2-Pyridyldimethylsilyl Group as a Removable Hydrophilic Group in Aqueous Organic Reactions: Formation of Molecular Aggregates and Dramatic Rate Enhancement in Diels–Alder Reactions

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Abstract: A novel methodology for aqueous organic reactions utilizing a 2-pyridyldimethylsilyl (2-PyMe_2Si) group as a removable hydrophilic group has been developed. It was found that 1,3-dienes bearing the 2-PyMe_2Si group form molecular aggregates in water when 1.0 equivalent of HCl was added, as evidenced by dynamic light-scattering experiments. The Diels–Alder reaction of 2-PyMe_2Si-substituted 1,3-dienes with various dienophiles took place in water at room temperature. The Diels–Alder reaction in organic solvents (Et_2O/toluene) under the same reaction temperature and time gave the cycloadduct in much lower yield, indicating the dramatic rate acceleration in water. The removal of the 2-PyMe_2Si group was accomplished by desilylation, oxidation, and electrophilic substitution.

Keywords: Diels–Alder reaction; removable hydrophilic group; water

Introduction

The continuing evolution of organic synthesis is heavily based on the discovery of reactions and strategies that allows the production of complex molecules in a safe, cheap, and environmentally acceptable fashion. Although the use of water as a solvent is most desirable in every sense, it is only recently that organic reactions in water have received much attention in synthetic organic chemistry.[1,2] This is mainly due to the solubility and stability problems of the reaction components in water. Therefore, many of the reported aqueous organic reactions have to rely on the use of organic co-solvents at the expense of the many inherent advantages and unique properties of water, such as hydrophobic effects, hydrogen-bonding effects, and polarity effects. Moreover, in today's economic and environmentally conscious climate, new strategies for the organic reactions in water, the only true environmentally benign solvent, are highly called for.[3]

Recently, we have developed the 2-pyridyldimethylsilyl (2-PyMe_2Si) group as a multifunctional phase tag for solution-phase synthesis, which relies on the miscibility of 2-PyMe_2Si-substituted molecules in acidic water (Figure 1).[4,5] Molecular aggregation seems to be involved in their dissolution so as to minimize the energetically unfavorable contact between water molecules and non-polar carbon chains. Indeed, dynamic light-scattering experiments on an aqueous solution (containing 1.0 equivalent of HCl) of dimethyl(*n*-octyl)(2-pyridyl)silane revealed the presence of molecular aggregates with average hydrodynamic radii of 61 nm. Moreover, we have already established that the 2-PyMe_2Si group can be easily removed from the organic molecule by several methods such as oxidation,[5c] protodesilylation,[5m] electrophilic substitution,[5h] and cross-coupling reaction.[5i] These facts led us to explore the concept of a removable hydrophilic group, which enables the induction of molecular aggregations in water and the removal from the molecules when needed.

We envisioned that, if the 2-PyMe_2Si group works as a removable hydrophilic group and induces molecular aggregation in water, organic reactions in aqueous molecular aggregates should be possible when the reaction site is located on a hydrophobic side chain of the 2-PyMe_2Si-substituted molecule (Figure 2).[6] The advantage of using the 2-PyMe_2Si group is apparent, as it can be readily removed from the molecule when required by utilizing the several methods described above. Moreover, easy separation and purification

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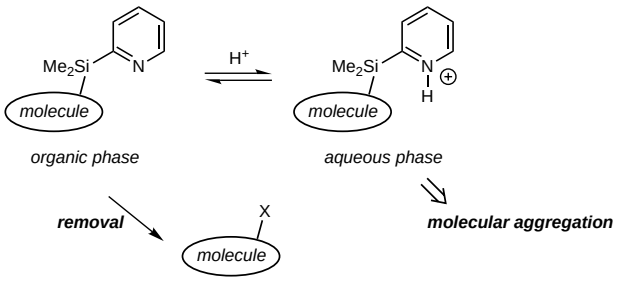


Figure 1.

processes (isolation of the product from the aqueous phase) are expected by taking advantage of the simple acid-base "phase switching" technique (Figure 1).[4] Recently, we reported the "proof-of-principle" of our strategy of using removable hydrophilic group in aqueous organic reactions by utilizing an intermolecular Diels–Alder reaction as a showcase.[7] In this paper, we report on the full details of this study.

Background on Aqueous Diels–Alder Reactions

The Diels–Alder reaction (DA reaction) is currently one of the most active areas of research where the use of water gives rise to exceptional rate enhancement and appreciable high stereoselectivity.[8–12] In 1980, half a century after the first discovery by Diels and Alder, Breslow made the first observation of dramatic rate acceleration of the DA reaction in water.[8] This rate enhancement is most likely attributed to the poor solubility of the reaction components in water, which causes an increase of hydrophobic interactions.[13] Enforced hydrophobic interactions and hydrogen-bonding effects have also been suggested as explanations for the enhanced rate of the DA reaction in water.[10,14]

An alternative approach toward the aqueous DA reaction is the use of a water-soluble diene and/or dienophile. Grieco reported that dienes bearing hydrophilic groups such as sodium salts of carboxylic or phosphoric acids, and ammonium salts undergo the DA reaction in water with enhanced rates and stereoselectivities.[9] Several other related approaches are also known.[11] In these aqueous DA reactions, the formation of molecular aggregates such as micelles by the water-soluble reactants has been suggested.[9a,9c,11] Rate acceleration by the formation of molecular aggregates stands in sharp contrast to the Breslow's observation that the addition of an external 'salting–in' agent such as guanidinium chloride to dissolve the non-polar reactant in water, most likely in a monomeric form, greatly decreases the rate of the reaction.[8] The only disadvantage of using water-soluble reactants might be that it is not easy to remove or convert those hydrophilic groups to other functional groups. This drawback profoundly diminishes the synthetic utility of the otherwise attractive methodology for organic reactions in water. Therefore, we thought that the use of a removable hydrophilic group should greatly expand the scope and limitation of this extremely interesting strategy for aqueous organic reactions.[15]

Results and Discussion

Synthesis of 2-PyMe$_2$Si-Substituted 1,3-Dienes

The 2-PyMe$_2$Si-substituted 1,3-dienes **1**, **2**, and **3** were prepared using our recently developed methods. Dienes **1** and **2** were prepared in one-pot by the Peterson-type reactions of (2-PyMe$_2$Si)$_2$CHLi with acrolein and methacrolein, respectively.[5h] In both cases, complete stereoselectivities (>99% *E*) were observed. Diene **3** was prepared by the reaction of 2-PyMe$_2$SiCH$_2$Li[5g] with (*E*,*E*)-1-bromo-2,4-hexadiene.[16] For comparison, we also prepared the PhMe$_2$Si-substituted 1,3-diene **4** (Figure 3).

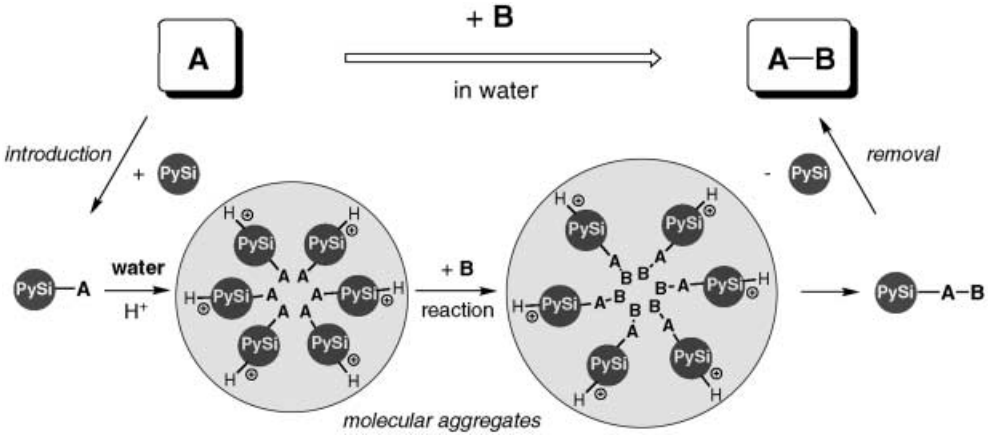


Figure 2.

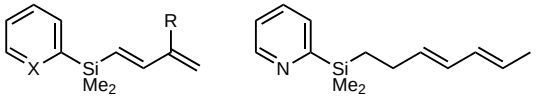


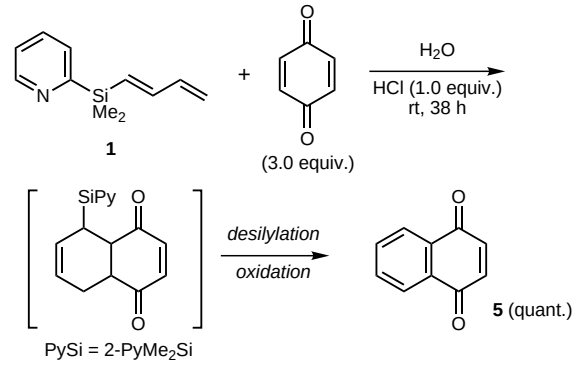
Figure 3.

Solution Behavior of 2-PyMe$_2$Si-Substituted 1,3-Dienes in Water

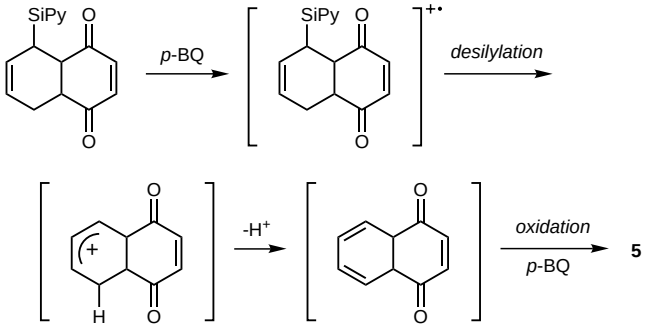
Before embarking on the aqueous DA reactions using 1,3-dienes bearing the 2-PyMe$_2$Si group (**1** – **3**), we examined if they form unambiguous molecular aggregates in water (containing 1.0 equivalent of HCl) as expected since there are no precedents for such surfactants. First, dynamic light-scattering experiments on aqueous solutions (containing 1.0 equivalent of HCl) of dienes **1**, **2**, and **3** were conducted at the concentration of 0.05 M. These experiments undoubtedly revealed the presence of molecular aggregates with average hydrodynamic radii of 197, 138, and 307 nm, respectively. However, the determination of the exact structure of the molecular aggregates must await further investigations. The large radii observed can probably be attributed to non-ordered structures of the molecular aggregates in aqueous solution. Short hydrophobic carbon chains (four and seven) may be the reason for the non-ordered structures of the molecular aggregates. Nevertheless, the detection of molecular aggregates led us to explore the aqueous reactions of **1** – **3**, irrespective of the structures of their molecular aggregations.

Aqueous Diels–Alder Reaction of 1 with *p*-Benzoquinone

Having substantiated the potential of the 2-PyMe$_2$Si group as a hydrophilic group, we investigated the intermolecular DA reactions. Throughout this work, the aqueous DA reactions were conducted at the concentration of 0.5 M of diene, which is greatly above the concentration we detected in molecular aggregates by dynamic light-scattering experiments. The DA reaction of **1** and *p*-benzoquinone occurred at room temperature in water (containing 1.0 equivalent of HCl) with simultaneous desilylation and oxidation to afford naphthoquinone **5** quantitatively (Scheme 1). In this case, an additional chemical operation was unnecessary for the removal of the 2-PyMe$_2$Si group. Interestingly, we found that this desilylation is not the ordinary protodesilylation under HCl/H_2O conditions.[17] Since there was no deuterium incorporation under DCl/D_2O conditions, desilylation most likely occurred by the electron transfer from an allylic silane intermediate to the *p*-benzoquinone and a subsequent desilylation and deprotonation sequence (Scheme 2).[18]



Scheme 1.



Scheme 2.

Several control experiments were conducted to assess the effects of the 2-PyMe$_2$Si group. When the DA reaction of **1** and *p*-benzoquinone was performed at elevated temperature (50 °C), the reaction rate did increase as expected. However, presumably because of the thermal instability of **1** in acidic aqueous media, the product **5** was obtained in lower yield (85% after 22 h). Therefore, all the control experiments were performed at room temperature (Table 1). Decreasing the amount of HCl added slowed down the reaction enormously and only a trace amount of **5** was formed with starting material **1** recovered (entries 2 and 3). On the other hand, the addition of 2.0 equivalents of HCl did not affect the rate and yield. We believe that at least 1.0 equivalent of HCl is required for the diene **1** to form molecular aggregates and that the reaction probably occurs in the interior of aggregates with enhanced hydrophobic interactions,[13] and not in the aqueous bulk phase.[8] The use of H_2SO_4 also gave rise to a rate enhancement, but not as dramatic as that with HCl (entry 4). In the reaction, the added HCl should play a major role as water-solubilizing agent for 2-PyMe$_2$Si-substituted diene by complexing with pyridyl group, but not as dienophile activator. In accord with this assumption, the reaction in Et_2O/toluene with HCl gave **5** in 22% yield after 38 h (entry 5). The reaction in Et_2O/

Table 1. Aqueous Diels–Alder reactions under various conditions.[a]

Entry	Diene	Solvent	Additive [equiv.]	Time [h]	Yield [%][b]
1	**1**	H_2O	HCl (1.0)[c]	38	quant.
2	**1**	H_2O	HCl (0.2)	47	2
3	**1**	H_2O	– –	89	4
4	**1**	H_2O	H_2SO_4 (1.0)	38	73
5	**1**	Et_2O/toluene	HCl (1.0)	38	22
6	**1**	Et_2O/toluene	–	38	6
7	**4**	H_2O	HCl (1.0)	38	0
8	1,3-pentadiene	H_2O	**7** (1.0) + HCl (1.0)	38	0

[a] All reactions were performed at room temperature using 1,3-diene (1.0 equivalent, 0.5 M concentration) and *p*-benzoquinone (3.0 equivalents).
[b] Isolated yields.
[c] The addition of 2.0 equivalents of HCl did not affect the rate and yield.

toluene without HCl also resulted in much lower yield of the product (6%) with 88% recovery of diene **1** (entry 6), indicating the huge rate acceleration in water. Fleming has reported that the related DA reaction of 1-trimethylsilyl-1,3-butadiene with substituted benzoquinone requires extremely harsh conditions (32% yield after 24 h at 140 °C).[19] The most striking contrast was seen in the reaction with the $PhMe_2Si$-substituted 1,3-diene **4** giving no cycloadduct at all in water (entry 7).

Next, we examined the aqueous reaction of 1,3-pentadiene with *p*-benzoquinone in the presence of protonated dimethyl(*n*-octyl)(2-pyridyl)silane (**7**) as a surfactant. The hard-to-dissolve 1,3-pentadiene dissolved in water when **7** and HCl were added. Thereafter, *p*-benzoquinone was added to the solution. However, in sharp contrast with the reaction of **1**, no cycloadduct was observed at room temperature (entry 8). These results are in line with the previous reports by other groups that the rate accelerations induced by external surfactants are generally modest and even retardations are observed.[8b,10g,10j,20] It is apparent that the use of a reacting surfactant has an advantage in terms of reactivity over the combined use of an external surfactant.

Aqueous Diels–Alder Reactions of 2-$PyMe_2Si$-Substituted 1,3-Dienes

Having established the viability of aqueous DA reactions, other 2-$PyMe_2Si$-substituted 1,3-dienes and dienophiles were subjected to the aqueous DA reaction (Table 2). The diene **2** also underwent DA reaction with *p*-benzoquinone to afford the substituted naphthoquinone **8** in quantitative yield (entry 1). The DA reaction of **1** with *N*-ethylmaleimide proceeded smoothly giving the cycloadduct **9** in 91% yield after 1 h. Unlike the reaction with *p*-benzoquinone, the initial adduct did not undergo the subsequent desilylation/oxidation sequence. Moreover, the reaction proceeded in a virtually completely diastereoselective fashion, following the usual *endo* selectivity. The relative stereochemistry was unambiguously confirmed by X-ray crystal structure analysis.

The aqueous DA reaction of **3** with *p*-benzoquinone was complete within 1 h to give the cycloadduct **10** (82% yield) after silica gel chromatography (entry 3). In this case, a catalytic amount of HCl (0.2 equivalents) was enough to promote the reaction. Interestingly, the formation of molecular aggregates (average hydrodynamic radii: 65 nm) was observed even at the end of the reaction. Moreover, the rate acceleration in water was again observed. Changing the solvent to Et_2O/toluene (containing 1.0 equivalent of HCl) resulted in 12% yield of **10** under otherwise identical conditions.

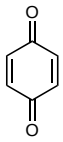
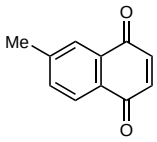
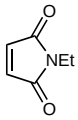
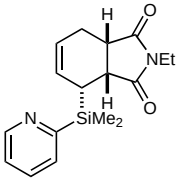
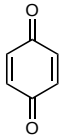
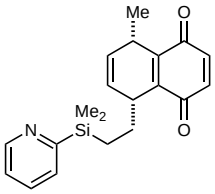
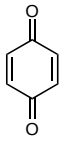
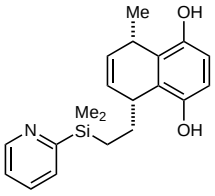
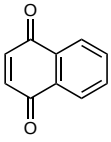
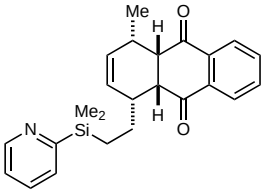
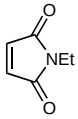
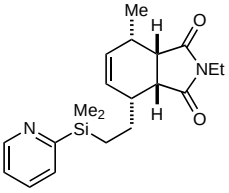
The formation of **10** may be worth a comment. Since we observed only the non-oxidized cycloadduct in the crude reaction mixture, the oxidation presumably took place on silica gel with *p*-benzoquinone which was employed in an excess amount (3.0 equivalents). In line with this assumption, the oxidized product **10** was not formed when the excess amount (2.0 equivalents) of **3** was employed (entry 4). In this case, initial adduct was isomerized to hydroquinone **11** during the silica gel chromatography.

The diene **3** also underwent aqueous DA reactions with naphthoquinone and *N*-ethylmaleimide giving the cycloadducts **12** and **13** in 90 and 88% isolated yield, respectively (entries 5 and 6). In these cases, the initial adducts were not oxidized. Again, the reaction proved to be *endo* selective. The ^1H NMR analysis and NOE experiments supported the proposed relative stereochemistry.

Removal of 2-$PyMe_2Si$ Group

In our strategy, the 2-$PyMe_2Si$ group must be removed after the aqueous reaction. First, we examined the direct removal of the 2-$PyMe_2Si$ group from the DA cycloadducts. For example, we subjected **13** to the typical 2-

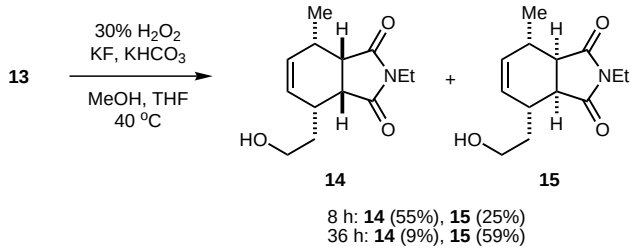
Table 2. Aqueous Diels–Alder reactions of 2-PyMe_2Si-substituted 1,3-dienes.

Entry	Diene	Dienophile	Product		Time [h]	Yield [%][c]
1[a]	**2**			**8**	38	quant.
2[b]	**1**			**9**	1	91
3[a]	**3**			**10**	1	82 (81)[d]
4[b]	**3**			**11**	1	91
5[b]	**3**			**12**	8	90
6[b]	**3**			**13**	0.5	88

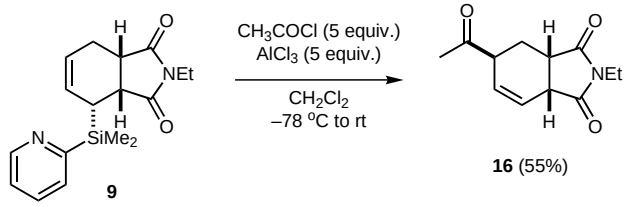
[a] The reactions were performed at room temperature using 1,3-diene (1.0 equivalent, 0.5 M concentration), dienophile (3.0 equivalents), and HCl (1.0 equivalent) in water.
[b] The reactions were performed at room temperature using 1,3-diene (2.0 equivalents, 0.5 M concentration), dienophile (1.0 equivalent), and HCl (2.0 equivalents) in water.
[c] Isolated yields.
[d] 0.2 equivalents of HCl were employed.

PyMe_2Si group oxidation conditions (H_2O_2/KF/$KHCO_3$ in MeOH/THF at 40 °C);[5c,21] this produced the corresponding alcohol **14**, together with the *exo* isomer **15** (**14**:**15** = 69:31; Scheme 3). Under the prolonged reaction time, the selective production of **15** is possible (**14**:**15** = 13:87). We assume that the isomerization to the *exo* isomer most likely occurred *via* enolization under the slightly basic nature of the reaction media, but not *via* the retro-DA reaction. In practice, the cycloadduct **13** did not undergo either a retro-DA reaction or isomerization under thermal conditions (40 °C in THF/MeOH).

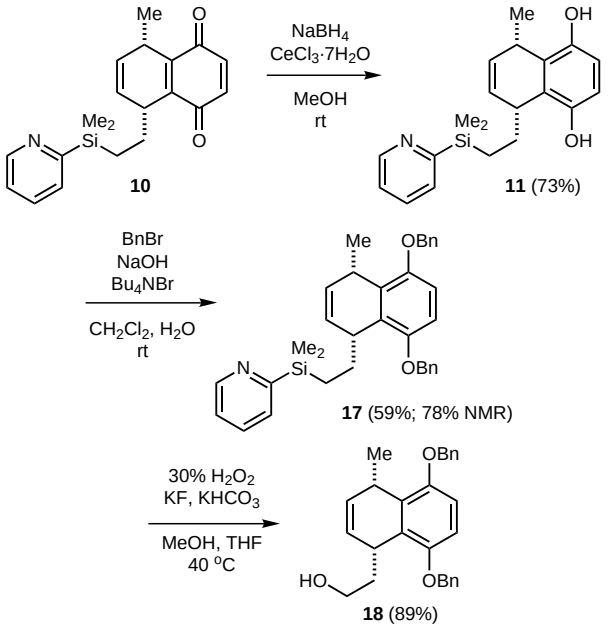
By taking advantage of the allylic silane nature of the cycloadduct **9**, electrophilic substitution can also be



Scheme 3.



Scheme 4.



Scheme 5.

utilized as a protocol for the removal of the 2-$PyMe_2Si$ group. For example, treatment of **9** with CH_3COCl in the presence of $AlCl_3$ afforded the methyl ketone **16** in 55% yield (Scheme 4). The reaction proved to be highly stereoselective following the usual *anti* attack of the electrophile.[22] The relative stereochemistry was confirmed by the ^1H NMR analysis and NOE experiments. Quite interestingly, however, the allylic silane **9** exhibits remarkably high stability toward protic acids. The treatment of **9** with TsOH (3 equivalents) under reflux in benzene or with HCl (10 equivalents) under reflux in water did not cause any protodesilylation (**9** was recovered in over 80% yield in both cases). These results were in sharp contrast with those of Fleming, where the similar allylic silane underwent facile protodesilylation with TsOH under reflux in benzene.[19]

Since the 2-$PyMe_2Si$ group is quite stable under various reaction conditions,[5] the intervention of several synthetic manipulations between the aqueous reaction and the final removal step is also feasible (Scheme 5). For example, the reduction of **10** in $NaBH_4/CeCl_3$ system afforded the substituted hydroquinone **11** in 73% yield. The protection of the phenolic hydroxy groups with benzyl groups afforded **17** in 59% yield (78% by NMR spectroscopy). Importantly, the 2-$PyMe_2Si$ group was unaffected throughout these transformations, which indicates the reasonable chemical stability of this group. Finally, the oxidation of **17** with H_2O_2 afforded **18** in 89% isolated yield without affecting the C–C double bond and benzyl protecting group or eroding the stereochemistry at the allylic carbon atoms. This specific 2-$PyMe_2Si$ group removing protocol substantially augments the value of our methodology.

Conclusions

A novel methodology for aqueous organic reactions utilizing a removable hydrophilic group has been developed. The 2-$PyMe_2Si$ group was successfully exploited as such a removable hydrophilic group. It was found that organic compounds having a 2-$PyMe_2Si$ group do form molecular aggregates in water when 1.0 equivalent of HCl is added, as evidenced by dynamic light-scattering experiments. Dramatic rate accelerations were observed in the aqueous DA reactions of 2-$PyMe_2Si$-substituted 1,3-dienes with dienophiles. The removal of the 2-$PyMe_2Si$ group from the products was easily accomplished by desilylation, H_2O_2 oxidation, or electrophilic substitution. Importantly, the strategy described herein should not be limited to the aqueous Diels–Alder reaction and can in principle be applied to the other aqueous organic reactions as well. The extensions to the other aqueous organic reactions as well as the development of other removable hydrophilic groups are currently underway.

Experimental Section

General Methods

NMR spectra were recorded on Varian GEMINI-2000 (^1H 300 MHz, ^{13}C 75 MHz), JEOL A-400 (^1H 400 MHz, ^{13}C 100 MHz), and JEOL A-500 (^1H 500 MHz, ^{13}C 125 MHz) spectrometers in $CDCl_3$ with internal standards (7.26 ppm ^1H, 77.0 ppm ^{13}C). Mass spectra (EI) were recorded on a JMS-SX102A spectrometer. Infrared spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer. Gel permeation

chromatography was carried out with Japan Analytical Industry LC-918. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. 3-Phenyldimethylsilylpropenal,[23] 2-PyMe$_2$Si-substituted 1,3-dienes **1** and **2**,[5h] (*E*,*E*)-1-bromo-2,4-hexadiene,[16] and dimethyl(*n*-octyl)(2-pyridyl)silane (**7**) [5c] were prepared according to the published procedures.

2-PyMe$_2$Si-Substituted Diene 3

To a solution of 2-pyridyltrimethylsilane (201 mg, 1.33 mmol) in dry Et$_2$O (2 mL) was added dropwise a solution of *t*-BuLi (1.58 mmol, 1.37 M solution in pentane) at $-78\,^{\circ}$C. The mixture was stirred for additional 30 min. To the resultant solution of [(2-pyridyldimethylsilyl)methyl]lithium was added (*E*,*E*)-1-bromo-hexa-2,4-diene (256 mg, 1.59 mmol) at $-78\,^{\circ}$C and the mixture was stirred for 1 h. After stirring the mixture at room temperature for 11 h, the reaction was quenched with water. Extractive work-up and subsequent silica gel chromatography (hexane/EtOAc = 10/1 as eluents) afforded **3** as a colorless oil; yield: 147 mg (48%); ^{1}H NMR (300 MHz): $\delta = 0.32$ (s, 6H), 0.90 – 0.96 (m, 2H), 1.70 (d, J = 6.3 Hz, 3H), 2.06 – 2.14 (m, 2H), 5.47 – 5.60 (m, 2H), 5.90 – 6.02 (m, 2H), 7.18 (ddd, J = 7.5, 4.5, 1.5 Hz, 1H), 7.47 (dt, J = 7.5, 1.5 Hz, 1H), 7.57 (td, J = 7.5, 1.5 Hz, 1H), 8.77 (dt, J = 4.5, 1.5 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = -3.6$, 14.5, 18.0, 26.7, 122.7, 126.6, 129.06, 120.07, 131.6, 133.9, 134.3, 150.1, 167.5. IR (neat): $\nu = 3015$, 2957, 1576, 1418, 1248 cm^{-1}; anal. calcd. for $C_{14}H_{21}NSi$: C 72.66, H 9.15, N 6.05; found: C 72.68, H 9.25, N 6.00; HRMS: *m/z* calcd. for $C_{14}H_{21}NSi$: 231.1443; found: 231.1444.

PhMe$_2$Si-Substituted Diene 4

To a suspension of methyltriphenylphosphonium bromide (1.43 g, 4.0 mmol) in Et$_2$O (4 mL) was added BuLi (4.0 mmol, 1.50 M in hexane) at room temperature. After stirring the mixture for 1 h, 3-phenyldimethylsilylpropenal (745 mg, 4.0 mmol) was added and the mixture was refluxed for 15 h. Filtration, extractive work-up, and subsequent silica gel chromatography (hexane as eluent) afforded **4** as a colorless oil; yield: 319 mg (42%); ^{1}H NMR (300 MHz): $\delta = 0.37$ (s, 6H), 5.15 (dd, J = 9.9, 1.8 Hz, 1H), 5.25 (dd, J = 16.8, 1.8 Hz, 1H), 6.00 (dd, J = 18.0, 0.6 Hz, 1H), 6.39 (dtd, J = 16.8, 9.9, 0.6 Hz, 1H), 6.59 (dd, J = 18.0, 9.9 Hz, 1H), 7.34 – 7.39 (m, 3H), 7.51 – 7.55 (m, 2H); ^{13}C NMR (75 MHz): $\delta = -2.8$, 118.3, 127.9, 129.1, 132.4, 133.9, 138.6, 139.8, 146.3. IR (neat): $\nu = 2954$, 1572, 1428, 1248 cm^{-1}; anal. calcd. for $C_{12}H_{16}Si$: C 76.53, H 8.56; found: C 76.34, H 8.70; HRMS: *m/z* calcd. for $C_{12}H_{16}Si$: 188.1021; found: 188.1024.

Typical Procedure for the Diels–Alder Reaction of 2-PyMe$_2$Si-Substituted 1,3-Diene with Dienophile (Scheme 1)

To a solution of HCl (0.5 mmol) in water (1 mL) was added **1** (95 mg, 0.5 mmol) and the mixture was stirred at room temperature for 10 min. To this mixture was added *p*-benzoquinone (162 mg, 1.5 mmol) in one portion. After stirring the mixture at room temperature for 38 h, $NaHCO_3$ was added to the mixture until the aqueous phase became neutral. Extractive work-up and subsequent silica gel chromatography afforded naphthoquinone; yield: 79 mg (quantitative).

Cycloadduct 9

^{1}H NMR (300 MHz): $\delta = 0.47$ (s, 3H), 0.56 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H), 2.12 – 2.22 (m, 2H), 2.63 (ddd, J = 15.0, 6.0, 1.8 Hz, 1H), 3.09 (ddd, J = 8.7, 7.8, 1.8 Hz, 1H), 3.27 (dd, J = 8.7, 6.0Hz, 1H), 3.44 (q, J = 7.2 Hz, 2H), 5.86 – 5.99 (m, 2H), 7.21 – 7.25 (m, 1H), 7.61 – 7.66 (m, 2H), 8.76 (dm, J = 4.8 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = -3.9$, -3.4, 13.3, 23.1, 24.4, 33.9, 41.0, 41.7, 123.0, 129.3, 129.7, 129.9, 134.4, 150.1, 167.4, 179.6, 180.2; IR (KBr): $\nu = 1692$, 1410, 1347, 1246, 1229 cm^{-1}. HRMS: *m/z* calcd. for $C_{17}H_{22}N_2O_2Si$: 314.1451; found: 314.1451.

The relative stereochemistry of **9** was determined by an X-ray crystal structure analysis (Figure 4). Crystal data: $C_{17}H_{22}N_2O_2Si$, M = 314.46, orthorhombic, space group *Pbca* (No. 61), a = 8.4169(3) Å, b = 18.1734(5) Å, c = 22.1037(8) Å, V = 3381.1(2) Å^3, $Z = 8$, $D_c = 1.235$ g/cm^3. Intensity data were measured on a Rigaku RAXIS imaging plate area detector with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å). The data were collected at 23 ± 1 °C to a maximum 2θ value of 55.0 . Of the 28282 reflections that were collected, 4311 were unique ($R_{int} = 0.038$); equivalent reflections were merged. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement on F was based on 2614 observed reflections ($I > 3.00\sigma(I)$) and 222 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of $R = 0.056$ ($R_w = 0.059$). The standard deviation of an observation of unit weight was 1.74. All calculations were performed using the CrystalStructure crystallographic software package. Tables of atomic coordinates, anisotropic displacement parameters, bond lengths, bond angles, and torsion angles are listed in the Supporting Information. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-176393. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax.: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

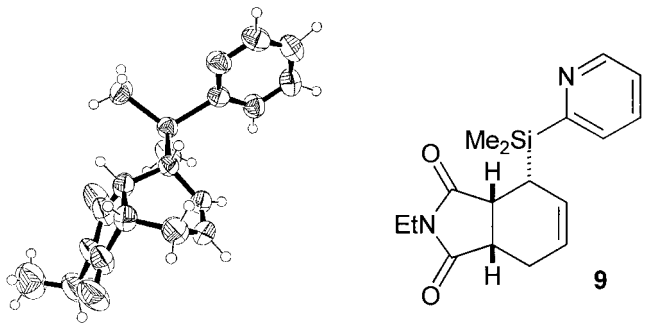


Figure 4.

Cycloadduct 10

^{1}H NMR (400 MHz): δ = 0.26 (s, 3H), 0.28 (s, 3H), 0.83 – 0.89 (m, 2H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.35 – 1.46 (m, 1H), 1.66 – 1.77 (m, 1H), 3.31 – 3.40 (m, 2H), 5.76 – 5.83 (m, 2H), 6.64 (d, *J* = 10.1 Hz, 1H), 6.67 (d, *J* = 10.1 Hz, 1H), 7.15 (ddd, *J* = 7.5, 5.1, 1.8 Hz, 1H), 7.43 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.54 (td, *J* = 7.5, 1.8 Hz, 1H), 8.71 (ddd, *J* = 5.1, 1.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz): δ = – 3.9, – 3.8, 11.6, 22.5, 29.7, 30.8, 36.6, 122.8, 126.8, 129.1, 130.0, 133.9, 136.36, 136.37, 143.2, 144.8, 150.1, 167.1, 186.8, 186.9; IR (neat): ν = 2961, 1651, 1453, 1294, 1248, 841, 750 cm^{-1}; HRMS: *m/z* calcd. for $C_{20}H_{23}NO_2Si$: 337.1498; found: 337.1512.

Cycloadduct 12

^{1}H NMR (500 MHz): δ = 0.30 (s, 3H), 0.32 (s, 3H), 0.70 (d, *J* = 7.6 Hz, 3H), 0.76 (td, *J* = 12.8, 4.6 Hz, 1H), 0.96 (td, *J* = 12.9, 4.6 Hz, 1H), 1.74 – 1.82 (m, 1H), 1.88 – 1.95 (m, 1H), 2.25 – 2.30 (m, 1H), 2.70 – 2.75 (m, 1H), 3.38 (dd, *J* = 7.4, 5.2 Hz, 1H), 3.50 (dd, *J* = 5.2, 5.2 Hz, 1H), 5.57 (dt, *J* = 10.4, 3.4 Hz, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 7.22 – 7.24 (m, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.68 – 7.72 (m, 2H), 7.87 – 7.90 (m, 1H), 8.03 – 8.06 (m, 1H), 8.74 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (75 MHz): δ = – 3.9, – 3.8, 12.9, 18.4, 26.4, 32.0, 40.1, 48.4, 52.4, 122.7, 125.8, 126.4, 128.8, 129.0, 129.9, 133.5, 134.0, 134.1, 135.3, 137.6, 149.9, 167.2, 198.5, 199.2; IR (KBr): ν = 1690, 1248 cm^{-1}; HRMS: *m/z* calcd. for $C_{24}H_{27}NO_2Si$: 389.1811; found: 389.1809.

The relative stereochemistry of **12** was determined on the basis of the coupling constants and the NOE experiments described below (Figure 5).

Cycloadduct 13

^{1}H NMR (300 MHz): δ = 0.36 (s, 6H), 1.03 (tm, *J* = 7.2 Hz, 5H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.77 – 1.89 (m, 1H), 1.93 – 2.06 (m, 1H), 2.11 – 2.14 (m, 1H), 2.31 – 2.36 (m, 1H), 2.89 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.08 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.41 (q, *J* = 7.2 Hz, 2H), 5.60 (dt, *J* = 9.0, 2.7 Hz, 1H), 5.67 (dt, *J* = 9.0, 2.7 Hz, 1H), 7.19 (dd, *J* = 4.8, 2.4 Hz, 1H), 7.53 (dm, *J* = 7.2 Hz, 1H), 7.59 (tm, *J* = 7.2 Hz, 1H), 8.76 (dm, *J* = 4.8 Hz, 1H); ^{13}C NMR (125 MHz): δ = – 3.8, – 3.6, 13.0, 13.4, 16.6, 25.1, 31.1, 33.2, 39.8, 43.4, 45.3, 122.7, 129.1, 133.0, 133.9, 134.0, 150.0, 167.4, 177.3 (two carbons); IR (neat): ν = 1698, 1404, 1352, 1246, 1231 cm^{-1}; HRMS: *m/z* calcd. for $C_{20}H_{28}N_2O_2Si$: 356.1919; found: 356.1920.

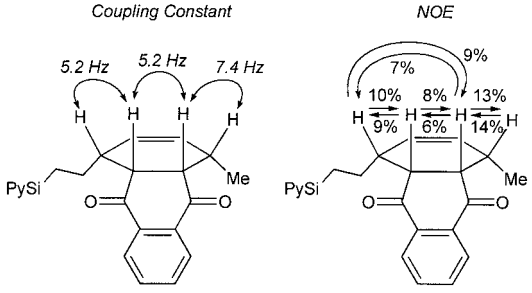


Figure 5.

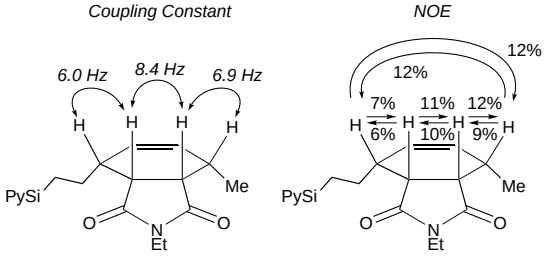


Figure 6.

The relative stereochemistry of **13** was determined on the basis of the coupling constants and the NOE experiments described below (Figure 6).

Procedure for the Direct Oxidative Removal of 2-PyMe$_2$Si Group from the Diels–Alder Cycloadduct

To a mixture of KF (24.6 mg, 0.41 mmol) and $KHCO_3$ (41.3 mg, 0.41 mmol) in MeOH (1 mL) and THF (1 mL) were added **13** (71.6 mg, 0.20 mmol) and then 30% aqueous H_2O_2 (0.68 g, 6.00 mmol). The mixture was stirred at 40 °C for 8 h. After being cooled at room temperature, the reaction mixture was treated with water (3 mL). The mixture was extracted with EtOAc and the combined organic phase was washed successively with 15% aqueous $Na_2S_2O_3$ (3 mL). Drying over $MgSO_4$ and subsequent gel permeation chromatography afforded **14** (yield: 26.4 mg, 55%) and **15** (yield: 11.8 mg, 25%).

Alcohol 14: ^{1}H NMR (300 MHz): δ = 1.07 (t, *J* = 7.2 Hz, 3H), 1.46 (d, *J* = 7.5 Hz, 3H), 1.83 (s, 1H), 2.00 – 2.10 (m, 1H), 2.20 – 2.32 (m, 1H), 2.43 – 2.49 (m, 2H), 2.99 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.27 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.45 (q, *J* = 7.2 Hz, 2H), 3.75 – 3.83 (m, 1H), 3.91 – 3.98 (m, 1H), 5.61 – 5.70 (m, 2H); ^{13}C NMR (125 MHz): δ = 13.1, 16.6, 31.1, 33.4, 33.6, 33.8, 43.7, 45.3, 61.4, 132.4, 134.6, 177.3, 178.2. IR (neat): ν = 3440, 1684, 1406, 1352, 1231 cm^{-1}. HRMS: *m/z* calcd. for $C_{13}H_{19}NO_3$: 237.1365; found: 237.1368.

The relative stereochemistry of **14** was determined on the basis of the coupling constants and the NOE experiments described below (Figure 7).

Alcohol 15: ^{1}H NMR (500 MHz): δ = 1.16 (t, *J* = 7.3 Hz, 3H), 1.34 (d, *J* = 7.1 Hz, 3H), 1.83 – 1.87 (m, 1H), 1.88 – 1.96 (m, 1H), 2.19 (tm, *J* = 7.1 Hz, 2H), 2.45 – 2.48 (m, 2H), 2.79 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.85 (m, 2H), 5.66 – 5.71 (m, 2H); ^{13}C NMR (125 MHz): δ = 13.0, 20.9, 30.2, 30.7, 33.6, 39.0, 43.7, 45.9, 59.9, 130.9, 132.9, 178.7, 180.4; IR (neat): ν = 3447, 1698, 1404, 1350, 1227 cm^{-1}; HRMS: *m/z* calcd. for $C_{13}H_{19}NO_3$: 237.1365; found: 237.1366.

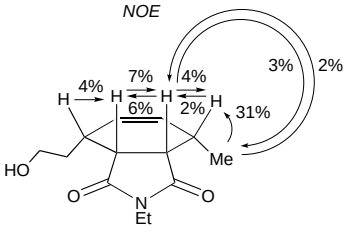


Figure 7.

The relative stereochemistry of **15** was determined on the basis of the coupling constants and the NOE experiments described below (Figure 8).

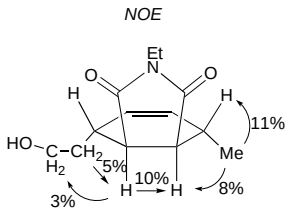


Figure 8.

Procedure for the Acylation of Allylic Silane 9

To a mixture of CH_3COCl (40.8 mg, 0.52 mmol) and $AlCl_3$ (68.2 mg, 0.51 mmol) in CH_2Cl_2 (0.5 mL) was added slowly a solution of **9** (32.0 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL) at $-78\,^{\circ}C$. After stirring the mixture for 24 h at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$. Drying over Na_2SO_4 and subsequent gel permeation chromatography afforded **16** (319 mg, 42%) as a colorless oil; yield: 319 mg (42%); ^1H NMR (500 MHz): $\delta = 1.14$ (t, $J =$ 7.3 Hz, 3H), 1.98 (ddd, $J = 13.7$, 8.6, 5.8 Hz, 1H), 2.18 – 2.25 (m, 1H), 2.23 (s, 3H), 3.05 – 3.09 (m, 1H), 3.23 (dt, $J = 8.3$, 5.8 Hz, 1H), 3.39 – 3.43 (m, 1H), 3.53 (q, $J = 7.3$ Hz, 2H), 6.01 (ddd, $J = 10.1$, 4.0, 2.5 Hz, 1H), 6.12 (dm, $J = 10.1$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 13.0$, 23.1, 28.4, 33.8, 37.5, 40.9, 45.4, 123.8, 127.6, 176.3, 178.4, 206.8; IR (neat): $\nu = 1698$, 1404, 1352, 1225 cm^{-1}; HRMS: *m/z* calcd. for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1052.

The relative stereochemistry of **16** was determined on the basis of the NOE experiments described below (Figure 9).

Synthetic Transformation/2-PyMe$_2$Si Group Removal Sequence from the Diels–Alder Cycloadduct

Reduction of 10: To a solution of **10** (2.27 g, 6.73 mmol) in MeOH (20 mL) were added $CeCl_3 \cdot 7H_2O$ (8.78 g, 23.6 mmol) and $NaBH_4$ (872 mg, 23.1 mmol) at 0 °C. After stirring the mixture at 0° for 30 min, the reaction was quenched with 1 N aqueous HCl (10 mL). Extractive work-up and subsequent silica gel chromatography (hexane/EtOAc = 5/1 to 1/1 as eluents) afforded **11**; yield: 1.67 g (73%); ^1H NMR (300 MHz): $\delta = 0.34$ (s, 3H), 0.38 (s, 3H), 0.90 – 1.11 (m, 2H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.50 – 1.62 (m, 1H), 2.07 – 2.18 (m, 1H), 3.53 – 3.59 (m, 2H), 5.96 (dd, $J = 9.9$, 4.8 Hz, 1H), 6.03 (dd, $J =$ 9.9, 4.8 Hz, 1H), 6.53 (d, $J = 8.9$ Hz, 1H), 6.64 (d, $J = 8.9$ Hz, 1H) 7.25 (ddd, $J = 7.5$, 4.8, 1.5 Hz, 1H), 7.54 (ddd, $J = 7.5$, 1.5, 1.2 Hz, 1H), 7.64 (td, $J = 7.5$, 1.5 Hz, 1H), 8.87 (ddd, $J = 4.8$, 1.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = -3.5$, -2.9, 12.2, 22.7, 30.1, 32.4, 36.7, 113.2, 113.8, 123.3, 127.8, 128.2, 128.3, 129.7, 131.6, 134.9, 146.5, 147.9, 149.8, 167.3; IR (neat): $\nu = 2442$, 1487, 1250 cm^{-1}. HRMS: *m/z* calcd. for $C_{20}H_{25}NO_2Si$: 339.1655; found: 339.1671.

Protection of 11: To a solution of **11** (87 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) was added 1 N aqueous solution of NaOH (0.5 mL, 0.5 mmol). To this solution were added tetrabutylammonium bromide (8.9 mg, 0.028 mmol) in CH_2Cl_2 (0.5 mL) and H_2O (0.5 mL), and then benzyl bromide (219 mg, 1.28 mmol). The reaction mixture was further stirred at room temperature for 40 min. Extractive work-up and subsequent silica gel chromatography (hexane/EtOAc = 10/1 as eluents) afforded **17**; yield: 78 mg (59%); ^1H NMR (300 MHz): $\delta = 0.26$ (s, 6H), 0.86 – 1.08 (m, 2H), 1.30 (d, $J = 6.9$ Hz, 3H), 1.41 – 1.54 (m, 1H), 1.97 – 2.08 (m, 1H), 3.62 – 3.75 (m, 2H), 4.99 (s, 2H), 5.01 (d, $J =$ 12.0 Hz, 1H), 5.06 (d, $J = 12.0$ Hz, 1H), 5.96 (dd, $J = 9.9$, 4.5 Hz, 1H), 6.03 (dd, $J = 9.9$, 4.8 Hz, 1H), 6.70 (s, 2H), 7.15 (ddd, $J =$ 7.5, 4.8, 1.5 Hz, 1H), 7.29 – 7.46 (m, 11H), 7.50 (td, $J = 7.5$, 1.5 Hz, 1H), 8.74 (dt, $J = 4.8$, 1.2 Hz, 1H); ^{13}C NMR (100 MHz): $\delta = -3.9$, -3.7, 12.4, 23.0, 30.2, 32.2, 37.6, 70.0, 70.1, 108.75, 108.77, 122.6, 126.9, 127.0, 127.55, 127.59, 128.2, 128.45, 128.46, 129.1, 130.1, 131.2, 131.5, 134.0, 137.78, 137.79, 149.9, 150.00, 150.04, 167.6; IR (neat): $\nu = 2957$, 1599, 1480, 1453, 1256, 1107 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{34}H_{37}NO_2Si$: 519.2594; found: 519.2588.

H_2O_2 Oxidation of 18: To a mixture of KF (15 mg, 0.26 mmol) and $KHCO_3$ (27 mg, 0.27 mmol) in MeOH (1 mL) and THF (1 mL) were added **17** (71 mg, 0.14 mmol) and then 30% aqueous H_2O_2 (0.47 g, 4.12 mmol). The mixture was stirred at 40 °C for 14 h. After being cooled at room temperature, the reaction mixture was treated with water (2 mL). The mixture was extracted with EtOAc (5 × 5 mL), and the combined organic phase was washed successively with 15% aqueous $Na_2S_2O_3$ (5 mL). Drying over Na_2SO_4 and removal of the solvents under reduced pressure afforded the crude product. Silica gel chromatography (hexane/EtOAc = 5/1 as eluents) of the crude product afforded **18**; yield: 49 mg (89%); ^1H NMR (300 MHz): $\delta = 1.35$ (d, $J = 6.6$ Hz, 3H), 1.50 – 1.80 (br, 1 H) 1.85 – 1.93 (m, 2H), 3.66 (t, $J = 6.0$ Hz, 2H), 3.72 – 3.86 (m, 2H), 4.98 – 5.11 (m, 4H), 5.96 – 6.04 (m, 2H), 6.75 (d, $J = 9.0$ Hz, 1H), 6.79 (d, $J = 9.0$ Hz, 1H), 7.33 – 7.47 (m, 10 H); ^{13}C NMR (75 MHz): $\delta = 22.6$, 30.2, 31.4, 41.7, 60.9, 70.1, 70.9, 109.0, 109.2, 127.0, 127.5, 127.7, 128.1, 128.5, 128.6, 128.7, 129.4, 131.4, 131.6, 137.1, 137.6, 150.0, 150.4; IR (neat): $\nu = 3029$, 1599, 1482, 1453, 1258, 793, 737, 696 cm^{-1}. HRMS: *m/z* calcd. for $C_{27}H_{28}O_3$: 400.2038; found: 400.2037.

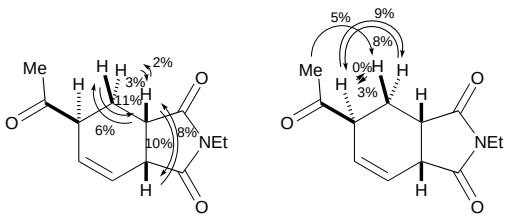


Figure 9.

Acknowledgements

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