Tetrahedron 69 (2013) 7308–7313

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of functionalized cyclotriveratrylene analogues with C_1-symmetry and the application for 1,4-Michael addition of alcohols to unsaturated aryl ketone

Jing-Ru Song, Zhi-Tang Huang, Qi-Yu Zheng *

Beijing National Laboratory for Molecular Science, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

ARTICLE INFO

Article history:
Received 11 April 2013
Received in revised form 27 May 2013
Accepted 21 June 2013
Available online 28 June 2013

Keywords:
Cyclotriveratrylene
C_1-symmetry
Chemical resolution
N-Heterocyclic carbene
Michael addition

ABSTRACT

C_1-symmetric cyclotriveratrylene analogues **2**–**8** with various functional groups at one benzene moiety were prepared starting from the selectively demethylated compound **1**. Through the chemical resolution, a pair of enantiomers of C_1-symmeric compound **1** could be separated with gram scale. Compound **8**, which possessed an N-linked imidazolium unit at the upper rim of the macrocyclic skeleton through a methylene linker, was successfully applied to 1,4-Michael addition reaction of alcohol to unsaturated aryl ketone. Its supramolecular catalytic activity as an NHC precursor was demonstrated by the chemselectivity to aromatic alcohol than alkyl alcohol.

1. Introduction

Cyclotriveratrylene (CTV) is a kind of macrocyclic host with a bowl-shaped cavity.[1] Since of the discovery, a great deal of its analogues with different functional groups and extended arms have been synthesized.[2] The excellent binding modes and deeper cavity make CTV and its analogues get broad usages in selective recognition,[2h,3] liquid crystal,[4] supramolecular assemblies,[5] porous materials,[6] xenon biosensing,[7] and fullerene separations.[3b,8] If the substituents of the upper rim are different, CTV analogues may be chiral.[9] Though much attention has been focused on this macrocycle and numerous achievements have been made, C_1-symmetric analogues, such as mono-functionalized or the derivatives bearing two different functional groups at only one of the three benzene units have rarely been reported. To the best of our knowledge, there are only two relative reports involving the synthesis, which bear hydroxyl or methyl group instead of one methoxy of the cyclotriveratrylene molecule.[1b,10] C_1-symmetric CTV analogues can be generated by two different methods. The first way is to directly introduce a benzene unit with two different groups. This is much difficult upon condensation due to the different electron-giving capability of the substituents at the benzene.[1b] Another way is originating from the cyclotriveratrylene through selective demethylation and then incorporation of the new functional group(s).

On the other side, oxa-Michael reaction is one of the most effective routes to form the C–O bond, which is a key component of many biologically active compounds. Many research groups have reported relative investigations with great progress.[11] However, there still remains challenge due to the undesired oligomerization of the Michael acceptor. Recently, *N*-heterocyclic carbenes (NHCs) have emerged as a powerful and effective organic catalyst to various reactions.[12] In 2010, Scheidt group reported the conjugated addition of alcohol using a free carbene without oligomerization of the substrate.[13]

In this paper, we demonstrated the second synthetic route for C_1-symmetric CTV analogues and firstly prepared three useful macrocycles bearing one formyl group (**4**), double functionalities (**5**) like salicylaldehyde and N-linked imidazolium group (**8**), respectively. We also attempted the resolution of C_1-symmetric CTV analogue to explore the feasibility of the chemical resolution method. Simultaneously, with compound **8** in hand, we further investigated its supramolecular catalytic activity as an NHC precursor to the 1,4-Michael addition reaction of alcohol to unsaturated aryl ketone.

* Corresponding author. Tel.: +86 10 6265 2811; fax: +86 10 6255 4449; e-mail address: zhengqy@iccas.ac.cn (Q.-Y. Zheng).

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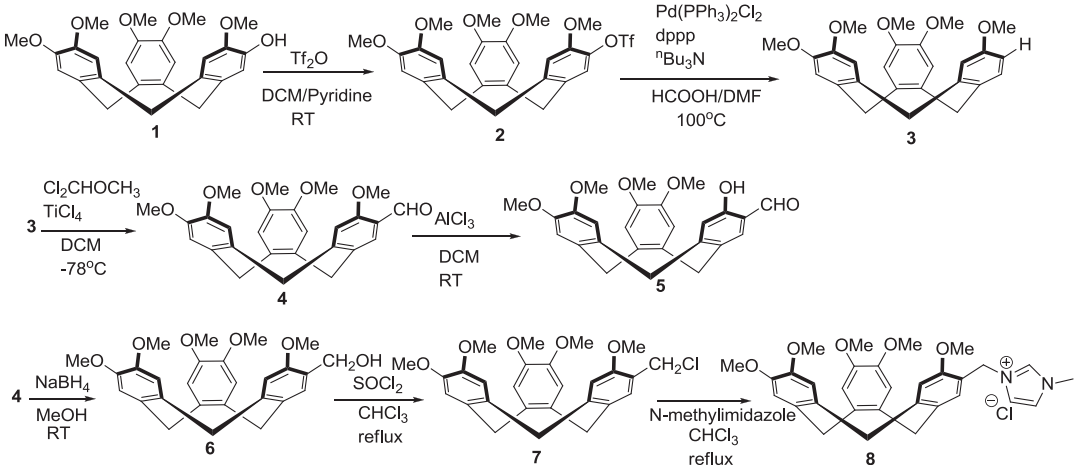
http://dx.doi.org/10.1016/j.tet.2013.06.077

2. Result and discussion

2.1. Synthesis

The synthetic route to the corresponding molecules is described in Scheme 1. Treating compound **1**[10] with trifluoromethanesulfonic anhydride in a mixed solvent of dichloromethane and pyridine, compound **2** was obtained in virtually quantitative yield.



Scheme 1. The synthetic route to compounds **2**–**8**.

After removing the ester group, compound **3** was obtained. Then introduction of a formyl group into compound **3** by using 1,1-dichloromethyl methyl ether in the presence of titanium tetrachloride was achieved in moderate yield to give the monoformyl group compound **4**. Compound **5** was prepared by selective demethylation of compound **4**. Reduction of the formyl group of compound **4** using sodium borohydride followed by chloromethylation with thionyl chloride, and finally alkylation of the 1-methylimidazole afforded N-linked imidazolium unit compound **8**. All of the products were confirmed by NMR, IR, MS spectra, and elemental analysis.

2.2. Crystal structure of compound 5

By slow evaporation the solution of compound **5** in dichloromethane and acetone, colorless crystal suitable for X-ray diffraction was obtained. Compound **5** crystallizes in the monoclinic $P2_1/n$ with the asymmetric unit having one molecule **5** (Fig. 1). There is a typical intramolecular hydrogen bond between the hydroxyl group and formyl group (O—H···O distance 2.060 Å and O···O distance 2.667 Å). In a crystal cell, the molecules with same chirality stack staggered in column along *b* axis, and one methyl group of upper CTV is included by the cavity of lower molecule with C—H···π interactions. The adjacent column is stacked by the opposite chiral substrate with opposite orientation. Thus, the whole crystal is racemic. Weak C—H···O interactions (C—H···O distance 2.475 Å and C···O distance 3.409 Å) between the formyl groups and methoxy groups connect these two columns.

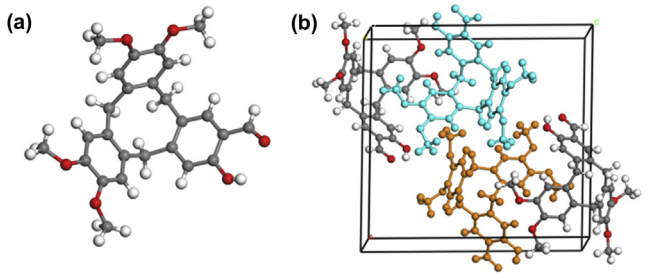
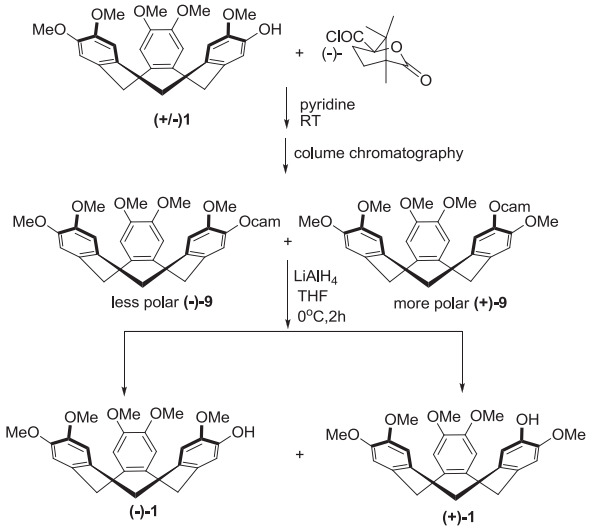


Fig. 1. Crystal structure of compound **5**. (a) Ball and stick view of the asymmetric unit. C: gray, H: white, O: red. (b) Ball and stick view of the molecules in one cell. C: gray, O: red, H: white. Specially, one enantiomer molecule was shown light blue, and the opposite enantiomer molecule was shown brown.

2.3. Chemical resolution of compound 1

C_3-symmetric CTV analogues can be resolved to obtain optically active isomers.[5f,14] However there is no trial to resolve the C_1-symmertric molecule. Here we make the first attempt to prepare the optically pure C_1-symmetric CTV analogues by chemical resolution (Scheme 2). Firstly, the diastereoisomer mixture **9** was prepared starting from the racemic compound **1** with (−)-camphanic acid chloride. Upon column chromatography, this mixture could be separated easily with $[\alpha]_D^{20}$ ($CHCl_3$, *c* 0.0102) values +22.5° and −21.6°, respectively. Then reductive cleavage of the chiral auxiliary group, optically pure (+)-**1** and (−)-**1** were obtained with $[\alpha]_D^{20}$ ($CHCl_3$, *c* 0.002) values +80° and −84°, respectively. The CD spectra of (+)-**1** and (−)-**1** were measured and they showed mirror images of each other, indicating the success of the separation



Scheme 2. Chemical resolution of compound **1**.

method (Fig. 2). The excited result proves the feasible chemical resolution of C_1-symmetric CTV analogues, which is important for optical resolution on a larger scale, laying foundation for the further application research of chiral C_1-symmetric analogues.

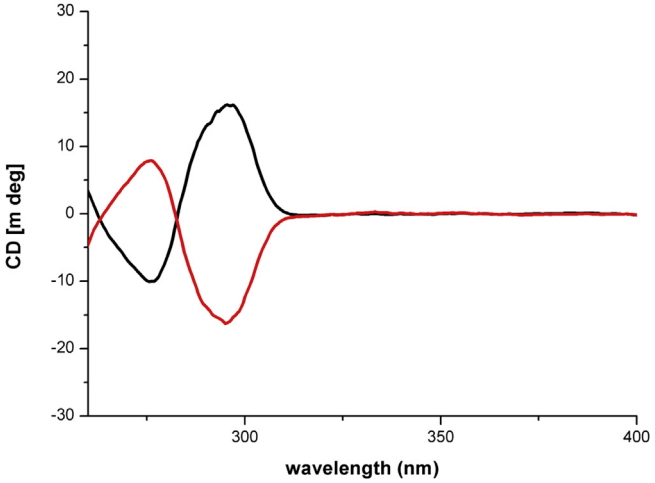
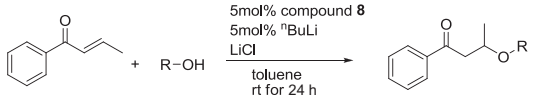


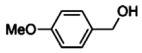
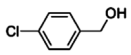
Fig. 2. CD spectra of (+)/(−)-**1** (c=2.3×10^{-4} M in DCM).

2.4. 1,4-Michael addition of alcohol

To test the catalytic activity of compound **8**, 1,4-Michael addition of alcohol to α,β-unsaturated ketone was applied. We began our study using the reaction condition reported by Scheidt with a little modification. The results are summarized in Table 1.

Table 1
1,4-Michael addition of alcohol



Entry	Substrate	Product	Yield[a] (%)
1		**10**	73
2		**11**	76
3		**12**	68
4		**13**	74
5		**14**	65
6	H_3C−OH	**15**	46
7		**16**	50
8		**17**	45

[a] Isolation yield based on substrate.

Compound **8** showed good activity in the addition reaction with the alcohol, with the reactivity toward the benzyl alcohol and analogues, unexpected, higher than that toward the alkyl alcohols, which did not manifest in other simple NHC catalytic reactions.[13] Reacting the ketone with benzyl alcohol and methanol in one pot, we got a mixed product with a **10**/**15**=5:1 molar proportion from ^{1}H NMR (Fig. 3), another proof to the higher activity toward aromatic alcohols. The chem-selectivity may result from the host–guest interaction (π···π interaction) of the CTV cavity and aromatic alcohol, which does not exist when using the alkyl alcohols. That was typical molecular recognition in supramolecular catalysis.[15]

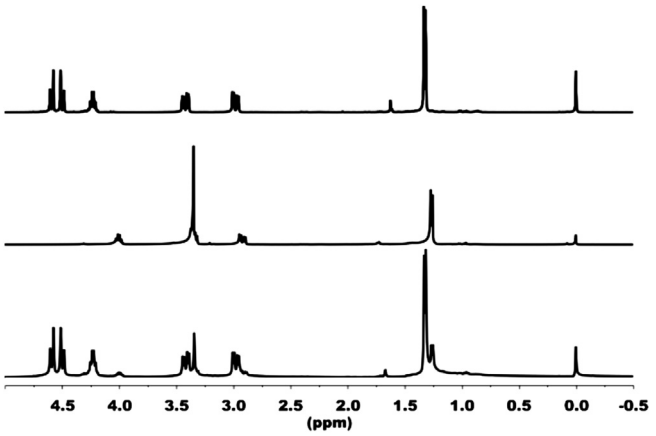


Fig. 3. ^{1}H NMR spectra: compound **10** (top); compound **15** (middle); the mixture by one-pot reaction (bottom).

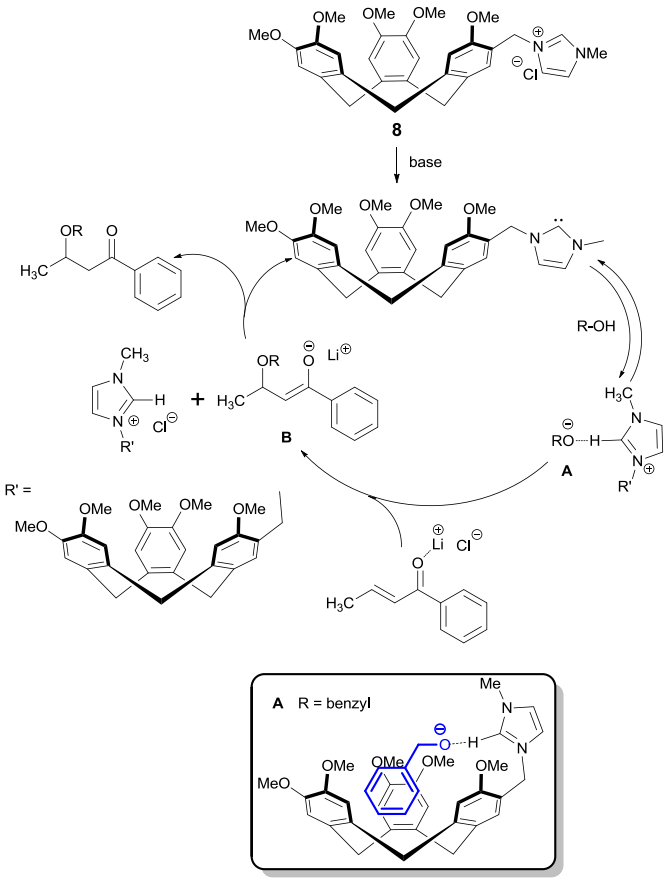
Sémeril and Matt synthesized calix[4]arene-based monophosphanes showing a fast Suzuki–Miyaura cross-coupling.[16] Yasuda and Baba had designed a tripodal cage-shaped catalyst, which can accelerate the hetero-Diels–Alder addition of benzaldehyde more effectively than that of butanal.[17] Both of the two manifested a cavity inclusion action that assisted the reaction. Similarly, our carbene catalyst gave the same influence to the alcohol substrates and presented the chem-selectivity to aromatic substrate with a high ratio in the competitive reaction.

For aromatic alcohols, regardless of the electron-donating or the electron-withdrawing groups, high yields were obtained (Table 1, entries 2 and 3) though a little lower toward electron-withdrawing alcohol. Addition of the primary alcohols gave higher yields than the secondary alcohols for aromatic nucleophiles (Table 1, entries 1 and 5), while the alkyl nucleophiles did not show obvious difference (Table 1, entries 6 and 8). Unexpectedly, 3-hydroxymethyl pyridine only gave the oligomerized product of the unsaturated ketone. The intermolecular hydrogen bond between the nitrogen atom and hydroxyl group of substrates may hinder the activation of the alcohol by the NHC.

The proposed mechanism is illustrated in Scheme 3. Macrocyclic carbene catalyst is generated from compound **8** under the base, and then NHC–alcohol complex **A** and activated ketone by lithium salt accelerate the 1,4-addition of the alcohol. For the aromatic alcohol, inclusion between the catalyst and substrate by π···π interaction facilitates the reaction, thus inducing the chem-selectivity. Hydrogen bonds between the 3-hydroxymethyl pyridine block the formation of complex **A**, and result in the unsuccessful addition.

3. Conclusion

Starting from the selectively demethylated compound **1**, we synthesized several C_1-symmetric cyclotriveratrylene analogues with various functional groups at one benzene moiety. Through the chemical resolution, a pair of enantiomers of C_1-symmeric CTV analogues has been successfully separated with gram scale firstly. Especially, the 1,4-Michael addition reaction catalyzed by one derivative contained a flexible N-linked imidazolium unit has been investigated. The CTV-based catalyst presents an outstanding activity to the conjugate addition that demonstrates the macrocyclic NHC precursor as an efficient catalyst compared to traditional carbenes. Interestingly, the catalyst showed an uncommon higher



Scheme 3. The proposed mechanism for the 1,4-addition reaction.

activity to aromatic substrates than the alkyl substrates, which may result from the molecular recognition between the substrate and catalyst, and this is also the first example of CTV-based catalyst performing the chem-selectivity.

4. Experimental section

4.1. General information

Melting points were taken on an electrothermal melting point apparatus and without correction. FT-IR spectra were recorded on a Thermo-Nicolet 6700 spectrometer using KBr discs for solid products and neat for oil products. Elemental analysis for C, H, and N were performed by a Flash EA 1112 elemental analyzer. H NMR and C NMR spectra were recorded at ambient temperature on a Bruker (400 MHz) NMR spectrometer. X-ray diffraction data on single crystals were collected on a Rigaku RAXISRAPID diffractometer with graphite monochromated Mo K_α radiation ($\lambda_{Mo\ K\alpha}$=0.71073 Å) at 173 K. CD spectra were conducted on JASCO J-810 spectropolarimeter. Compound **1** was synthesized according to the literature method.[10] Methanol, ethanol, isopropyl alcohol, dichloromethane, chloroform, and toluene were dried by standard procedures. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification.

4.2. Synthesis of cyclotriveratrylene analogues 2–9

*4.2.1. Compound **2**.* A solution of triflic anhydride was slowly added under nitrogen to an ice-cooled solution of **1** (1.9 g, 4.35 mmol) in a mixture of pyridine (16 ml) and dichloromethane (50 ml). The solution was warmed to room temperature and stirred for 18 h. Water was then added, and the mixture was extracted three times with dichloromethane. The combined organic layer was washed with water, brine, and then dried with sodium sulfate. Filtration and evaporation of the solvent afforded a residue, which was purified by column chromatography (PE/EA=2:1) to obtain a pale yellow solid (2.43 g, 98%). Mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 6.82 (s, 2H), 6.74 (s, 1H), 4.82–4.71 (m, 3H), 3.86–3.84 (m, 15H), 3.62–3.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 149.60, 148.18, 148.01, 140.73, 137.27, 133.02, 132.45, 131.51, 130.82, 130.27, 123.71, 114.63, 113.33, 113.26, 113.04, 112.90, 56.32, 56.23, 56.11, 56.04, 36.89, 36.67, 36.16; FT-IR ν 3439, 2936, 2847, 1612, 1510, 1446, 1418, 1236, 1252, 1221, 1141, 1089, 999, 942, 882 cm^{-1}; MS (ESI): m/z 568.5 ([M]$^+$). Anal. Calcd for $C_{27}H_{27}F_3O_8S\cdot 2/3H_2O$: C, 55.85; H, 4.92. Found: C, 55.86; H, 4.72.

*4.2.2. Compound **3**.* Compound **2** (1.987 g, 3.5 mmol), dppp (22 mg, 0.053 mmol), $Pd(PPh_3)_2Cl_2$ (25 mg, 0.035 mmol), tributylamine (3 ml), formic acid (2 ml), DMF (20 ml) were mixed in a 100 ml flask. The mixture was heated to 100 °C for 18 h under nitrogen. Then, water was added, and the mixture was extracted with dichloromethane for three times. The organic phase was washed with water, brine, and then dried with sodium sulfate. Filtration and evaporation of the solvent afforded a residue, which was purified by column chromatography (PE/EA=1:1) to obtain a white solid (1.32 g, 89%). Mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 6.82 (s, 3H), 6.67 (d, 1H, J=8 Hz), 4.81–4.73 (m, 3H), 3.84 (m, 12H), 3.75 (s, 3H), 3.62–3.54 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.33, 147.90, 140.91, 132.28, 132.08, 131.32, 131.02, 115.88, 113.34, 113.06, 112.04, 56.15, 55.34, 37.11, 36.71, 36.19; FT-IR ν 3441, 2990, 2927, 2829, 1609, 1577, 1517, 1478, 1463, 1393, 1263, 1225, 1203, 1147, 1089, 1037, 991, 846 cm^{-1}; MS (ESI): m/z 421.4 ([M+H]$^+$). Anal. Calcd for $C_{27}H_{28}O_5\cdot 0.3H_2O$: C, 73.32; H, 6.77. Found: C, 73.58; H, 6.71.

*4.2.3. Compound **4**.* Titanium tetrachloride (0.8 ml) was added to a solution of **3** (1.318 g, 3.13 mmol) in dichloromethane (30 ml) under nitrogen at −78 °C. Then, 1,1-dichloromethyl methyl ether (0.55 ml) was slowly added with syringe. The mixture was stirred at −78 °C for 5 h. Then the solution was poured into a beaker with ice-water and stirred for 10 min. The aqueous phase was extracted with dichloromethane for three times. The organic phase was washed with water, 10% $NaHCO_3$ aqueous solution, brine, and then dried with sodium sulfate. Filtration and evaporation of the solvent afforded a residue, which was purified by column chromatography (EA/DCM=1:25) to obtain a white solid (1.09 g, 77%). Mp 224–227 °C; ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 7.82 (s, 1H), 6.94 (s, 1H), 6.84 (t, 3H), 6.80 (s, 1H), 4.86–4.71 (m, 3H), 3.89 (s, 3H), 3.84 (m, 12H), 3.68–3.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 189.16, 160.34, 148.18, 148.05, 147.86, 147.79, 132.56, 132.48, 131.36, 131.17, 129.88, 129.75, 123.70, 113.20, 113.12, 112.94, 112.86, 112.79, 56.13, 56.03, 56.00, 55.65, 37.41, 36.60, 35.79; FT-IR ν 3440, 2930, 2843, 1677, 1608, 1517, 1462, 1394, 1265, 1227, 1144, 1089, 999, 740, 612 cm^{-1}; MS (ESI): m/z 449.5 ([M+H]$^+$). Anal. Calcd for $C_{27}H_{28}O_6\cdot 0.4H_2O$: C, 71.16; H, 6.37. Found: C, 71.14; H, 6.29.

*4.2.4. Compound **5**.* $AlCl_3$ (599 mg, 4.54 mmol) was added to a solution of **4** (503 mg, 1.12 mmol) in dichloromethane. The mixture was stirred for 20 h at room temperature. Then the solution was poured into a breaker with ice-water. The aqueous phase was extracted with dichloromethane for three times. The organic phase was washed with water, brine, and then dried with sodium sulfate. Filtration and evaporation of the solvent afforded a residue, which was purified by column chromatography (EA/DCM=1:25) to obtain a white solid (220 mg, 45%). Mp 257–259 °C; ^{1}H NMR ($CDCl_3$) δ 10.72 (s, 1H), 9.81 (s, 1H), 7.48 (s, 1H), 6.99 (s, 1H), 6.82 (br, 4H), 4.80–4.68 (m, 3H), 3.86–3.84 (m, 12H), 3.66–3.56 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 195.64, 159.91, 150.01, 148.14, 147.99, 134.97, 132.05, 132.01, 131.98, 130.96,

129.33, 119.76, 118.36, 113.15, 113.06, 112.89, 56.28, 56.14, 56.04, 55.99, 37.09, 36.648, 35.76; FT-IR ν 3440, 2931, 2843, 1653, 1608, 1519, 1478, 1448, 1393, 1351, 1262, 1225, 1144, 1088, 1031, 997, 848, 811, 740, 613 cm^{-1}; MS (MALDI-TOF): m/z 434.0 ($[M]^+$). Anal. Calcd for $C_{26}H_{26}O_6 \cdot 0.8H_2O$: C, 69.57; H, 6.20. Found: C, 69.64; H, 5.99.

4.2.5. Compound ***6***. $NaBH_4$ (880 mg, 23 mmol) was added to an ice-cooled solution of **4** (1.30 g, 2.9 mmol) in methanol (10 ml) under nitrogen. Upon 10 min, the solution was warmed to room temperature and stirred overnight. After evaporation of the solvent, water was added, and the aqueous phase was extracted with dichloromethane for three times. The organic phase was washed with water, brine, and then dried with sodium sulfate. Filtration and evaporation of the solvent afforded a white solid, which was used next step without further purification (1.228 g, 94%). Mp 215–216 °C; ^1H NMR ($CDCl_3$) δ 7.25 (d, 1H, J=4.8 Hz), 6.85–6.82 (m, 5H), 4.83–4.71 (m, 3H), 4.66–4.53 (m, 2H), 3.84 (s, 15H), 3.62–3.54 (m, 3H), 2.16 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 156.00, 147.86, 147.75, 140.14, 132.12, 131.93, 131.83, 131.70, 131.29, 130.45, 127.80, 113.29, 113.11, 111.61, 61.70, 56.20, 56.10, 55.40, 37.04, 36.58, 36.03; FT-IR ν 3415, 2932, 2844, 2247, 1611, 1578, 1514, 1478, 1464, 1394, 1262, 1222, 1194, 1143, 1087, 996, 922, 847, 725, 617 cm^{-1}; MS (MALDI-TOF): m/z 450.0 ($[M]^+$). Anal. Calcd for $C_{27}H_{30}O_6 \cdot 0.85H_2O$: C, 69.61; H, 6.86. Found: C, 69.31; H, 6.37.

4.2.6. Compound ***7***. A solution of $SOCl_2$ (1 ml) in 2 ml $CHCl_3$ was added slowly to an ice-cooled solution of **6** (258 mg, 0.57 mmol) in $CHCl_3$ (5 ml). After addition, the mixture was warmed to 70 °C under nitrogen for 2 h. Evaporation of the solvent afforded a viscous liquid. Diethyl ether was added to the residue, stirred for 5 h, and then filtrated, dried in vacuum afford a white solid for the next step without further purification (155 mg, 58%). Mp 227–229 °C; ^1H NMR ($CDCl_3$) δ 7.34 (s, 1H), 6.85–6.81 (m, 5H), 4.83–4.73 (m, 3H), 4.65–4.50 (m, 2H), 3.84 (s, 15H), 3.62–3.54 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 155.94, 148.00, 147.84, 141.39, 132.25, 132.18, 131.80, 131.65, 131.05, 124.50, 113.31, 113.23, 113.11, 112.22, 56.20, 56.16, 55.79, 41.38, 37.15, 36.66, 36.05; FT-IR ν 3441, 2931, 2905, 2842, 1610, 1520, 1460, 1394, 1350, 1262, 1226, 1194, 1143, 1090, 999, 848, 741 cm^{-1}; MS (MALDI-TOF): m/z 467.0 ($[M-H]^+$). Anal. Calcd for $C_{27}H_{29}ClO_5 \cdot 0.25H_2O$: C, 68.49; H, 6.28. Found: C, 68.79; H, 6.11.

4.2.7. Compound ***8***. Compound **7** (155 mg, 0.33 mmol), 1-methylimidazole (33 mg, 0.4 mmol), and 5 ml $CHCl_3$ were mixed. The mixture was heated to 70 °C under nitrogen for 48 h. After evaporation of the solvent, diethyl ether was added to the residue, stirred overnight, then filtrated, dried in vacuum afford a white solid without further purification (170 mg, 93%). Mp 196–198 °C; ^1H NMR ($CDCl_3$) δ 10.97 (s, 1H), 7.98 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 6.98 (s, 1H), 6.84–6.78 (m, 4H), 5.56–5.39 (m, 2H), 4.84–4.67 (m, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 3.82 (s, 9H), 3.75–3.53 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 155.65, 148.21, 147.96, 147.63, 142,73, 138.37, 133.91, 133.15, 132.39, 131.82, 131.09, 130.70, 122.28, 122.04, 120.44, 113.67, 113.18, 113.06, 112.77, 11.92, 57.10, 56.15, 56.03, 55.94, 55.68, 47.95, 37.07, 36.56, 36.39, 35.63; FT-IR ν 3420, 3102, 2957, 2842, 1612, 1571, 1518, 1461, 1446, 1395, 1268, 1223, 1197, 1148, 1086, 993, 739, 617 cm^{-1}; MS (ESI): m/z 515.2 ($[M]^+$). Anal. Calcd for $C_{31}H_{35}ClN_2O_5 \cdot 3H_2O$: C, 61.53; H, 6.83; N, 4.63. Found: C, 61.16; H, 6.43; N, 4.93.

4.2.8. Compound ***9***. (−)-Camphanic acid chloride (330 mg, 1.52 mmol) was added to the solution of compound **1** (430 mg, 0.98 mmol) in 10 ml dry pyridine. The mixture was stirred at room temperature overnight. Then, water was added and pale yellow precipitate was obtained. After filtration and wash with water, the residue was dried in vacuum and then purified by column chromatography ($CHCl_3$/EA=50:1) to afford white solid of (+)-**9** (174 mg) and (−)-**9** (229 mg). (−)-**9**: mp 171–174 °C; ^1H NMR ($CDCl_3$) δ 7.04 (s, 1H), 6.94 (s, 1H), 6.85–6.82 (m, 3H), 6.77 (s, 1H), 4.82–4.72 (m, 3H), 3.85–3.78 (m, 12H), 3.78 (s, 3H), 3.61–3.54 (m, 3H), 2.59–2.53 (m, 1H), 2.22–2.15 (m, 1H), 2.01–1.94 (m, 1H), 1.77–1.72 (m, 1H), 1.15 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.21, 165.34, 148.99, 147.95, 147.90, 147.82, 138.76, 137.51, 132.49, 132.11, 131.81, 131.36, 131.02, 123.78, 113.96, 113.31, 113.08, 91.25, 56.37, 56.12, 55.88, 55.03, 54.75, 36.86, 36.65, 36.18, 30.88, 29.10, 16.67, 16.60, 9.88; FT-IR ν 2932, 2850, 1787, 1609, 1510, 1464, 1395, 1342, 1315, 1261, 1224, 1195, 1088, 1047, 996 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 639.2564, found: 639.2561.

(+)-**9**: mp 168–174 °C; ^1H NMR ($CDCl_3$) δ 7.05 (s, 1H), 6.94 (s, 1H), 6.83–6.81 (m, 3H), 6.76 (s, 1H), 4.81–4.73 (m, 3H), 3.85–3.83 (m, 12H), 3.78 (s, 3H), 3.61–3.54 (m, 3H), 2.60–2.53 (m, 1H), 2.21–2.14 (m, 1H), 2.00–1.94 (m, 1H), 1.79–1.70 (m, 1H), 1.15–1.11 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 178.32, 165.53, 149.07, 147.99, 147.88, 147.84, 138.68, 137.62, 132.58, 132.22, 131.65, 131.27, 130.92, 123.75, 114.07, 113.17, 113.09, 113.01, 91.26, 56.29, 56.14, 55.96, 55.06, 54.76, 36.90, 36.67, 36.23, 30.87, 29.02, 16.75, 16.72, 9.93; FT-IR ν 2932, 2848, 1768, 1609, 1510, 1464, 1446, 1395, 1315, 1261, 1224, 1195, 1144, 1088, 1045, 996 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 639.2564; found: 639.2559.

4.3. General procedure for the 1,4-Michael addition

To an oven-dried vial equipped with magnetic stirring bar were added compound **8** (19 mg, 0.0345 mmol) and LiCl (29 mg, 0.69 mmol) under nitrogen atmosphere. The vial was then sealed. Under nitrogen atmosphere, toluene (1 ml) was added. The reaction was cooled to −78 °C and ^{n}BuLi (14 μL, 0.0336 mmol, 2.4 M in hexanes) was added through a syringe. The reaction was allowed to warm to room temperature. After 10 min, a mixture of ketone (100 mg, 0.685 mmol), alcohol (2.055 mmol), and toluene (1 ml) was added to the vial through a syringe. The mixture was stirred under N_2 atmosphere at room temperature for 24 h. Upon completion of the reaction, the mixture was concentrated and the residue was purified by column chromatography with EtOAc/petroleum=1:30 to afford the corresponding products.

*4.3.1. 3-Benzyloxy-1-phenylbutane-1-one (****10****).* Yellow oil (126.4 mg, 73%). ^1H NMR ($CDCl_3$) δ 7.97 (d, 2H, J=7.2 Hz), 7.57 (t, 1H, J=7.2 Hz), 7.46 (t, 2H, J=7.6 Hz), 7.32–7.25 (m, 5H), 4.55 (dd, 2H, J=11.6, 25.6 Hz), 4.26–4.22 (m, 1H), 3.43 (dd, 1H, J=7.2, 9.6 Hz), 2.99 (dd, 1H, J=6.0, 10.0 Hz), 1.33 (d, 3H, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 198.82, 138.64, 137.40, 133.20, 128.68, 128.42, 128.33, 127.79, 127.61, 72.12, 71.12, 46.03, 20.35.

*4.3.2. 3-(4-Methoxybenzyloxy)-1-phenylbutane-1-one (****11****).* Colorless oil (146 mg, 76%). ^1H NMR ($CDCl_3$) δ 7.96–7.94 (m, 2H), 7.58–7.54 (m, 1H), 7.47–7.44 (m, 2H), 7.20 (d, 2H, J=8.8 Hz), 6.83 (d, 2H, J=8.8 Hz), 4.52 (d, 1H, J=10.8 Hz), 4.43 (d, 1H, J=8.8 Hz), 4.23–4.19 (m, 1H), 3.78 (s, 3H), 3.40 (dd, 1H, J=6.4, 10 Hz), 2.97 (dd, 1H, J=6.4, 10 Hz), 1.31 (d, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ 198.84, 159.17, 137.39, 133.16, 130.73, 129.37, 128.65, 128.31, 113.82, 71.76, 70.77, 55.35, 46.05, 20.37.

*4.3.3. 3-(4-Chlorobenzyloxy)-1-phenylbutane-1-one (****12****).* Colorless oil (138 mg, 68%). ^1H NMR ($CDCl_3$) δ 7.98–7.91 (m, 2H), 7.60–7.56 (m, 2H), 7.49–7.46 (m, 2H), 7.28–7.20 (m, 3H), 4.56 (d, 1H, J=12 Hz), 4.46 (d, 1H, J=12 Hz), 4.25 (t, 1H, J=6 Hz), 3.42 (dd, 1H, J=6.8, 16 Hz), 2.98 (dd, 1H, J=6.8, 16 Hz), 1.34 (d, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ 198.64, 137.28, 137.15, 133.22, 129.02, 128.66, 128.48, 128.27, 72.22, 70.26, 45.92, 20.26; FT-IR ν 3060, 2971, 2930, 1684, 1597, 1580, 1491, 1448, 1373, 1339, 1296, 1133, 1087, 1015, 808, 753, 690 cm^{-1}; HRMS (ESI) calcd for $[M+Na^+]$: m/z 311.0809; found: 311.0803.

*4.3.4. 3-(1-Naphthalenemethoxy)-1-phenylbutane-1-one (****13****).* Yellow oil (154 mg, 74%). ^1H NMR ($CDCl_3$) δ 7.93–7.78 (m, 5H),

7.57–7.39 (m, 7H), 5.05 (d, 1H, J=11.2 Hz), 4.964 (d, 1H, J=11.2 Hz), 4.40–4.35 (m, 1H), 3.46 (dd, 1H, J=6.8, 9.6 Hz), 3.01 (dd, 1H, J=6, 10 Hz), 1.38 (t, 3H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 198.83, 137.30, 134.02, 133.82, 133.16, 131.82, 128.67, 128.63, 128.53, 128.30, 128.16, 126.59, 126.19, 125.78, 125.31, 124.24, 72.14, 69.66, 46.07, 20.29; FT-IR ν 3058, 2966, 2924, 1676, 1596, 1510, 1447, 1370, 1333, 1196, 1132, 1077, 999, 791, 772, 750 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 305.1536; found: 305.1533.

*4.3.5. 3-(1-Phenylethoxy)-1-phenylbutane-1-one (**14**).* Yellow oil (120 mg, 65%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1H), 7.84 (d, 1H), 7.57–7.22 (m, 8H), 4.58–4.51 (m, 1H), 4.12–3.95 (m, 1H), 3.42–3.22 (m, 1H), 2.96–2.88 (m, 1H), 1.41–1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 199.18, 198.62, 144.52. 143.83, 137.43, 137.20, 133.14, 132.98, 128.63, 128.51, 128.40, 128.32, 128.29, 127.50, 127.43, 126.38, 126.32, 75.15, 70.56, 69.44, 46.76, 45.92, 24.57, 24.11, 21.68, 19.96; FT-IR ν 3060, 2971, 2927, 1682, 1596, 1447, 1367, 1281, 1210, 1196, 1132, 1078, 999, 751, 690 cm^{-1}; HRMS (ESI) calcd for $[M+Na^+]$: m/z 291.1355; found: 291.1351.

*4.3.6. 3-Methoxy-1-phenylbutane-1-one (**15**).* Yellow oil (56 mg, 46%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 2H, J=7.6 Hz), 7.56 (t, 1H, J=7.2 Hz), 7.46 (t, 2H, J=7.6 Hz), 4.02–3.97 (m, 1H), 3.36–3.31 (m, 4H), 2.94–2.88 (m, 1H), 1.25 (d, 3H, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 198.77, 133.21, 128.68, 128.27, 73.61, 56.56, 45.56, 19.69.

*4.3.7. 3-Ethoxy-1-phenylbutane-1-one (**16**).* Colorless oil (66 mg, 50%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 2H, J=7.6 Hz), 7.55 (t, 1H, J=7.2 Hz), 7.45 (t, 2H, J=7.6 Hz), 4.10–4.07 (m, 1H), 3.60–3.55 (m, 1H), 3.48–3.42 (m, 1H), 3.36–3.32 (m, 1H), 2.94–2.89 (m, 1H), 1.25 (d, 3H, J=6.4 Hz), 1.14 (t, 3H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 198.94, 137.45, 133.13, 128.64, 128.28, 71.95, 64.23, 45.97, 20.46, 15.61; FT-IR ν 3060, 2972, 2928, 1685, 1597, 1448, 1372, 1293, 1211, 1132, 1096, 1001, 752, 690 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 193.1223; found: 193.1221.

*4.3.8. 3-Isopropoxy-1-phenylbutane-1-one (**17**).* Colorless oil (64 mg, 45%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 2H, J=7.6 Hz), 7.54 (t, 1H, J=7.2 Hz), 7.45 (t, 2H, J=7.6 Hz), 4.15 (m, 1H), 3.66 (m, 1H), 3.30 (dd, 1H, J=6.8, 9.2 Hz), 2.60 (dd, 1H, J=6, 10 Hz), 1.24 (d, 3H, J=6 Hz), 1.13 (d, 3H, J=6 Hz), 1.05 (d, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ 199.24, 133.11, 128.76, 128.62, 128.51, 128.34, 128.15, 69.77, 69.72, 46.52, 23.15, 22.49, 21.51; FT-IR ν 3060, 2970, 2930, 1683, 1597, 1580, 1448, 1376, 1330, 1213, 1001, 752, 690 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: 207.1379; found: 207.1377.

4.4. Crystal structure of 5

$C_{26}H_{26}O_6$, M=434.47, monoclinic, a=16.340(3) Å, b=7.6251(15) Å, c=16.917(3) Å, α=90.00°, β=91.81(3)°, γ=90.00°, V=2106.7(7), T=173(2) K, space group $P2(1)/n$, Z=4, μ(Mo Kα)=0.097 mm^{-1}, 10,723 reflections measured, 4799 independent reflections (R_{int}=0.0317). The final R_1 values were 0.0748 ($I>2\sigma(I)$). The final wR (F^2) values were 0.1509 ($I>2\sigma(I)$). The final R_1 values were 0.0853 (all data). The final wR (F^2) values were 0.1569 (all data). The goodness of fit on F^2 was 1.172. CCDC number: 932872.

Acknowledgements

This work was supported by the Major State Basic Research Development Program of China (2011CB932501), the National Nature Science Foundation of China (20932004), and the Chinese Academy of Science.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.077.

References and notes

1. (a) Robinson, G. M. *J. Chem. Soc.* **1915**, *107*, 267; (b) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685.
2. (a) Umezawa, B.; Hoshio, O.; Hara, H.; Ohyama, K.; Mitsubay, S.; Sakakiba, J. *Chem. Pharm. Bull.* **1969**, *17*, 2240; (b) Umezawa, B.; Hoshio, O.; Sakakiba, J. *Chem. Pharm. Bull.* **1968**, *16*, 177; (c) Sato, T.; Akima, T.; Uno, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 891; (d) Poupko, R.; Luz, Z.; Spielberg, N.; Zimmermann, H. *J. Am. Chem. Soc.* **1989**, *111*, 6094; (e) Garcia, C.; Malthete, J.; Collet, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 93; (f) Ahmad, R.; Hardie, M. J. *Supramol. Chem.* **2006**, *18*, 29; (g) Sanseverino, J.; Aubert, E.; Espinosa, E.; Chambron, J. C. *J. Org. Chem.* **2011**, *76*, 1914; (h) Arduini, A.; Calavacca, F.; Demuru, D.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2004**, *69*, 1386; (i) Yu, J.-T.; Huang, Z.-T.; Sun, J.; Zheng, Q.-Y. *Org. Biomol. Chem.* **2012**, *10*, 1359; (j) Peyrard, L.; Dumartin, M. L.; Chierici, S.; Pinet, S.; Jonusauskas, G.; Meyrand, P.; Gosse, I. *J. Org. Chem.* **2012**, *77*, 7023; (k) Han, X.-N.; Chen, J.-M.; Huang, Z.-T.; Zheng, Q.-Y. *Eur. J. Org. Chem.* **2012**, 6895.
3. (a) Eckert, J. F.; Byrne, D.; Nicoud, J. F.; Oswald, L.; Nierengarten, J. F.; Numata, M.; Ikeda, A.; Shikai, S.; Armaroli, N. *New J. Chem.* **2000**, *24*, 749; (b) Huetra, E.; Isla, H.; Perez, E. M.; Bo, C.; Martin, N.; de Mendoza, J. *J. Am. Chem. Soc.* **2010**, *132*, 5351; (c) Konarev, D. V.; Khasanov, S. S.; Vorontsov, I. I.; Saito, G.; Antipin, M. Y.; Otsuka, A.; Lyubovskaya, R. N. *Chem. Commun.* **2002**, 2548; (d) Konarev, D. V.; Khasanov, S. S.; Saito, G.; Otsuka, A.; Yoshida, Y.; Lyubovskaya, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 10074.
4. (a) Malthéte, J.; Collet, A. *J. Am. Chem. Soc.* **1987**, *109*, 7544; (b) Zimmermann, H.; Bader, V.; Poupko, R.; Wachtel, E. J.; Luz, Z. *J. Am. Chem. Soc.* **2002**, *124*, 15286.
5. (a) Sumby, C. J.; Hardie, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6395; (b) Ronson, T. K.; Fisher, J.; Harding, P.; Hardie, M. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9086; (c) Westcott, A.; Fisher, J.; Harding, L. P.; Rizkallah, P.; Hardie, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2950; (d) Ronson, T. K.; Fisher, J.; Harding, L. P.; Rizkallan, P. J.; Warren, J. E.; Hardie, M. J. *Nature* **2009**, *1*, 212; (e) Abrahams, B. F.; FitzGerald, N. J.; Robson, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 2896; (f) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520.
6. (a) McKeown, N. B.; Gahnem, B.; Msayib, K. J.; Budd, P. M.; Tattershall, C. E.; Mahmood, K.; Tan, S.; Book, D.; Langmi, H. W.; Walton, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1804; (b) Yu, J.-Y.; Sun, J.; Huang, Z.-T.; Zheng, Q.-Y. *CrystEngCommun* **2012**, *14*, 112; (c) Yu, J.-Y.; Chen, Z.; Sun, J.; Huang, Z.-T.; Zheng, Q.-Y. *J. Mater. Chem.* **2012**, *22*, 5369.
7. (a) Zhang, S.; Echegoyen, L. *J. Am. Chem. Soc.* **2005**, *127*, 1315; (b) Abrahams, B. F.; FitzGerald, N. J.; Hudson, T. H.; Robson, R.; Waters, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3129; (c) Schröder, L.; Lowery, T. J.; Hilty, C.; Wemmer, D. E.; Pines, A. *Science* **2006**, *314*, 446; (d) Aaron, J. A.; Chambers, J. M.; Jude, K. M.; Costanzo, L. D.; Dmochowski, I. J.; Christianson, D. W. *J. Am. Chem. Soc.* **2008**, *130*, 6942; (e) Ruiz, E. J.; Sears, D. N.; Pines, A.; Jameson, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 16980.
8. (a) Steed, J. W.; Junk, P. C.; Atwood, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 10346; (b) Wang, L.; Wang, G.-T.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. *J. Org. Chem.* **2011**, *76*, 3531.
9. (a) Collet, A.; Gabard, J.; Jacques, J.; Cesario, M.; Guilhem, G.; Pascard, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1630; (b) Colletand, A.; Gabard, J. *J. Org. Chem.* **1980**, *45*, 5400.
10. Chakrabarti, A.; Chawla, H. M.; Hundal, G.; Pant, N. *Tetrahedron* **2005**, *61*, 12323.
11. (a) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555; (b) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.
12. (a) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107; (b) Sarkar, D. S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266; (c) Kang, Q.; Zhang, Y. *Org. Biomol. Chem.* **2011**, *9*, 6715; (d) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080; (e) Chen, X.-Y.; Wen, M.-W.; Ye, S.; Wang, Z.-X. *Org. Lett.* **2011**, *13*, 1138; (f) Shen, L.-T.; Sun, L.-H.; Ye, S. *J. Am. Chem. Soc.* **2011**, *133*, 15894.
13. Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179.
14. Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299.
15. (a) Wezenberg, S. J.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 2354; (b) Richeter, S.; Julius Rebek, J. *J. Am. Chem. Soc.* **2004**, *126*, 16280; (c) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117; (d) Hu, S.; Li, J.; Xiang, J.; Pan, J.; Luo, S.; Cheng, J.-P. *J. Am. Chem. Soc.* **2010**, *132*, 7216.
16. Monnereau, L.; Sémeril, D.; Matt, D.; Toupet, L. *Chem.—Eur. J.* **2010**, *16*, 9237.
17. Nakajima, H.; Yasuda, M.; Takeda, R.; Baba, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3867.