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Tetrahedron 62 (2006) 7380–7389
Tetrahedron

Regioselectivity in the 1,3-dipolar cycloaddition of adamantylidenefulvene and its modification by inclusion in cyclodextrins' solutions

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Received 21 February 2006; revised 10 May 2006; accepted 11 May 2006
Available online 5 June 2006

Abstract—The 1,3-dipolar cycloaddition of adamantylidenefulvene (**1**) with 2 equiv of nitrile oxides **2a–d** gave 1/1 cycloadducts, **3a–d** and **4a–d**, as the major products, and four other 1/2 minor cycloadducts **5–8a**,**b**. The ratios of 1/1 cycloadducts **3a–d** to **4a–d** in THF solution were about 1/1 in the four different nitrile oxides **2a–d** studied and microwave was found to accelerate the reactions and enhance their yields. It is noteworthy that the regioselectivity of **3a**/**4a** was enhanced to 71/29 in β-cyclodextrin (β-CD) aqueous solution compared to that of 40/60 in the absence of β-CD. The regioselectivity of **3b**/**4b** was further enhanced to 99/1 when 4-*tert*-butylphenyl hydroximinoyl chloride (**9b**) was complexed with β-CD and then proceeded to react with **1**; this is in sharp contrast with that of 33/67 in the absence of β-CD. The binding constant of **1**·β-CD in acetone-d_6/D_2O (1/1) was determined to be 188±9 M^{-1} by ^1H NMR titration experiments. The binding mode of **1**·β-CD was further determined by ROESY experiment. Furthermore, molecular dynamic simulations were carried out to provide information of the complexation modes of **1**·β-CD, **3a**·β-CD, **4a**·β-CD, **9a**·β-CD, and **9b**·β-CD. It was found that both steric and electrostatic effects play important roles in determining the regio- and stereochemistry of 1,3-dipolar cycloaddition of **1**. Finally, β-CD is shown to serve as a chiral shift reagent to differentiate the enantiomers of **4a** in ^1H NMR.

1. Introduction

Cycloaddition reactions on fulvenes have attracted much attention because there are many possible reaction pathways involved in them and their reaction products are usually versatile and complicated.[1] Compounds containing isoxazolines or isoxazoles have also received considerable attention[2] because they are excellent precursors in transforming to a variety of bifunctional compounds[3] and they show diverse biological activity.[4] 1,3-Dipolar cycloaddition of fulvenes with benzonitrile oxide (**2a**) was first reported by Grünanger and co-workers in 1952,[5a] and recently elaborated by Nair and co-workers using 6-(2-phenylethenyl)fulvene.[5c] In their studies, at least 2–5 products that contained 1/1 and 1/2 cycloadducts were reported.[5] Even though the reactions of fulvenes with nitrile oxides lead to complex isoxazolines products, they provide us an opportunity to fine tune or control the reaction products.

Cyclodextrins (CDs) can be described as a truncated cone with the narrow rim bearing the primary hydroxy groups and the secondary hydroxy groups as the wider rim, and they possess hydrophobic cavities that enable them to include a variety of organic compounds in aqueous solution[6,7] (Chart 1). Because of their inclusion ability, CDs have become one of the most commonly used host systems and have shown great potential in areas such as drug delivery[6,8] and chromatographic separations.[6,9] Furthermore, CDs have been found to enhance reaction rates and control product

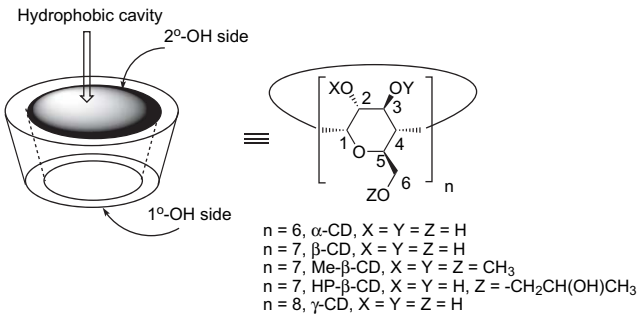

Chart 1.

Keywords: Regioselectivity; Fulvene; Steric effect; Inclusion complex; 1,3-Dipolar cycloaddition; Chiral shift reagent; Molecular reactor.
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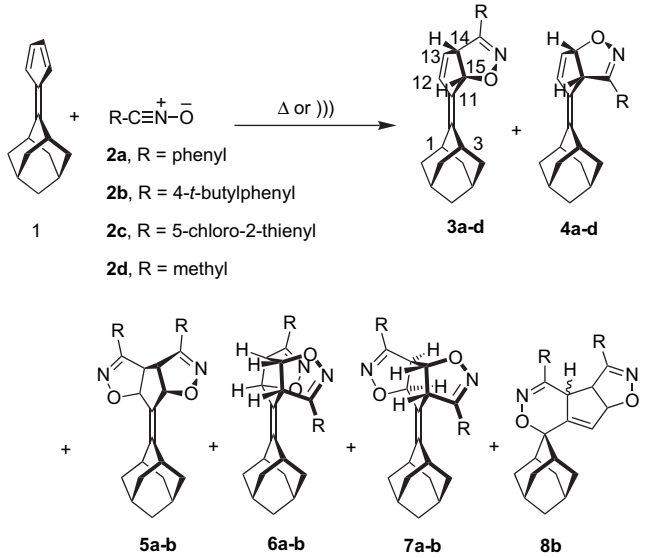
doi:10.1016/j.tet.2006.05.021

distribution in various reactions including nucleophilic substitution,[6,7,10] electrophilic substitution,[6,11] Diels–Alder reactions,[6,12] and [2+2] photochemical cycloadditions.[6,13]

Rama Rao and co-workers have exploited the use of both CDs and baker's yeast together to enhance the enantioselectivity and regioselectivity of the 1,3-dipolar cycloadditions in several molecular systems;[14] however, Simpson and co-workers later reported that baker's yeast was not required to achieve the high selectivities.[15a] Moreover, Easton and co-workers have elegantly demonstrated that the regioselectivity can be *dramatically reversed* by a dipolarophile (e.g., terminal alkyne) tethered β-CD in 1,3-dipolar cycloaddition.[15] As advocated by Easton and co-workers[3b,c,9b,15] and our continuous interests in using CDs as molecular reactors,[7e,12f,g,13a,c] we report here our studies of the 1,3-dipolar cycloaddition of adamantylidenefulvene (**1**) with nitrile oxides **2a–d** and the application of CDs to modulate the regio- and stereochemistry of the reaction, and indeed, a highly regioselective product distribution is achieved (vide infra).

2. Results and discussion

Adamantylidenefulvene (**1**) was prepared using a literature procedure.[16] The 1,3-dipolar cycloaddition of **1** with 2 equiv of nitrile oxides **2a–d** (R = phenyl, 4-*tert*-butylphenyl, 5-chloro-2-thienyl, and methyl) prepared in situ in THF solution gave a mixture of 2–6 products in total yields of 40–60%. The reaction took 24 h under reflux condition but was completed within 20 min under microwave irradiation and concurrently with higher yields (ca. 50–80%). Column chromatography on silica gel with *n*-hexane and ethyl acetate (20/1) as eluent afforded two major 1/1 cycloadducts **3** and **4** and 2–4 minor 1/2 cycloadducts **5–8** (Scheme 1). The ratios and yields of the major products **3** and **4** are shown in Table 1 and the minor 1/2 cycloadducts are: **5a** (8%), **6a** (6%), and **7a** (6%) when reacting with **2a**; **5b** (15%), **6b** (9%), **7b** (12%), and **8b** when reacting with **2b** (total yields, 50–80%).



Scheme 1.

Table 1. Ratios (**3/4**) of the 1/1 cycloadducts from 1,3-dipolar cycloaddition of **1** with nitrile oxides **2a–d** in THF under thermal condition or microwave irradiation

Entry	Nitrile oxide	**3/4** ratio[a] (yield, %)	
		Thermal reaction[b]	Microwave irradiation[c]
1	**2a**, R = phenyl	60/40 (41%)	66/34 (59%)
2	**2b**, R = 4-*tert*-butylphenyl	51/49 (60%)	64/36 (51%)
3	**2c**, R = 5-chloro-2-thienyl	50/50 (40%)	60/40 (50%)
4	**2d**, R = methyl	49/51 (45%)	45/55 (60%)

[a] Product ratios were determined by ^{1}H NMR at 300 and 500 MHz; error limit ±5%.
[b] The reaction was refluxed in THF for 24 h.
[c] Microwave irradiation (20 min) was set at 300 W and temperature was controlled below 66 °C.

In principle, a [6+3] cycloaddition product (e.g., **8**) is also possible[1c,5b] in the 1,3-dipolar cycloaddition of **1** with nitrile oxides **2a–d**, however, only a trace of [6+3] product **8b** was observed in ^{1}H NMR spectra of the crude products. The molar ratio between **1** and benzonitrile oxide (**2a**) was varied to look for possible variation in product distribution, however, no obvious change was found despite that products' yield increased slightly at higher concentrations of the nitrile oxide. The reactions of **1** with four different nitrile oxides **2a–d** gave 1/1 cycloadducts **3a–d** and **4a–d** as the major products. In order to rationalize product distribution of the reactions, AM1 calculation was carried out and the HOMO and LUMO energies of **1** and **2a–d** are summarized in Figure S-1. As can be seen, the HOMO energy of **1** is higher than those of the four dipoles, thus, the 1,3-dipolar cycloadditions of **1** with **2a–c** (but not **2d**), are believed to be $LUMO_{(dipole)}$–$HOMO_{(dipolarophile)}$ controlled reactions. For the reaction of **1** with **2d**, both the $LUMO_{(dipole)}$–$HOMO_{(dipolarophile)}$ and $HOMO_{(dipole)}$–$LUMO_{(dipolarophile)}$ interactions are important.

The structures of all cycloadducts were determined by ^{1}H, ^{13}C NMR, H,H-COSY, H,C-COSY, MS, and NOE spectral data. The regio and stereo structural assignments of a 1/1 cycloadduct **3b** is described as follows. Compound **3b** is assigned to be a 1/1 head-to-tail adduct of nitrile oxide on **1** where the C_{14} (one of the aliphatic tertiary carbon next to carbon atoms, δ 58.6) and C_{15} (a tertiary carbon next to one oxygen atom, δ 83.7) of the fused dihydrocyclopentaisoxazolines can be readily assigned from its ^{13}C NMR and DEPT. H_{14} and H_{15} can then be assigned through H,C-COSY from the identified C_{14} and C_{15}. From H,H-COSY, we found that H_{14} not only coupled with H_{15} and H_{13} but also coupled with H_{12}, therefore, NOE experiments were carried out to assist the assignment of H_{12} and H_{13}. When H_{14} was irradiated, substantial NOE was found on H_{15} (8.1%), H_{13} (3.6%), and on the *ortho*-protons of the aryl group (5.6%), whereas no NOE was found on H_{12}. In contrast, when H_{12} was irradiated, intense NOE was found on H_1 (15.1%) and H_{13} (6.4%), however, no NOE was found on H_{14}. Based on these observations, H_{12} and H_{13} can be assigned unambiguously and the results of NOE experiments on **3b** are summarized in Figure 1a. The peaks for C_{12} and C_{13} can subsequently be assigned from H,C-COSY through correlation with H_{12} and H_{13}, respectively. Finally, the structure of **3b** was confirmed by a single crystal

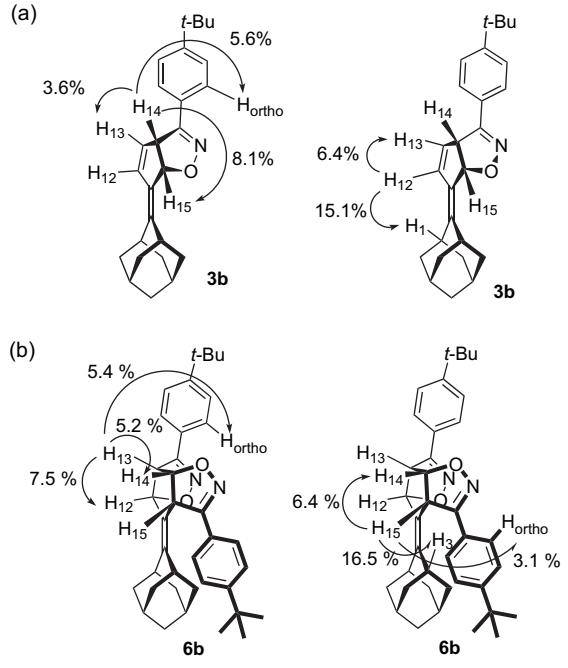


Figure 1. NOE results of (a) compound **3b** and (b) compound **6b**.

X-ray crystallography analysis to be a 1/1 head-to-tail cycloadduct (Fig. 2a).

The detailed regio and stereo structural assignment of a 1/2 cycloadduct **6b** is described in Supplementary data. NOE results (Fig. 1b) and single crystal X-ray crystallography of a 1/2 cycloadduct **6a**, an analogue of **6b**, confirmed the structure to be a *syn* head-to-tail biscycloadduct (Fig. 2b). The characteristic ^{1}H and ^{13}C NMR of all cycloadducts on the fused dihydro- and tetrahydrocyclopentaisoxazolines are summarized in Supplementary data (Tables S-1 and S-2).

2.1. Control of regioselectivity by reacting in CDs

After structural assignments of all products, we then explored the application of CDs on the control of regioselectivity of 1,3-dipolar cycloaddition of **1** with benzonitrile oxides (**2a**,**b**). The regioselectivity (**3a/4a**) of the 1,3-dipolar cycloaddition of **1** with **2a** changed from 60/40 in THF to 40/60 in acetone/water (v/v = 1/1) co-solvent.[17] It is noteworthy that the regioselectivity of **3/4** can be dramatically reversed when the 1,3-dipolar cycloaddition (between **1** and **2**) is executed in the presence of CDs (see Table 2). The regioselectivity reached a maximum value of 83/17 for **3a/4a** but was further enhanced to 99/1 for **3b/4b** when 6 equiv of β-CD versus **1** was added to the reaction mixture (Fig. 3a,b, and S-3). Interestingly, higher values of **3/4** were achieved if inclusion complex of hydroximinoyl chlorides (**9a**,**b**)·β-CD were prepared first (instead of **1**·β-CD), and then proceeded to react with the dipolarophile **1** (filled circles in Fig. 3a,b). The results imply that the hydroximinoyl chlorides **9a**,**b** form stronger complexes with β-CD than **1** does, because electrostatic interactions are involved between them.

There was basically no effect on the product distribution when either α- or γ-CD was used. This is understandable

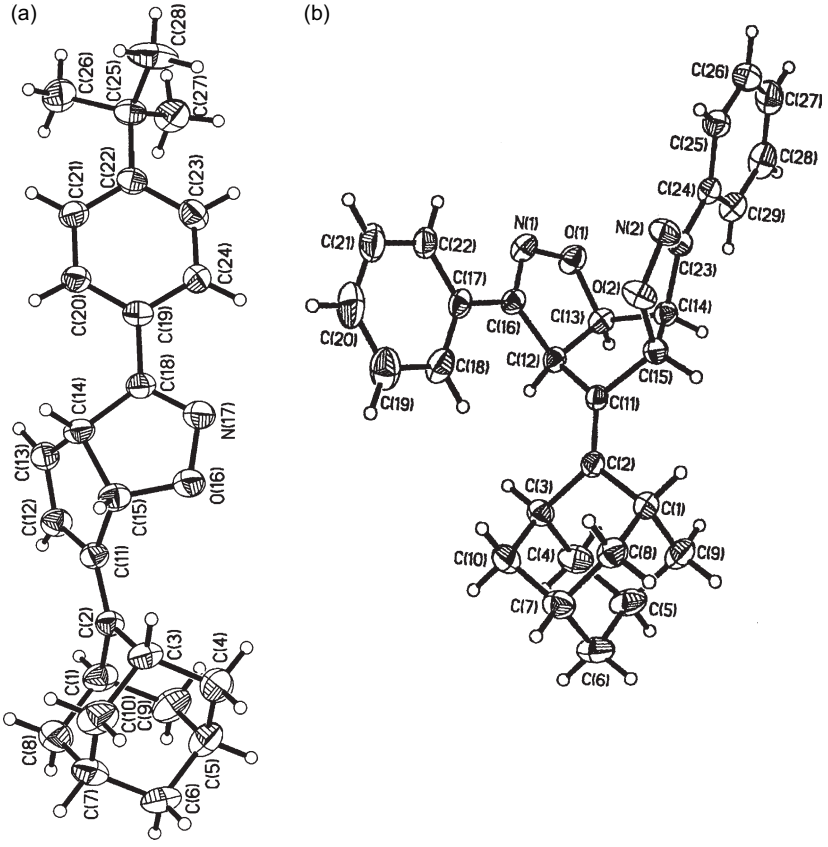


Figure 2. ORTEP structures of (a) compound **3b** and (b) compound **6a**.

Table 2. Ratios of cycloadducts (**3/4**) from 1,3-dipolar cycloaddition of **1** with benzonitrile oxide (**2a**) and 4-*tert*-butylphenyl nitrile oxide (**2b**) in various CD solutions at 310 K[a,b]

Entry	[CDs]/[**1**]	**3a/4a**		**3b/4b**	
		β-CD[c]	β-CD[d]	β-CD[c]	β-CD[d]
1	0	40/60	40/60	33/67	33/67
2	1.0	43/57	43/57	37/63	39/61
3	3.0	58/42	64/36	49/51	48/52
4	5.0	68/32	78/22	57/43	77/21
5	6.0	71/29	83/17	80/20	99/1

[a] Solvent system was acetone/H_2O (v/v = 1/1).
[b] The product ratio was determined by ^1H NMR integration; error limit is ±5%.
[c] Complex of **1**·β-CD was prepared first, followed by adding phenyl hydroximinoyl chloride **9a** or **9b** into the solution.
[d] Complex (**9a** or **9b**)·β-CD was prepared first, followed by adding **1** into the solution.

since the cavity of α-CD is known to bind adamantane moiety only shallowly; and the cavity of γ-CD is too large for a snug fit of the adamantane moiety. Permethylation on all hydroxyl groups of β-CD (i.e., Me–β-CD) or perhydroxypropylation on all primary alcohols of the β-CD (i.e., HP–β-CD), highly enhanced their water solubility, however, not much change on the regioselectivity was found in either cases. Furthermore, it is noteworthy that product yields of the reaction were in the range of 40–45% when [β-CD] was below 3 mM, but they decreased to 20–30% when [β-CD] was above 6 mM. In other words, our results show that a higher regioselectivity was accompanied with a lower reaction yield at high concentrations of β-CD. These results suggest that β-CD plays as a 'steric shield' instead of a 'promoter' in the 1,3-dipolar reactions studied here.

Evidences for complexation of **1** with β-CD came from ^1H NMR spectra, which showed that H_3 ($\Delta\delta=-0.03$ ppm) and H_5 ($\Delta\delta=-0.04$ ppm) of β-CD, oriented toward the interior of the CD cavity, were considerably upfield shifted in the presence of **1**. By contrast, H_1, H_2, H_4, and H_6 all located on the exterior wall of β-CD, either showed little downfield shifts or were unaffected (Fig. 4). These observations are consistent with the notion that a complex is formed between β-CD and **1**, and they most likely have 1/1 stoichiometric ratios, similar to those of adamantane derivatives found in several X-ray crystallography data.[18] The binding constant for complexation of **1** with β-CD was determined to be 188±9 M^{-1} by Benesi–Hilderbrand plot,[19] where the reciprocal chemical shift differences of guest **1** are plotted with the reciprocal concentration of β-CD (See Fig. S-2).

The regioselective results of 1,3-dipolar cycloadditions of **1** in β-CD can be explained by complexes **A** or **B**, where the hydrophilic nitrile oxide can only attack the fulvene from sterically less hindered sites. Complexes **C** and **D** are less likely because the cavity of β-CD is too small to accommodate both fulvene **1** and nitrile oxide **2a** concomitantly (Chart 2). Had complexes **C** and **D** been the favored complexes, one would have observed predominant formation of **4a**; however, **3a** became the major product when high equivalent of β-CD versus **1** was used. Furthermore,

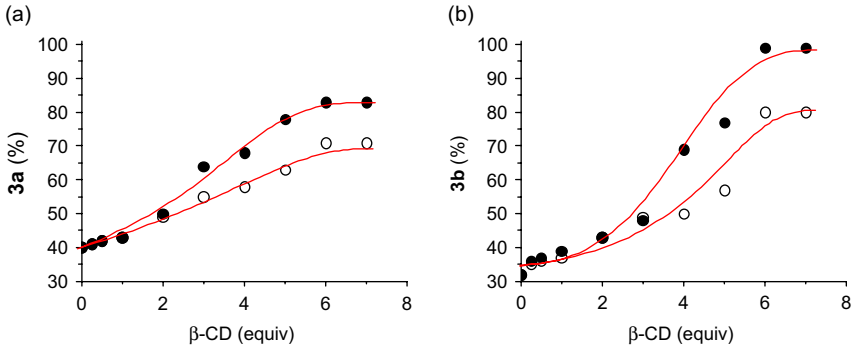


Figure 3. The percentage of (a) **3a** over **4a** and (b) **3b** over **4b** in the 1,3-dipolar cycloadditions of **1** (5 mM) with **2a** and **2b** (10 mM) in aqueous solution as a function of [β-CD]. Where ● denotes data obtained when inclusion complex of hydroximinoyl chloride (**9a** or **9b**)·β-CD was prepared first and proceeded to react with **1**, and ○ denotes data obtained when inclusion complex of **1**·β-CD was prepared first then proceeded to react with corresponding dipoles **2a** or **2b**.

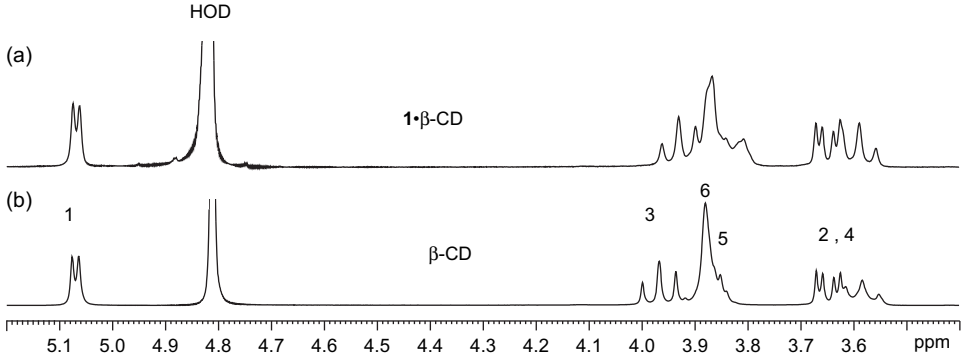


Figure 4. ^1H NMR spectra of (a) **1**·β-CD where [**1**]=[β-CD]=2 mM in D_2O, and (b) [β-CD]=5 mM in D_2O at 300 K.

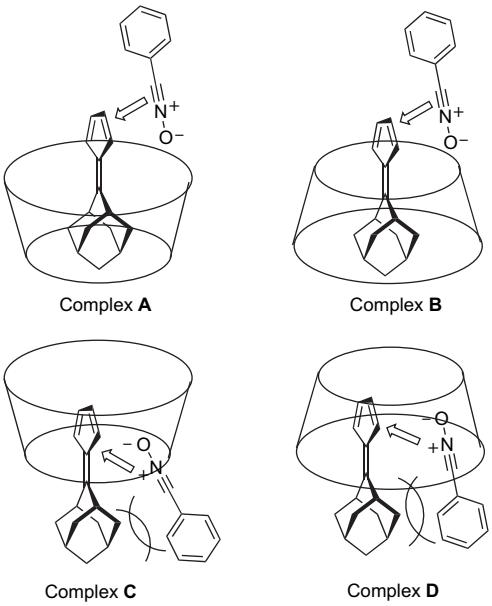


Chart 2.

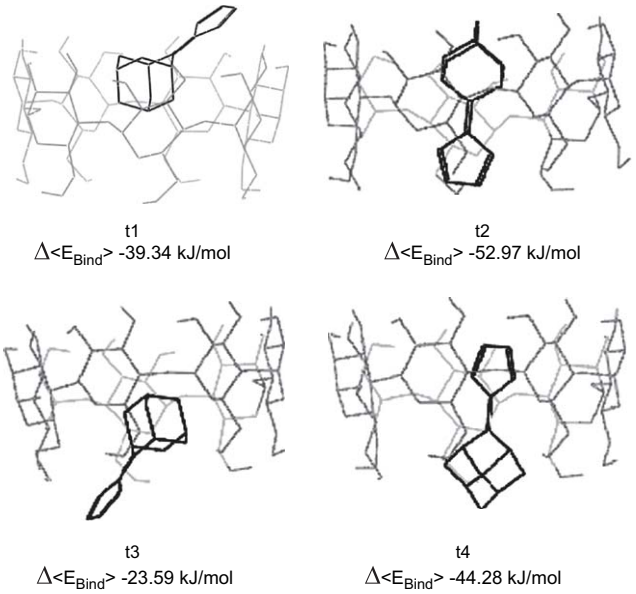


Figure 5. The calculated $\Delta\langle E_{\text{Bind}}\rangle$ of **1**·β-CD from four trajectories (t1–t4), each starting from a different binding configuration (see Supplementary data). For each trajectory, the lowest energy structure obtained from optimization of sampled structures during 5000 ps MD is shown. Hydrogen atoms are omitted for clarity, and all structures are shown with the wider secondary hydroxyl rim of β-CD on the top.

cycloadducts **3a** and **4a** were proven to be stable under the reaction conditions; therefore, they are formed in kinetically controlled processes. ROESY experiment (Fig. S-4)[20d] was carried out on **1**·β-CD (acetone-d_6/D_2O = 1/1), which suggests that complex **B** is the favored binding mode; namely, the reactive fulvene group is pointing toward the primary side of β-CD.

Previously, we have shown that molecular dynamic (MD) simulations[22–24] with a multi-trajectory approach are useful in explaining the product preference in a β-CD mediated Diels–Alder reaction;[12g] each trajectory starts with distinctly different host·guest geometry. The same approach was used here to examine the complexes of **1**·β-CD, **3a**·β-CD, **4a**·β-CD, **3a-TS**·β-CD, **4a-TS**·β-CD (TS stands for transition state structure, which was located quantum mechanically),[25] **9a**·β-CD, and **9b**·β-CD. MD simulations of **1**·β-CD showed trajectory t2, with the reactive fulvene pointing toward the primary side of β-CD, to be the statistically most stable binding mode and this is in agreement with the observed spectroscopic data (Figs. 5 and S-4). The calculated results of the products and their transition state structures with β-CD showed that on average both **3a** and **3a-TS** bound more tightly within β-CD than **4a** and **4a-TS** (see Supplementary data). For example, for **3a-TS**·β-CD the calculated $\Delta\langle E_{\text{Bind}}\rangle$ from different trajectories ranged from −38.03 to −70.62 kJ mol^{-1}, which are more stable than **4a-TS**·β-CD with $\Delta\langle E_{\text{Bind}}\rangle$ in the range of −26.41 to −60.11 kJ mol^{-1} (Tables S-6 and S-7). These results support the notion that the CD cavity provides steric control stabilizing the formation of the transition state structure **3a-TS**, giving **3a** as the major product.

It is noteworthy that the **3a/4a** product ratio reversed from 60/40 in THF to 40/60 in acetone/water (1/1). This may imply that when reacted in acetone/water (1/1) the transition state leading to **3a** is relatively destabilized compared to that leading to **4a**. Higher regioselectivity was achieved in the 1,3-dipolar cycloaddition of **1** when phenyl hydroximinoyl chloride (**9a**) was complexed with β-CD first and then proceeded to react with **1**. MD simulations of **1**·β-CD showed that, with the presence of adamantane moiety, the stability of **1**·β-CD is very dependent on how the guest molecule is bound in the CD cavity; the calculated binding energy, $\Delta\langle E_{\text{Bind}}\rangle$, of four different trajectories t1–t4 are −39.34, −52.97, −23.59, and −44.28 kJ mol^{-1}, respectively. It can be seen in Figure 5 that t2 and t4 enjoy stronger binding energy at the expense of blocking the ene group from reaction. For **9a**·β-CD, $\Delta\langle E_{\text{Bind}}\rangle$ is less trajectory dependent with a phenyl core (−47.01 and −51.00 kJ mol^{-1} for hydroximinoyl chloride pointing to the top and bottom rims of CD, respectively). In each trajectory, the hydroximinoyl chloride part moves in and out of β-CD rather frequently. The calculated results indicate that while **1**·β-CD might have binding modes with stronger binding energies, the modes effective for 1,3-dipolar cycloaddition are in fact having weaker binding energies than those of **9a**·β-CD. This explains the smaller regioselectivity when **1**·β-CD was prepared first.

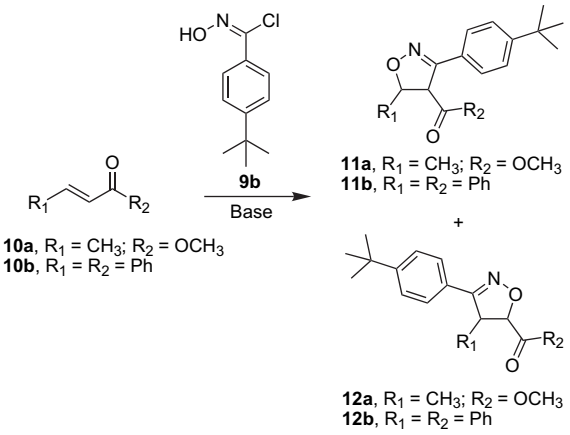
Easton and co-workers reported that 1,3-dipolar cycloaddition of a dipolarophile tethered β-CD with 4-*tert*-butylphenyl nitrile oxide (**2b**) led to an excellent regioselective product.[15a–c] Indeed, **3b** became the exclusive product and almost no **4b** was found when 4-*tert*-butylphenyl hydroximinoyl chlorides (**9b**) formed a complex with β-CD first and then proceeded to react with fulvene **1**. It would be desirable to obtain binding constants of the aryl hydroximinoyl chlorides **9a** and **9b** (precursors for nitrile oxides **2a** and **2b**) with β-CD, however, we were not successful in both cases. The two aryl hydroximinoyl chlorides **9a** and **9b** were too unstable to be detected in D_2O even in the presence of β-CD, and they tend to form diphenyl- and di-*tert*-butylphenyl furoxanes (dimers of the nitrile oxides) instead of the intended cycloaddition with **1**. The latter fact explains why the yields

of 1,3-dipolar cycloaddition of **2a** and **2b** in water are usually below 50%.

MD simulations of **9b**·β-CD showed that it has a higher binding affinity than **9a**·β-CD ($\Delta\Delta\langle E_{\text{Bind}}\rangle = -6.21$ and -4.74 kJ mol^{-1} with the hydroximinoyl chloride pointing to the top and bottom rims of CD, respectively) (Tables S-4 and S-5). Thus the *tert*-butyl group helps to anchor **9b** in the CD cavity and sterically blocking reactant **1** from approaching in the *syn* position relative to **9b**, preventing the formation of product **4b**.

It is possible though not necessary that a reaction in the chiral CD cavity may lead to induced optical activity in the product.[20a–c] This possibility was investigated for the 1,3-dipolar cycloaddition of benzonitrile oxide (**2a**) with **1** in D_2O. In the presence of β-CD, the ^{1}H NMR spectrum of the product **4a** showed two well resolved doublets around δ 6.8 for methine proton H_{12}; without β-CD, only a doublet is showed around δ 7.2 (Fig. S-5). Any enantiomeric excess can thus be determined from the area ratios of the respective isoxazolines; however, the enantiomers are present in 1/1 ratio within experimental error. Unfortunately, spectrum of **3a**·β-CD was not obtained due to its poor solubility in D_2O.

In order to exploit the high regioselectivity of **9b**·β-CD in 1,3-dipolar cycloaddition, we tested its reaction with other dipolarophiles such as methyl *trans*-crotonate **10a** and *trans*-chalcone **10b** (Scheme 2). The product ratio of **11a/12a** was found to be enhanced from 65/35 in THF[21] to that of 86/14 in acetone/water (1/1). The product ratio of **11b/12b** enhanced from 36/64 in THF[21] to that of >99/1 in acetone/water (1/1). Unfortunately, no further improvement in regioselectivity was found when the above reactions were carried out in acetone/water (1/1) in the presence of β-CD (**11a/12a**, 82/18 and **11b/12b**, >99/1, respectively). The results suggest that solvent polarity alone has a strong influence on the regioselectivity of 1,3-dipolar cycloadditions of **10a**,**b** with **9b**.



Scheme 2.

3. Conclusion

The 1,3-dipolar cycloaddition of adamantylidenefulvene **1** with aryl and alkyl nitrile oxides **2a–d** under thermal and microwave reactions gave 1/1 cycloadducts, **3a–d** and **4a–d**, as the major products, and four other 1/2 cycloadducts **5–8a–d** as minor products. All the isoxazolines adducts **3a–7a**, **3b–7b**, **3c**, **4c**, **3d**, and **4d** were isolated and fully characterized by ^{1}H, ^{13}C NMR, MS, NOE, H,H-COSY, and H,C-COSY spectral data. Furthermore, the regioselectivity of the 1,3-dipolar cycloaddition of **1** with nitrile oxides **2a** or **2b** was highly enhanced by inclusion in β-CD solution. MD simulation results support that the *CD cavity provides steric control stabilizing the formation of the transition state structure* **3a**-**TS** (or **3b**-**TS**), giving **3a** (or **3b**) as the major product. The results further expand the scope of using CDs as a molecular reactor in a regio- and stereo-selective fashion. Finally, β-CD was found to be a useful chiral shift reagent for the differentiation of enantiomers of **4a**.

4. Experimental

4.1. General

^{1}H NMR spectra were measured on a 300, 500, and 600 MHz spectrometer. Natural abundance ^{13}C NMR spectra were measured using pulse Fourier transform, on a 300 MHz NMR spectrometer operating at 75.4 MHz. Broad-band decoupling, DEPT, NOE, H,H-COSY, and H,C-COSY were carried out to simplify the spectra and aid peak identification. Chemical shifts are given in parts per million (ppm) and coupling constant J in hertz (Hz) for both nuclei, with the solvent (usually $CDCl_3$) peak as an internal standard. The reference peak for ^{1}H is at δ 7.25 of $CHCl_3$, and for ^{13}C it is the central peak at δ 77. All reported yields here were from an average of three runs and were based on uncovered starting materials. The microwave reactions were carried out in a CEM MARS-5 magnetron with temperature controller.

4.2. Computation details

Stochastic molecular dynamics simulations were carried out using MacroModel V 8.0[22] with an all-atom amber* forcefield[23] in a continuum GB/SA model[24] for water. Default amber* charges were used except for **3a**-**TS** and **4a**-**TS**, which were obtained from CHELPG electrostatic potential fitting using Gaussian 03 at the HF/6-31G* level.[25] Geometric constraint to the optimized HF geometries for **3a**-**TS** and **4a**-**TS** was also applied. Constant dielectric treatment was used to estimate electrostatic interactions. A 200 ps equilibration step with 1 fs time step was followed by a 5000 ps MD run with 1 fs time step at 300 K. Structures were sampled at regular interval of 1 ps during the simulations. The sampled structures were then minimized using PR conjugated gradient method to obtain the lowest energy structure in each simulation.

4.3. General procedures for the reaction of 1 with 2a–c

To a well-stirred solution of **1** (100.0 mg, 0.50 mmol) with hydroximinoyl chloride (**9a**: 155.4 mg, 1.00 mmol; **9b**: 211.3 mg, 1.00 mmol; **9c**: 196.6 mg, 1.00 mmol) in THF (or benzene) (15 mL) was added triethylamine (15 drops) and refluxed for 24 h. After cooled to rt, the solution was washed with water (10 mL) and the water layer was

extracted three times with methylene chloride (10 mL×3). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel column by elution with *n*-hexane/ethyl acetate (20/1) to give **3a**–**8a** 50%; **3b**–**8b** 60%; **3c**–**4c** 40%.

4.3.1. 6-Adamantan-2-ylidene-3-phenyl-3*a*,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 3a. Colorless solid; mp 154–155 °C; δ_H 1.80–2.12 (m, 12H), 2.90 (br s, 1H), 3.01 (br s, 1H), 4.74 (ddd, *J*=8.8, 2.4, 2.3 Hz, 1H), 5.81 (d, *J*=8.8 Hz, 1H), 5.97 (dd, *J*=5.8, 2.4 Hz, 1H), 6.48 (dd, *J*=5.8, 2.3 Hz, 1H), 7.39–7.45 (m, 3H), 7.74–7.80 (m, 2H); δ_C 28.1 (2×CH), 35.3 (CH), 35.5 (CH), 37.1 (CH_2), 39.0 (CH_2), 39.1 (CH_2), 39.2 (CH_2), 39.7 (CH_2), 58.5 (CH), 84.0 (CH), 126.8 (CH), 128.3 (CH), 128.7 (CH), 129.7 (CH), 131.1 (CH), 132.2 (Cq), 149.0 (Cq), 156.3 (Cq); MS (EI, *m*/*z*) 317 (M^+, 83), 300 (43), 198 (100); HRMS *m*/*z* calcd for $C_{22}H_{23}NO$: 317.1780; found: 317.1776. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41; found: C, 82.85; H, 7.37; N, 4.37.

4.3.2. 4-Adamantan-2-ylidene-3-phenyl-3*a*,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 4a. Colorless solid; mp 126–128 °C; δ_H 0.40–0.46 (m, 1H), 1.30–1.37 (m, 1H), 1.46–1.55 (m, 1H), 1.64–1.93 (m, 9H), 2.51 (br s, 1H), 2.82 (br s, 1H), 4.74 (d, *J*=8.2 Hz, 1H), 5.86 (dd, *J*=8.2, 2.1, 0.8 Hz, 1H), 5.94 (dd, *J*=5.8, 2.1 Hz, 1H), 6.63 (dd, *J*=5.8, 0.8 Hz, 1H), 7.34–7.43 (m, 5H); δ_C 27.7 (CH), 28.0 (CH), 35.2 (CH), 35.9 (CH), 36.7 (CH_2), 37.6 (CH_2), 38.5 (CH_2), 39.4 (CH_2), 39.5 (CH_2), 54.8 (CH), 88.8 (CH), 127.5 (Cq), 128.2 (CH), 128.3 (CH), 129.1 (CH), 130.5 (Cq), 130.6 (CH), 132.8 (CH), 144.9 (Cq), 159.0 (Cq); MS (EI, *m*/*z*) 317 (M^+, 43), 300 (52), 198 (100); HRMS *m*/*z* calcd for $C_{22}H_{23}NO$: 317.1780; found: 317.1776.

4.3.3. 7-Adamantan-2-ylidene-3,4-diphenyl-3*a*,3*b*,6*a*,7*a*-tetrahydro-3*aH*-cyclopenta-[2,1-*d*:3,4-*d*′]diisoxazole 5a. Colorless solid; mp 230–231 °C; δ_H 1.87–2.04 (m, 12H), 3.03 (br s, 2H), 4.07 (d, *J*=7.6 Hz, 1H), 5.79 (d, *J*=7.6 Hz, 2H), 7.20–7.27 (m, 4H), 7.35–7.41 (m, 6H); δ_C 27.9 (CH), 36.1 (CH), 36.9 (CH_2), 38.9 (CH_2), 39.5 (CH_2), 56.6 (CH), 87.2 (CH_2), 126.2 (Cq), 127.8 (CH), 128.2 (Cq), 128.7 (CH), 130.1 (CH), 158.9 (2×Cq); MS (EI, *m*/*z*) 436 (M^+, 68), 317 (100), 198 (56), 119 (46), 91 (35), 77 (36); HRMS *m*/*z* calcd for $C_{29}H_{28}N_2O_2$: 436.2152; found: 436.2153. Anal. Calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.47; N, 6.42; found: C, 79.88; H, 6.67; N, 6.13.

4.3.4. (3*aR*,3*bR*,6*aS*,7*aR*)-7-Adamantan-2-ylidene-3,6-diphenyl-3*a*,3*b*,6*a*,7*a*-tetrahydro-3*aH*-cyclopenta[1,2-*d*:3,4-*d*′]diisoxazole 6a. Colorless solid; mp 237–238 °C; δ_H 0.98–1.03 (m, 1H), 1.58–1.97 (m, 11H), 2.68 (br s, 1H), 3.01 (br s, 1H), 4.17 (dd, *J*=8.7, 8.7 Hz, 1H), 4.96 (d, *J*=8.7 Hz, 1H), 5.57 (dd, *J*=8.7, 8.7 Hz, 1H), 5.71 (d, *J*=8.7 Hz, 1H), 7.30–7.53 (m, 8H), 7.71–7.75 (m, 2H); δ_C 27.5 (CH), 27.9 (CH), 35.3 (CH), 35.7 (CH), 36.6 (CH_2), 37.8 (CH_2), 38.8 (CH_2), 39.3 (CH_2), 39.5 (CH_2), 57.5 (CH), 58.0 (CH), 85.7 (CH), 86.2 (CH), 121.4 (Cq), 127.2 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.3 (Cq), 129.4 (CH), 129.7 (CH), 130.2 (Cq), 153.0 (Cq), 158.7 (Cq), 158.9 (Cq); MS (EI, *m*/*z*) 436 (M^+, 100), 408 (32), 317 (44), 289 (40), 198 (34), 104 (40), 91 (33), 77 (58); HRMS *m*/*z* calcd for $C_{29}H_{28}N_2O_2$: 436.2152; found: 436.2158.

X-ray crystal data for compound **6a**: $C_{29}H_{28}N_2O_2$, *M*=436.53, monoclinic, *a*=11.3842(2) Å, *b*=17.894(3) Å, *c*=11.099(2) Å, *α*=90°, *β*=97.291(1)°, *γ*=90°, *V*=2085.6(3) Å^3, *V*=2242.5(7) Å^3, space group $P2_1/c$, *Z*=4, calculated density 1.293 Mg m^{-3}, crystal dimensions (mm^3): 0.60×0.50×0.40, *T*=293(2) K, *λ* (Mo K*α*)=0.71073 Å, *μ*=0.081 mm^{-1}, 3958 reflections collected, 3958 independent (R_{int}=0.0000), 299 parameter refined on F^2, R_1=0.0422, $wR2[F^2]$=0.1198 (all data), GOF on F^2 1.099, $\Delta\rho_{max}$=0.162 eÅ^{-3}. Crystallographic data for the structure have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606881. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk].

4.3.5. 6-Adamantan-2-ylidene-3-(4-*tert*-butyl-phenyl)-6,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 3b. Colorless solid; mp 172–173 °C; δ_H 1.32 (s, 9H), 1.78–2.07 (m, 12H), 2.90 (br s, 1H), 3.01 (br s, 1H), 4.72 (ddd, *J*=8.8, 2.3, 2.3 Hz, 1H), 5.79 (d, *J*=8.8 Hz, 1H), 5.97 (dd, *J*=5.8, 2.3 Hz, 1H), 6.47 (dd, *J*=5.8, 2.3 Hz, 1H), 7.42 (d, *J*=8.7 Hz, 2H), 7.68 (d, *J*=8.7 Hz, 2H); δ_C 28.2 (2×CH), 31.2 (CH_3), 34.8 (Cq), 35.3 (CH), 35.5 (CH), 37.1 (CH_2), 39.0 (CH_2), 39.1 (CH_2), 39.2 (CH_2), 39.7 (CH_2), 58.6 (CH), 83.7 (CH), 125.7 (CH), 126.6 (CH), 126.6 (Cq), 128.5 (CH), 131.0 (CH), 132.3 (Cq), 148.9 (Cq), 153.0 (Cq), 156.1 (Cq); MS (EI, *m*/*z*) 373 (M^+, 47), 356 (39), 225 (14), 198 (100), 161 (23), 91 (14); HRMS *m*/*z* calcd for $C_{26}H_{31}NO$: 373.2406; found: 373.2408.

X-ray crystal data for compound **3b**: $C_{26}H_{31}NO$, *M*=373.52, monoclinic, *a*=16.5261(13) Å, *b*=10.5956(9) Å, *c*=11.9249(9) Å, *α*=90°, *β*=92.796(2)°, *γ*=90°, *V*=2085.6(3) Å^3, space group $P2_1/c$, *Z*=4, calculated density 1.19 Mg m^{-3}, crystal dimensions (mm^3): 0.45×0.30×0.13, *T*=295(2) K, *λ* (Mo K*α*)=0.71073 Å, *μ*=0.071 mm^{-1}, 16867 reflections collected, 3670 independent (R_{int}=0.0506), 272 parameter refined on F^2, R_1=0.0862, $wR2[F^2]$=0.2483 (all data), GOF on F^2 1.049, $\Delta\rho_{max}$=0.383 eÅ^{-3}. Crystallographic data for the structure have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606882. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk].

4.3.6. 4-Adamantan-2-ylidene-3-(4-*tert*-butyl-phenyl)-4,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 4b. Colorless solid; mp 145–146 °C; δ_H 0.26–0.35 (m, 1H), 1.21–1.29 (m, 1H), 1.29 (s, 9H), 1.44–1.53 (m, 1H), 1.60–1.90 (m, 9H), 2.47 (br s, 1H), 2.81 (br s, 1H), 4.71 (d, *J*=8.2 Hz, 1H), 5.4 (ddd, *J*=8.2, 2.0, 0.7 Hz, 1H), 5.93 (dd, *J*=5.8, 2.0 Hz, 1H), 6.62 (dd, *J*=5.8, 0.7 Hz, 1H), 7.27 (d, *J*=8.4 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H); δ_C 27.7 (CH), 28.0 (CH), 31.2 (CH_3), 34.7 (Cq), 35.2 (CH), 35.8 (CH), 36.8 (CH_2), 37.4 (CH_2), 38.5 (CH_2), 39.4 (CH_2), 39.5 (CH_2), 55.0 (CH), 88.7 (CH), 125.1 (CH), 127.5 (Cq), 127.6 (Cq), 128.0 (CH), 130.6 (CH), 132.7 (CH), 144.9 (Cq), 152.2 (Cq), 159.0 (Cq); MS (EI, *m*/*z*) 373 (M^+, 87), 356 (39), 225 (17), 198 (100), 161 (18), 91

(9); HRMS *m/z* calcd for $C_{26}H_{31}NO$: 373.2406; found: 373.2404.

4.3.7. 7-Adamantan-2-ylidene-3,4-bis-(4-*tert*-butyl-phenyl)-3*b*,6*a*,7,7*a*-tetrahydro-3*aH*-cyclopenta[2,1-*d*:3,4-*d*′]-diisoxazole 5b. Colorless solid; mp 218–219 °C; δ_H 1.32 (s, 18H), 1.83–2.08 (m, 12H), 3.01 (br s, 2H), 4.06 (d, *J*=7.7 Hz, 2H), 5.75 (d, *J*=7.7 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 4H), 7.33 (d, *J*=8.5 Hz, 4H); δ_C 27.9 (CH), 31.2 (CH_3), 34.8 (Cq), 36.0 (CH), 36.9 (CH_2), 38.8 (CH_2), 39.5 (CH_2), 56.4 (CH), 87.2 (CH), 125.3 (Cq), 125.5 (CH), 126.2 (Cq), 127.6 (CH), 153.4 (Cq), 156.6 (Cq), 158.9 (Cq); MS (EI, *m/z*) 548 (M^+, 6), 373 (33), 356 (39), 225 (17), 198 (100), 91 (9); HRMS *m/z* calcd for $C_{37}H_{44}N_2O_2$: 548.3403; found: 548.3394.

4.3.8. (3*aR*,3*bR*,6*aS*,7*aR*)-7-Adamantan-2-ylidene-3,6-bis-(4-*tert*-butyl-phenyl)-3*b*,6*a*,7,7*a*-tetrahydro-3*aH*-cyclopenta[1,2-*d*:3,4-*d*′]diisoxazole 6b. Colorless solid; mp 238–239 °C; δ_H 0.93–1.02 (m, 1H), 1.28 (s, 9H), 1.32 (s, 9H), 1.56–1.96 (m, 11H), 2.68 (br s, 1H), 3.02 (br s, 1H), 4.13 (dd, *J*=8.6, 8.6 Hz, 1H), 4.93 (d, *J*=8.6 Hz, 1H), 5.55 (dd, *J*=8.6, 8.6 Hz, 1H), 5.68 (d, *J*=8.6 Hz, 1H), 7.34 (d, *J*=6.8 Hz, 2H), 7.41 (d, *J*=6.8 Hz, 2H), 7.44 (d, *J*=6.8 Hz, 2H), 7.66 (d, *J*=6.8 Hz, 2H); δ_C 27.6 (CH), 28.0 (CH), 31.2 (CH_3), 34.7 (Cq), 34.8 (Cq), 35.2 (CH), 35.7 (CH), 36.6 (CH_2), 37.6 (CH_2), 38.7 (CH_2), 39.4 (CH_2), 39.5 (CH_2), 57.6 (CH), 58.1 (CH), 85.6 (CH), 86.1 (CH), 121.7 (Cq), 125.1 (CH), 125.5 (CH), 126.4 (Cq), 126.9 (CH), 127.4 (Cq), 128.0 (CH), 152.4 (Cq), 152.7 (Cq), 152.8 (Cq), 158.5 (Cq), 158.6 (Cq); MS (EI, *m/z*) 548 (M^+, 100), 520 (91), 373 (49), 345 (64), 259 (60), 214 (41), 198 (61), 144 (28), 91 (19); HRMS *m/z* calcd for $C_{37}H_{44}N_2O_2$: 548.3403; found: 548.3402.

4.3.9. (3*aS*,3*bS*,6*aR*,7*aR*)-7-Adamantan-2-ylidene-3,4-bis-(4-*tert*-butyl-phenyl)-3*b*,6*a*,7,7*a*-tetrahydro-3*aH*-cyclopenta[2,1-*d*:3,4-*d*′]diisoxazole 7b. Colorless solid; mp 245–246 °C; δ_H 0.68–0.80 (m, 1H), 1.31 (s, 9H), 1.34 (s, 9H), 1.35–1.47 (m, 1H), 1.56–2.03 (m, 10H), 2.48 (br s, 1H), 3.00 (br s, 1H), 4.18 (dd, *J*=10.6, 4.2 Hz, 1H), 4.83 (d, *J*=8.6 Hz, 1H), 5.16 (dd, *J*=8.6, 4.2 Hz, 1H), 5.69 (d, *J*=10.6 Hz, 1H), 7.39 (br s, 4H), 7.47 (d, *J*=8.4 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H); δ_C 27.4 (CH), 27.9 (CH), 31.1 (CH_3), 34.8 (Cq), 34.9 (Cq), 36.2 (CH), 36.3 (CH), 36.7 (CH_2), 37.3 (CH_2), 38.2 (CH_2), 39.6 (CH_2), 39.7 (CH_2), 58.1 (CH), 60.8 (CH), 85.2 (CH), 88.0 (CH), 123.6 (Cq), 125.3 (CH), 125.5 (Cq), 125.9 (CH), 126.2 (Cq), 127.0 (CH), 128.0 (CH), 152.9 (Cq), 153.5 (Cq), 153.9 (Cq), 157.0 (Cq), 159.4 (Cq); MS (EI, *m/z*) 548 (M^+, 65), 520 (39), 373 (62), 356 (42), 345 (36), 259 (30), 214 (35), 198 (100), 144 (28), 91 (14); HRMS *m/z* calcd for $C_{37}H_{44}N_2O_2$: 548.3403; found: 548.3399.

4.3.10. Compound 8b. It is a mixture of at least two stereoisomers, and the ratio of the two isomers is ca. 3/1; colorless solid; mp>320 °C (decomp.); δ_H 1.29 (s, 18H), 1.30 (s, 18H), 1.74–1.94 (m, 10H), 1.97–2.06 (m, 2H), 2.08–2.23 (m, 4H), 2.31–2.40 (m, 4H), 2.41–2.53 (m, 4H), 2.70–2.79 (m, 2H), 3.02 (d, *J*=9.0 Hz, 1H), 3.08 (d, *J*=9.0 Hz, 1H), 4.42 (dd, *J*=9.5, 9.5 Hz, 1H), 4.43 (dd, *J*=9.5, 9.5 Hz, 1H), 6.09 (d, *J*=9.5 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 4H), 7.39 (d, *J*=8.4 Hz, 4H), 7.47 (d, *J*=8.4 Hz, 4H), 7.56 (d, *J*=8.4 Hz, 4H); MS (EI, *m/z*) 548 (M^+, 50), 373 (74), 356 (34), 198 (62), 161 (50), 97 (42), 91 (17), 85 (60), 57 (100); HRMS *m/z* calcd for $C_{37}H_{44}N_2O_2$: 548.3403; found: 548.3406.

4.3.11. 6-Adamantan-2-ylidene-3-(5-chloro-thiophen-2-yl)-6,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 3c. Light yellow solid; mp 144–145 °C; δ_H 1.77–2.10 (m, 12H), 2.89 (br s, 1H), 2.97 (br s, 1H), 4.61 (ddd, *J*=8.9, 2.3, 2.3 Hz, 1H), 5.80 (d, *J*=8.9 Hz, 1H), 5.93 (dd, *J*=5.7, 2.3 Hz, 1H), 6.49 (dd, *J*=5.7, 2.3 Hz, 1H), 6.88 (d, *J*=3.9 Hz, 1H), 7.05 (d, *J*=3.9 Hz, 1H); δ_C 28.1 (2×CH), 35.3 (CH), 35.6 (CH), 37.0 (CH_2), 38.9 (CH_2), 39.1 (2×CH_2), 39.7 (CH_2), 39.1 (CH_2), 58.7 (CH), 84.5 (CH), 126.3 (CH), 126.7 (CH), 127.6 (CH), 131.1 (Cq), 131.6 (CH), 131.8 (Cq), 132.8 (Cq), 149.7 (Cq), 151.9 (Cq); MS (EI, *m/z*) 359 (M^++2, 34), 357 (M^+, 87), 340 (53), 327 (86), 198 (100), 129 (28), 91 (32); HRMS *m/z* calcd for $C_{20}H_{20}{}^{35}ClNOS$: 357.0954; found: 357.0952.

4.3.12. 4-Adamantan-2-ylidene-3-(5-chloro-thiophen-2-yl)-4,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 4c. Light yellow oil; δ_H 1.43–1.52 (m, 1H), 1.67–2.04 (m, 11H), 2.81 (br s, 1H), 2.88 (br s, 1H), 4.60 (d, *J*=7.9 Hz, 1H), 5.84 (ddd, *J*=7.9, 1.9, 0.8 Hz, 1H), 5.90 (dd, *J*=5.8, 1.9 Hz, 1H), 6.65 (dd, *J*=5.8, 0.8 Hz, 1H), 6.83 (d, *J*=3.9 Hz, 1H), 6.96 (d, *J*=3.9 Hz, 1H); δ_C 27.8 (CH), 28.1 (CH), 35.3 (CH), 36.1 (CH), 36.8 (CH_2), 37.8 (CH_2), 38.1 (CH_2), 39.7 (CH_2), 40.1 (CH_2), 53.6 (CH), 89.7 (CH), 126.2 (CH), 127.3 (CH), 127.5 (Cq), 130.1 (Cq), 130.3 (CH), 132.0 (Cq), 133.1 (CH), 145.1 (Cq), 153.0 (Cq); MS (EI, *m/z*) 357 (M^+, 51), 340 (100), 325 (68), 198 (97), 91 (26), 71 (29), 57 (36); HRMS *m/z* calcd for $C_{20}H_{20}{}^{35}ClNOS$: 357.0954; found: 357.0951.

4.4. General procedures for the reaction of 1 with 2d

To a well-stirred solution of **1** (68.0 mg, 0.34 mmol), nitroethane (50.0 mg, 0.69 mmol), and phenyl isocyanate (163.2 mg, 1.14 mmol) in THF (or benzene) (10 mL) was added triethylamine (10 drops) and then refluxed for 24 h. After cooled to rt, to the solution was added 1–2 mL of water and stirring was continued for 30 min in an ice bath; the solution was filtered to remove urea and dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel column by eluting with *n*-hexane/ethyl acetate (20/1) to give **3d** and **4d** in a combined yield of 45%.

4.4.1. 6-Adamantan-2-ylidene-3-methyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 3d. Light yellow oil; δ_H 1.73–2.05 (m, 12H), 1.98 (s, 3H), 2.87 (br s, 1H), 2.94 (br s, 1H), 4.15 (ddd, *J*=8.9, 2.4, 2.2 Hz, 1H), 5.61 (d, *J*=8.9 Hz, 1H), 5.86 (dd, *J*=5.8, 2.4 Hz, 1H), 6.64 (dd, *J*=5.8, 2.2 Hz, 1H); δ_C 12.4 (CH_3), 28.1 (2×CH), 35.2 (CH), 35.4 (CH), 37.0 (CH_2), 38.9 (CH_2), 39.1 (CH_2), 39.2 (CH_2), 39.6 (CH_2), 62.0 (CH), 82.4 (CH), 127.4 (CH), 131.2 (CH), 132.6 (Cq), 148.7 (Cq), 154.9 (Cq); MS (EI, *m/z*) 255 (M^+, 33), 238 (12), 214 (18), 198 (100), 129 (14), 91 (18); HRMS *m/z* calcd for $C_{17}H_{21}NO$: 255.1623; found: 255.1627.

4.4.2. 4-Adamantan-2-ylidene-3-methyl-4,6*a*-dihydro-3*aH*-cyclopenta[*d*]isoxazole 4d. Light yellow oil; δ_H

1.69–2.07 (m, 12H), 1.92 (s, 3H), 2.75 (br s, 1H), 2.90 (br s, 1H), 4.20 (dd, J=8.2, 1.0 Hz, 1H), 5.66 (ddd, J=8.2, 2.0, 1.0 Hz, 1H), 5.87 (dd, J=5.9, 2.0 Hz, 1H), 6.54 (dd, J=5.9, 1.0 Hz, 1H); δ_C 12.5 (CH_3), 28.0 (CH), 28.1 (CH), 35.1 (CH), 35.8 (CH), 36.9 (CH_2), 38.6 (CH_2), 39.3 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 54.9 (CH), 87.6 (CH), 128.2 (Cq), 131.4 (CH), 132.2 (CH), 144.0 (Cq), 155.9 (Cq); MS (EI, *m/z*) 255 (M^+, 17), 238 (9), 214 (14), 198 (100), 155 (10), 128 (9), 115 (9), 91 (10); HRMS *m/z* calcd for $C_{17}H_{21}NO$: 255.1623; found: 255.1619.

The ratio of cycloadducts and their isolated yields are summarized in Table 1. Compounds **3**–**8** were eluted (*n*-hexane/ethyl acetate = 6/1) in the following sequence (R_f): **3a** (0.38), **4a** (0.43), **5a** (0.48), **6a** (0.69); **3b** (0.69), **4b** (0.50), **5b** (0.53), **6b** (0.36), **7b** (0.57), **8b** (0.50); **3c** (0.26), **4c** (0.35); **3d** (0.65) and **4d** (0.53). Although, compound **7a** was not isolated its existence can be assured by comparing its ^{1}H NMR spectrum with that of **7b**.

4.5. Synthesis of compound 11a,b and 12a,b

The synthetic procedures of **11a**,**b** and **12a**,**b** are similar to those of compounds **3**–**8**. The amount of reagent used in the reaction was as follows: compound **10a** (200 mg, 2.00 mmol), **9b** (365 mg, 3.00 mmol), Et_3N (320 mg, 3.17 mmol), THF (10 mL). The combined yield of compound **11a** and **12a** was 70% and the isolated yield of compounds **11b** and **12b** was 85%.

4.5.1. 3-(4-*tert*-Butyl-phenyl)-5-methyl-4,5-dihydro-isoxazole-4-carboxylic acid methyl ester 11a. Colorless oil; δ_H 1.31 (s, 9H), 1.43 (d, J=6.4 Hz, 3H), 3.71 (s, 3H), 4.06 (d, J=5.8 Hz, 1H), 5.01–5.10 (m, 1H), 7.40 (d, J=8.6 Hz, 2H), 7.62 (d, J=8.6 Hz, 2H); δ_C 20.8 (CH_3), 31.1 (CH_3), 34.8 (Cq), 52.9 (CH_3), 60.1 (CH), 82.1 (CH), 125.7 (CH), 125.9 (Cq), 126.5 (CH), 153.5 (Cq), 153.6 (Cq), 170.0 (Cq); MS (EI, *m/z*) 275 (M^+, 24), 260 (100), 160 (13), 116 (8), 91 (5); HRMS *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1520.

4.5.2. 3-(4-*tert*-Butyl-phenyl)-4-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 12a. Colorless oil; δ_H 1.32 (s, 9H), 1.42 (d, J=7.2 Hz, 3H), 3.78 (s, 3H), 3.92–4.02 (m, 1H), 4.77 (d, J=3.9 Hz, 1H), 7.42 (d, J=8.7 Hz, 2H), 7.62 (d, J=8.7 Hz, 2H); δ_C 18.2 (CH_3), 31.1 (CH_3), 34.9 (Cq), 47.1 (CH), 52.7 (CH_3), 84.8 (CH), 124.7 (Cq), 125.8 (CH), 127.1 (CH), 153.9 (Cq), 160.3 (Cq), 171.1 (Cq); MS (EI, *m/z*) 275 (M^+, 32), 260 (65), 216 (100), 188 (19), 91 (8); HRMS *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1529.

4.5.3. [3-(4-*tert*-Butyl-phenyl)-5-phenyl-4,5-dihydro-isoxazol-4-yl]-phenyl-methanone 11b. Colorless oil; δ_H 1.27 (s, 9H), 5.36 (d, J=6.6 Hz, 1H), 5.74 (d, J=6.6 Hz, 1H), 7.31–7.42 (m, 7H), 7.48–7.55 (m, 4H), 7.62–7.69 (m, 1H), 7.90–7.95 (m, 2H); δ_C 31.1 (CH_3), 34.8 (Cq), 65.0 (CH), 87.6 (CH), 125.6 (Cq), 125.8 (CH), 125.9 (CH), 126.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 134.3 (CH), 135.2 (Cq), 139.8 (Cq), 153.6 (Cq), 155.2 (Cq), 195.4 (Cq); MS (EI, *m/z*) 383 (M^+, 2), 105 (100), 77 (19); HRMS *m/z* calcd for $C_{26}H_{25}NO_2$: 383.1885; found: 383.1888.

4.5.4. [3-(4-*tert*-Butyl-phenyl)-4-phenyl-4,5-dihydro-isoxazol-5-yl]-phenyl-methanone 12b. Colorless oil; δ_H 1.26 (s, 9H), 5.41 (d, J=4.6 Hz, 1H), 5.65 (d, J=4.6 Hz, 1H), 7.25–7.64 (m, 12H), 8.03–8.08 (m, 2H); δ_C 31.1 (CH_3), 34.8 (Cq), 55.3 (CH), 90.0 (CH), 125.2 (Cq), 125.6 (CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.7 (CH), 129.4 (CH), 129.6 (CH), 133.9 (CH), 134.4 (Cq), 138.5 (Cq), 153.5 (Cq), 158.4 (Cq), 193.6 (Cq); MS (EI, *m/z*) 383 (M^+, 4), 278 (100), 207 (37), 105 (90), 91 (39), 77 (40); HRMS *m/z* calcd for $C_{26}H_{25}NO_2$: 383.1885; found: 383.1885.

Acknowledgements

We thank the National Science Council of Republic of China for financial support. We also thank Ms. J.-L. Peng at the Instrumentation Center of National Tsing Hua University Taiwan, for her help in ROESY experiment.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.021.

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