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Tetramethyleneethane Equivalents: Recursive Reagents for Serialized Cycloadditions

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ABSTRACT: New reactions and reagents that allow for multiple bond-forming events per synthetic operation are required to achieve structural complexity and thus value with step-, time-, cost- and waste-economy. Here we report a new class of reagents that function like tetramethyleneethane (TME), allowing for back-to-back [4+2] cycloadditions, thereby amplifying the complexity-increasing benefits of Diels-Alder and metal-catalyzed cycloadditions. The parent recursive reagent, DMTB (2,3-dimethylene-4-trimethylsilylbutan-1-ol), is readily available from the metathesis of ethylene and THP-protected 4-trimethylsilylbutyn-1-ol. DMTB and related reagents engage diverse dienophiles in an initial Diels-Alder or metal-catalyzed [4+2] cycloaddition, triggering a subsequent vinylogous Peterson elimination that recursively generates a new diene for a second cycloaddition. Overall, this multi-component catalytic cascade produces in one operation carbo- and hetero-bicyclic building blocks for the synthesis of a variety of natural products, therapeutic leads, imaging agents, and materials. Its application to the three step synthesis of a new solvatochromic fluorophore, 6-DMA (*N*-ethyl(6-*N,N*-dimethylaminoanthracene-2,3-dicarboximide)), and the photophysical characterization of this fluorophore, are described.

Introduction

The success of a synthesis is generally measured in terms of cost, time, yield, waste, and length; metrics influenced to varying degrees, but mainly, by step economy.¹ In general, synthetic strategies with the greatest number of target relevant bond forming events per synthetic operation are the most step economical.² However, most reactions, including the venerable Diels-Alder cycloaddition, form at most only two new bonds per operation. To achieve greater step economy in accessing targets of value, new reactions, reagents, and strategies that would increase this bonds-per-operation count are required. Nature's solution to this problem is instructive, often taking the form of recursive reactions in which a single bond forming event is serially repeated. Biosynthetic cation-alkene cyclizations^{3,4} are quintessential examples of how complexity is amplified through such recursive processes. Given the exceptional synthetic utility of the Diels-Alder and related metal-catalyzed [4+2] cycloadditions, we wondered whether they could be deployed recursively in a diene-based cycloaddition that regenerates another diene.^{5,6} This intriguing 4-bond disconnection strategy to bicyclo[4.4.0]ring systems – a common feature in natural products,⁷ materials,⁸ imaging agents^{9,10}, and potentially oligomeric acenes – leads conceptually to the tetramethyleneethane diradical (TME) as a key species capable of

connecting back-to-back cycloadditions (Figure 1).

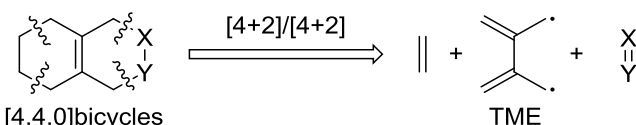


Figure 1. Retrosynthetic analysis of [4.4.0]bicycles into two dienophiles and the tetramethyleneethane (TME) diradical

However, as shown in a brilliant series of studies by Dowd, TME itself has a half-life of only 20 minutes at -196 °C and preparations of its precursors can be lengthy.¹¹ Predating these studies, Alder and Ackermann serendipitously uncovered a TME equivalent, reporting that allene and maleic anhydride when heated in a “Bombenrohr” for 3 days at 175 °C produce an octahydronaphthalene product in 16% yield, putatively through the formation and reaction of 1,2-bis-methylenecyclobutane (BMCB).¹² Unfortunately, the volatility and reactivity of BMCB limits its use in recursive processes. Other creative concepts for diene-generating diene cycloadditions have since been reported; however, these involve multistep sequences, harsh conditions, or volatile or difficult to access reactants that limit utility.^{12–23} Here we report the design and development of a versatile TME equivalent, DMTB (2,3-dimethylene-4-trimethylsilylbutan-1-ol: **1**), that is readily prepared and safely handled on scale. This TME

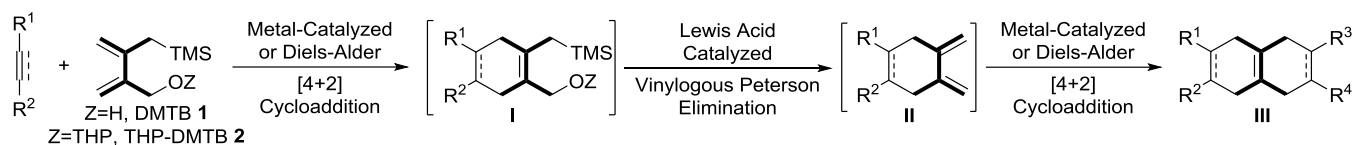


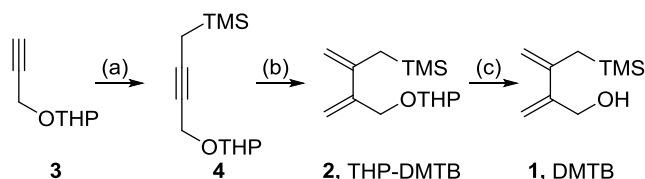
Figure 2. DMTB and THP-DMTB: tetramethyleneethane equivalents for recursive cycloadditions.

equivalent efficiently engages dienophiles in an initial Diels-Alder or metal-catalyzed [4+2] cycloaddition, which then allows for a catalyzed vinylogous Peterson elimination²⁴ to produce a second diene captured in a subsequent [4+2] cycloaddition (Figure 2). A single dienophile can be used in both cycloadditions to produce 2:1 products or different dienophiles can be deployed to produce 1:1:1 bicyclic products. Thus, in one synthetic operation, this three component process involving as many as three catalytic cycles efficiently produces four new bonds and a carb- or hetero[4.4.0]bicyclic product, a core subunit found in many synthetic targets, and here applied to the synthesis of a new solvatochromic imaging agent with excellent photophysical properties for biological applications.^{9,10}

Results and Discussion

The synthesis of our parent TME reagent (Scheme 1: DMTB, **1**) uses a strategy that would be generally applicable to the synthesis of many related reagents. Commercially available alkyne **3** is first alkylated using a previously published procedure²⁵ and the resulting alkyne **4** is converted to THP-DMTB (**2**) through an enyne metathesis conducted under one atmosphere of ethylene gas using Grubbs' Second Generation catalyst. While previous studies have used higher catalyst loadings and elevated temperatures for similar substrates,^{26,27} the conditions employed here for the synthesis of THP-DMTB (**2**) are unexpectedly efficient and can be conducted on a multi-gram scale. The hydrolysis of THP-DMTB (**2**) to the desired alcohol **1** was accomplished with boric acid in refluxing ethanol which gave DMTB in 70% yield with a minor amount (6 %) of the protodesilylated alcohol product.²⁸ DMTB can be prepared on gram-scale and is readily purified by column chromatography. It is an air-stable liquid and can be stored at -20 °C for months. In practice, the THP-DMTB is an effective storage point and can be used as a TME equivalent on its own or converted as needed to DMTB.

Scheme 1. A simple, scalable synthesis of tetramethyleneethane equivalents, DMTB and THP-DMTB^a



^a(a)i. *n*-BuLi, ii. TMSCH₂I, THF, 90%; (b) Grubbs II, 1 atm ethylene, DCM, RT, 16 h, 95%; (c) B(OH)₃, EtOH, reflux, 1 h, 70%

To investigate whether DMTB would serve as a TME equivalent capable of connecting back-to-back cycloadditions, we combined it with an excess of *N*-phenylmaleimide in 1,2-dichloroethane (Figure 3). After 4 hours, cycloadduct **5** formed cleanly, and was transformed to diene **6** upon addition of [(naph)Rh(COD)]SbF₆.²⁹ Over the course of 2 days at room temperature, diene **6** was converted to the 2:1 cycloadduct **7** in 96% overall yield (dr 8:1 favoring the cis-anti-cis isomer, See Supplementary Information). To determine whether other conditions would effect the intervening Peterson 1,4-elimination,^{30,31} cycloadduct **5**, obtained in 98% yield from the reaction of DMTB with *N*-phenylmaleimide, was used as a test substrate (Table 1). Both protic and Lewis acid catalysts were found to work well, leading, in the preferred cases, to rapid (<3 hours) and efficient (>90%) conversion to diene **6** even at room temperature.

Scheme 2. DMTB (**1**) functions as a TME equivalent in single-flask operations under a variety of conditions.

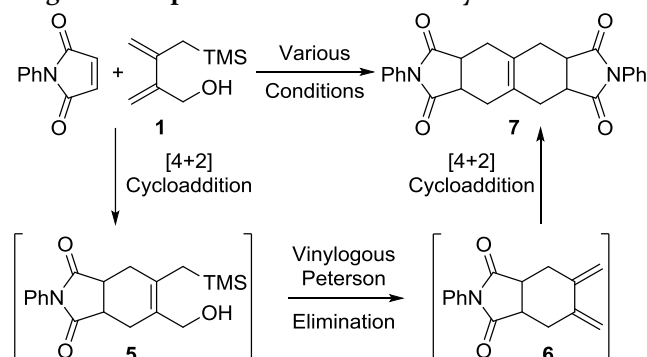


Table 1. Conditions for the elimination of **5** to **6**

Entry	Catalyst	mol%	Solvent	[5] (M)	T (°C)	Time (h)	Yield (%)
1	-	-	toluene	0.25	111	>24	- ^a
2	HCl	200	ethanol	0.1	40	1	92
3	ZnCl ₂	25	THF	0.1	23	>48	- ^b
4	ZnCl ₂	5	DCE	0.1	60	0.33	95
5	AlCl ₃	25	THF	0.1	RT	2.25	99
6	FeCl ₃	25	THF	0.1	RT	5	94
7	Rh(I)	3	DCE	0.5	RT	>48	92
8	Rh(I)	3	THF	0.25	RT	>72	- ^b
9	Rh(I)	3	THF	0.25	66	4	90
10	Rh(I)	1.5	acetone	0.5	56	1.25	98
11	Rh(I)	1	acetone	1.0	56	<1.25	98

All reactions in the table above were monitored by TLC analysis for consumption of the cycloadduct **5**. ^aComplex mixture formed. ^bNo conversion observed by TLC analysis.

Table 2. Summary of one-flask [4+2]/elimination/[4+2] reactions using tetramethyleneethane equivalents DMTB and THP-DMTB.

Diels-Alder / Lewis Acid Adducts ^a				Diels-Alder / Rhodium(I) Adducts ^a				Diels-Alder / Rhodium(I) Adducts Continued ^a			
Product	Catalyst (%)	Time ^b	Yield	Product	Catalyst (%) ^f	Time ^b	Yield	Product	Catalyst (%) ^f	Time ^b	Yield
7	AlCl ₃ (40)	1.6 h	97% ^c	13a	Rh(I) (5)	23 h	83%	14	Rh(I) (5)	11 h	92%
8	ZnCl ₂ (10)	16 h	95%	13b	Rh(I) (5)	21 h ^g	70%	15	Rh(I) (5)	11 h	99%
9^d	AlCl ₃ (25)	3 h	78%	13c	Rh(I) (5)	42 h	85%	16a	Rh(I) (5)	28 h	83%
9^e	AlCl ₃ (100)	16 h	73%	13d	Rh(I) (5)	24 h	86%	16b	Rh(I) (5)	28 h	79%
10	ZnCl ₂ (10)	6.25 h	72%	13e	Rh(I) (5)	39 h	83%	16c	Rh(I) (5)	28 h	76%
11	ZnCl ₂ (10)	22 h	62%	13f	Rh(I) (5)	23 h	78% ^h	16d	Rh(I) (5)	28 h	79%
12	ZnCl ₂ (10)	2.25 h	92%	13g	Rh(I) (5)	25 h	85%	16e	Rh(I) (5)	28 h	80%
				13h	Rh(I) (5)	21 h ^g	81%	17	Rh(I) (5)	24 h	79%

All reactions were performed in oven dried glassware using pure reagents. All reported yields are of pure isolated products. ^aZ=H. ^bTime reflects the full reaction time for all three steps. See Supplementary Information for detailed conditions. ^cProduct is a 15:1 mixture of diastereomers favoring the cis-anti-cis. See Supplementary Information. ^d*N*-phenylmaleimide used as first dienophile. ^eDimethylfumarate used as first dienophile. ^fRh(I) catalyst used was [(naph)Rh(COD)]SbF₆ in all cases. ^gSecond [4+2] cycloaddition was run at 50 °C. ^hProcedure was slightly different from other entries. See Supplementary Information. ⁱZ=THP.

The diverse and effective conditions for the vinylogous Peterson elimination make possible a range of one-operation cycloaddition/elimination/cycloaddition options, including consecutive Diels-Alder or metal-catalyzed processes or a mixture of the two with the same or different dienophiles. Initial work focused on using DMTB to connect two Diels-Alder cycloadditions; either with two equivalents of a single dienophile or with two different dienophiles added in a serialized fashion. Thus, with AlCl₃ as the Lewis acid instead of Rh(I), DMTB and *N*-phenylmaleimide provide compound **7** (Table 2) in one operation in greatly reduced reaction times (1.5 h) and in high yield (97%). Similarly, the use of 1,4-naphthoquinone as a dienophile and ZnCl₂ as the Lewis acid leads, in one operation, to the hexacene precursor **8**,³²⁻³⁴ in 95% yield. Complementing this route to 2:1 adducts, the 1:1:1 adduct **9** is obtained in 78% yield by using 1 equivalent of *N*-phenylmaleimide first and then dimethyl fumarate as a second component. Interestingly, switching the order of the addition (dimethyl fumarate then *N*-phenylmaleimide) results in a similar outcome (73%).

Activated acetylenes (e.g. dimethyl acetylenedicarboxylate : DMAD) were also shown to be effective Diels-Alder partners in our system (**10**). As exemplified by **11** and **12** (Table 2), heteroatomic dienophiles such as 4-phenyl-1,2,4-triazoline-3,5-dione and diethyl oxomalonate both function effectively in this reaction, providing facile access to a diverse array of heterocyclic compounds of the isochromane and pyridazine families.

We and others have previously shown that certain transition metals can effectively catalyze multi-step diene-dienophile cycloadditions that are otherwise electronically disfavored under Diels-Alder conditions due to a poor highest occupied molecular orbital (HOMO) - lowest unoccupied molecular orbital (LUMO) gap.^{24,35-38} Phenylacetylene, for example, is an ineffective dienophile under conventional thermal Diels-Alder conditions involving **1**. When it is combined with an activated dienophile (DMAD) and **1**, cycloaddition occurs only with DMAD. However, addition of [(naph)Rh(COD)]SbF₆ to this mixture results in elimination and subsequent Rh(I) catalyzed cycloaddition to afford cycloadduct **13a** in high yield. With Rh(I) catalysis, a large variety of commercially

available alkynes can be employed in the same fashion as post-Peterson elimination dienophiles providing the corresponding cycloadducts in one operation in good to excellent yields (**13a-h**, **14**, **15**, Table 2). Internal and terminal alkynes worked equally well. Of further synthetic note, the resultant tetrahydronaphthalenes can be readily transformed to the fully aromatic naphthalene core using DDQ, as exemplified by the transformation of **13a** to its naphthalene derivative in 80% yield (See Supplementary Information).

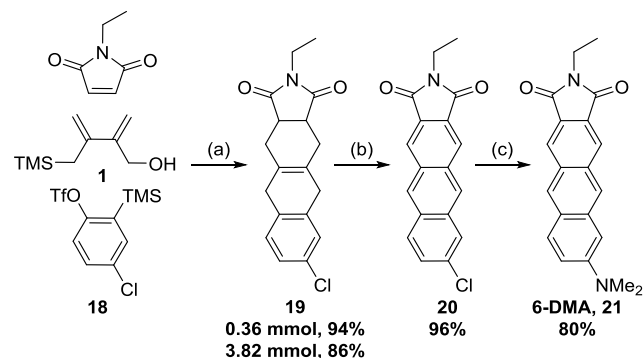
Initial attempts to perform sequential metal-catalyzed [4+2] cycloadditions between DMTB and alkynes, i.e. involving catalysis of each step of the cycloaddition/elimination/cycloaddition sequence, led to low yields due to decomposition of DMTB under the reaction conditions. The use of THP-DMTB circumvented this problem and allowed for successful conversion to 2:1 adducts of an alkyne and TME equivalent (**17**, Table 2). Due to the facility of the elimination at room temperature, the conditions used for the synthesis of **17** were not amenable to accessing 1:1:1 adducts resulting from the use of different alkynes. However, a change in solvent and reduction in temperature (0 °C) for the initial cycloaddition markedly reduces the rate of elimination while allowing the initial rhodium-catalyzed [4+2] cycloaddition to proceed. Allowing the reaction to warm to room temperature and addition of a second alkyne leads efficiently to 1:1:1 cycloadducts (**16a-e**, Table 2). Utilizing this optimized procedure in which a single catalyst under different conditions is capable of effecting multiple reactions, a topic of understandably great current interest,³⁹ the synthesis of a number of tetrahydronaphthalene structures resulting from unactivated alkynes was achieved in high yield.

This recursive process provides highly step-economical access to numerous targets of interest. Pertinent to our studies on drug delivery,⁴⁰ this process can be used to access solvatochromic dyes (e.g., 6-DMN⁴¹ and ANTHRADAN⁴²). Such agents report on their local molecular environments through changes in their observable fluorescent properties and have found considerable use in studies on DNA binding to proteins,⁴³ protein-protein interactions,^{9,44} membrane viscosity, dynamics, and permeation,^{45,46} and protein structure.⁴⁷ Using our recursive strategy, we set out to make 6-DMA (**21**), a new and potentially broadly useful solvatochromic dye, as it would be expected to exhibit enhanced photophysical properties in biological applications relative to 6-DMN (Scheme 3).

The synthesis of the 6-DMA fluorophore also presented a new direction for our TME studies as it required compatibility between our reagent and conditions required for aryne generation and cycloaddition. Significantly, in one synthetic operation, initiated by *N*-ethylmaleimide cycloaddition with DMTB, followed by zinc catalyzed elimination and TBAF triggered aryne formation using an easily synthesized chloroaryne equivalent, **18**⁴⁸, afforded the desired dye precursor **19** in 94% yield. To avoid an undesirable exotherm on larger scales,

a 1 M solution of DMTB and the chloroaryne precursor **18** were added to a solution of *N*-ethylmaleimide. Under these conditions (See Supplementary Information), 1.2 g of the desired hexahydroanthracene **19** was obtained in 86% yield. Oxidation of **19** utilizing a modified Wohl-Ziegler procedure furnished the desired anthracene core **20**⁴⁹ (96% yield) and modified C-N coupling chemistry readily produced the desired 6-DMA (**21**) in 80% yield.⁵⁰ This new fluorophore is thus formed in only three synthetic operations in 72% overall yield from chloroaryne precursor **18** and DMTB.

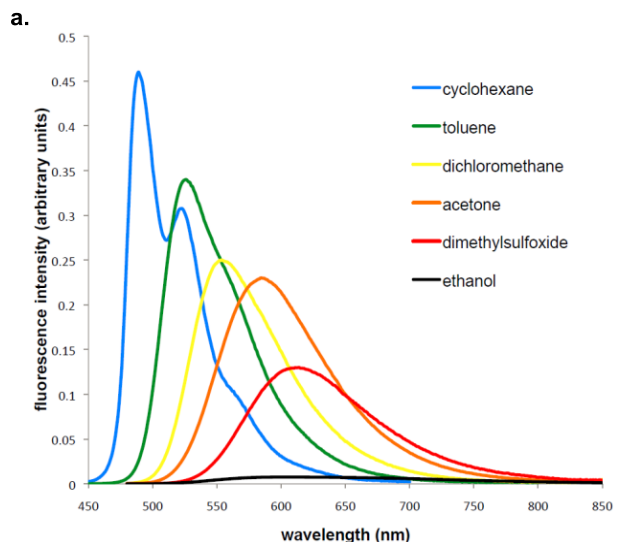
Scheme 3. The synthesis of novel fluorophore 6-DMA^a



^a(a)i. DCE, reflux, ii. 1-5% ZnCl₂, 60 °C, iii. TBAF, 0 °C; (b)i. NBS, (PhCOO)₂, CCl₄, reflux, 17 h, ii. NEt₃, RT, 20 min; (c) HNMe₂, 5% RuPhos Pd G2, 5:1 Toluene/*t*-BuOH, Cs₂CO₃, 100 °C, 8.5 h

The photophysical properties of the novel dye **21** are summarized in Figure 3a and 3b. 6-DMA exhibits an acute sensitivity to its environment. The maximum emission occurs at 527 nm in toluene and 691 nm in methanol. This corresponds to a large spectral red-shift of 164 nm in contrast to the lower benzolog 6-DMN, which displays a spectral red-shift of only 100 nm in the same solvents.⁴⁰ Despite the large difference in emission, the solvatochromic shift in absorption is minimal: changing only 7 nm between the two solvents. In addition, the extension of the chromophore from a naphthalene to an anthracene core results in approximately a 40 nm increase in the wavelength of maximum absorption. This is a useful property in that lower energy light minimizes stimulating cellular autofluorescence.⁵¹ Another important quality of solvatochromic dyes is their ability to exhibit on/off fluorescence between aprotic and protic environments respectively. To investigate the potential of 6-DMA as an on/off fluorophore the quantum yields were determined in a number of common solvents. The highest quantum yield (QY, Φ) observed for 6-DMA was in 1,4-dioxane (Φ = 0.48) and the lowest was in methanol (Φ = 0.0027). The difference in quantum yields corresponds to a 180-fold decrease in fluorescence intensity, which is an order of magnitude more than 6-DMN (18-fold decrease in QY). Research is currently underway for the derivatization of

this new class of solvatochromic dyes to allow for incorporation into biological systems and will be reported on in due course.



b.

solvent	6-DMA, 21			6-DMN ⁴¹			ANTHRADAN ⁴²		
	λ_{abs}	λ_{em}	Φ	λ_{abs}	λ_{em}	Φ	λ_{abs}	λ_{em}	Φ
cyclohexane	409	489	0.46	-	-	-	-	-	-
toluene	415	527	0.34	373	491	0.21	447	507	0.58
chloroform	423	539	0.18	380	509	0.23	458	536	-
1,4-dioxane	412	539	0.48	372	498	0.22	-	-	-
DCM	422	555	0.25	379	517	0.21	-	-	-
THF	416	562	0.36	373	510	0.15	450	529	-
acetone	416	589	0.23	375	532	0.15	452	557	0.51
acetonitrile	418	591	0.16	380	545	0.14	455	557	-
DMF	423	606	0.07	380	549	0.16	458	557	-
DMSO	425	612	0.13	-	-	-	-	-	-
2-propanol	423	593	0.023	385	589	0.018	-	-	-
ethanol	423	602	0.0076	379	584	0.027	452	601	0.41
methanol	422	691	0.0027	382	589	0.012	-	-	-

Figure 3. Photophysical data for fluorophore 6-DMA. a. Selected emission spectra of 6-DMA in various solvents. Emission maxima are scaled relative to quantum yield. b. Comparative analysis of 6-DMA and related fluorophores

Here, we have introduced recursive reagents that function like tetramethylethane equivalents, bringing together, through back-to-back cycloadditions, common building blocks in the form of alkynes, alkenes, arynes, and heteroatomic dienophiles and efficiently producing in one operation polycyclic ring systems of potential use in the synthesis of natural and designed molecules. The reagents allow for the coupling of two Diels-Alder cycloadditions, a Diels-Alder cycloaddition and a metal-catalyzed cycloaddition, or two metal-catalyzed cycloadditions with the same or different dienophiles. A range of conditions for the crucial Peterson 1,4-elimination enables these recursive cycloadditions to be achieved in one operation. The use of [(naph)Rh(COD)]SbF₆ provides a highly effective example of a catalytic cascade in which three operations are controlled by the same catalyst. These new reagents

allow facile access to commonly encountered ring systems, herein illustrated in a three-step synthesis of a promising new solvatochromic fluorophore (**21**). Further studies on these fluorophores and other applications of this methodology are ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Detailed experimental procedures and characterization of new compounds. Experimental procedures for 6-DMA fluorescence measurements and photophysical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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