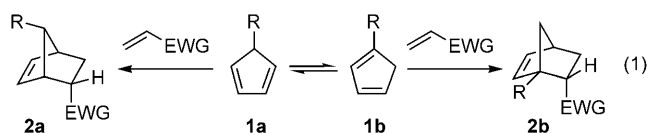


Diels–Alder Reactions

Stable 5-Substituted Cyclopentadienes for the Diels–Alder Cycloaddition and their Application to the Synthesis of Palau'amine**

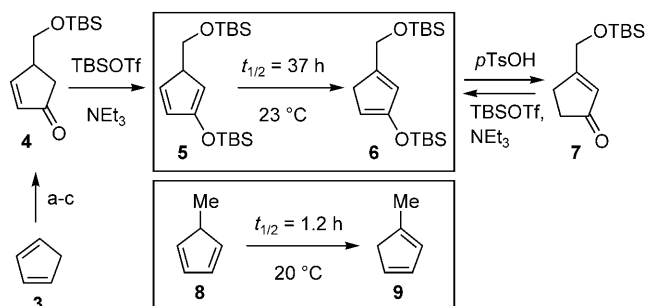
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The Diels–Alder cycloaddition reaction is one of the most fundamental synthetic transformations and has been the cornerstone in countless total syntheses. Surprisingly, cyclopentadiene, the most common diene employed in asymmetric synthesis methods, is used only rarely in total synthesis. Moreover, substituted variants are almost never used, with the notable exception of the landmark synthesis of the prostaglandins by Corey et al.^[1a] Substituted cyclopentadienes, particularly those substituted at the 5 position, are very attractive substrates as they lead to structures of high complexity and can provide functional handles for further transformation.^[2] The main obstacle to their use is the need to prepare, isolate, and employ the diene at temperatures $\leq 0^\circ\text{C}$ to prevent a facile [1,5]-sigmatropic shift, which can lead to mixtures of cycloadducts (e.g. Eq. (1); EWG = electron with-



drawing group).^[1–3] Although this problem may be circumvented in certain instances by removing the offending hydrogen atom, no direct solution to this long-standing problem has been reported.^[4] Herein, we demonstrate that the incorporation of a 2-silyloxy group greatly stabilizes 5-substituted cyclopentadienes toward [1,5]-sigmatropic shifts, for the first time making their use practical for Diels–Alder cycloaddition reactions conducted at room temperature. We further demonstrate the potential of this method by applying it to the synthesis of a key ring in the marine alkaloid palau'amine.

5-Substituted cyclopentadiene **5** is easily prepared by enolsilylation of 4-substituted cyclopentenone **4** (Scheme 1). The latter is prepared from cyclopentadiene by an easily scalable, three-step procedure involving a Prins reaction with formaldehyde, selective allylic oxidation with the reagent



Scheme 1. Synthesis of the stable 5-substituted cyclopentadiene **5**. Reagents and conditions: a) HCHO , HCO_2H , TsOH ; then NaOH (43 %, 55:45 regioisomers); b) 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate; c) TBSCl , imid; then regioisomer separation (45 % over 2 steps). imid = imidazole, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

developed by Bobbitt, and protection of a primary alcohol.^[5,6] Silyl enol ether formation from **4** may be accomplished under either soft (R_3SiOTf , NEt_3) or hard (lithium diisopropylamide, R_3SiCl) enolization reaction conditions.^[7] In this way, the *tert*-butyldimethylsilyl (TBS), triethylsilyl, or trimethylsilyl enol ethers may be prepared, with the former being preferred because of the increased hydrolytic stability of the diene and the subsequent cycloadducts. In all cases, the cross-conjugated diene is formed exclusively and may be isolated by a simple extractive workup and used directly in subsequent cycloaddition reactions.

Diene **5** undergoes a [1,5]-sigmatropic shift of a hydrogen atom at a considerably slower rate than normal 5-substituted cyclopentadienes. Monitoring a solution of **5** in $[\text{D}_6]\text{benzene}$ by ^1H NMR spectroscopy demonstrated that it rearranges with a half-life of 37 hours at 23°C , and it was found that **5** could be stored at -20°C for up to a month with no significant rearrangement or dimerization observed. By contrast, 5-methylcyclopentadiene (**8**) is reported to rearrange with a half life of only 1.2 hours at 20°C , thus indicating a greater than 30-fold increase in stability upon incorporation of the 2-silyloxy group.^[8] Although the rearrangement product could not be separated from **5**, its ^1H NMR spectrum, the isolation of enone **7** upon mild acid workup, and its regeneration upon enolsilylation of **7** were fully consistent with **6** as the major rearrangement product. The increased stability of **5** undoubtedly arises from donation of electron density from the silyloxy substituent.^[9] Density functional calculations at the B3LYP/6-31G* level showed a reasonable correlation between the predicted activation enthalpy for a [1,5]-sigmatropic shift and the electron donor ability of substituents at the 2 position of the diene (See the Supporting Information for details).^[10,11]

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Diene **5** proved to be highly competent in Diels–Alder cycloadditions with a wide variety of dienophiles under very mild reaction conditions ($[\mathbf{5}] = 0.5\text{ M}$, $[\text{dienophile}] = 1.5\text{ M}$, CH_2Cl_2 , 23°C ; Table 1). The cycloadducts were isolated as the versatile silyl enol ethers after chromatography on neutral alumina (Brockman Grade IV). Cycloaddition reactions were rapid with dienophiles such as benzoquinone (Table 1,

Table 1: Diels–Alder cycloaddition reactions of cyclopentadiene **5**.^[a]

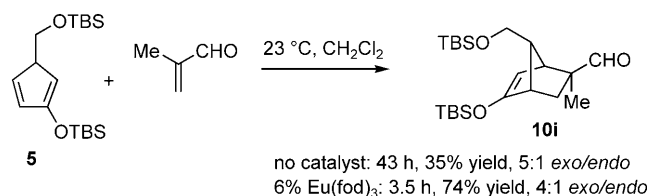
Entry	Dienophile	Product	<i>t</i> [h]	Yield [%] ^[b]	<i>endo/exo</i>
1			0.15	66	> 95:5
2			0.5	79	> 95:5
3			0.75	79	–
4			2	71	1.6:1
5			4	67	2:1
6			3.5	73	3.2:1
7			20	68	1.2:1
8			24	65	2.3:1

[a] Reactions were carried out with excess dienophile (3 equiv) in CH_2Cl_2 with a diene concentration of 0.5 M at 23°C . [b] Overall yields of isolated products (*endo* + *exo*) starting from enone **4**.

entry 1), *N*-methylmaleimide (entry 2), and dimethylacetylene dicarboxylate (entry 3), as well as being highly *endo* selective in the first two cases. Cycloaddition reactions with slightly less reactive dienophiles such as acrolein (entry 4), methyl vinyl ketone (entry 5), and chloroacrylonitrile (entry 6) also proceeded efficiently at room temperature in just 2–4 hours. Finally, the reaction of **5** with acrylonitrile (entry 7) and methyl acrylate (entry 8) also afforded cycloadducts in good yields at room temperature, even with extended reaction times (20–24 h); these reaction conditions would clearly be unsuitable for simple 5-substituted cyclopentadienes. In all cases, the cycloaddition reactions proceeded with excellent diastereofacial selectivity, where the

approach of the dienophile is from the face opposite to the 5-silyloxymethyl group, and provided *endo/exo* ratios comparable to those observed with cyclopentadiene.^[12]

Diene **5** is compatible with the use of mild Lewis acids. The cycloaddition of **5** with methacrolein proceeded very slowly at room temperature, and afforded only a 35 % yield of isolated **10i** after 43 hours (Scheme 2). However, the use of 6 % $\text{Eu}(\text{fod})_3$ as a catalyst allowed the reaction to proceed to completion in just 3.5 hours at 23°C , and gave the cycloadduct **10i** in 74 % yield as a 4:1 mixture of *exo/endo* isomers.^[13]

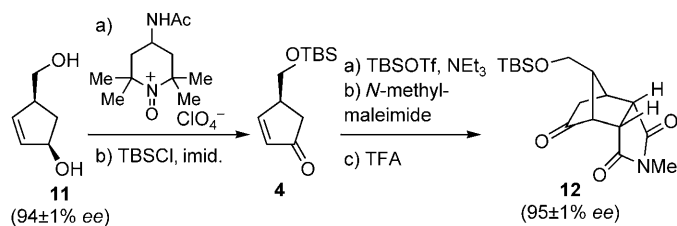


Scheme 2. Lewis acid catalysis with diene **5**. fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl 3,5-octanedionate.

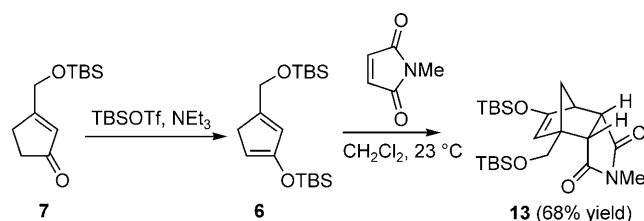
Diene **5** offers an additional advantage over simple 5-substituted cyclopentadienes in that it is chiral and, as can be seen in Table 1, it provides excellent regioselectivity and diastereofacial control with respect to both the 2- and 5-substituents. Diene **5** may be prepared in an enantiomerically enriched form from **11** ($94 \pm 1\%$ *ee*; Scheme 3), which is available from the procedure developed by Hodgson et al.,^[14] by using selective allylic oxidation and silylation.^[6] Cycloaddition of enantiomerically enriched **5** with *N*-methylmaleimide and subsequent selective desilylation of the enol ether afforded ketone **12** as a single diastereomer in $95 \pm 1\%$ *ee*, thus indicating that the diene does not racemize during formation nor during successive reversible [1,5]-sigmatropic shifts.

The concept of stabilization by a silyloxy group is not limited to diene **5**. Diene **6**, produced cleanly by enolsilylation of enone **7**, is even more stable than **5** to [1,5]-sigmatropic shifts (Scheme 4).^[15] Exposure of **6** to *N*-methylmaleimide for 30 minutes under our standard cycloaddition reaction conditions afforded *endo* cycloadduct **13** in 68 % yield as a single regio- and diastereomer. Presumably, this silyloxy stabilization can be incorporated in other diene substitution patterns.

As a demonstration of the synthetic utility of **5**, we applied it to the significant synthetic challenge presented by the oroidin alkaloid palau'amine.^[16] This marine alkaloid pos-

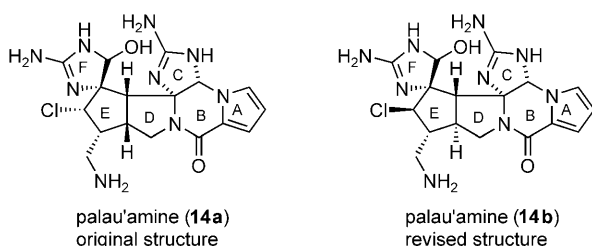


Scheme 3. The preparation and use of the enantioenriched diene **5**. TFA = trifluoroacetic acid.



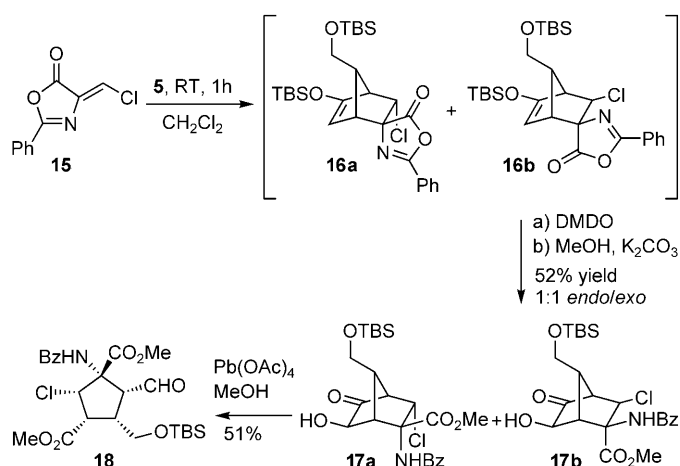
Scheme 4. 2,4-Disubstituted cyclopentadiene **6** in a Diels-Alder cycloaddition reaction.

sesses a hexacyclic structure containing two guanidine-containing rings and a densely functionalized E ring, the configuration about which has been a matter of significant debate.^[17] The original structure assignment suggested that the D/E ring junction was *cis* fused and that the chlorine substituent of the E ring was on the α face (**14a**).^[16] Several groups have recently proposed that the D/E ring junction is *trans* fused and that the chlorine substituent is on the β face (**14b**).^[18] Both of these stereoarrays represent demanding synthetic challenges. Despite significant efforts by many research groups, the original all-*cis* E ring stereoarray of the originally reported structure has only recently been synthesized.^[19]



One potential route to give the configuration of the E ring of the original structure is through the cycloaddition of a 5-substituted cyclopentadiene with a β -chlorodehydroalanine derivative and subsequent oxidative ring-opening of the cycloadduct.^[20,21] We found that the cycloaddition of **5** with chloromethyleneoxazolone **15**^[22] proceeds rapidly in dichloromethane at room temperature (Scheme 5). The resulting 1:1 mixture of cycloadducts was not stable to chromatography and therefore was treated directly with dimethyldioxirane (DMDO) and subsequent methanolysis of the oxazolone afforded hydroxy ketones **17a** and **17b** in 52% yield over three steps. Subsequent cleavage of the hydroxy ketone of **17a** with lead tetraacetate in methanol afforded the hexasubstituted cyclopentane **18**, which possesses the same configuration as the E ring in **14a**. This is a successful preparation of the E ring of palau'amine with the all-*cis* configuration.

In conclusion, we have shown that 2-silyloxy substitution markedly stabilizes 5-substituted cyclopentadienes towards [1,5]-sigmatropic shifts, thus allowing the facile preparation and efficient use of this important class of diene. Furthermore, the diene may be easily prepared in enantiomerically enriched form and undergoes cycloaddition with excellent



Scheme 5. Application of **5** to the synthesis of the E ring of palau'amine. Bz = benzyl.

regio- and diastereocontrol with no loss of enantiopurity. It is expected that this versatile new diene will find application in the synthesis of complex molecules.^[23]

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