Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3122

www.rsc.org/obc

PAPER

Selective oxidation of unactivated C–H bonds by supramolecular control†

Yat-Sing Fung, Siu-Cheong Yan and Man-Kin Wong*

Received 10th December 2011, Accepted 22nd February 2012
DOI: 10.1039/c2ob07069c

Efficient methods for dioxirane-based selective C–H bond oxidation by supramolecular control in H_2O have been developed. With β-cyclodextrin as the supramolecular host, site-selective oxidation of the terminal over the internal tertiary C–H bond of 3,7-dimethyloctyl esters **3a–c** was achieved. In addition, β-cyclodextrin selectively enhanced the C–H bond oxidation of cumene in a mixture of cumene and ethyl benzene in H_2O. Through ^1H NMR studies, the selectivity in C–H bond oxidation could be attributed to the inclusion complex formation between β-cyclodextrin and the substrates.

Introduction

Selective C–H bond oxidation is a great challenge in organic synthesis.[1] By selective oxidation of C–H bonds, functional groups can be strategically incorporated at the desired positions of hydrocarbons, providing an efficient method for the synthesis of structurally diverse organic molecules.[2] Over the decades, significant advancements have been made in selective C–H bond oxidation based on electronic,[3] steric,[4] and substrate-based directing[5] factors. However, these approaches are limited by the inherent structural properties of the substrates. Thus, it remains a great interest to develop new strategies for selective C–H bond oxidation to cater for a wide diversity of substrates.

Supramolecular host–guest chemistry provides a promising means to achieve selectivity in a wide range of organic reactions.[6] In general, supramolecular hosts function in two ways for selectivity enhancement in organic reactions. One way is by positioning the target sites of the substrates close to the reaction centre, and hence the target sites are preferentially reacted. Another way is by obstructing the approach of the non-target sites of the substrates to the reaction centre through inclusion complex formation. As a result, the selectivity of reaction at the target sites would be enhanced.

Cyclodextrins (CDs) are water-soluble supramolecular compounds with hydrophobic cavity and hydrophilic surface (Fig. 1) which have been extensively employed as ideal hosts in supramolecular catalysis.[7] For C–H bond oxidation by cyclodextrin-based catalysts, the selectivity enhancement by directing the target site to the reaction centre has been widely investigated. Breslow and Dong reported pioneering work on selective C–H bond oxidations of steroids using cyclodextrin-attached metalloporphyrins as catalysts.[7d] However, selective C–H bond oxidation by obstructing the approach of non-target C–H bonds to the reaction centre using cyclodextrins remains largely unexplored.[8]

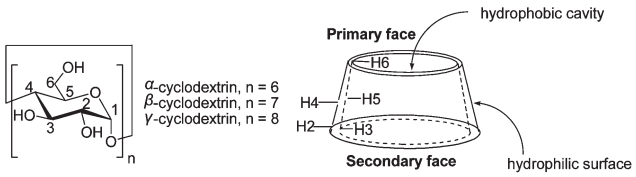


Fig. 1 General structure of cyclodextrins.

Dioxiranes are powerful oxidants which can be generated *in situ* from ketones and Oxone for oxidation of organic compounds,[9] including C–H bond oxidation.[10,11] In 2003, we employed cyclodextrin-ketoester as a supramolecular catalyst for stereoselective alkene epoxidation.[12] Bols and co-workers developed cyclodextrin ketones for organic oxidations.[13]

In this work, we report efficient methods for selective C–H bond oxidation by a supramolecular approach. Cyclodextrins were chosen as the supramolecular host, and dioxiranes generated *in situ* were used as the oxidant. Selective C–H bond oxidation was achieved by obstructing the approach of dioxiranes to the C–H bond with higher induced steric hindrance through inclusion complex formation with cyclodextrins. As a result, the unbound C–H bonds far away from cyclodextrins would be preferentially oxidized.

Results and discussion

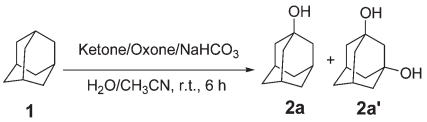
Optimization of reaction conditions for C–H bond oxidation by dioxiranes generated *in situ*

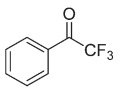
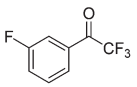
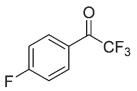
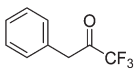
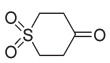
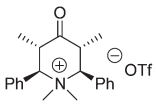
To increase the efficiency of C–H bond oxidation by dioxiranes generated *in situ* from ketones and Oxone, reaction temperature,

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China. E-mail: bcmkwong@inet.polyu.edu.hk; Fax: +(852)2364 9932; Tel: +(852)3400 8701

†Electronic supplementary information (ESI) available: Data for optimization of adamantane oxidation and selective C–H bond oxidations of **3a–d**; LC-MS spectra of β-CD; NMR spectra; GC calibration curve; GC temperature program and GC chromatograms. See DOI: 10.1039/c2ob07069c

Table 1 Studies on activities of ketones towards C–H bond oxidation of adamantane (**1**)[a]

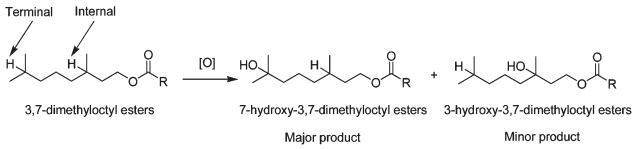


Entry	Ketone	**1** : **2a** : **2a′**[b]	Conv. (%)
1		7 : 50 : 43	93
2		14 : 71 : 15	86
3		43 : 52 : 5	57
4		24 : 66 : 10	76
5		52 : 43 : 5	48
6		61 : 35 : 4	39
7		22 : 61 : 17	78
8		60 : 40 : 0	40

[a] Reactions were conducted with **1** (0.1 mmol) and ketone (0.1 mmol) in H_2O (1 mL) and CH_3CN (1.5 mL) at room temperature with Oxone (0.5 mmol × 3) and $NaHCO_3$ (1.55 mmol × 3) added at 0 h, 2 h and 4 h (total reaction time: 6 h). [b] Determined by ^1H NMR analysis of the crude reaction mixture.

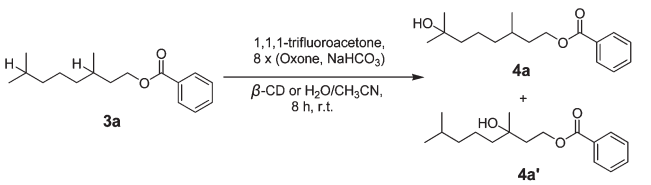
choice of base, and amounts of Oxone, base, and ketones have been optimized using adamantane (**1**) as the substrate (see ESI†). It was noted that the conversion of C–H bond oxidation could be enhanced by portion-wise additions of Oxone and base. Based on the optimized reaction conditions, the activities of a variety of ketones towards C–H bond oxidation were examined.

As shown in Table 1, the C–H bond oxidation of adamantane (**1**) (0.1 mmol) was conducted with ketone (0.1 mmol), Oxone (0.5 mmol × 3), and $NaHCO_3$ (1.55 mmol × 3) in H_2O (1 mL) and CH_3CN (1.5 mL) at room temperature for 6 h. It was found that 1,1,1-trifluoroacetone exhibited the highest activity towards adamantane oxidation (entry 1), and it converted 93% of **1** to **2a** and **2a′**. This would be attributed to the strong electron-withdrawing trifluoromethyl group. Methyl pyruvate with an electron-withdrawing ester group also gave high conversion of adamantane oxidation (entry 2, 86%). Yet, ketones with a phenyl group (entries 3–6) gave lower conversion (39–76%). Despite their possession of the electron-withdrawing trifluoromethyl group, the lower conversion would be due to the unfavorable steric effect of the phenyl ring. Cyclic ketones[14] (entries 7 and 8) gave moderate to good conversion (78% and 40%, respectively).



Scheme 1 Oxidation of 3,7-dimethyloctyl esters.

Table 2 Studies on the effect of β-CD on site-selective C–H bond oxidation of **3a**[a]



Entry	β-CD	H_2O (mL)	CH_3CN (mL)	Conv.[b] (%)	Yield[c] (%)	**4a** : **4a′**[d]
1	1.1 equiv	10	—	40	71	20 : 1
2	—	4	6	35	96	7 : 1
3	1.1 equiv	4	6	34	75	7 : 1
4	—	10	—	4	34	5 : 1

[a] Reactions were conducted with **3a** (0.2 mmol), 1,1,1-trifluoroacetone (0.2 mmol) at room temperature with Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) for 8 h. [b] Conversion was calculated from the amount of substrate recovered by flash column chromatography. [c] Yield based on conversion. [d] Determined by ^1H NMR.

Design of substrates for site-selective C–H bond oxidation

To investigate the effect of cyclodextrins on the site-selectivity of C–H bond oxidation, 3,7-dimethyloctyl esters with two tertiary C–H bonds located at the terminal and internal positions were chosen as the substrate (Scheme 1). Owing to the electronic effect, 7-hydroxy-3,7-dimethyloctyl esters are expected to be the major product through oxidation at the terminal C–H bond.[3b]

Effect of β-CD on site-selective C–H bond oxidation of 3a

β-Cyclodextrin (β-CD) was chosen for studying the effect of cyclodextrins on site-selective C–H bond oxidation with 3,7-dimethyloctyl benzoate (**3a**) as the substrate. The reaction was conducted with **3a** (0.2 mmol), 1,1,1-trifluoroacetone (0.2 mmol) and β-CD (0.22 mmol, 1.1 equiv) in the presence of Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) in H_2O (10 mL) at room temperature for 8 h (Table 2, entry 1). **4a** and **4a′** were obtained in 71% yield based on 40% conversion with a product ratio of 20 : 1. We have studied the effect of the equivalent of β-CD (Table S6 in ESI†). With 0.1 and 0.5 equiv of β-CD, lower conversion (23–32%), yield (40–50%), and selectivity (~7 : 1) were obtained. Increasing the amount of β-CD to 2, 5, and 10 equiv led to enhanced selectivity of 25 : 1, 29 : 1, and 30 : 1 yet with reduced yield. Monitored by LC-MS, no significant change on β-CD was observed during the course of the reaction (see ESI†). A comparable conversion (35%) and yield (96%) was obtained for oxidation conducted in H_2O (4 mL) and CH_3CN (6 mL) without β-CD. However, the ratio of **4a** to **4a′**

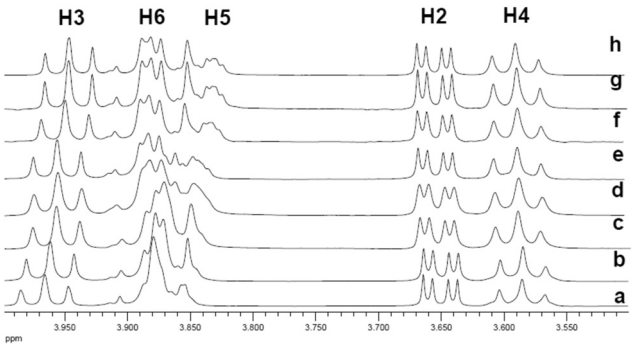


Fig. 2 Partial ^{1}H NMR spectra of a mixture of **3a** and β-CD in D_2O (signals of β-CD). Ratios of **3a** : β-CD: (a) 0 : 10, (b) 1 : 9, (c) 2 : 8, (d) 3 : 7, (e) 4 : 6, (f) 5 : 5, (g) 6 : 4, (h) 7 : 3.

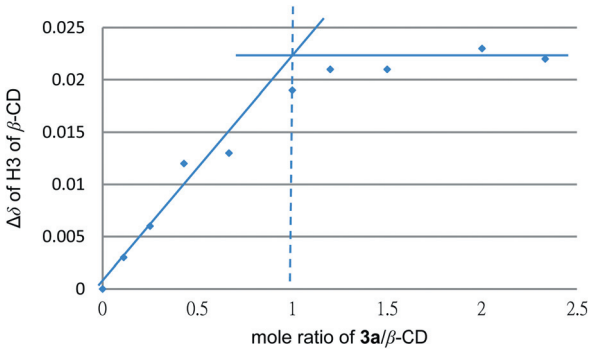


Fig. 3 ^{1}H NMR titration curve for **3a** and β-CD.

was only 7 : 1, which is consistent with the literature reports based on the electronic effect of the substrates.[3b] A control experiment was performed in H_2O (10 mL) without β-CD (entry 4). Only poor conversion could be obtained (34% yield based on 4% conversion), probably due to the low solubility of **3a** in H_2O.

These findings indicated that β-CD could provide enhanced site-selectivity for C–H bond oxidation (20 : 1 *vs.* 7 : 1), probably by obstructing the approach of dioxirane to the internal C–H bond of **3a** through inclusion complex formation in H_2O. Moreover, β-CD could act as a reaction vessel to give comparable conversion and yield of C–H bond oxidation as that of the reaction performed in a mixture of H_2O and CH_3CN, by assisting the dispersion of **3a** in H_2O.

^{1}H NMR titration for binding of 3a to β-CD

We studied the inclusion complex formation between β-CD and **3a** by ^{1}H NMR titration.[15] The inclusion complexation between β-CD and **3a** was confirmed by ^{1}H NMR titration (Fig. 2). The signals of H3 and H5 were shifted upfield significantly when the amount of **3a** presented in the aqueous solution of β-CD increased, whereas the signals of H2 and H4 remained unchanged. This reflects the fact that **3a** interacts with the protons inside β-CD.

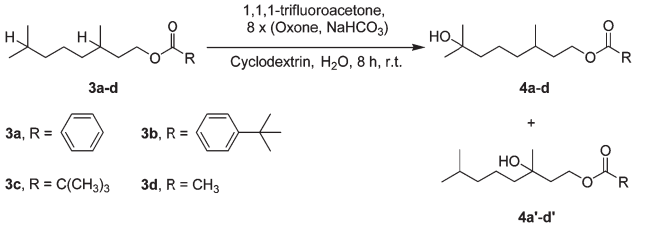
A ^{1}H NMR titration curve was obtained by plotting the change of chemical shift of H3 against the ratio of **3a** to β-CD (Fig. 3). The stoichiometry for the inclusion complex formation was 1 : 1, determined by extrapolating the curve. The association constant of the inclusion complex was 210 M^{-1}, determined by Scott's method.[16]

Effect of different substituents on the site-selectivity of C–H bond oxidation of 3a–d in the presence of cyclodextrins

Upon confirmation of the inclusion complex formation between 3,7-dimethyloctyl benzoate (**3a**) and β-CD, the effect of cyclodextrins on the C–H bond oxidations of 4-*tert*-butylbenzoate **3b**, pivalate **3c**, and acetate **3d** were studied. The results are summarized in Table 3.

In the presence of β-CD, **3a–d** (Table 3, entries 2, 6, 10 and 14) were oxidized to **4a–d** and **4a′–d′**. β-CD in H_2O gave

Table 3 Effect of substituents and α-, β- and γ-CDs on site-selective C–H bond oxidation of **3a–d**[a]



Entry	Substrate	CD	Conv.[c] (%)	Yield[d] (%)	**4a–d** : **4a′–d′**[e]
1	**3a**	α	6	55	6 : 1
2	**3a**	β	40	71	20 : 1
3	**3a**	γ	17	81	7 : 1
4[b]	**3a**	—	35	96	7 : 1
5	**3b**	α	34	23	11 : 1
6	**3b**	β	40	40	12 : 1
7	**3b**	γ	28	22	5 : 1
8[b]	**3b**	—	52	56	7 : 1
9	**3c**	α	41	18	3 : 1
10	**3c**	β	61	20	12 : 1
11	**3c**	γ	45	19	4 : 1
12[b]	**3c**	—	54	39	4 : 1
13	**3d**	α	64	5	n.d.
14	**3d**	β	68	24	5 : 1
15	**3d**	γ	73	39	10 : 1
16[b]	**3d**	—	54	61	4 : 1

[a] Unless otherwise indicated, reactions were conducted with substrate (0.2 mmol), 1,1,1-trifluoroacetone (0.2 mmol) and α-, β- or γ-CD (0.22 mmol) in H_2O (10 mL) at room temperature with Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) for 8 h. [b] The reaction was carried out in H_2O (4 mL) and CH_3CN (6 mL). [c] Conversion was calculated from the amount of substrate recovered by flash column chromatography. [d] Yield based on conversion. [e] Determined by ^{1}H NMR.

enhancement of the site-selectivity of C–H bond oxidations of **3a**, **3b**, and **3c** (entries 2, 6 and 10), as compared to the oxidations performed in H_2O (4 mL) and CH_3CN (6 mL) without β-CD (entries 4, 8 and 12) *i.e.*, **4a** : **4a′** (20 : 1 *vs.* 7 : 1); **4b** : **4b′** (12 : 1 *vs.* 7 : 1); **4c** : **4c′** (12 : 1 *vs.* 4 : 1). The site-selectivity obtained in the presence of β-CD was two-to-three fold higher than that controlled by the inherent electronic effect of the

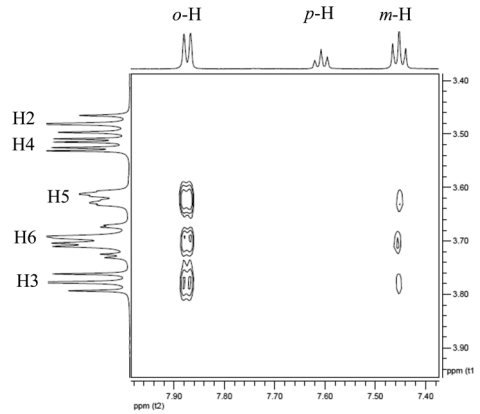


Fig. 4 Partial contour plot of 600 MHz 2D ROESY spectrum for binding of **4a** (phenyl ring moiety) to β-CD in D_2O.

substrates.[3b,f] For **3d**, the site-selectivity of the C–H bond oxidation was enhanced by γ-CD (entry 15, **4d** : **4d′** = 10 : 1) rather than β-CD (entry 14, **4d** : **4d′** = 5 : 1). In the presence of α-CD or γ-CD, the oxidation of **3a–c** generally gave poor conversion and yield, and the site-selectivity was not enhanced.

The stoichiometries of the inclusion complexes of **3a–c** and β-CD were found to be 1 : 1 with similar association constants (**3a**: 210 M^{-1}; **3b**: 220 M^{-1}; **3c**: 325 M^{-1}). In this regard, the difference in site-selectivity (20 : 1 *vs.* 12 : 1) for **3a** and **3b–c** could not be accounted for by the stoichiometries and the association constants of **3a–c** and β-CD. We decided to study the binding geometry of **3a–c** to β-CD by 2D ROESY experiments[15] in order to provide hints on the different site-selectivities.

However, owing to the low solubility of **3a–c** in D_2O, attempts to perform 2D ROESY experiments for the inclusion complexes between **3a–c** and β-CD were not successful (the signals of **3a–c** in 2D ROESY spectra are too weak in D_2O). Therefore, we performed the 2D ROESY experiment for the binding of **4a** (as a model of **3a**).

Studies on the binding geometries between 4a to β-CD through 2D ROESY experiments

The 2D ROESY spectrum for the binding of **4a** and β-CD showed that H3, H5, and H6 of β-CD have NOE correlation signals with the phenyl ring (Fig. 4) and the 3,7-dimethyloctyl carbon chain (Fig. 5) of **4a**.

The NOE correlation signals of the phenyl ring of **4a** with H3, H5, and H6 of β-CD (Fig. 4) suggested that the phenyl ring binds to the cavity of β-CD. The absence of the NOE signals of the *p*-H of **4a** indicated that the phenyl ring is deeply included in the cavity of β-CD. Apart from this, the NOE correlation signals of the 3,7-dimethyloctyl carbon chain of **4a** with H3, H5, and H6 of β-CD (Fig. 5) revealed that the 3,7-dimethyloctyl carbon chain of **4a** would also bind into the cavity of β-CD.

Thus, based on the 2D ROESY spectrum of the inclusion complex of **4a** and β-CD, β-CD would bind to **3a** with two possible binding modes. It is proposed that β-CD would affect the site-selectivity through binding to the phenyl substituent of the **3a** (Fig. 6, Binding mode A), and no C–H bond oxidation is expected to occur when β-CD binds to the 3,7-dimethyloctyl carbon chain of **3a** (Fig. 6, Binding mode B).

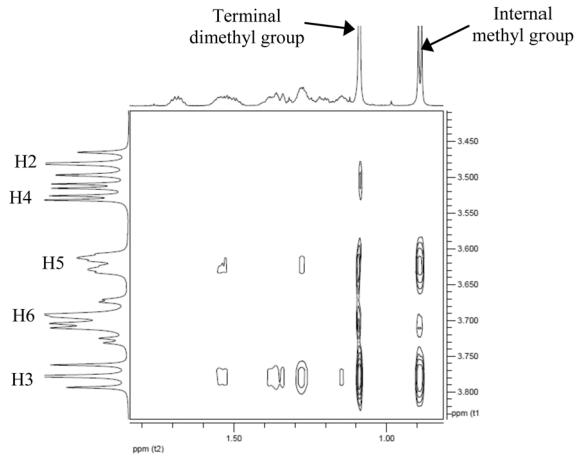


Fig. 5 Partial contour plot of 600 MHz 2D ROESY spectrum for binding of **4a** (3,7-dimethyloctyl carbon chain) to β-CD in D_2O.

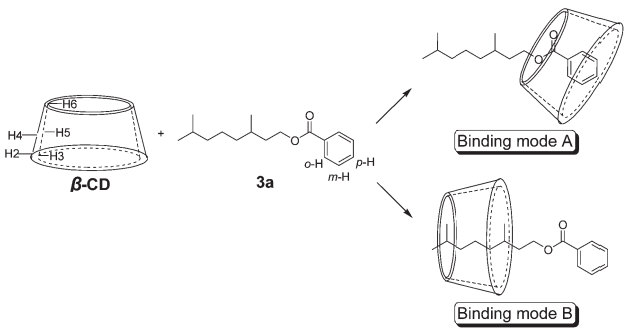


Fig. 6 Proposed binding geometry for the inclusion of **3a** in β-CD.

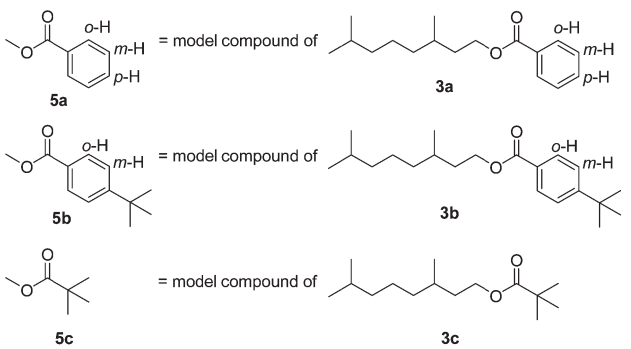


Fig. 7 **5a–c** as model compounds of **3a–c** for 2D ROESY experiments.

Studies on the binding geometries between model compounds of 3a–c to β-CD through 2D ROESY experiments

After establishment of the two possible binding geometries of **3a** to β-CD, the effect of different substituents on the binding geometries was studied. In this part, methyl benzoate (**5a**), methyl 4-*tert*-butylbenzoate (**5b**), and methyl pivalate (**5c**) were chosen as the model compounds of **3a**, **3b**, and **3c**, respectively (Fig. 7).

From the 2D ROESY spectra for the binding of **5a–c** to β-CD (see ESI†), it was found that **5a–c** would bind into the β-CD cavity with different depth (Fig. 8). **5a** was deeply included into

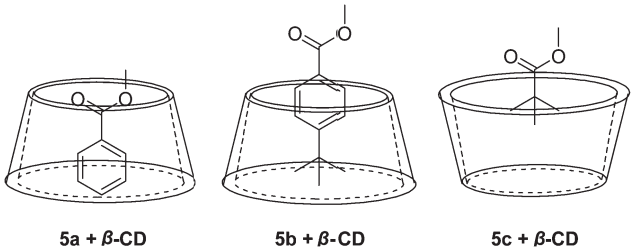


Fig. 8 Proposed binding geometries of **5a–c** to β-CD.

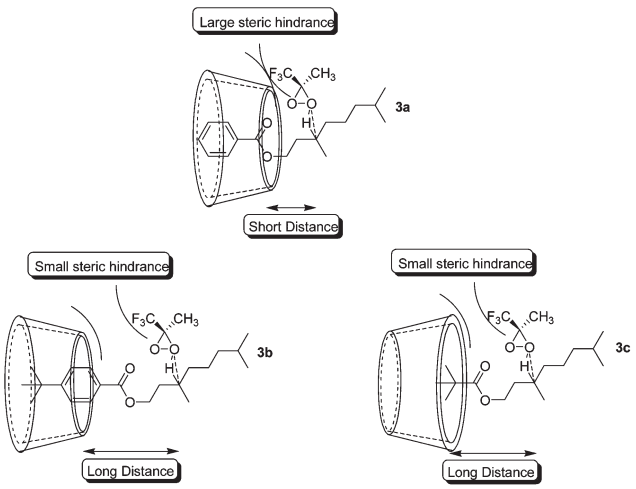


Fig. 9 Schematic diagrams for site-selective C–H bond oxidation of **3a–c**.

the β-CD cavity. For **5b**, only the *tert*-butyl moiety and a half of the phenyl ring were included into the β-CD cavity. The *tert*-butyl moiety of **5c** was included close to the secondary face of β-CD.

Proposed relationship between binding geometries and site-selective C–H bond oxidation of 3a–c

Based on the 2D ROESY studies of binding geometries of **5a–c** to β-CD, it is expected that the different binding geometries of the substituents to β-CD could affect the site-selectivity (Fig. 9).

A deep inclusion of the phenyl ring of **3a** into the β-CD cavity leading to significant steric hindrance induced by the β-CD could effectively obstruct the approach of dioxirane to the internal tertiary C–H bond of **3a**, resulting in the highest site-selectivity in C–H bond oxidation (**4a** : **4a′** = 20 : 1). In the case of **3b**, the inclusion of the *tert*-butyl moiety and only half of the phenyl ring into the β-CD cavity led to a longer distance between the internal tertiary C–H bond and the β-CD. The reduced steric hindrance induced by β-CD on the internal tertiary C–H bond gave lower site-selectivity in C–H bond oxidation (**4b** : **4b′** = 12 : 1). The *tert*-butyl group of **3c** was in close proximity to H3 located at the rim of β-CD and not as deeply included as the phenyl group of **3a**. Thus, β-CD provides less effective obstruction to the approach of dioxirane to the internal tertiary C–H bond, leading to the lower site-selectivity in the C–H bond oxidation (**4c** : **4c′** = 12 : 1).

As shown in Table 3, α-CD and γ-CD could not give enhancement of the site-selectivity of C–H bond oxidation of **3a–c**. It may be because the size of the cavity of α-CD did not fit the substrates; and the structure of γ-CD was too flexible to bind with the substrates (the changes of the chemical shift of H3 and H5 of γ-CD induced by the inclusion complexation between γ-CD and the substrates were very small, see ESI†). Apart from the site-selectivity, the low yields and conversions obtained with α-CD or γ-CD could be due to the undesirable binding.

Effect of CDs on the site-selectivity of C–H bond oxidation of 3d

Unlike the results obtained from **3a–c**, β-CD did not improve the site-selectivity of C–H bond oxidation of **3d**. The stoichiometry of the inclusion complex of **3d** to β-CD was found to be 2 : 1 by ^{1}H NMR titration. The 2D ROESY experiment for the binding of **3d** to β-CD has been conducted (see ESI†). The results showed that β-CD bound to the 3,7-dimethyloctyl carbon chain of **3d**. Thus, no C–H bond oxidation of **3d** would occur based on this binding mode. The C–H bond oxidation of **3d** was likely to occur with poor site-selectivity in aqueous medium (Table 3, entry 14). Interestingly, γ-CD gave a two-fold improvement on the site-selectivity of C–H bond oxidation of **3d** (Table 3, entry 15). The stoichiometry of the inclusion complex of **3d** to γ-CD was found to be 1 : 1 by ^{1}H NMR titration. However, it was not possible to study the binding geometry of **3d** to γ-CD due to the weak NOE signal between **3d** and γ-CD.

Selective C–H bond oxidation of hydrocarbon mixtures by supramolecular approach

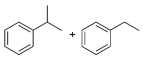
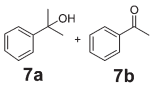
As β-CD gave an enhancement of the conversion and site-selectivity of C–H bond oxidation, it was interesting to study the selectivity in C–H bond oxidation of hydrocarbon mixtures by supramolecular approach. In this regard, cumene (**6a**) and ethyl benzene (**6b**) were used as the substrates.

The oxidation of **6a** in the presence of β-CD gave cumyl alcohol (**7a**) in 32% yield with 38% recovery of **6a** (Table 4, entry 1). However, no **7a** was obtained with only 3% recovery of **6a** in the absence of β-CD (entry 2). It is known that **6a** has low solubility in H_2O and would evaporate during the course of reaction. Comparing the findings in entries 1 and 2, it was suggested that β-CD could enhance the reaction yield by acting as a reaction vessel and minimizing the evaporation of volatile **6a** through inclusion complex formation.[17] In H_2O (4 mL) and CH_3CN (6 mL), **7a** in 4% yield with 63% recovery of **6a** was obtained (entry 3). The poor oxidation efficiency of **6a** would be due to the biphasic separation of H_2O and CH_3CN during the reaction.

β-CD exhibited a similar effect on the oxidation of **6b** to afford **7b** in 15% yield with 65% recovery of **6b** (entry 4). Without β-CD, no oxidation of **6b** occurred and only 3% of **4b** was recovered (entry 5). The oxidation of **6b** in H_2O (4 mL) and CH_3CN (6 mL) gave **7b** in 4% yield with 73% recovery of **6b** (entry 6).

In a mixture of **6a** and **6b**, the oxidation of **6a** was selectively enhanced in the presence of β-CD. With β-CD, **7a** (23% yield; 50% recovery) and **7b** (3% yield; 59% recovery) were obtained

Table 4 Effect of β-CD on dioxirane-based oxidation of **6a**, **6b**, and their mixture

Entry	Substrate	Conditions	Product	Yield[d] (%) (Recovery of starting materials (%))
1	 **6a**	H_2O + β-CD[a]	 **7a**	32 (38)
2		H_2O[b]		0 (3)
3		H_2O + CH_3CN[c]		4 (63)
4	 **6b**	H_2O + β-CD[a]	 **7b**	15 (65)
5		H_2O[b]		0 (3)
6		H_2O + CH_3CN[c]		4 (73)
7	 **6a** **6b**	H_2O + β-CD[a]	 **7a** **7b**	**7a**: 23 (50); **7b**: 3 (59)
8		H_2O + CH_3CN[c]		**7a**: 9 (71); **7b**: 4 (59)

[a] The reaction was conducted by stirring substrate (0.2 mmol), 1,1,1-trifluoroacetone (0.2 mmol) and β-CD (0.22 mmol) in H_2O (10 mL) at room temperature with Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) for 8 h. [b] The reaction was performed in H_2O (10 mL) without β-CD. [c] The reaction was performed in H_2O (4 mL) and CH_3CN (6 mL) without β-CD. [d] Obtained by GC analysis of crude reaction mixture using authentic standards.

(entry 7). The experiment conducted in H_2O–CH_3CN gave **7a** (9% yield; 71% recovery) and **7b** (4% yield; 70% recovery) without notable selectivity. It should be pointed out that the binding constant of **6a** to β-CD (1.2×10^3 M^{-1}) is about four-fold higher than that of **6b** to β-CD (3.3×10^2 M^{-1}).[18] Thus, the preferential binding of **6a** to β-CD would probably lead to an enhanced oxidation efficiency of **6a** over **6b**.

Conclusions

In summary, we have developed efficient methods for C–H bond oxidation by dioxiranes generated *in situ* in aqueous medium. With portion-wise additions of Oxone and $NaHCO_3$, the conversion and yield would be increased. Site-selective C–H bond oxidation of aliphatic esters was achieved by obstructing the approach of dioxiranes to the C–H bond with higher steric hindrance induced through inclusion complexation with β-CD in H_2O. In addition, using β-CD, cumene was preferentially oxidized in a mixture of cumene and ethyl benzene.

Experimental

General information

Reagents and solvents purchased from commercial sources were used without further purification. Flash column chromatography was performed using silica gel 60 (230-400 mesh ASTM) with ethyl acetate–*n*-hexane as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian AS-500 spectrometer. Chemical shifts (ppm) were referred to TMS (internal standard). The 2D ROESY spectra were recorded using Brucker Avance III 600. IR spectra were reported with a Thermo Scientific Nicolet 380 FT-IR spectrometer. Mass spectra were measured using a Q-TOF 2^{TM} mass spectrometer with an ESI source (Waters-Micromass, Manchester, UK). Gas chromatography experiments were carried out with gas chromatograph system (Hewlett Packard 5890 series II) equipped with a flame ionization detector operated at 280 °C. The injector temperature was set to be 250 °C. The column used was HP-5 column (30 m × 0.32 mm × 0.25 μm film thickness). The carrier gas was nitrogen at 12 psi. The running mode was splitless. The sample injection was done by auto-sampler. 1 μL of solution was injected for each run.

General procedure for C–H bond oxidation of adamantane (Table 1)

To a stirring solution of adamantane (**1**) (0.1 mmol) in a mixture of H_2O (1 mL) and CH_3CN (1.5 mL), 1,1,1-trifluoroacetone (0.1 mmol) was added, followed by 3 additions of Oxone (0.5 mmol × 3) and $NaHCO_3$ (1.55 mmol × 3) at 0 h, 2 h and 4 h. After an additional stirring of 2 h, H_2O (4 mL) was added, and the resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent evaporated under reduced pressure. The residue was analyzed by ^{1}H NMR.

Preparation of 3a–d

To 0.1 mmol of DMAP in 5 mL of distilled dichloromethane under nitrogen atmosphere, 1 mmol of 3,7-dimethyl 1-octanol was added, followed by addition of 5 mmol of triethylamine and dropwise addition of 1.2 mmol of acyl chloride (For preparation of **3d**, 1.2 mmol of acetic anhydride was used instead of acyl chloride). After stirring the reaction mixture overnight under nitrogen atmosphere, the reaction was quenched by addition of 10 mL of H_2O. The resulting solution was extracted with 10 mL of dichloromethane. The organic extract was then washed with 10 mL of 3.7% hydrochloric acid, 10 mL of saturated sodium bicarbonate solution and 10 mL of brine, followed by drying with anhydrous Na_2SO_4. The organic solvent was filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate–hexane as eluent.

3,7-Dimethyloctyl benzoate (3a).[3a] Colorless liquid; analytical TLC (silica gel 60) (2% EtOAc in hexane), R_f = 0.5; δ_H (500 MHz; $CDCl_3$) 8.04 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 8.2 Hz, 2H), 4.40–4.32 (m, 2H), 1.85–1.77

(m, 1H), 1.70–1.48 (m, 3H), 1.38–1.12 (m, 6H), 0.96 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.8 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 166.7, 132.9, 130.8, 129.7, 128.5, 63.7, 39.4, 37.4, 35.8, 30.2, 28.2, 24.9, 22.8, 19.8.

3,7-Dimethyloctyl 4-*tert*-butylbenzoate (3b). Colorless liquid; yield: 97% (0.308 g, 0.97 mmol); analytical TLC (silica gel 60) (2% EtOAc in *n*-hexane), R_f = 0.45; δ_H (500 MHz, $CDCl_3$) 7.98–7.96 (d, 2H), 7.46–7.44 (d, 2H), 4.38–4.30 (m, 2H), 1.83–1.76 (m, 1H), 1.67–1.60 (m, 1H), 1.59–1.49 (m, 1H), 1.38–1.22 (m, 12H), 1.18–1.13 (m, 3H), 0.96–0.95 (d, 3H), 0.87–0.86 (d, 6H); δ_C (125 MHz, $CDCl_3$) δ 166.8, 156.54, 129.63, 128.02, 125.46, 63.52, 39.45, 37.41, 35.88, 35.24, 31.35, 30.22, 28.17, 24.88, 22.92, 22.83, 19.85; IR (KBr): = 2956, 2869, 1721, 1276, 855, 755, 708 cm^{-1}; HRMS (ESI) *m/z* for $C_{21}H_{34}O_2Na$ $[M + Na]^+$ calcd: 341.2457, found: 341.2466.

3,7-Dimethyloctyl pivalate (3c).[20] Colorless liquid; analytical TLC (silica gel 60) (2% EtOAc in *n*-hexane), R_f = 0.55; δ_H (500 MHz, $CDCl_3$) 4.15–4.04 (m, 2H), 1.59–1.49 (m, 2H), 1.47–1.38 (m, 1H), 1.36–1.25 (m, 3H), 1.19 (s, 9H), 1.17–1.11 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 178.7, 63.0, 39.3, 38.8, 37.3, 35.7, 30.0, 28.1, 27.3, 24.8, 22.8, 22.7, 19.7.

3,7-Dimethyloctyl acetate (3d).[3f] Colorless liquid; analytical TLC (silica gel 60) (2% EtOAc in *n*-hexane), R_f = 0.6; δ_H (500 MHz, $CDCl_3$) 4.15–4.04 (m, 2H), 2.03 (s, 3H), 1.70–1.09 (m, 10H), 0.90 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 7.1 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 171.0, 63.0, 39.3, 37.2, 35.6, 29.9, 28.0, 24.7, 22.7, 22.6, 21.0, 19.6.

Procedure for site-selective C–H bond oxidation of 3a with β-CD (Table 2, entry 1)

To a mixture of **3a** (0.2 mmol) and β-CD (0.22 mmol), H_2O (10 mL) was added, followed by the addition of 1,1,1-trifluoroacetone (0.2 mmol). Then, the reaction mixture was treated with 8 additions of Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) at an interval of 1 h. After stirring for a total of 8 h at room temperature, the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. The residue was then dissolved in $CDCl_3$ for analysis of the product ratio by ^1H NMR spectroscopy. The yield and conversion were obtained by flash column chromatography of the residue.

Experimental procedures for ^1H NMR titration experiment

To the solutions of β-cyclodextrin of different concentrations in D_2O (0.5 mL) in NMR tubes at room temperature, different volumes of the solution of substrates in D_6-acetone (0.5 M) were added (the ratio of β-cyclodextrin to substrate = 0 : 10, 1 : 9, 2 : 8, 3 : 7, 4 : 6, 5 : 5, 5.5 : 4.5, 6 : 4, 6.7 : 3.3, 7 : 3). The resulting solutions were analyzed by ^1H NMR spectrometer immediately after being shaken vigorously with cover. Using the chemical shift of H4 as internal reference (as the chemical shift of H4 is least affected during inclusion complex formation), the curve of ^1H NMR titration was obtained by plotting the change of chemical shift of H3 against the mole ratio of substrate to cyclodextrin.

General procedure for site-selective C–H bond oxidation of 3,7-dimethyloctyl esters 3a–d with cyclodextrins (Table 3)

To a mixture of 3,7-dimethyloctyl ester (0.2 mmol) and cyclodextrin (0.22 mmol), H_2O (10 mL) was added, followed by addition of 1,1,1-trifluoroacetone (0.2 mmol). Then, the reaction mixture was treated with 8 additions of Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) at an interval of 1 h. After stirring for a total of 8 h at room temperature, the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. The residue was then dissolved in $CDCl_3$ for analysis of the product ratio by ^1H NMR spectroscopy. The yield and conversion were obtained by flash column chromatography of the residue.

7-Hydroxy-3,7-dimethyloctyl benzoate (4a).[3a] Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.35; δ_H (500 MHz, $CDCl_3$) 8.04 (d, J = 7.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 4.40–4.31 (m, 2H), 1.85–1.79 (m, 1H), 1.71–1.55 (m, 3H), 1.48–1.32 (m, 5H), 1.21 (s, 6H), 0.973 (d, J = 6.6 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 166.7, 132.8, 130.5, 129.5, 128.3, 70.9, 63.5, 44.1, 37.4, 35.6, 30.1, 29.2, 29.2, 21.6, 19.6; MS (ESI) *m/z* 301 $[M + Na]^+$.

3-Hydroxy-3,7-dimethyloctyl benzoate (4a′).[19] Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.45; δ_H (500 MHz, $CDCl_3$) 8.03 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 4.50 (t, J = 6.9 Hz, 2H), 2.01–1.92 (m, 2H), 1.57–1.50 (m, 3H), 1.40–1.33 (m, 2H), 1.27 (s, 3H), 1.20–1.15 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 166.9, 133.1, 130.5, 129.7, 128.6, 72.2, 62.0, 43.1, 40.0, 39.7, 28.2, 27.4, 22.8, 22.8, 22.0; MS (ESI) *m/z* 301 $[M + Na]^+$.

7-Hydroxy-3,7-dimethyloctyl 4-*tert*-butylbenzoate (4b). Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.48; δ_H (500 MHz, $CDCl_3$) 7.97 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 4.39–4.31 (m, 2H), 1.84–1.78 (m, 1H), 1.71–1.62 (m, 1H), 1.61–1.54 (m, 1H), 1.47–1.32 (m, 15H), 1.27–1.22 (m, 1H), 1.21 (s, 6H), 0.97 (d, J = 6.8 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 166.7, 156.4, 129.4, 127.7, 125.3, 70.9, 63.3, 44.1, 37.4, 35.6, 31.1, 30.0, 29.3, 29.2, 21.6, 19.6; IR (KBr): = 3449, 2966, 2870, 1720, 1278, 855, 776, 708 cm^{-1}; MS (ESI) *m/z* 335 $[M + H]^+$; HRMS (ESI) *m/z* for $C_{21}H_{35}O_3$ $[M + H]^+$ calcd: 335.2586, found: 335.2598.

3-Hydroxy-3,7-dimethyloctyl 4-*tert*-butylbenzoate (4b′). Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.52; δ_H (500 MHz, $CDCl_3$) 7.95 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 4.48 (t, J = 6.8 Hz, 2H), 2.00–1.91 (m, 2H), 1.64–1.48 (m, 5H), 1.35–1.32 (m, 12H), 1.27 (s, 3H), 0.86 (d, J = 6.6 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 166.8, 156.8, 129.6, 127.7, 125.6, 72.2, 61.8, 43.1, 40.1, 39.7, 35.3, 31.3, 28.2, 27.4, 22.8, 22.8, 22.0; MS (ESI) *m/z* 335

$[M + H]^+$; HRMS (ESI) *m/z* for $C_{21}H_{35}O_3$ $[M + H]^+$ calcd: 335.2586, found: 335.2573.

7-Hydroxy-3,7-dimethyloctyl pivalate (4c).[20] Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.38; δ_H (500 MHz, $CDCl_3$) 4.15–4.04 (m, 2H), 1.72–1.63 (m, 1H), 1.61–1.53 (m, 1H), 1.49–1.29 (m, 7H), 1.22 (s, 6H), 1.20 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 178.7, 70.9, 62.9, 44.1, 38.7, 37.4, 35.5, 29.9, 29.3, 29.2, 27.2, 21.7, 19.5; MS (ESI) *m/z* 281 $[M + Na]^+$.

3-Hydroxy-3,7-dimethyloctyl pivalate (4c′). Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.48; δ_H (500 MHz, $CDCl_3$) 4.23 (t, J = 6.6 Hz, 2H), 1.87–1.77 (m, 2H), 1.59–1.50 (m, 2H), 1.49–1.44 (m, 2H), 1.38–1.31 (m, 3H), 1.22 (s, 3H), 1.20 (s, 9H), 0.88 (d, J = 8.1 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 178.7, 72.2, 61.5, 43.0, 40.0, 39.7, 38.9, 28.2, 27.4, 27.2, 22.8, 22.8, 21.9; MS (ESI) *m/z* 281 $[M + Na]^+$; HRMS (ESI) *m/z* for $C_{15}H_{31}O_3$ $[M + H]^+$ calcd: 259.2273, found: 259.2273.

7-Hydroxy-3,7-dimethyloctyl acetate (4d).[3b] Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.27; δ_H (500 MHz, $CDCl_3$) 4.14–4.06 (m, 2H), 2.04 (s, 3H), 1.71–1.24 (m, 10H); 1.22 (s, 6H), 0.92 (d, J = 6.8 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 171.3, 71.0, 63.0, 44.1, 37.4, 35.5, 29.8, 29.3, 29.2, 21.6, 21.0, 19.5; MS (ESI) *m/z* 217 $[M + H]^+$.

3-Hydroxy-3,7-dimethyloctyl acetate (4d′).[3b] Colorless liquid; analytical TLC (silica gel 60) (20% EtOAc in hexane), R_f = 0.20; δ_H (500 MHz, $CDCl_3$) 4.24 (t, J = 7Hz, 2H), 2.05 (s, 3H), 1.87–1.77 (m, 2H), 1.60–1.15 (m, 7H), 1.21 (s, 3H), 0.88 (d, J = 6.6 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 171.0, 71.9, 61.3, 42.8, 39.6, 39.4, 28.0, 27.1, 22.6, 21.7, 21.1; MS (ESI) *m/z* 239 $[M + Na]^+$.

General procedure for C–H bond oxidation of 6a or 6b with β-CD (Table 4)

To a mixture of substrate (0.2 mmol) and β-CD (0.22 mmol), H_2O (10 mL) was added, followed by addition of 1,1,1-trifluoroacetone (0.2 mmol). Then, the mixture was treated with 8 additions of Oxone (0.5 mmol × 8) and $NaHCO_3$ (1.55 mmol × 8) at an interval of 1 h. After stirring for 8 h at room temperature, the resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered. Then, 0.4 mL of the extract was mixed with a hexane solution of *n*-decane as internal standard, and made up to 0.9 mL solution by *n*-hexane in a 1.5 mL vial for GC analysis.

Acknowledgements

We thank the financial support of Hong Kong Research Grants Council (PolyU 7052/07p) and The Hong Kong Polytechnic University (A-PK37, PolyU Departmental General Research Funds, Competitive Research Grants for Newly Recruited Junior Academic Staff and SEG PolyU01).

Notes and references

1 (*a*) A. E. Shilov and G. B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, Kluwer Academic Publishers, 2000; (*b*) K. I. Goldberg and A. S. Goldman, *Activation and Functionalization of C–H Bonds*, Oxford University Press, 2004; (*c*) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (*d*) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879; (*e*) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698; (*f*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507.

2 (*a*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077; (*b*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*d*) R. Mas-Ballesté and L. Que Jr., *Science*, 2006, **312**, 1885; (*e*) H. M. L. Davies, *Angew. Chem., Int. Ed.*, 2006, **45**, 6422; (*f*) C. I. Herrerías, X. Yao, Z. Li and C.-J. Li, *Chem. Rev.*, 2007, **107**, 2546; (*g*) L. Que Jr and W. B. Tolman, *Nature*, 2008, **455**, 333; (*h*) H. M. L. Davies, *Nat. Chem.*, 2009, **1**, 519; (*i*) K. Chen and P. S. Baran, *Nature*, 2009, **459**, 824; (*j*) G. B. Shul'pin, *Org. Biomol. Chem.*, 2010, **8**, 4217; (*k*) D.-H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315; (*l*) M. Chen and M. C. White, *Science*, 2010, **327**, 566; (*m*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (*n*) M. A. Bigi, S. A. Reed and M. C. White, *Nat. Chem.*, 2011, **3**, 216; (*o*) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976.

3 (*a*) B. H. Brodsky and J. Du Bois, *J. Am. Chem. Soc.*, 2005, **127**, 15391; (*b*) M. Chen and M. C. White, *Science*, 2007, **318**, 783; (*c*) L. V. Desai, K. J. Stowers and M. S. Sanford, *J. Am. Chem. Soc.*, 2008, **130**, 13285; (*d*) N. D. Litvinas, B. H. Brodsky and J. Du Bois, *Angew. Chem., Int. Ed.*, 2009, **48**, 4513; (*e*) H.-Q. Do and O. Daugulis, *Chem. Commun.*, 2009, **42**, 6433; (*f*) L. Gómez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas and M. Costas, *Angew. Chem., Int. Ed.*, 2009, **48**, 5720.

4 (*a*) Y. Asakawa, R. Matsuda, M. Tori and T. Hashimoto, *Phytochemistry*, 1988, **27**, 3861; (*b*) Ref. 3b (*c*) Ref. 3f (*d*) L. Li, W. W. Brennessel and W. D. Jones, *Organometallics*, 2009, **28**, 3492.

5 (*a*) D. H. R. Barton, *Pure Appl. Chem.*, 1968, **16**, 1; (*b*) R. H. Hesse, *Adv. Free Radical Chem.*, 1969, **3**, 83; (*c*) Y. L. Chow, W. C. Danen, S. F. Nelsen and D. H. Rosenblatt, *Chem. Rev.*, 1978, **78**, 243; (*d*) C. Walling and D. Bristol, *J. Org. Chem.*, 1972, **37**, 3514; (*e*) C. G. Espino, P. M. Wehn, J. Chow and J. Du Bois, *J. Am. Chem. Soc.*, 2001, **123**, 6935; (*f*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (*g*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*h*) K. Chen, J. M. Richter and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7247.

6 (*a*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995; (*b*) J. K. M. Sanders, in *Supramolecular Science: Where It Is and Where It Is Going*, ed. R. Ungaro and E. Dalcanale, Kluwer, Dordrecht, The Netherlands, 1999; (*c*) J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, Wiley, England, 2000; (*d*) Y. Murakami, J. I. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721; (*e*) J. Kang, J. Santamaría, G. Hilmersson and J. Rebek Jr., *J. Am. Chem. Soc.*, 1998, **120**, 7389; (*f*) M. C. Feiters, A. E. Rowan and R. J. M. Nolte, *Chem. Soc. Rev.*, 2000, **29**, 375; (*g*) W. B. Motherwell, M. J. Bingham and J. Six, *Tetrahedron*, 2001, **57**, 4663; (*h*) D. H. Leung, D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem., Int. Ed.*, 2004, **43**, 963; (*i*) M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem., Int. Ed.*, 2009, **48**, 3418; (*j*) G. B. Shul'pin, *Org. Biomol. Chem.*, 2010, **8**, 4217; (*k*) S. Liu, H. Gan, A. T. Hermann, S. W. Rick and B. C. Gibb, *Nat. Chem.*, 2010, **2**, 847; (*l*) Y. Inokuma, M. Kawano and M. Fujita, *Nat. Chem.*, 2011, **3**, 349.

7 (*a*) J. Szejtli and T. Osa, Cyclodextrins, in *Comprehensive Supramolecular Chemistry*, ed. J.-M. Lehn, J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vogtle, Pergamon, New York, vol. 3, 1996; (*b*) K. A. Connors, *Chem. Rev.*, 1997, **97**, 1325; (*c*) J. Szejtli, *Chem. Rev.*, 1998, **98**, 1743; (*d*) R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997; (*e*) K. Takahashi, *Chem. Rev.*, 1998, **98**, 2013; (*f*) M. Bols and L. Marinescu, *Curr. Org. Chem.*, 2010, **14**, 1380.

8 K. Oiwka and K. Furuya, *Ekcmchintica Acta*, 1992, **37**, 1135.

9 (*a*) W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, 1989, **22**, 205; (*b*) R. W. Murray, *Chem. Rev.*, 1989, **89**, 1187; (*c*) W. Adam and L. Hadjiarapoglou, *Top. Curr. Chem.*, 1993, **164**, 45; (*d*) S. E. Denmark and Z. Wu, *Synlett*, 1999, 847; (*e*) W. Adam, C. R. Saha-Möller and C.-G. Zhao, *Org. React.*, 2002, **61**, 219; (*f*) Y. Shi, *Acc. Chem. Res.*, 2004, **37**, 488; (*g*) D. Yang, *Acc. Chem. Res.*, 2004, **37**, 497;

(*19*) W. Adam, C.-G. Zhao and K. Jakka, *Org. React.*, 2007, **69**, 1; (*i*) O. A. Wong and Y. Shi, *Chem. Rev.*, 2008, **108**, 3958.
10 (*a*) R. Curci, L. D'Accolti and C. Fusco, *Acc. Chem. Res.*, 2006, **39**, 1; (*b*) R. W. Murray, R. Jeyaraman and L. Mohan, *J. Am. Chem. Soc.*, 1986, **108**, 2470; (*c*) G. Asensio, M. E. G. Nunez, C. B. Bernardini, R. Mello and W. Adam, *J. Am. Chem. Soc.*, 1993, **115**, 7250; (*d*) K. Chen, A. Eschenmoser and P. S. Baran, *Angew. Chem., Int. Ed.*, 2009, **48**, 9705; (*e*) S. Kasuya, S. Kamijo and M. Inoue, *Org. Lett.*, 2009, **11**, 3630.
11 (*a*) D. Yang, M.-K. Wong, X.-C. Wang and Y.-C. Tang, *J. Am. Chem. Soc.*, 1998, **120**, 6611; (*b*) M.-K. Wong, N.-W. Chung, L. He and D. Yang, *J. Am. Chem. Soc.*, 2003, **125**, 158; (*c*) M.-K. Wong, N.-W. Chung, L. He, X.-C. Wang, Z. Yan, Y.-C. Tang and D. Yang, *J. Org. Chem.*, 2003, **68**, 6321.
12 W.-K. Chan, W.-Y. Yu, C.-M. Che and M.-K. Wong, *J. Org. Chem.*, 2003, **68**, 6576.
13 (*a*) C. Rousseau, B. Christensen, T. E. Petersen and M. Bols, *Org. Biomol. Chem.*, 2004, **2**, 3476; (*b*) L. Marinescu, M. Mølbach, C. Rousseau and M. Bols, *J. Am. Chem. Soc.*, 2005, **127**, 17578; (*c*) J. Bjerre, T. H. Fenger, L. G. Marinescu and M. Bols, *Eur. J. Org. Chem.*, 2007, 704; (*d*) T. H. Fenger, L. G. Marinescu and M. Bols, *Org. Biomol. Chem.*, 2009, **7**, 933; (*e*) T. H. Fenger, L. G. Marinescu and M. Bols, *Eur. J. Org. Chem.*, 2011, 2339.
14 (*a*) D. Yang, Y.-C. Yip, G.-S. Jiao and M.-K. Wong, *J. Org. Chem.*, 1998, **63**, 8952; (*b*) D. Yang, G.-S. Jiao, Y.-C. Yip and M.-K. Wong, *J. Org. Chem.*, 1999, **64**, 1635.
15 (*a*) P. V. Demarco and A. L. Thakkar, *J. Chem. Soc., Chem. Commun.*, 1970, 2; (*b*) A. Botsi, K. Yannakopoulou, B. Perly and E. Hadjoudis, *J. Org. Chem.*, 1995, **60**, 4017; (*c*) D. Salvatierra, C. Jaime, A. Virgili and F. Sanchez-Ferrando, *J. Org. Chem.*, 1996, **61**, 9578; (*d*) A. Botsi, B. Perly and E. Hadjoudis, *J. Chem. Soc., Perkin Trans. 2*, 1997, 89; (*e*) H. J. Schneider, F. Hacket and V. Rüdiger, *Chem. Rev.*, 1998, **98**, 1755; (*f*) D. Salvatierra, X. Sanchez-Ruiz, R. Garduno, E. Cervello, C. Jaime, A. Virgili and F. Sanchez-Ferrando, *Tetrahedron*, 2000, **56**, 3035; (*g*) M. Zubiaur and C. Jaime, *J. Org. Chem.*, 2000, **65**, 8139.
16 R. L. Scott, *Recl. Trav. Chim. Pays-Bas*, 1956, **75**, 787.
17 H. M. C. Marques, *Flavour Fragr. J.*, 2010, **25**, 313.
18 I. Sanemasa and Y. Akamine, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2059.
19 L. F. Tietze, S. Biller and T. Wolfram, *Synlett*, 2010, **14**, 2130.
20 E. McNeill and J. Du Bois, *J. Am. Chem. Soc.*, 2010, **132**, 10202.

