Trimethylaluminum−Triflimide Complexes for the Catalysis of Highly Hindered Diels−Alder Reactions
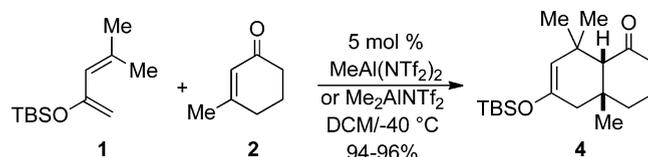
Michael E. Jung* and Mikhail Guzaev

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

jung@chem.ucla.edu

ABSTRACT

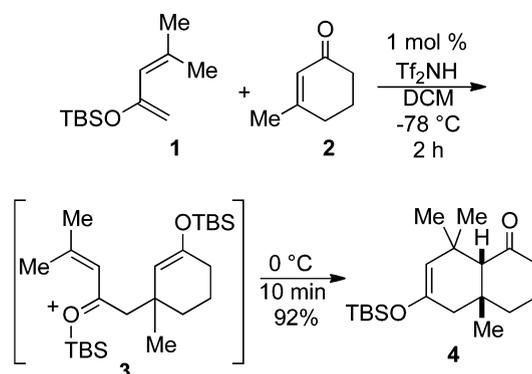Two catalysts, Me_2AlNTf_2 and $MeAl(NTf_2)_2$, derived from the mixing of trimethylaluminum with triflimide, proved to be highly effective catalysts in hindered Diels−Alder reactions, generating the desired Diels−Alder cycloadducts from both hindered 2-silyloxydienes and hindered dienophiles. Thus reaction of **1** with **2** afforded the hindered cycloadduct **4** in excellent yield in 0.5−1.5 h at −40 °C.

The Diels−Alder reaction is ubiquitous in organic synthesis.[1] In particular substituted silyloxydienes have proved very useful in this reaction.[2] We have previously found two very effective catalyst systems, namely a 5:1 mixture of aluminum tribromide ($AlBr_3$) and trimethylaluminum ($AlMe_3$) and *tert*-butyldimethylsilyl triflamide ($TBSNTf_2$), prepared in situ from triflimide (Tf_2NH) and a silyl enol ether. These have proven to be valuable and potent catalysts for more challenging transformations of this kind.[3] However, in our studies of a novel synthetic approach toward Rhodexin A, neither of these methods provided satisfactory results.[4] Yamamoto and co-workers recently reported the generation of highly active Lewis acid species through the formation of triflimide complexes of

Scheme 1. Triflimide-Catalyzed Diels−Alder Reaction

trimethylaluminum.[5] However, to the best of our knowledge these species have never been applied to the Diels−Alder reaction. We therefore wanted to explore their synthetic viability in this reaction.

We recently reported a triflimide promoted stepwise Mukaiyama−Michael vinylogous aldol addition of hindered silyloxy dienes **1** to hindered enones **2** to give formal Diels−Alder cycloadducts (Scheme 1).[3] This method allows easy synthetic access to highly hindered systems that are difficult to obtain via alternative Lewis acid catalysis or

(1) For reviews of Diels−Alder reactions, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–98. (b) Hayashi, Y. *Cycloaddit. React. Org. Synth.* **2002**, 5–55. (c) Whiting, A. *Adv. Asymmetric Synth.* **1996**, 126–145. (d) Oppolzer, W. Intermolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 4.1, pp 315–99.

(2) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406.

(3) (a) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–51. (b) Jung, M. E.; Ho, D. *Org. Lett.* **2007**, *9*, 375–78. (c) Jung, M. E.; Chu, H. V. *Org. Lett.* **2008**, *10*, 3647–49.

(4) For the synthesis of Rhodexin A, see: Jung, M. E.; Yoo, D. *Org. Lett.* **2011**, *13*, 2698–01 and references therein.

(5) (a) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178–81. (b) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127–29. (c) Brady, P. B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1942–46.

indeed by any other synthetic route. Although good yields could be obtained in many systems, transformations were complicated by considerably prolonged reaction times under AlBr$_3$–AlMe$_3$ catalysis and the tendency of triflimide catalysis to stop at the Mukaiyama–Michael intermediates, such as the enone derived by desilylation of **3**, without proceeding to the cyclized product **4**. In an attempt to improve upon these conditions, we explored the use of the potentially more highly active Lewis acid systems described by Yamamoto and co-workers and here report the results.

The reaction of the silyl enol ether **1** with 3-methyl-2-cyclohexen-1-one **2** has previously been shown to yield the desired cycloadduct **4** in 92% yield under Tf$_2$NTBS catalysis (prepared in situ from reaction of **1** with triflimide) (Table 1, entry 1).[3] We observed that Me$_2$AlNTf$_2$ (prepared by mixing Me$_3$Al with equimolar amounts of Tf$_2$NH) resulted in a marked rate acceleration of this reaction, while affording comparable yields of the cycloadduct **4**, 96% in 1.5 h (Table 1, entry 2). Use of an additional equivalent of triflimide (to generate MeAl(NTf$_2$)$_2$) provided further rate acceleration with a similar yield, 94% in 0.5 h (Table 1, entry 3). Based on these findings, we have identified Me$_2$AlNTf$_2$ and MeAl(NTf$_2$)$_2$ as potentially useful catalysts for highly hindered Diels–Alder cycloadditions. We found that a Me$_2$AlNTf$_2$ catalyst loading of 3–10% gave excellent yields. Interestingly, the

Table 1. Aluminum–Triflimide Catalysts for the Preparation of **4**
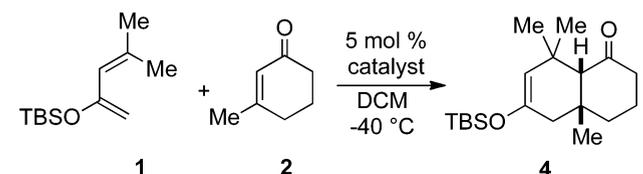
entry	catalyst	time (h)	yield (%)[a]
1	Tf$_2$NH	4	92
2	Me$_2$AlNTf$_2$	1.5	96
3	MeAl(NTf$_2$)$_2$	0.5	94
4	Al(NTf$_2$)$_3$	0.1	N/A

[a] Isolated yield based on 3-methyl-2-cyclohexen-1-one.

tris(triflimido)aluminum species, Al(NTf$_2$)$_3$,[6] did not result in constructive catalysis, creating instead a complex mixture of products (Table 1, entry 4). In addition, the use of solvents other than dichloromethane, including toluene, benzene, diethyl ether, and tetrahydrofuran, gave poorer results.[7]

Based on these results, we then proceeded to screen Me$_2$AlNTf$_2$ as a catalyst in a series of Diels–Alder cycloadditions with hindered dienes and/or dienophiles (Table 2). Initially we focused on improving the extensive

(6) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H.; Maruta, M. *Synlett* **1996**, 171–2.

(7) The catalyst system was poorly soluble in toluene and benzene, the yields decreased dramatically in diethyl ether, and THF was highly prone to polymerization under these conditions.
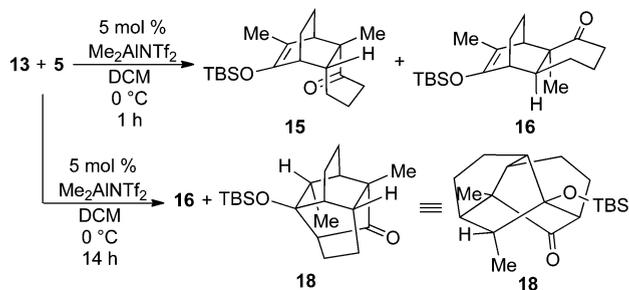
Table 2. Me$_2$AlNTf$_2$ Catalyzed Diels–Alder Cycloadditions

entry	diene	dienophile	temp (°C); time (h)	product	yield % (endo:exo)
1	**1**	**2**	0; 0.5	**4**	96
2	**1**	**5**	0; 1	**6**	71
3	**1**	**7**	0; 1	**8**	68
4	**9**	**2**	0; 2	**10n** and **10x**	99 (5:2)
5	**9**	**5**	0; 3	**11n** and **11x**	41 (1:1)
6	**9**	**7**	0; 2	**12**	56
7	**13**	**2**	0; 3	**14n** and **14x**	48 (~5:4)
8	**13**	**5**	0; 1	**15** (endo) and **16** (exo)	92 (3:2)
9	**13**	**7**	0; 1	**17**	45

reaction times and/or difficult conditions of a number of substrates that have been reacted with the mixed Lewis acid catalyst (AlBr$_3$–Me$_3$Al) or Tf$_2$NTBS. Using Me$_2$AlNTf$_2$ as the catalyst, we reacted the silyl enol ether **1** with the enone **2** to produce the desired cycloadduct **4** in excellent yield under mild conditions (0 °C, 0.5 h) (Table 2, entry 1).[8] Similarly, reaction of **1** with the enone **5** afforded the previously obtained product **6** in 71% yield, with the reaction time drastically reduced from the reported 48 h.[3b] As we had seen earlier, the double bond of the silyl enol

(8) In all cases, 1.3 equiv of the silyloxydiene were used.

Scheme 2. Formation of Twistanone **18** from **13** and **5**

Interestingly, when silyloxycyclohexadiene **13** and the enone **5** were left under the same reaction conditions, that is, Me₂AlNTf₂ in DCM at 0 °C for 14 h, we isolated, in addition to the expected exo adduct **16**, the novel twistanone **18** (Scheme 2). It is likely that this compound is formed via enolization of the cyclohexanone **15** to give an enol derivative **19** (A = H, Tf) followed by protonation of the silyl enol ether from the less hindered exo face to give the stabilized carbocation **20** and final C−C bond formation via an aldol-like reaction (Scheme 3). This finding proved helpful in elucidating the diastereoselectivity of the reaction, as this structure is geometrically accessible only via the endo Diels−Alder product **15**.

Scheme 3. Possible Mechanism for Formation of Twistanone **18**
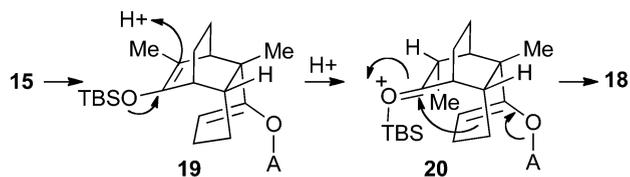
In summary, we have demonstrated the efficacy of complexes of Me₃Al in combination with Tf₂NH in catalyzing very hindered Diels−Alder reactions. The reactivity of Me₂AlNTf₂ has permitted isolation of products that are either difficult to obtain or inaccessible through conventional Tf₂NH catalysis. In addition, MeAl(NTf₂)₂ shows promise as a more powerful Lewis acid with even greater rate acceleration. Further studies on the use of these complexes in natural product synthesis are in progress.

Supporting Information Available. Experimental procedures and proton and carbon NMR for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

ether migrated easily to the allylic position and yielded exclusively the migrated product **6** (Table 2, entry 2). Likewise the reaction of **1** with the hindered enone **7** gave the desired cycloadduct **8** in good yield under much milder conditions than those previously used (Table 2, entry 2).[3b] The hindered cyclopentenyl diene system **9** also reacted well with the dienophiles **2**, **5**, and **7** under Me₂AlNTf₂ catalysis to afford the cycloadducts **10**, **11**, and **12** in fair to excellent yields (41−99%). In the first two cases, a mixture of diastereomers was obtained, 5:2 for **10nx** and 1:1 for **11nx**,[9] while in the last case the pure diastereomer was able to be separated out[10] (Table 2, entries 4−6). In order to investigate the formation of bridged polycyclic compounds, we prepared the cyclic diene, 2-trialkylsilyloxy-3-methyl-1,3-cyclohexadiene **13**, and reacted it with the same series of dienophiles. With the dienophile **2**, we obtained an approximate 5:4 mixture of the endo and exo adducts **14nx** in 48% yield, whereas the dienophile **5** gave a 3:2 mixture of endo and exo diastereomers **15** and **16** in 92% yield[9] (Table 2, entries 7−8). Finally the very hindered dienophile **7** afforded the endo adduct **17** in fair yield (Table 2, entry 9). All of the cycloadditions shown in Table 2 occurred under very mild conditions even though the products were quite hindered, thus showing the efficacy of this new catalyst system.

(9) The structures of the major and minor diastereomers have not been rigorously proven and are assigned based on mechanistic reasons.

(10) Interestingly, the reaction of **5** and **9** at 0 °C for only 1 h gave mainly the simple Mukaiyama−Michael product.[3b]