

[AlCl₃ + 2THF]: A New and Efficient Catalytic System for Diels–Alder Cycloaddition of α,β -Unsaturated Carbonyl Compounds under Solvent-Free Conditions

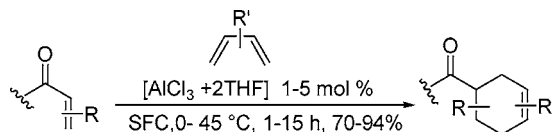
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ABSTRACT



[AlCl₃ + 2THF] is a new catalytic system for the Diels–Alder cycloaddition under SFC and air atmosphere. By using equimolar amounts of reactants, this catalyst prevents the polymerization of the diene and allows the corresponding adducts to be isolated with high regio- and stereocontrol and in excellent yields.

The Diels–Alder cycloaddition is one of the best known processes in organic chemistry and has been carried out under a variety of reaction conditions, mainly in organic solvent and in the presence of a catalyst.¹

Surprisingly, this reaction has been scarcely investigated under solvent-free conditions (SFC).¹ To our knowledge, only one example of Lewis acid-catalyzed hetero-Diels–Alder of aromatic aldehydes with the highly reactive Danishefsky's diene has been reported under SFC to date.²

It is known that a Lewis acid catalyst activates the dienophile but also favors the polymerization of the diene, and consequently, an excess of diene is generally used to achieve the complete conversion of the dienophile.³

(1) (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; John Wiley & Sons: New York, 1990. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439–457. (c) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; John Wiley & Sons: Chichester: UK, 2002. (d) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K., Eds; Wiley-VCH: Weinheim, Germany, 2002.

(2) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11.

The use of SFC is playing an important role in the development of modern and green organic synthesis.⁴ There is a growing number of examples in which the rate, the selectivity, and the yields obtained under SFC are better than those obtained in organic solvent.^{2,4,5}

In the past few years, we have been contributing in the development of organic processes in water⁶ and under SFC.⁵ According to this research and to our continuous efforts to study Diels–Alder cycloadditions,^{1a–c} we have started a

(3) Cationic polymerization of a diene is catalyzed by Lewis acids, such as AlCl₃; Elias, G.-H. *An Introduction to Polymer Science*; Wiley-VCH: Weinheim, Germany, 2005; p 73.

(4) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998. (b) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975–2978. (c) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074. (d) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198. (f) Cave, G. W. V.; Raston, C.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169. (e) Toda, F. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.

(5) For some recent examples from our group, see: (a) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 8780–8785. (b) Fringuelli, F.; Pizzo, F.; Vittorini, C.; Vaccaro, L. *Chem. Commun.* **2004**, 2586–2687. (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526–6529.

project aimed at defining a general protocol for realizing this important reaction under environmentally friendly conditions.

Considering our previous interest in the use of AlCl_3 in the Diels–Alder cycloaddition of α,β -cycloalkenones in organic solvents,^{7d} we intend to investigate this process under SFC.

Since Yates and Eaton's pioneering work in the 1960s,^{7a} AlCl_3 has been known as an efficient catalyst for the Diels–Alder cycloaddition of α,β -unsaturated carbonyl compounds,^{1,7} but in the past decade, its use has been made less frequent due to its very high acidity, which is responsible for the significant polymerization of the diene and/or the dienophile.^{7b–e}

We maintain that by lowering the Lewis acidity of AlCl_3 , while increasing the reactivity by using SFC, it is possible to avoid the polymerization of the diene and the dienophile allowing the use of stoichiometric amounts of reagents. We planned to realize the Diels–Alder cycloadditions of α,β -unsaturated esters, ketones, aldehydes, anhydrides, and amides with 1,3-butadienes by operating (a) under SFC, (b) at room temperature, and (c) with equimolar amounts of diene and dienophile that it is possible only if polymerization of the diene is avoided.

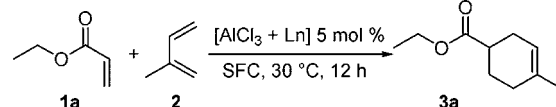
In this communication, we report the results of the Diels–Alder cycloadditions of dienes **2**, **4**, and **5** with dienophiles **1a–l** catalyzed by AlCl_3 catalysts.

We initially performed the reaction of ethyl acrylate (**1a**) with isoprene (**2**) (equimolar amounts) under SFC at 30 °C in the presence of 5 mol % of AlCl_3 . The conversion of **1a** to cycloadduct **3a** after 12 h was 80% (Table 1, entry 1). The reaction did not reach completion because 20% of isoprene (**2**) polymerized.

It is known that the catalytic ability of the Lewis acid can be strongly influenced by using ligands, such as ethers, thioethers, and amines.⁸ Therefore, to carry the AlCl_3 -catalyzed cycloaddition of **1a** and **2a** to completion, we employed tetrahydrofuran (THF), diethylene glycol (DEG), diethyl sulfide (DES), and triethylamine (TEA) as representative ligands.

Equimolar amounts of **1a** and **2** were added at 30 °C to 5 mol % of a 1:2 mixture of AlCl_3 and THF ($[\text{AlCl}_3 + 2\text{THF}]$) under air atmosphere. After 12 h, the adduct **3a** was formed in a 95:5 *para:meta* ratio, and it was isolated in an almost quantitative yield (Table 1, entry 3). When the reaction was carried out with 5 mol % of $[\text{AlCl}_3 + 1\text{THF}]$, no positive effect was detected (Table 1, entry 2). By using a combina-

Table 1. $[\text{AlCl}_3 + 2\text{THF}]$ -Catalyzed Diels–Alder Reaction of Ethyl Acrylate (**1a**) with Isoprene (**2**) under SFC at 30 °C



| entry | catalyst | C ^a (%) | polymerization (%) ^b |
|-------|---------------------------------|--------------------|---------------------------------|
| 1 | AlCl_3 | 80 | 20 |
| 2 | $[\text{AlCl}_3 + 1\text{THF}]$ | 83 | 17 |
| 3 | $[\text{AlCl}_3 + 2\text{THF}]$ | >99 ^c | – |
| 4 | $[\text{AlCl}_3 + 3\text{THF}]$ | 70 | – |
| 5 | $[\text{AlCl}_3 + 4\text{THF}]$ | 37 | – |
| 6 | AlCl_3 in THF | – | – |
| 7 | $[\text{AlCl}_3 + 1\text{DEG}]$ | 20 | – |
| 8 | $[\text{AlCl}_3 + 2\text{DES}]$ | – | – |
| 9 | $[\text{AlCl}_3 + 2\text{TEA}]$ | – | – |

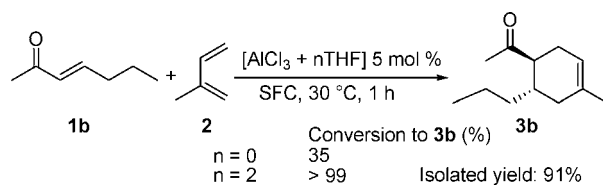
^a C = Conversion (determined by ¹H NMR analysis). ^b Polymerization was evaluated by ¹H NMR analysis by using *p*-nitroanisole as internal standard. ^c Isolation yield = 92%.

tion of AlCl_3 and 3 or 4 equiv of THF, the process was significantly slower (Table 1, entries 4 and 5). Expectedly, when THF was used as reaction medium, adduct **3a** was not detected at all (Table 1, entry 6).

The catalytic activity of AlCl_3 was reduced in the presence of 1 equiv of DEG, while it was completely depressed by 2 equiv of DES or TEA (Table 1, entries 7–9).

The effect of THF in the AlCl_3 -catalyzed reaction of equimolar amounts of 3-hepten-2-one (**1b**) with isoprene (**2**) is even more evident (Scheme 1). In fact, in the absence of

Scheme 1. $[\text{AlCl}_3 + 2\text{THF}]$ -Catalyzed Cycloadditions of 3-Hepten-2-one (**1b**) with Isoprene (**2**) under SFC at 30 °C



THF, only 35% conversion was reached after 1 h and the polymerization of **2** was mainly obtained, while a complete conversion to **3b** was accomplished in the presence of 2 equiv of THF.

$\text{AlCl}_3 \cdot \text{THF}^{\text{9a}}$ and $\text{AlCl}_3 \cdot 2\text{THF}^{\text{9b}}$ are known complexes. We have not identified the actual catalytic species acting in the reactions of **1a** and **1b** with **2**, and therefore, we refer to a catalytic system identified as $[\text{AlCl}_3 + 2\text{THF}]$, indicating that we have used AlCl_3 and THF in a 1:2 molar ratio.

The catalytic efficiency of $[\text{AlCl}_3 + 2\text{THF}]$ was confirmed in the cycloadditions of **1a** with 1,3-dienes **4** and **5** (Scheme

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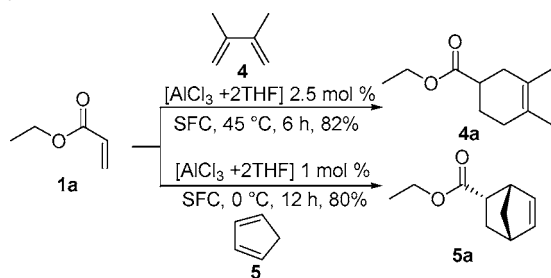
(6) For recent papers, see: (a) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041–7045. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263–9268. (c) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Org. Lett.* **2005**, *7*, 4411–4414.

(7) (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437. (b) Inumai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 1121–1123. (c) Inumai, T.; Kojima, T. *J. Org. Chem.* **1970**, *35*, 1342–1348. (d) Fringuelli, F.; Guo, M.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 710–712 (part 16). (e) Bueno, M. P.; Cativiela, C. A.; Mayoral, J. A. *J. Org. Chem.* **1991**, *56*, 6551–6555. (f) Shing, T. K. M.; Lo, H. Y.; Mak, T. C. W. *Tetrahedron* **1999**, *55*, 4643–4648. (g) Yin, D.; Yin, D.; Fu, Z.; Li, Q. *J. Mol. Catal. A* **1999**, *148*, 87–95.

(8) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 1999.

2). In the presence of 2.5 or 5 mol % of $[\text{AlCl}_3 + 2\text{THF}]$,

Scheme 2. $[\text{AlCl}_3 + 2\text{THF}]$ -Catalyzed Diels–Alder Cycloadditions of **1a** with 1,3-Butadienes **4** and **5** at 30 °C



and by using equimolar amounts of reagents, the cycloadducts **4a** and **5a** were isolated in 82 and 80% yields, respectively. The stereoselectivity was high in the case of cyclopentadiene (**5**) where the adduct **5a** was formed in a 5:95 *exo/endo* ratio.

The $[\text{AlCl}_3 + 2\text{THF}]$ -catalyzed protocol was then extended to the cycloadditions of **1c–l** with isoprene (**2**) (Table 2).¹⁰ The results were in all cases excellent, and the polymerization of the diene was always avoided. The regiochemistry of the reactions was exclusively *para*, except in the case of crotonaldehyde (**1h**), which was converted to adduct **3h** in a 4:1 *para/meta* ratio.

The reaction of **1k** with **2** was also performed on a 50 mmol scale, and similarly, to the 1.0 mmol scale, product **3k** was isolated in 93% yield. The reaction was exothermic, and a careful control of temperature (ice bath) together with the use of a mechanical stirrer was necessary for achieving the best results.

To understand the precise role of THF, further studies are necessary. We hypothesize that $[\text{AlCl}_3 + 2\text{THF}]$ possesses a lower acidic character compared to AlCl_3 , being still able to activate the dienophile via oxygen complexation but not to react with the diene and to induce the polymerization. The use of THF as a solvent, obviously preventing the complexation, depresses both polymerization and cycloaddition.

In conclusion, in the reactions of **1a–l** with **2**, **4**, and **5**, we have shown that the use of SFC and $[\text{AlCl}_3 + 2\text{THF}]$ allowed the corresponding cycloadducts to be isolated in high yields. It is noteworthy that by this approach the diene's polymerization is avoided, allowing equimolar amounts of reagents to be used. The combination of SFC and an adequate catalyst is a promising approach for improving both the chemical and the environmental efficiency of the Diels–Alder reaction.

(10) Typical procedure for the $[\text{AlCl}_3 + 2\text{THF}]$ -catalyzed reaction of **1a** with **2** under SFC: a screw-capped vial equipped with a magnetic stirrer was charged with 0.05 mmol (0.0066 g) of AlCl_3 and 0.10 mmol (0.0072 g) of THF. After 15 min, ethyl acrylate (**1a**) (1.0 mmol, 0.1002 g) and, after additional 15 min, isoprene (**2**) (1.0 mmol, 0.068 g) were added, and the mixture was left under stirring at 30 °C for 12 h. The final reaction mixture was purified by silica gel column chromatography (EtOAc/petroleum ether, 5/95 gradient), and cycloadduct **3a** was isolated in 92% yield (0.154 g).

Table 2. $[\text{AlCl}_3 + 2\text{THF}]$ -Catalyzed Diels–Alder Reactions of Dienophiles **1c–l** with Isoprene (**2**)¹⁰

| dienophile | <i>t</i> (h) | adduct | yield (%) ^a |
|------------|--------------|--------|------------------------|
| | 15 | | 92 ^b |
| | 1.5 | | 92 |
| | 6 | | 90 |
| | 24 | | 80 ^c |
| | 2.5 | | 91 ^{b,d} |
| | 5 | | 75 ^e |
| | 2 | | 70 |
| | 1 | | 94 |
| | 2.5 | | 94 |
| | 2 | | 93 |

^a Isolated yield. ^b With 1 mol % of catalyst. ^c With 2 equiv of isoprene (**2**). ^d Performed at 0 °C. ^e 4:1 *para/meta* ratio.

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Supporting Information Available: General experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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