaction step (Scheme 1), which to some extent produces a metal alcoholate connecting two diene molecules (**1**) to the same linker.

Scheme 2



1. mix AlX_2R and AlY_2R
2. heat at 160 °C
3. work-up

---

[9] (a) See refs 3a and 3b. (b) Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877.

[10] Haslinger, E.; Müller, A. *Liebigs Ann. Chem.* **1989**, 121.

An obvious extension of these reactions was to use an optically active third alcohol (instead of **5**) to make the reaction enantioselective. Disappointingly, when (−)-menthol or (−)-8-phenylmenthol was used as the third ligand in the reaction between **1** and **2c**, no enantiomeric excess (ee) in the products was obtained as shown by chiral-column HPLC analysis. However, application of 1 equiv of (*R*)-BINOL gave a 58% yield of an optically active 3:1 mixture of **3c** and **4c**, of which **3c** had an ee of 70%, the (+)-form dominating (Figure 1). We were not able to separate the enantiomers of **4c**. The (*R*)-BINOL was recovered in 70−75% yields.

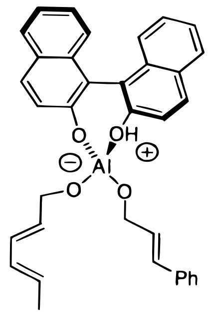


Figure 1. Hypothetical complex of the tethered Diels−Alder reaction using (*R*)-BINOL as the third ligand.

In summary, the present study shows that both $AlMe_3$ and $ZnMe_2$ can be used as linker reagents in a simple one-step procedure tethering usually nonreactive dienes and dienophiles in the IMDA reaction. Thus, in addition to increased reactivity and complete regioselectivity, considerable diastereoselectivity and enantioselectivity can be achieved.

Acknowledgment. We thank the Swedish Natural Science Research Council, The Knut and Alice Wallenberg Foundation, and The Crafoord Foundation for economic support. We also thank Ms. Vanessa Smith for performing some of the preliminary experiments and Mr. Adrian Scott Lindhurst for linguistic comments.

Supporting Information Available: General experimental procedure for the cycloaddition reactions and ^1H and ^{13}C NMR and HRMS data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0057232