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Fluorous Dienophiles Are Powerful Diene Scavengers in Diels–Alder Reactions[†]

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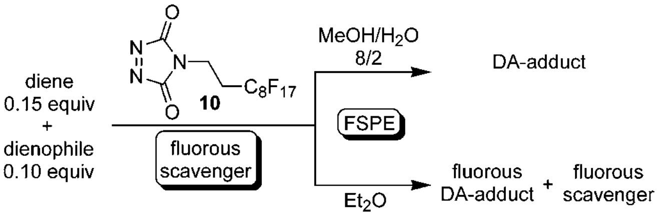
ABSTRACT



Three fluorous dienophiles have been synthesized, and their value in scavenging an excess diene after Diels–Alder reactions is shown. The resulting fluorous derivatives are separated by solid-phase extraction on fluorous silica gel (FSPE). The fluorous [1,2,4]triazoline-3,5-dione 10 reacted with most dienes within seconds or minutes.

Scavenging methods for removing excess reactants or reagents are increasingly popular, especially in solution-phase parallel synthesis. Many polymer-bound scavengers are now available;[1] however, large excesses are typically used, scavenging times can be long, and solvent use is sometimes limited by polymer swelling characteristics.

A series of recent papers suggests that fluorous scavengers typically do their job rapidly in solution, and large excesses are not needed.[2] After the reaction, the separation of target products from scavenged products and excess scavenger is readily accomplished by a fluorous solid-phase extraction (FSPE).[3] Fluorous compounds are retained on fluorous silica gel on a first-pass elution with MeOH/water, while the target non-fluorous compounds are not. A second-pass elution with diethyl ether then gives the fluorous compounds.

Current fluorous scavengers are mostly electrophiles or nucleophiles.[2] We present here the first fluorous dienophiles and validate their utility as diene scavengers. Target adducts and scavenged products are separated by FSPE.

We made three reactive fluorous dienophiles by the reactions summarized in Scheme 1. Using Toru's procedure[4] afforded the benzylmaleimide **4** and the phenylmaleimide **5** in 83 and 76% yields, respectively, starting from maleic anhydride **1** and commercially available fluorous amines **2** and **3**.[5] *N*-Phenyl maleimide **5** has no spacer and bears a shorter C_6F_{13} tag, while *N*-benzylmaleimide **4** has an ethylene spacer and a longer C_8F_{17} tag.

[1,2,4]Triazoline-3,5-diones are very reactive dienophiles, so we used Cookson's procedure[6] to make fluorous [1,2,4]-

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[†] Dedicated to Prof. Shuji Kanemasa on the occasion of his 60th birthday.

(1) (a) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18−26. (b) Parlow, J. J.; Devraj, R. V.; South, M, S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336. (c) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324−337. (d) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (e) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213−1224.

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(5) Commercially available from Fluorous Technologies, Inc., http://www.fluorous.com. DPC holds an equity interest in this company.

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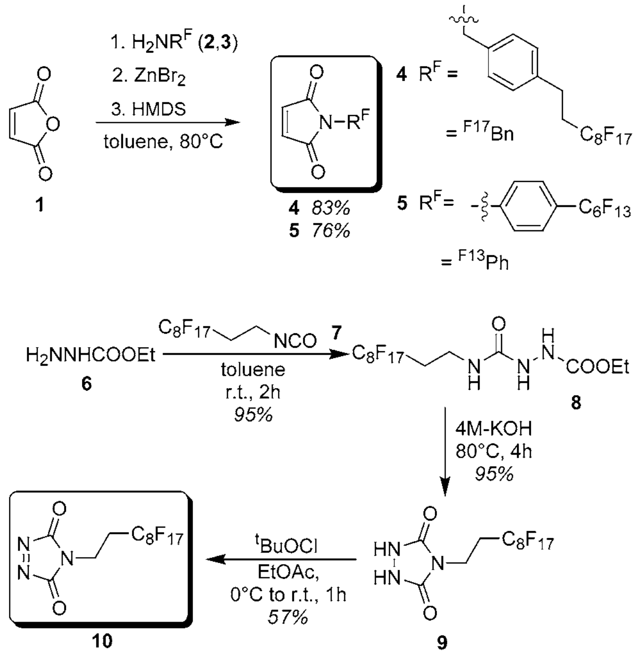
Scheme 1. Synthesis of Fluorous Dienophiles **4**, **5**, and **10**



triazoline-3,5-dione **10** from ethyl hydrazinecarboxylate **6** and the commercially available fluorous isocyanate **7**.[5] Ring closure of **8** with KOH and oxidation of **9** with ^{t}BuOCl[7] gave **10** in an overall yield of 51%. Triazoline dione **10** is a beautiful pink solid that was purified by sublimation. It decomposes on silica gel, allowing easy separation of Diels–Alder adducts from **10**.

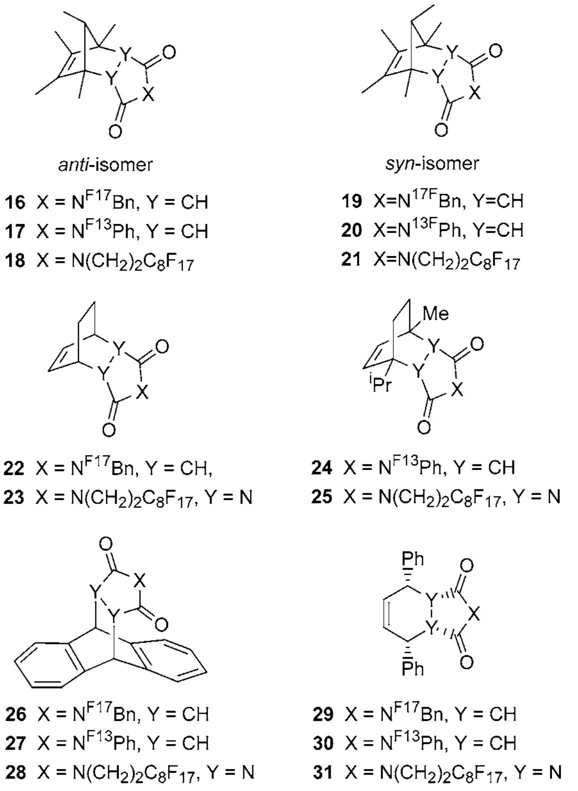


Figure 1. Structures **16**–**31**.

Next, we explored the reactivity of the three dienophiles in Diels–Alder reactions with 1,2,3,4,5-pentamethylcyclopentadiene (PMCP,**11**), cyclohexadiene (CHD, **12**), α-terpinene (TP, **13**), anthracene (ANT, **14**), and 1,4-diphenyl-1,3-butadiene (DPBD, **15**). The structures of the products obtained are shown in Figure 1, while the results are summarized in Table 1. We obtained the fluorous Diels–

Table 1. Diels–Alder Reactions of the Fluorous Dienophiles **4**, **5**, and **10**

entry	diene	fluorous dienophile	DA adduct	reaction conditions[a]	isomer ratio[b] (anti/syn)	isolated yield[c] (%)	retention time[d] (min)
1	PMCP**11**	**4**	**16** + **19**	DCM, 30 min, rt	83/17	68[e]	65.0 + 70.7
2	PMCP**11**	**5**	**17** + **20**	DCM, 30 min, rt	82/18	68[e]	13.4 + 14.3
3	PMCP**11**	**10**	**18** + **21**	THF, 1 s, rt	70/30	52[e]	31.2 + 33.3
4	CHD **12**	**4**	**22**	DCE, 2 day, 60 °C		96	26.0
5	CHD **12**	**10**	**23**	DCM, 1 s, rt		87	13.8
6	TP**13**	**5**	**24**	DCE, 1 day, 110 °C		73	14.9
7	TP**13**	**10**	**25**	DCM, 1 s, rt		87	25.1
8	ANT**14**	**4**	**26**	toluene, 1 day, 120 °C		93	26.0
9	ANT**14**	**5**	**27**	toluene, 1 day, 120 °C		85	8.5
10	ANT**14**	**10**	**28**	THF, 2 h, rt		69	14.8
11	DPBD**15**	**4**	**29**	toluene, 2 day, 155 °C		55	30.5
12	DPBD**15**	**5**	**30**	toluene, 2 day, 155 °C		66	9.3
13	DPBD**15**	**10**	**31**	THF, 20 min, rt		75	15.2
14		**4**[f]					24.7
15		**5**[f]					7.9

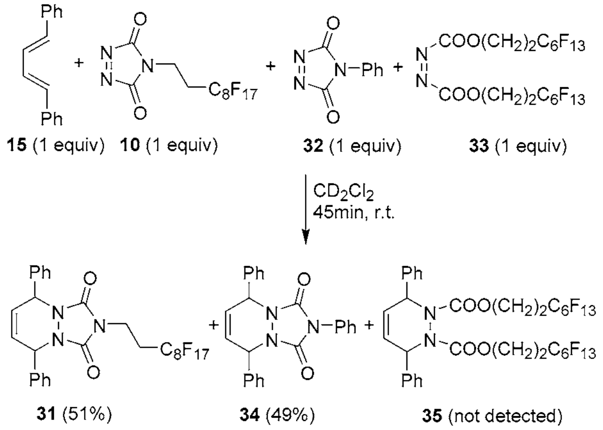
[a] Heated reactions were carried out in a pressure tube under 2 atm argon; DCM is dichloromethane; DCE is 1,2-dichloroethane. [b] By ^{1}H NMR integration. [c] After column chromatography. [d] Retention times of the Diels–Alder adducts using a FTI PF–C8 HPLC/LC column (150 × 4.6 mm) on a HP 1100 series MSD LC-MS system with UV-detection at 231 nm, elution with MeCN/H_2O 80/20, flow rate 1 mL/min; no retention time for **10** was available because of decomposition on silica gel. [e] After F-HPLC separation. [f] Retention times of dienophiles.

Alder adducts **16**−**31** in 52−96% yields. The Diels−Alder adducts **16**−**21** were obtained in about the same anti/syn ratios as the corresponding non-fluorous adducts.[8] Although the anti and the syn isomers **16**/**19**, **17**/**20**, and **18**/**21** have the same fluorous tag, they were easily separated on a semipreparative Fluoro*Flash* HPLC column.[9] In contrast, separation on a reverse-phase HPLC column[10] or on flash-grade silica gel was not possible.

Comparison of reaction times in Table 1 shows that the fluorous maleimides **4** and **5** have a similar reactivity, but that the fluorous [1,2,4]triazoline-3,5-dione **10** is much more reactive. Kinetic studies showed that **10** is at least 1000 times more reactive toward DPBD **15** than **4** or **5**.

We calibrated the reactivity of **10** against that of 4-phenyl-[1,2,4]triazoline-3,5-dione (**32**), which is one of the most reactive dienophiles known. These results are shown in Scheme 2.

Scheme 2. Competition Experiment between **10**, **32**, and **33**



Equimolar amounts of **10**, **32**, and ^{F}DEAD **33**[5,11] were allowed to compete for a deficiency of the diene **15** (0.33 equiv) in CD_2Cl_2 at rt. After 45 min, ^1H NMR analysis showed that diene **15** was consumed and **31** and **34** were present in a 51/49 ratio; **35** was not detected. This shows that **10** and **32** have similar reactivities and both are in turn much more reactive than **33**.

The last column of Table 1 also collects the retention times of all the adducts on a Fluoro*Flash* HPLC column eluting with 80/20 MeOH/water. Non-fluorous-tagged compounds elute at or near the solvent front under these conditions. The Diels−Alder adducts from **5** with the C_6F_{13}-tag showed shorter retention times than those from **4** and **10** with the C_8F_{17}-tag. Adducts from the more polar **10** eluted prior to adducts from **4** (compare entries 1/3, 4/5, etc.), even though all these adducts have C_8F_{17} tags. All Diels−Alder adducts from **4** and **5** had longer retention times than the corresponding polar dienophiles themselves (entries 14, 15). Small, nonpolar organic domains in the Diels−Alder adduct produced longer retention times than larger, more polar domains (compare **16**/**19** in entry 1 with **26** in entry 8, for example).

We used a standard protocol to compare fluorous dienophiles **4**, **5**, and **10** in typical scavenging reactions (Figure 2). An excess of a diene (0.15 mmol) was reacted with 0.10 mmol of maleic anhydride (MA, **1**), *N*-phenylmaleimide (PMI, **36**), or DMAD (**37**), respectively. When TLC analysis showed that the diene was consumed, a fluorous scavenger **4**, **5**, or **10** was added. Separation was done by FSPE on 5 g Fluoro*Flash* cartridges[5] eluting with MeOH/H_2O 8/2.

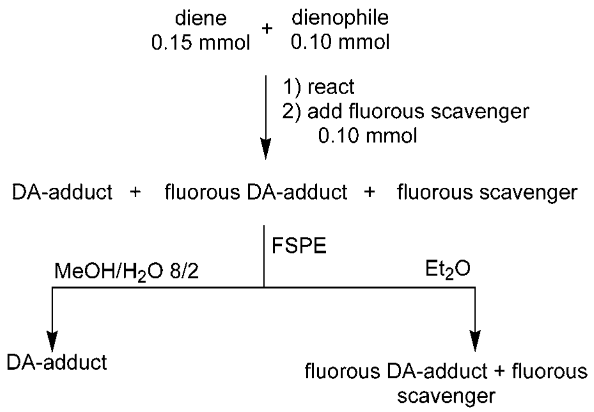


Figure 2. Standard Procedure for the Scavenging Reactions.

The results of a series of scavenging experiments are summarized in Table 2. After FSPE, the Diels−Alder adducts were isolated in 77−99% yield and in 84−97% purity. These adducts were analyzed by GC and their ^1H NMR spectra, which were consistent with literature data.[12,13] A second elution with diethyl ether provided the excess of the scavengers **4** and **5** and the corresponding fluorous Diels−Alder adducts, which had been previously prepared (Table 1). The excess of **10** decomposed on the fluorous silica gel, in those cases (Table 2, entries 4, 6, and 11) the diethyl ether elution gave pure compounds **18**/**21** or **28**. The anthracene/maleic anhydride adducts decomposed selectively in a methanolysis reaction to give the half-methyl ester (not shown; see Supporting Information) during the FSPE (entries 7 and 11). This problem was solved by using a MeCN/H_2O mixture for elution during FSPE instead of MeOH/H_2O. MeCN/H_2O in an 8/2 ratio was used for the C_8F_{17}-tagged scavenger **4** (entries 8 and 14), while for the C_6F_{13}-tagged scavenger **5**, the ratio was 6/4 (entries 9 and 10).

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(9) Fluoro*Flash* HPLC column (FTI), 20 × 250 mm.

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(13) Compounds **39**, **40**, **46**, and **47** were separately synthesized and characterized.

Table 2. Use of the Fluorous Dienophiles **4**, **5**, and **10** in Scavenging Excess Diene after a Diels−Alder Reaction[a]

entry	diene	dienophile	scavenger	DA adduct[b]	reaction conditions[c]	solvent for FSPE elution	yield (%)[d]	purity[e] (%)
1	PMCP**11**	MA**1**	**4**	**39** + **40**	DCM, 2 × 30 min, rt	MeOH/H_2O 8/2[f]	84	89
2	PMCP**11**	PMI**36**	**4**	**41** + **42**	DCM, 2 × 30 min, rt	MeOH/H_2O 8/2[f]	89	95
3	PMCP**11**	PMI**36**	**5**	**41** + **42**	DCM, 2 × 30 min, rt	MeOH/H_2O 8/2	97	91
4	PMCP**11**	PMI**36**	**10**	**41** + **42**	DCM, 30 min, rt; 1 s, rt	MeOH/H_2O 8/2	97	91
5	PMCP**11**	DMAD**37**	**4**	**43** + **44**	DCM, 2 × 30 min, rt	MeOH/H_2O 8/2	99	95
6	PMCP**11**	DMAD**37**	**10**	**43** + **44**	DCM, 30 min, rt; 1 s, rt	MeOH/H_2O 8/2	97	97
7	ANT**14**	MA**1**	**4**	**45**	toluene, 2 × 1 day, 120 °C	MeOH/H_2O 8/2	99	methanolysis[g]
8	ANT**14**	MA **1**	**4**	**45**	toluene, 2 × 1 day, 120 °C	MeCN/H_2O 8/2	93	96
9	ANT**14**	MA**1**	**5**	**45**	toluene, 2 × 1 day, 120 °C	MeCN/H_2O 8/2	-	47
10	ANT**14**	MA**1**	**5**	**45**	toluene, 2 × 1 day, 120 °C	MeCN/H_2O 6/4	82	97
11	ANT**14**	MA**1**	**10**	**45**	toluene, 1 day, 120 °C; 5 min, 70 °C	MeOH/H_2O 8/2	81	methanolysis[g]
12	ANT**14**	PMI**36**	**4**	**46**	toluene, 2 × 1 day, 120 °C	MeOH/H_2O 8/2[f]	81[h]	84
13	DPBD **15**	DMAD**37**	**4**	**47**	toluene, 6 h, 155 °C; 12 h 155 °C	MeOH/H_2O 8/2	77	96
14	ANT**14**	MA**1**	**4**	**45**	MW[i]: neat, 2 × 10 min, 160 °C	MeCN/H_2O 8/2	83	93
15	DPBD**15**	MA**1**	**5**	**48**	MW[i]: neat, 2 × 10 min, 160 °C	MeCN/H_2O 6/4	79	90

[a] Standard procedure: 0.15 mmol of the diene was allowed to react with 0.10 mmol of the dienophile. After the reaction was complete, 0.10 mmol of the fluorous scavenger was added. After the scavenging reaction was complete, the solvent was evaporated and the crude mixture was loaded in 0.6 mL of THF onto a 5 g Fluoro*Flash* cartridge[5] that had been preconditioned with MeOH/H_2O or MeCN/H_2O. The cartridge was eluted with 4 × 8 mL of the mentioned solvent mixture to give the non-fluorous Diels−Alder adducts, followed by elution with 2 × 8 mL of diethyl ether to give the excess of the fluorous scavenger and the scavenger adducts. [b] Non-fluorous Diels−Alder adduct from the mentioned diene and dienophile; structures not shown. [c] Reaction conditions for Diels−Alder reaction; reaction conditions for scavenging reaction. [d] After FSPE workup. [e] By GC analysis. [f] Purification by a 2 g Fluoro*Flash* cartridge is possible. [g] Only the Diels−Alder adduct and the corresponding methanolysis adduct could be detected by ^{1}H NMR. [h] Further elution is necessary. [i] CEM Microwave Reactor SP-1188 (ramp time, 1 min; power, 300 W).

We tested two scavengers in Diels−Alder reactions under microwave conditions.[14] The reactions of the dienes **14** and **15** with maleic anhydride were complete after 10 min of irradiation in a microwave reactor at 160 °C under solvent-free conditions. Under the same conditions, the scavengers **4** and **5** reacted with the excess diene, and the Diels−Alder adducts were obtained after FSPE in 79−83% yield and with a purity of 90−93% (entries 14 and 15).

The intense pink color of **10** allows scavenging reactions with reactive dienes to be conducted as titrations. For example, a solution of **10** in dichloromethane was used to scavenge an excess of PCMP **11** after reaction with DMAD (Figure 3). On dropwise addition of the pink solution of **10** to the reaction mixture, the color persisted only after all the excess PCMP **11** had reacted. The endpoint was readily detected even with dilute 0.005 M solutions **10**. For suitably reactive dienes, this titration method bypasses the need to use excess scavenger to ensure complete diene consumption.

Figure 3. Use of the scavenger **10** in a Diels−Alder titration experiment, scavenging an excess of **11** after a Diels−Alder reaction with DMAD: left, 0.005 M solution in CH_2Cl_2; middle, before equivalence point; right, at equivalence point.

In summary, we have synthesized three fluorous dienophiles and proved their usefulness as diene scavengers. The fluorous [1,2,4]triazoline-3,5-dione **10** shows superior reactivity, and its pink color allows convenient titrations in some cases. Triazoline diones are also reactive in ene and other reactions, so the scavenging ability of **10** extends beyond Diels−Alder reactions.

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Supporting Information Available: Procedures for dienophile synthesis and reactions, spectroscopic and analytical data for compounds **4**, **5**, **8**−**10**, **16**−**31**, **38**−**40**, **46**, and **47**, and descriptions of the reactivity studies, the competition experiment, and the titration experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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