

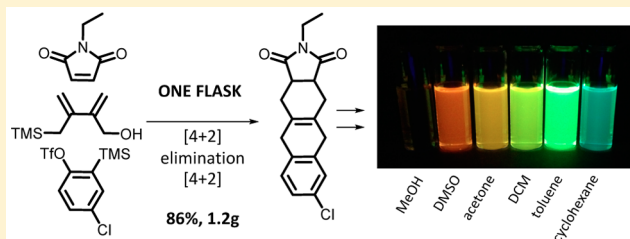
# Tetramethyleneethane Equivalents: Recursive Reagents for Serialized Cycloadditions

Paul A. Wender,\* Matthew S. Jeffreys,<sup>‡</sup> and Andrew G. Raub<sup>‡</sup>

Department of Chemistry, Department of Chemical and Systems Biology, Stanford University, Stanford, California 94305-5080, United States

**S** Supporting Information

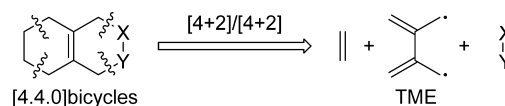
**ABSTRACT:** New reactions and reagents that allow for multiple bond-forming events per synthetic operation are required to achieve structural complexity and thus value with step-, time-, cost-, and waste-economy. Here we report a new class of reagents that function like tetramethyleneethane (TME), 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, 2,3-dimethylene-4-trimethylsilylbutan-1-ol (DMTB), 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 multicomponent catalytic cascade produces in one operation carbo- and heterobicyclic 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, *N*-ethyl(6-*N,N*-dimethylaminoanthracene-2,3-dicarboximide) (6-DMA), 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.<sup>1</sup> In general, synthetic strategies with the greatest number of target relevant bond-forming events per synthetic operation are the most step economical.<sup>2</sup> 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<sup>3,4</sup> 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.<sup>5,6</sup> This intriguing four-bond disconnection strategy to bicyclo[4.4.0]ring systems—a common feature in natural products,<sup>7</sup> materials,<sup>8</sup> imaging agents,<sup>9,10</sup> and potentially oligomeric acenes—leads conceptually to the tetramethyleneethane diradical (TME) as a key species capable of connecting back-to-back cycloadditions (Figure 1).

However, as shown in a brilliant series of studies by Dowd, TME itself has a half-life of only 20 min at  $-196\text{ }^{\circ}\text{C}$ , and

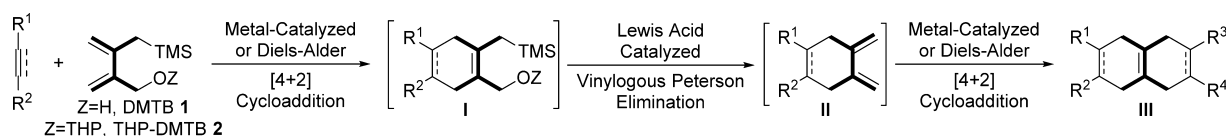


**Figure 1.** Retrosynthetic analysis of [4.4.0]bicycles into two dienophiles and the tetramethyleneethane (TME) diradical.

preparations of its precursors can be lengthy.<sup>11</sup> 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  $175\text{ }^{\circ}\text{C}$  produce an octahydronaphthalene product in 16% yield, putatively through the formation and reaction of 1,2-bis-methylenecyclobutane (BMCB).<sup>12</sup> Unfortunately, the volatility and reactivity of BMCB limit 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.<sup>12–23</sup> Here we report the design and development of a versatile TME equivalent, 2,3-dimethylene-4-trimethylsilylbutan-1-ol (DMTB, **1**), that is readily prepared and safely handled on scale. This TME equivalent efficiently engages dienophiles in an initial Diels–Alder or metal-catalyzed [4 + 2] cycloaddition, which then allows for a catalyzed vinylogous Peterson elimination<sup>24</sup> to produce a second diene captured in a

**Received:** April 20, 2015

**Published:** May 11, 2015



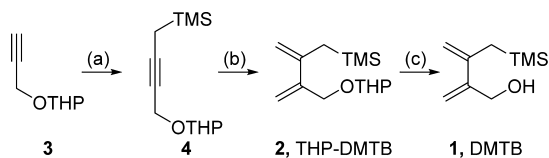
**Figure 2.** DMTB and THP-DMTB: tetramethyleneethane equivalents for recursive cycloadditions.

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 carbo- 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.<sup>9,10</sup>

## RESULTS AND DISCUSSION

The synthesis of our parent TME reagent (Scheme 1: DMTB, 1) uses a strategy that would be generally applicable to the

### Scheme 1. A Simple, Scalable Synthesis of Tetramethyleneethane Equivalents, DMTB and THP-DMTB<sup>a</sup>

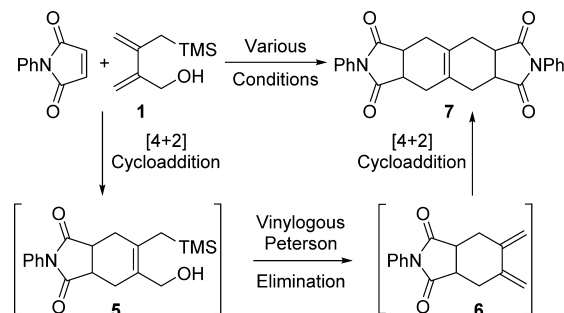


<sup>a</sup>(a) i. *n*-BuLi, ii. TMSCH<sub>2</sub>I, THF, 90%; (b) Grubbs' II, 1 atm ethylene, DCM, RT, 16 h, 95%; (c) B(OH)<sub>3</sub>, EtOH, reflux, 1 h, 70%.

synthesis of many related reagents. Commercially available alkyne **3** is first alkylated using a previously published procedure,<sup>25</sup> and the resulting alkyne **4** is converted to THP-DMTB (**2**) through an enyne metathesis conducted under 1 atm of ethylene gas using Grubbs' second generation catalyst. While previous studies have used higher catalyst loadings and elevated temperatures for similar substrates,<sup>26,27</sup> the conditions employed here for the synthesis of THP-DMTB (**2**) are unexpectedly efficient and can be conducted on a multigram 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.<sup>28</sup> 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  $-20\text{ }^{\circ}\text{C}$  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.

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 (Scheme 2). After 4 h, cycloadduct **5** formed cleanly and was transformed to diene **6** upon addition of [(naph)Rh(COD)]SbF<sub>6</sub>.<sup>29</sup> 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 Supporting Information). To determine whether other conditions would effect the intervening Peterson 1,4-

### Scheme 2. DMTB (1) Functions as a TME Equivalent in Single-Flask Operations under a Variety of Conditions



elimination,<sup>30,31</sup> 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

**Table 1.** Conditions for the Elimination of **5** to **6**<sup>a</sup>

entry	catalyst	mol %	solvent	[5] (M)	T (°C)	time (h)	yield (%)
1	—	—	toluene	0.25	111	>24	— <sup>b</sup>
2	HCl	200	ethanol	0.1	40	1	92
3	ZnCl <sub>2</sub>	25	THF	0.1	23	>48	— <sup>c</sup>
4	ZnCl <sub>2</sub>	5	DCE	0.1	60	0.33	95
5	AlCl <sub>3</sub>	25	THF	0.1	RT	2.25	99
6	FeCl <sub>3</sub>	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	— <sup>c</sup>
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

<sup>a</sup>All reactions in the table above were monitored by TLC analysis for consumption of the cycloadduct **5**. <sup>b</sup>Complex mixture formed. <sup>c</sup>No conversion observed by TLC analysis.

were found to work well, leading, in the preferred cases, to rapid (<3 h) and efficient (>90%) conversion to diene **6** even at room temperature.

The diverse and effective conditions for the vinyllogous 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 2 equiv of a single dienophile or with two different dienophiles added in a serialized fashion. Thus, with AlCl<sub>3</sub> 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 ZnCl<sub>2</sub> as the Lewis acid leads, in one operation, to the hexacene precursor **8**,<sup>32–34</sup> in 95% yield. Complementing this route to 2:1 adducts, the 1:1:1 adduct **9** is obtained in 78% yield by using 1 equiv of *N*-phenylmaleimide first and then

**Table 2. Summary of One-Flask [4 + 2]/Elimination/[4 + 2] Reactions Using Tetramethyleneethane Equivalents DMTB and THP-DMTB**

Diels-Alder / Lewis Acid Adducts <sup>a</sup>				Diels-Alder / Rhodium(I) Adducts <sup>a</sup>				Diels-Alder / Rhodium(I) Adducts Continued <sup>a</sup>			
Product	Catalyst (%)	Time <sup>b</sup>	Yield	Product	Catalyst (%) <sup>f</sup>	Time <sup>b</sup>	Yield	Product	Catalyst (%) <sup>f</sup>	Time <sup>b</sup>	Yield
<b>7</b>	AlCl <sub>3</sub> (40)	1.6 h	97% <sup>c</sup>	<b>13a</b>	Rh(I) (5)	23 h	83%	<b>14</b>	Rh(I) (5)	11 h	92%
<b>8</b>	ZnCl <sub>2</sub> (10)	16 h	95%	<b>13b</b>	Rh(I) (5)	21 h <sup>g</sup>	70%	<b>15</b>	Rh(I) (5)	11 h	99%
<b>9<sup>d</sup></b>	AlCl <sub>3</sub> (25)	3 h	78%	<b>13c</b>	Rh(I) (5)	42 h	85%	Rhodium(I) / Rhodium(I) Adducts <sup>i</sup>			
<b>9<sup>e</sup></b>	AlCl <sub>3</sub> (100)	16 h	73%	<b>13d</b>	Rh(I) (5)	24 h	86%	<b>16a</b>	Rh(I) (5)	28 h	83%
<b>10</b>	ZnCl <sub>2</sub> (10)	6.25 h	72%	<b>13e</b>	Rh(I) (5)	39 h	83%	<b>16b</b>	Rh(I) (5)	28 h	79%
<b>11</b>	ZnCl <sub>2</sub> (10)	22 h	63%	<b>13f</b>	Rh(I) (5)	23 h	78% <sup>h</sup>	<b>16c</b>	Rh(I) (5)	28 h	76%
<b>12</b>	ZnCl <sub>2</sub> (10)	2.25 h	92%	<b>13g</b>	Rh(I) (5)	25 h	85%	<b>16d</b>	Rh(I) (5)	28 h	79%
				<b>13h</b>	Rh(I) (5)	21 h <sup>g</sup>	81%	<b>16e</b>	Rh(I) (5)	28 h	80%
								<b>17</b>	Rh(I) (5)	24 h	79%

<sup>a</sup>Z = H. <sup>b</sup>Time reflects the full reaction time for all three steps. See Supporting Information for detailed conditions. <sup>c</sup>Product is a 15:1 mixture of diastereomers favoring the cis-anti-cis. See Supporting Information. <sup>d</sup>*N*-phenylmaleimide used as first dienophile. <sup>e</sup>Dimethylfumarate used as first dienophile. <sup>f</sup>Rh(I) catalyst used was [(naph)Rh(COD)]SbF<sub>6</sub> in all cases. <sup>g</sup>Second [4 + 2] cycloaddition was run at 50 °C. <sup>h</sup>Procedure was slightly different from other entries. See Supporting Information. <sup>i</sup>Z = THP.

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 oximalonate 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 multistep diene–dienophile cycloadditions that are otherwise electronically disfavored under Diels–Alder conditions due to a poor highest occupied molecular orbital–lowest unoccupied molecular orbital gap.<sup>24,35–38</sup> 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)]SbF<sub>6</sub> 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

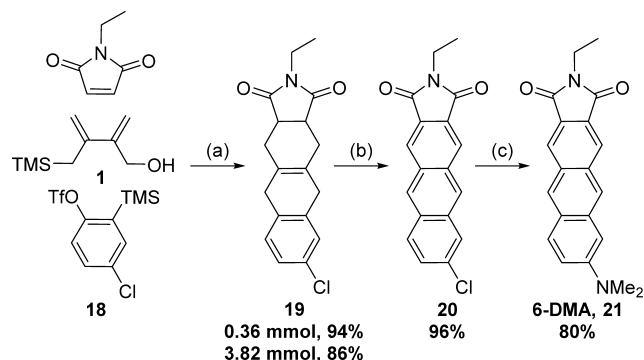
employed in the same fashion as post-Peterson elimination dienophiles providing the corresponding cycloadducts in one operation in good to excellent yields (**13a–h**, **14**, and **15**, Table 2). Internal and terminal alkynes worked equally well. Of further synthetic note, the resultant tetrahydronaphthalenes 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 Supporting 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 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,<sup>39</sup> 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,<sup>40</sup> this process can be used to access solvatochromic dyes (e.g., 6-DMN<sup>41</sup> and ANTHRADAN<sup>42</sup>). 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;<sup>43</sup> protein–protein interactions;<sup>9,44</sup> membrane viscosity, dynamics, and permeation;<sup>45,46</sup> and protein structure.<sup>47</sup> 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).

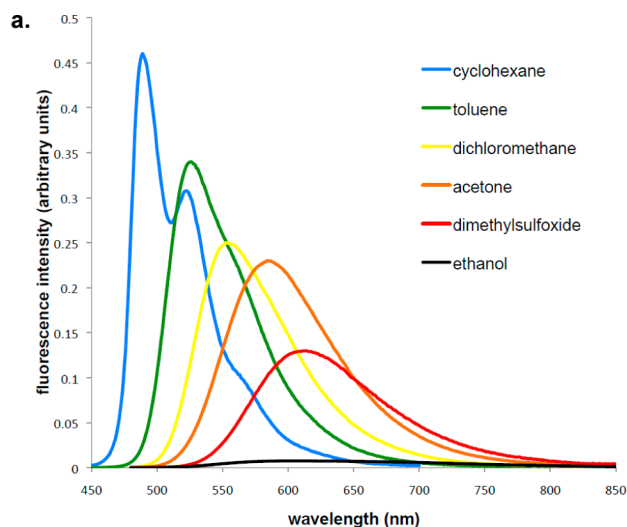
### Scheme 3. Synthesis of Novel Fluorophore 6-DMA<sup>a</sup>



<sup>a</sup>(a) i. DCE, reflux, ii. 1–5% ZnCl<sub>2</sub>, 60 °C, iii. TBAF, 0 °C; (b) i. NBS, (PhCOO)<sub>2</sub>, CCl<sub>4</sub>, reflux, 17 h, ii. NEt<sub>3</sub>, RT, 20 min; (c) HNMe<sub>2</sub>, 5% RuPhos Pd G2, 5:1 toluene/*t*-BuOH, Cs<sub>2</sub>CO<sub>3</sub>, 100 °C, 8.5 h

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**,<sup>48</sup> 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 Supporting 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**<sup>49</sup> (96% yield) and modified C–N coupling chemistry readily produced the desired 6-DMA (**21**) in 80% yield.<sup>50</sup> This new fluorophore is thus formed in only three synthetic operations in 72% overall yield from chloroaryne precursor **18** and DMTB.

The photophysical properties of the novel dye **21** are summarized in Figure 3. 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



solvent	6-DMA, <b>21</b>			6-DMN <sup>41</sup>			ANTHRADAN <sup>42</sup>		
	$\lambda_{\text{abs}}$	$\lambda_{\text{em}}$	$\Phi$	$\lambda_{\text{abs}}$	$\lambda_{\text{em}}$	$\Phi$	$\lambda_{\text{abs}}$	$\lambda_{\text{em}}$	$\Phi$
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.

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.<sup>40</sup> 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.<sup>51</sup> 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,  $\Phi$ ) observed for 6-DMA was in 1,4-dioxane ( $\Phi = 0.48$ ), and the lowest was in methanol ( $\Phi = 0.0027$ ). 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.

Here, we have introduced recursive reagents that function like tetramethyleneethane 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 1,4-Peterson elimination enables these recursive cycloadditions to be achieved in one operation. The use of [(naph)Rh(COD)]SbF<sub>6</sub> 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

### 📄 Supporting Information

Detailed experimental procedures and characterization of new compounds. Experimental procedures for 6-DMA fluorescence measurements and photophysical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04091.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*wenderp@stanford.edu

### Author Contributions

‡These authors contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was supported by the National Science Foundation (NSF, CHE1265956) and the National Institutes of Health (CA031845). M.S.J. gratefully acknowledges an Abbott Laboratories Stanford Graduate Fellowship.

## ■ REFERENCES

- Wender, P. A. *Nat. Prod. Rep.* **2014**, *31* (4), 433–440.
- (a) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Eds.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27–66. (b) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.
- Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105* (12), 4730–4756.
- Pronin, S. V.; Shenvi, R. A. *Nat. Chem.* **2012**, *4* (11), 915–920.
- Newton, C. G.; Drew, S. L.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Nat. Chem.* **2015**, *7* (1), 82–86.
- Souweha, M. S.; Enright, G. D.; Fallis, A. G. *Org. Lett.* **2007**, *9* (25), 5163–5166.
- Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130* (52), 17913–17927.
- Payne, M. M.; Parkin, S. R.; Anthony, J. E. *J. Am. Chem. Soc.* **2005**, *127* (22), 8028–8029.
- Loving, G. S.; Sainlos, M.; Imperiali, B. *Trends Biotechnol.* **2010**, *28* (2), 73–83.
- Benedetti, E.; Kocsis, L. S.; Brummond, K. M. *J. Am. Chem. Soc.* **2012**, *134* (30), 12418–12421.
- Dowd, P. *J. Am. Chem. Soc.* **1970**, *92* (4), 1066–1068.
- Alder, K.; Ackermann, O. *Chem. Ber.* **1954**, *87* (10), 1567–1571.
- Hosomi, A.; Otaka, K.; Sakurai, H. *Tetrahedron Lett.* **1986**, *27* (25), 2881–2884.
- Bauld, N. L.; Chang, C.-S. *J. Am. Chem. Soc.* **1972**, *94* (21), 7594–7595.
- Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104* (15), 4299–4301.
- Beetz, T.; Kellog, R. M. *J. Am. Chem. Soc.* **1973**, *95* (23), 7925–7926.
- Gaoni, Y.; Sadeh, S. *J. Org. Chem.* **1980**, *45* (5), 870–881.
- Markoulides, M. S.; Ioannou, G. I.; Manos, M. J.; Chronakis, N. *RSC Adv.* **2013**, *3* (14), 4750–4756.
- Hirata, G.; Yamada, N.; Sanada, S.; Onodera, G.; Kimura, M. *Org. Lett.* **2015**, *17* (3), 600–603.
- Takasu, K.; Tanaka, T.; Azuma, T.; Takemoto, Y. *Chem. Commun.* **2009**, *46* (43), 8246–8248.
- Alder, R. W.; Allen, P. R.; Edwards, L. S.; Fray, G. I.; Fuller, K. E.; Gore, P. M.; Hext, N. M.; Perry, M. H.; Thomas, A. R.; Turner, K. S. *J. Chem. Soc., Perkin Trans. 1 (1972-1999)* **1994**, No. 21, 3071–3077.
- Stephan, C.; Munz, C.; tom Dieck, H. *J. Organomet. Chem.* **1994**, *468* (1–2), 273–278.
- Suzuki, T.; Kubomura, K.; Takayama, H. *Chem. Pharm. Bull. (Tokyo)* **1991**, *39* (8), 2164–2166.
- Wender, P. A.; Fournogerakis, D. N.; Jeffreys, M. S.; Quiroz, R. V.; Inagaki, F.; Pfaffenbach, M. *Nat. Chem.* **2014**, *6* (5), 448–452.
- Malkov, A. V.; Kysilka, O.; Edgar, M.; Kadčiková, A.; Kotora, M.; Kočovský, P. *Chem. – Eur. J.* **2011**, *17* (26), 7162–7166.
- Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119* (50), 12388–12389.
- Gregg, T. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2013**, *135* (45), 16777–16780.
- Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1967**, No. 0, 431–434.
- Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41* (23), 4550–4553.
- Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97* (6), 2063–2192.
- Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1 (1972-1999)* **1998**, No. 17, 2749–2764.
- Anthony, J. E.; Eaton, D. L.; Parkin, S. R. *Org. Lett.* **2002**, *4* (1), 15–18.
- Zhang, J.; Smith, Z. C.; Thomas, S. W. *J. Org. Chem.* **2014**, *79* (21), 10081–10093.
- Webster, O. W.; Sharkey, W. H. *J. Org. Chem.* **1962**, *27* (9), 3354–3355.
- Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71* (1), 91–96.
- Liao, W.; Yu, Z.-X. *J. Org. Chem.* **2014**, *79* (24), 11949–11960.
- Hilt, G.; Danz, M. *Synthesis* **2008**, *14*, 2257–2263.
- Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111* (16), 6432–6434.
- Abou-Shehadeh, S.; Williams, J. M. *J. Nat. Chem.* **2014**, *6* (1), 12–13.
- Stanzl, E. G.; Trantow, B. M.; Vargas, J. R.; Wender, P. A. *Acc. Chem. Res.* **2013**, *46*, 2944–2954.
- Vázquez, M. E.; Blanco, J. B.; Imperiali, B. *J. Am. Chem. Soc.* **2005**, *127* (4), 1300–1306.
- Lu, Z.; Lord, S. J.; Wang, H.; Moerner, W. E.; Twieg, R. J. *J. Org. Chem.* **2006**, *71* (26), 9651–9657.
- Riedl, J.; Pohl, R.; Ernsting, N. P.; Orság, P.; Fojta, M.; Hocek, M. *Chem. Sci.* **2012**, *3* (9), 2797–2806.
- Cohen, B. E.; McAnaney, T. B.; Park, E. S.; Jan, Y. N.; Boxer, S. G.; Jan, L. Y. *Science* **2002**, *296* (5573), 1700–1703.
- Klymchenko, A. S.; Kreder, R. *Chem. Biol.* **2014**, *21* (1), 97–113.
- Kreder, R.; Pyrshev, K. A.; Darwich, Z.; Kucherak, O. A.; Mély, Y.; Klymchenko, A. S. *ACS Chem. Biol.* [Online early access]. DOI: 10.1021/cb500922m. Published online: February 24, 2015. <http://>

pubs.acs.org/doi/abs/10.1021/cb500922m (accessed March 10, 2015).

- (47) Macgregor, R. B.; Weber, G. *Nature* **1986**, 319 (6048), 70–73.
- (48) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, No. 10, 1454–1458.
- (49) Wang, Z.; Kim, C.; Facchetti, A.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, 129 (44), 13362–13363.
- (50) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, 130 (21), 6686–6687.
- (51) Berezin, M. Y.; Achilefu, S. *Chem. Rev.* **2010**, 110 (5), 2641–2684.