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Ditopic Cyclodextrin-Based Receptors: New Perspectives in Aqueous Organometallic Catalysis

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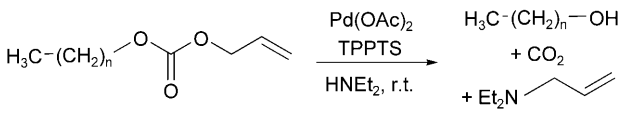
Abstract: The mass transfer properties of mono- and ditopic β-cyclodextrin-based receptors have been evaluated in a biphasic palladium-catalyzed Tsuji–Trost reaction and compared to one of the best mass-transfer promoters, namely the randomly methylated β-cyclodextrin. While monotopic receptors appeared to be poor mass-transfer promoters of long alkyl chain allyl carbonates or urethanes, cooperative effects have been evidenced with ditopic cyclodextrin-based receptors, opening new perspectives in aqueous organometallic catalysis.

Keywords: cooperative effects; cyclodextrins; host-guest systems; inclusion compounds; structure-activity relationships; supramolecular chemistry

Introduction

The design of environment-benign and ecological chemical processes has become a major challenge in our present consuming world. In this context, the use of water as non-polluting solvent was thought to be the most obvious solution for transition metal-catalyzed reactions.[1] Nevertheless, the insolubility of most organic molecules in water limits its industrial use to the transformation of hydrophilic substrates. Although solutions have been developed for hydrophobic substrates,[2] none of the proposed solutions was completely satisfying. For example, the use of molecular receptors such as chemically modified β-cyclodextrins (β-CDs) has been intensely investigated during the past decade.[3] In fact, CDs can mask the substrate hydrophobic character by including the hydrophobic moiety in their cavity, thus favoring interfacial catalysis. Interesting results were obtained in various catalytic reactions such as aldehyde hydrogenation,[4] olefin hydroformylation[5] or allyl carbonate cleavage (Tsuji–Trost reaction).[6] However, with very hydrophobic substrates, the catalytic performances are significantly affected.[7]

To circumvent this technological lock, more elaborated CD structures have been recently synthesized starting from the mono-azide β-CD and terminal alkynes using the Cu(I)-catalyzed azide-alkyne cycloaddition.[8] Herein, we evaluate the catalytic performances of the synthesized mono- and ditopic β-CD-based receptors in a Pd-catalyzed cleavage reaction of alkyl allyl carbonates (Scheme 1). The two main parameters controlling the efficiency of the supramolecular β-CD receptors are discussed, namely their ability to adsorb at the organic/aqueous interface and the ease with which a substrate is included in their cavities. We bring proof of the synergetic interactions displayed by well-designed ditopic CD-based receptors to supramolecularly recognize long alkyl chain substrates and efficiently convert them into products.



Scheme 1. The Tsuji–Trost reaction.

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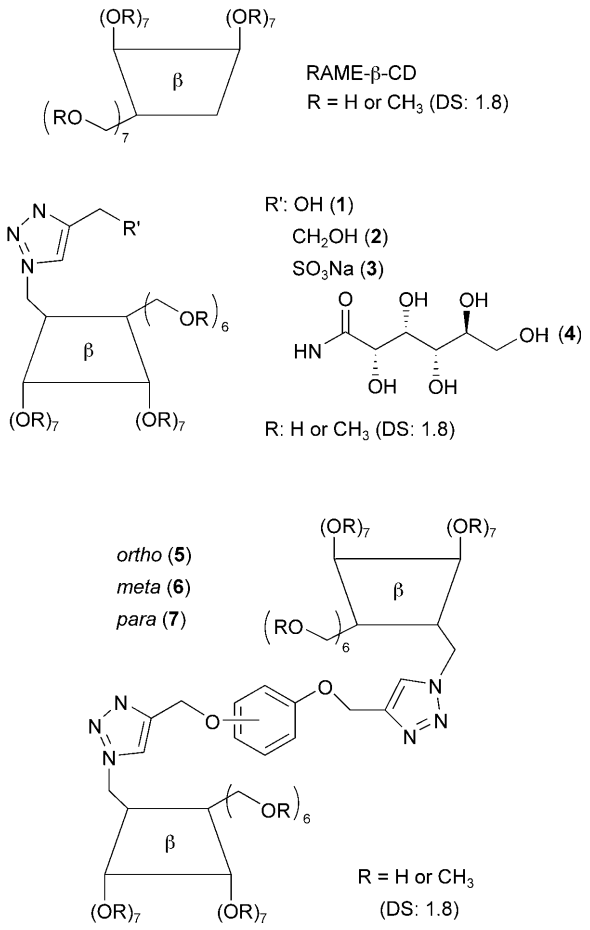
Results and Discussion

The structure of the CDs used in this study are described in Scheme 2 (see also Supporting Information). Only randomly methylated derivatives have been considered as it has previously been clearly established that their adsorption properties at the organic/aqueous interface are better than those of their hydroxylated counterparts.[9] Apart from the well-known randomly methylated β-CD (RAME-β-CD), all the CDs are mono-substituted on their primary face by a triazole group, itself substituted in the 4-position by various organic moieties.

The Tsuji–Trost reactions have been performed at room temperature under nitrogen using palladium acetate as catalyst, TPPTS (sodium salt of the *meta*-trisulfonated triphenylphosphine) as hydrosoluble ligand, diethylamine as allyl scavenger and undecyl (**8**), tridecyl (**9**), hexadecyl (**10**) and octadecyl (**11**) allyl carbonates as substrates. In Figure 1 are summarized the catalytic results obtained with monotopic β-CDs receptors **1**–**4** and RAME-β-CD, one of the best mass-transfer promoters. Using **8** as a substrate,



Scheme 2. Mono- and ditopic β-CDs. DS: degree of substitution.

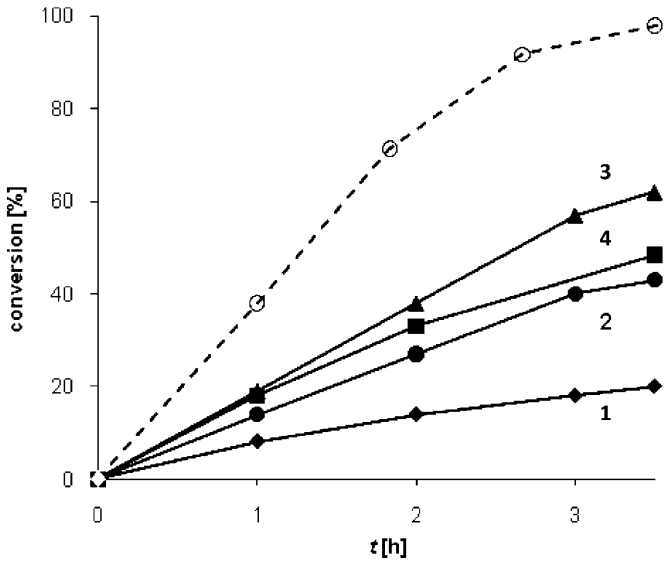


Figure 1. Conversion of allyl undecyl carbonate (**8**) as a function of time in a Pd-catalyzed cleavage reaction with RAME-β-CD (-·-·-), **1** (-◆-), **2** (-●-), **3** (-▲-) and **4** (-■-) as additives.

RAME-β-CD appears a better mass-transfer promoter than **1**–**4**. Among the triazole randomly methylated β-CDs, **2**, **3** and **4** give similar results while **1** appears less efficient. Note that without CD, the conversion is only 0.5% after 3.5 h. Tensiometric measurements have been carried out to tentatively explain the above results.

As shown in Figure 2, all the curves describing the variation of the surface tension (γ) as a function of the concentration are gathered in a quite narrow beam, suggesting that the surface active properties of these mono-substituted β-CDs is not the determining factor influencing the mass transfer between the or-

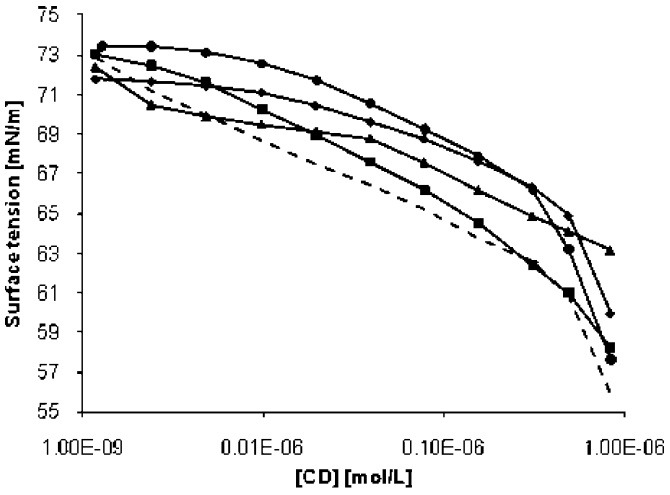


Figure 2. Surface tension curves of RAME-β-CD (-·-·-), **1** (-◆-), **2** (-●-), **3** (-▲-) and **4** (-■-) in water at 20 °C.

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ganic and the aqueous phase. In fact, the lower efficiency of **1**–**4** with respect to RAME-β-CD is a consequence of the steric hindrance generated by the substituted triazole group. The approach of the substrate is then disfavored for the recognition process to take place. Moreover, a capping process of the CD cavity by the triazole substituant has also been highlighted. This phenomenon has especially been evidenced for **2** through a detailed NMR analysis. Varying the concentration of **2** in D_2O results in a cross shift of two broad signals in the triazole proton chemical shift range in the ^1H NMR spectrum, indicative of two different species **A** and **B** in slow equilibrium (Figure 3). From a 2D T-ROESY NMR experiment, it can be inferred that **A** is a self-included structure as correlation peaks were identified between the triazole moiety and the CD cavity, contrary to **B** (non-included form) for which no correlation could be detected (Figure 4). The magnitude in chemical shift variation for each signal confirms this assertion as $\Delta\delta$ is larger for **B** (0.3 ppm) than for **A** (0.05 ppm), which is logically attributed to a greater dependence of the more water-exposed **B** form towards the concentration. At a low 5 mmol·L^{-1} concentration, the proportions of **A** and **B** were determined by integration of the triazole signals in the ^1H NMR spectrum. A slight excess of **A** (54% *vs.* 46% for **B**) was calculated. Note that no variation in the NMR signal was detected when increasing the temperature (even at 80 °C) suggesting a rather strong interaction of the triazole moiety with the CD cavity. Of interest, at 5 mmol·L^{-1}, both signals evolve, after 20 days, to a predominant resonance that has been attributed to another species **C**. The structure of **C** could be deduced from a comparison of its triazole proton resonance with that obtained from a 1:1 mixture of **2** and RAME-β-CD (Figure 5). Actually, with **2** and RAME-β-CD in stoichiometric proportions, the free RAME-β-CD cavity is available and

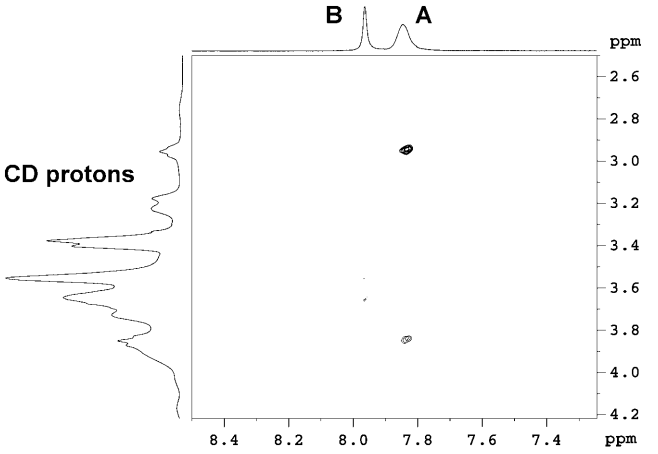

Figure 4. Partial T-ROESY spectrum of **2** (36 mmol·L^{-1}) in D_2O at 25 °C.

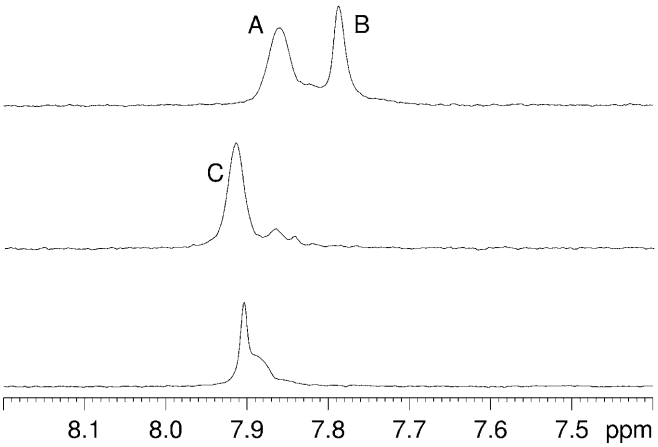

Figure 5. Partial ^1H NMR spectra at 25 °C in D_2O of 5 mM solutions of freshly prepared **2** (*top*), **2** after 20 days (*middle*) and freshly prepared equimolar mixture of **2** and RAME-β-CD (*bottom*).

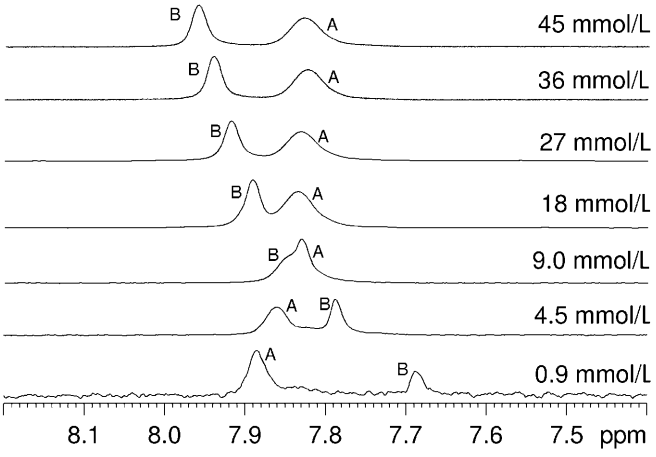

Figure 3. Chemical shift variation of **2** in water at 25 °C as a function of the concentration.

the triazole substituent of **2** has then a natural tendency to include inside this cavity rather than the cavity of its own CD. The self-inclusion process (**A** form) is then disfavored. As both the triazole proton resonances of **C** and the above mixture could be nearly superimposed, we contend that the triazole substituent of **C** is embedded in the cavity of another **2** receptor (inter-inclusion) (Scheme 3).[10]

A 2D T-ROESY spectrum of **C** unambiguously confirms the inclusion of the triazole group as cross peaks were detected between the triazole proton and the inner protons of the CD (H-3 and H-5) (see Supporting Information). As a conclusion, **2** is a mixture of self-included and non-included structures whose proportions depend upon the concentration and the time in solution.

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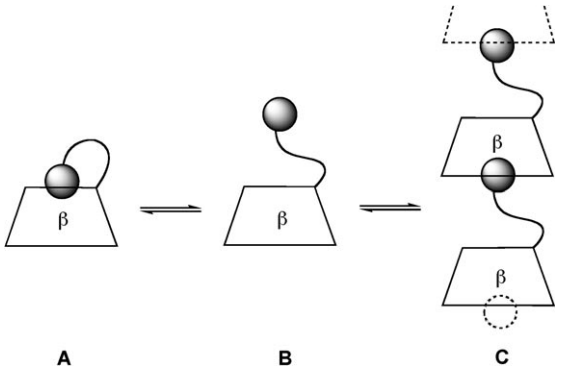

Scheme 3. Equilibriums between the non-included form **A** and self-included forms **B** and **C**.

This capping phenomenon has also been highlighted with **1** (see Supporting Information). In that case, integration of the triazole protons led to 72% of self-included form and 28% of CDs with their substituent free in solution. Conversely, the effect is less marked for the more hydrophilic receptors **3** and **4** as no contacts were detected in their T-ROESY spectra. This is corroborated by the ^{1}H NMR spectrum as only one triazole signal was detected suggesting 100% of the free form. Nevertheless, although not included, the presence of the sulfonated or carbohydrate triazole group over the primary face of the CD significantly hampers the substrate recognition. Consequently, **3** and **4** are better mass-transfer promoters than **1** and **2** but remain less efficient than RAME-β-CD. Hence, the lower catalytic efficiency of **1**–**4** with respect to RAME-β-CD is a consequence of both steric effects and a partial capping phenomenon of the CD cavity by the triazole substituent. The substrate recognition process is then hindered, resulting in lower initial activities.

The use of monotopic receptors has been extended to the Pd-catalyzed cleavage reaction of **9**, **10** and **11**. With **3** as mass-transfer promoter, increasing the alkyl chain length has a detrimental impact on the initial activity, indicative of a bad substrate recognition process at the interface (Figure 6). Similar results have been obtained with **4** as additive (see Supporting Information). Thus, in addition to the above capping phenomenon, this outcome illustrates the requisite adequacy between the CD host and the guest substrate. Long alkyl chain substrates are too large to be properly accommodate in a single CD cavity. In fact, two CD-based receptors would be needed as demonstrated in the solid state with 1,12-dodecanediol as guest.[11] In solution, the inclusion process of a long alkyl chain into two CDs is statistically disfavored.

Hence, monotopic CD-based receptors suffer from several drawbacks and do not constitute a viable alternative to promote the mass transfer at the aqueous/organic interface. To circumvent this difficulty, it

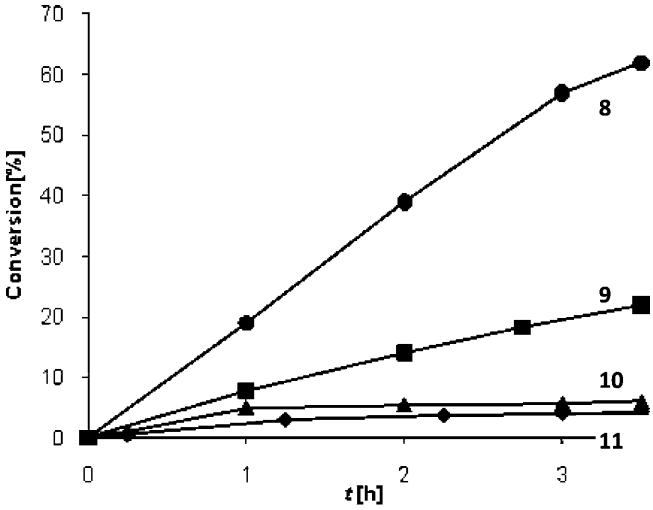

Figure 6. Impact of **3** on the cleavage reactions of **8** (-●-), **9** (-■-), **10** (-▲-) and **11** (-◆-).

seemed appropriate to use ditopic species such as **5**, **6** and **7**. The closeness of two CDs linked together by a short organic tether should improve the substrate recognition process. Moreover, the linker being attached to another CD moiety, its self-inclusion process (capping) should be disfavored.

Very interestingly, the catalytic performances of these ditopic β-CD-based receptors are in high contrast with those obtained with their monotopic counterparts (Figure 7). Note that, for the results to be comparable, the molar amount of RAME-β-CD was twice that of the dipotic receptors. A host structure-dependent recognition process seems to occur during the cleavage reaction. As evidenced through the analysis of the initial activities, RAME-β-CD is more appropriate than the ditopic receptors to recognize **8** and **9**, indicative of a better ability to mask the hydrophobic character of middle-length alkyl chain substrates.[12] Conversely, RAME-β-CD and **6** give similar results for the Pd-catalyzed cleavage of **10** while **5** and **6** prove more efficient than RAME-β-CD to help converting **11** into alcohols, suggesting cooperative effects resulting from synergetic interactions between **5** or **6** and the substrates. Hence, RAME-β-CD appears inappropriate to recognize subtrates with long alkyl chains since the catalytic activity decreases when the substrate alkyl chain is lengthened. On the contrary, with the ditopic β-CDs as receptors, almost no variation in catalytic performances is noticed whatever the length of the substrate alkyl chain. For example, when the conversion remains rather constant with **6** after 3.5 h reaction time (in the range 47–64%), the conversion measured with RAME-β-CD dramatically drops from 100 to 29% when increasing the alkyl chain length from eleven to eighteen carbons. Also note that the *p*-isomer receptor **7** leads to poor activities whatever the substrates.

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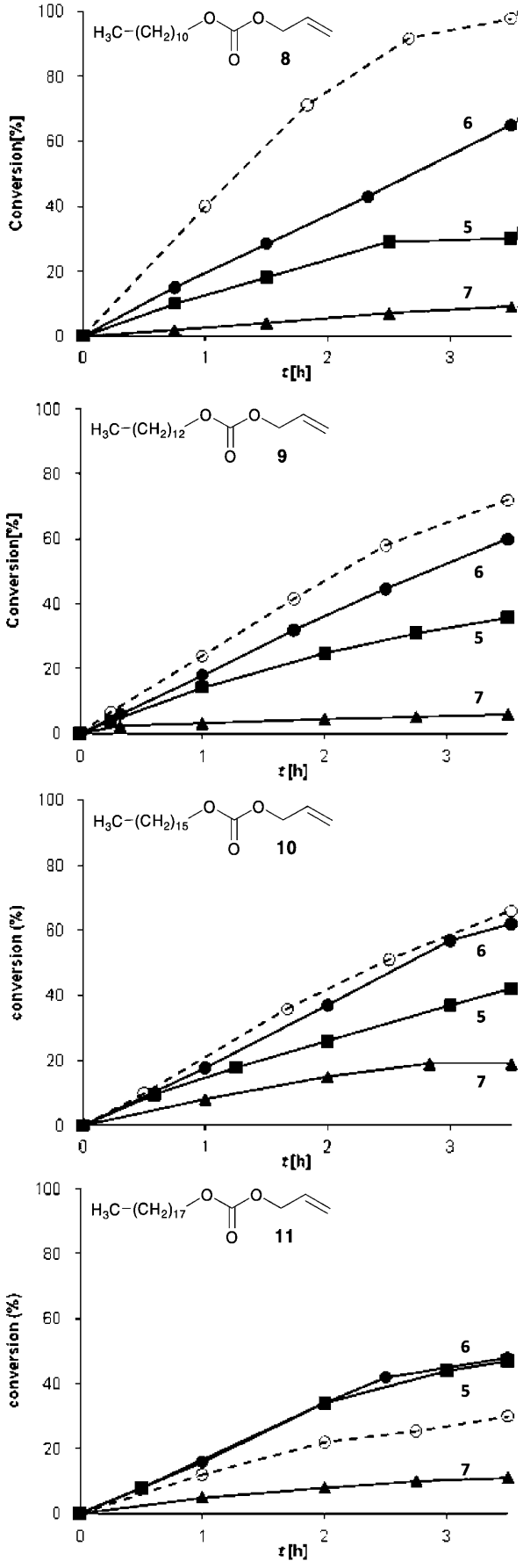

Figure 7. Structure/activity dependence of RAME-β-CD (-○-), **5** (-■-), **6** (-●-) and **7** (-▲-) on the cleavage reactions of **8–11**.

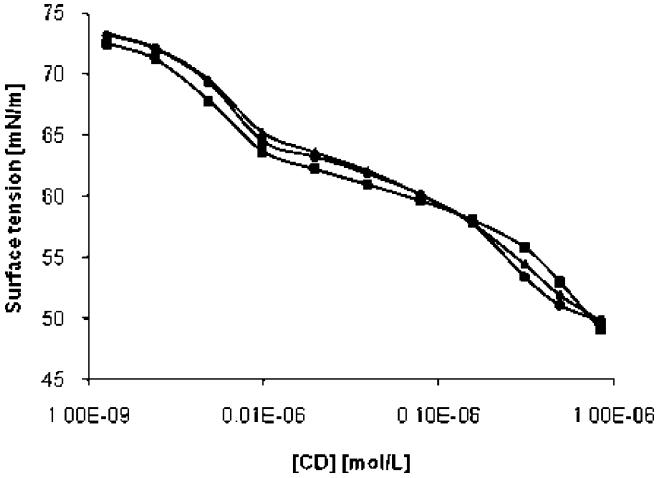

Figure 8. Surface tension curves of **5** (-■-), **6** (-●-) and **7** (-▲-) in water at 20 °C.

Figure 8 definitely confirms that, here again, the surface active properties of the mass-transfer promoters do not constitute the key parameter allowing a satisfactory explanation of the catalytic results. Indeed, no significant difference could be detected as the three curves are superimposed over a broad concentration range. However, contrary to what was demonstrated with monotopic receptors, no clear evidence of a self-inclusion process was established for **5**, **6** and **7** as ^{1}H and ^{13}C NMR prove inappropriate to bring clues on their geometry as the spectra show most of the resonances to be clustered together, giving very broad and shouldered peaks. Nonetheless, a comparison with their hydroxylated counterparts for which contacts were previously detected on the T-ROESY spectrum tend to prove that at least a partial inclusion of the linker in the CD cavities may occur, especially for the *p*-isomer **7**.[8a] This is in line with other previous studies on bridged bis(β-CD)s for which the substituent is also embedded in the CD cavity.[13]

Thus, when comparing the catalytic results obtained with **5**, **6** and **7**, it appears that the structure of the ditopic host is of importance as it governs the substrate recognition process and consequently the catalytic performances of the system. In particular, it can be assumed from the catalytic results that the recognition process of long alkyl chain substrates occurs according to a "sandwich" binding mode for **5** and **6** (Scheme 4a).[14] Actually, in that case, the linear substrate can probably penetrate deeply into the β-CD cavities from the longitudinal direction to be fully in-

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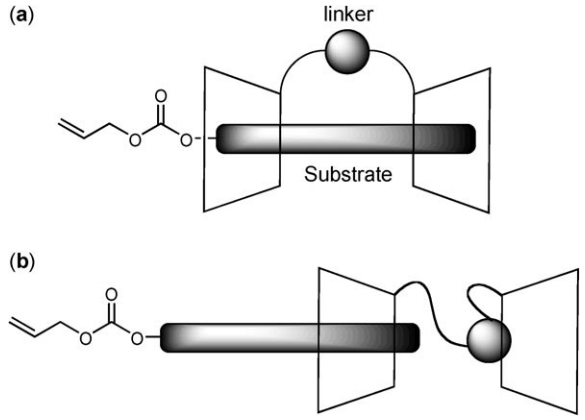


Scheme 4. "Sandwich" binding mode (**a**) and host-linker-guest co-inclusion mode (**b**).

cluded at the end of the recognition process. This channel-type supramolecular assembly displays a high binding ability through the cooperative binding of two adjacent CD units, resulting in increased contacts between the substrate and the organometallic catalyst. These results are in line with previous studies where well-suited bridged bis(CD)s displayed an enhanced molecular binding ability for large substrates through the cooperativity of two hydrophobic cavities located in a closely vicinity.[15]

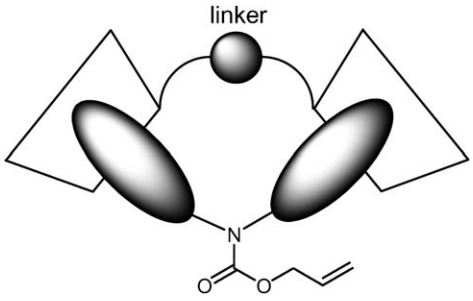
Conversely, a host-linker-guest co-inclusion binding mode (Scheme 4b) is certainly preferred for **7** as the initial activity is low whatever the alkyl chain length. In that case, the linker caps one of the CD cavities, preventing the substrate to be properly recognized.

Extension of the above results to other hydrophobic substrates such as urethanes gave us valuable insights into the recognition process involving ditopic CDs. Two sets of experiments have been carried out. The first one concerned the linear allyl-dodecyl-urethane **12** and the one the branched allyl-dihexyl-urethane **13** (Scheme 5).

The results obtained with **12** are in good agreement with what was observed above with carbonates. The *ortho*-isomer **6** is still the best mass-transfer promoter while the *para*-isomer **7** remains the worst. However, in these conditions, RAME-β-CD and **6** have a similar ability to recognize **12**, the performances of RAME-β-CD slightly decreasing with time.

Of interest, the catalytic results obtained with **13** clearly demonstrated that ditopic receptors **5**, **6** and **7**

Scheme 5. Linear and branched alkyl-allyl-urethanes.



Scheme 6. Possible cyclic supramolecular intermediate between ditopic receptors **5**, **6** and **7** and the branched substrate **13**.

are 4-fold more efficient than RAME-β-CD at converting branched urethanes into amines. The poor ability of RAME-β-CD to recognize branched structures was previously demonstrated.[16] Conversely, the results obtained with **5**, **6** and **7** are far better than expected and suggest that a bent structure favors the cooperativity existing between two linked CDs. Thus, when a "sandwich" binding mode is believed to take place for **12**, we propose an "open wings" cyclic supramolecular structure as intermediate of the recognition process between the *n*-hexyl chains of **13** and the CD cavities of **5**, **6** and **7** (Scheme 6 and Figure 9).

Contrary to linear substrates such as **8**–**11**, note that the bent structure of **13** allows unblocking of the CD cavities of **7** as an increase in activity was observed. This is in sharp contrast with the above results obtained with linear substrates and for which no increase in activity was noticed for **7**. The molecular recognition process between **7** and **13** likely involves two interactions, the first interaction with the host guiding the second one. Indeed, once an *n*-hexyl chain is included in a CD cavity, the other chain could then be able to expel the triazole group from the second CD cavity. Its hydrophobic character being properly masked, **13** could then efficiently react with the palladium catalyst.

Conclusions

To sum up, the use of ditopic β-CD-based receptors appears a promising approach to solve the mass-transfer limitation in aqueous organometallic catalysis provided that the receptor conformation was appropriate with the substrate geometry. Two tethered CDs are much more efficient as mass-transfer promoters than RAME-β-CD to recognize substrates that are too large to be accommodated in a single CD cavity but are less efficient than RAME-β-CD in binding small substrates which can be completely included in a single cavity. This unambiguously proves that multiple simultaneous hydrophobic interactions have collective

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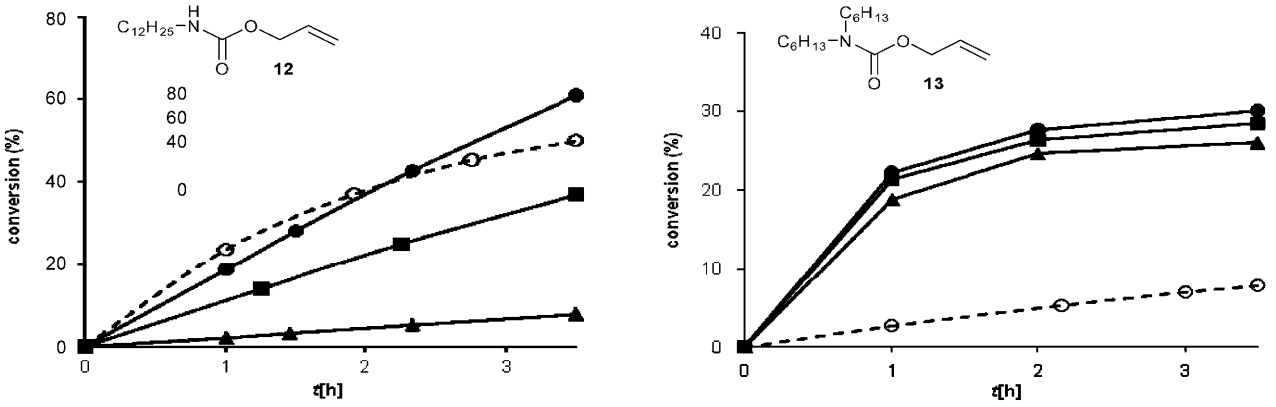

Figure 9. Impact of RAME-β-CD (-○-), **5** (-■-), **6** (-●-) and **7** (-▲-) on the cleavage reactions of **12** and **13**.

properties whose contribution to the mass-transfer process is greater than that displayed by individual interactions for which the constituents interact monovalently. This study constitutes the first example of cooperative hydrophobic interactions between two CD cavities and a substrate at the organic/aqueous interface of a biphasic system. Thus, thanks to cooperative effects exhibited by ditopic hosts, an important gap could be filled in biphasic catalysis, especially for the transformation of very hydrophobic substrates.

Experimental Section

All chemicals were purchased from Strem Chemicals and Aldrich Chemicals in their highest purity. Distilled water was used in all experiments. All solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze-pump-thaw cycles. The syntheses of **1**, **2**, **5**, **6** and **7** have previously been described.[8] NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei, 75 MHz for ^{13}C nuclei and 121.49 MHz for ^{31}P nuclei. $CDCl_3$ (99.50% isotopic purity), DMSO-d_6 (99.80% isotopic purity) and D_2O (99.92% isotopic purity) was purchased from Euriso-Top. Signals are recorded in terms of chemical shifts and are expressed in parts per million (δ), multiplicity, coupling constants (in Hz, rounded to one decimal place), integration and assignments in that order. The correct assignments of the chemical shifts were confirmed when necessary by two-dimensional correlation measurements attained by ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC or ^{1}H-^{13}C HMBC experiments. The 2D T-ROESY experiments were run using the software supplied by Bruker. T-ROESY experiments were preferred to classical ROESY experiments as this sequence provides reliable dipolar cross-peaks with a minimal contribution of scalar transfer. Mixing times for TROESY experiments were set at 300 ms. The data matrix for the T-ROESY was made of 512 free induction decays, 1 K points each, resulting from the co-addition of 32 scans. The real resolution was 1.5–6.0 Hz/point in F2 and F1 dimensions, respectively. They were transformed in the non-phase-sensitive mode after QSINE window processing. Mass spectra were recorded on a MALDI-TOF/TOF Bruker Daltonics Ultraflex II in positive reflectron mode with 2,5-DHB as matrix. Gas chromatographic analyses were carried out on a Shimadzu GC-17 A gas chromatograph equipped with a methyl silicone capillary column (25 m × 0.25 mm; film thickness: 0.25 μm) and a flame ionization detector (GC:FID).

Synthesis of Sodium [1-(Randomly Methylated 6^{A}-Deoxy-β-D-cyclodextrinyl)-1*H*-1,2,3-triazol-4-yl]-methanesulfonate (3)

Randomly methylated mono-6-azido-6^{A}-deoxy-β-D-cyclodextrin (1.5 mmol) and hydrated copper sulfate (3 mmol) were added to a solution of sodium propargylsulfonate (1.8 mmol) in DMF (40 mL). After the subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (6 mmol) dissolved in water (5 mL), the solution was stirred for 18 h at room temperature. After evaporation of the solvent, the crude product was dissolved in an ammonia solution (8%) and stirred 2 h before being purified by column chromatography on silica gel with water as eluent to give the product as a white powder. After evaporation of the solvent, the product was dissolved in 25 mL of water and extracted by 500 mL of chloroform (2 × 250 mL). The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and concentrated. The product was dissolved in 50 mL of water and 25 g of Amberlyst 15 resin (Na form) was then added. The resin was filtered off on a glass filter and washed with 15 mL of water. The solution was lyophilized to give a yellowish powder; yield: 1.25 g (55%). ^{1}H NMR (300 MHz, D_2O): $\delta = 8.12$ (s, 1H), 5.34 (m, 5.1H), 5.02 (m, 4.1H), 4.60 (m, 4.6H), 4.06–3.92 (m, 13.2H), 3.83–3.39 (m, 57.8H), 3.21–3.12 (m, 5.7H), 2.43–2.28 (m, 2.4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 20 °C): $\delta = 140.1$, 126.8, 103.2–101.3, 84.2–79.3, 74.3, 73.4–70.9, 61.6–59.1, 52.0, 47.9, 29.9; MS: m/z (%) = 1478.51 (2.2) (calcd. for $[C_{56}H_{94}N_3NaO_{37}S + Na]^+$: 1478.51), 1492.93 (27.2) (calcd. for $[C_{57}H_{96}N_3NaO_{37}S + Na]^+$: 1492.52), 1506.96 (60.1) (calcd. for $[C_{58}H_{98}N_3NaO_{37}S + Na]^+$: 1506.54), 1520.97 (9.5) (calcd. for $[C_{59}H_{100}N_3NaO_{37}S + Na]^+$: 1520.56), 1534.98 (0.9) (calcd. for $[C_{60}H_{102}N_3NaO_{37}S + Na]^+$: 1534.57).

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Synthesis of *N*-[1-(Randomly Methylated 6^A-Deoxy-β-D-cyclodextrinyl)-1*H*-1,2,3-triazol-4-yl]methyl-D-gluconoamide (4)

Randomly methylated mono-6-azido-6^A-deoxy-β-D-cyclodextrin (1.5 mmol) and hydrated copper sulfate (3 mmol) were added to a solution of the *N*-propargyl-D-gluconoamide (1.8 mmol) in DMF (40 mL). After the subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (6 mmol) dissolved in water (5 mL), the solution was stirred for 18 h at room temperature. After evaporation of the solvent, the crude product was dissolved in an ammonia solution (8%) and stirred 2 h before being purified by column chromatography on silica gel with water as eluent to give the product as a white powder. After evaporation of the solvent the product was dissolved in 50 mL of water and extracted by 500 mL of chloroform (2×250 mL). The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and concentrated to give a yellowish powder; yield: 1.85 g (77%). ^{1}H NMR (300 MHz, D_2O): $\delta = 7.97$ (s, 1H), 5.33 (m, 6.5H), 4.98 (m, 5.4H), 4.56 (m, 4.0H), 3.18 (m, 3.2H), 3.99–3.86 (m, 17.5H), 3.71–3.53 (m, 69.9H), 3.37–3.14 (m, 29.4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 20 °C): $\delta = 173.0$, 144.0, 124.8, 102.6–100.7, 92.9–81.4, 79.0, 73.8, 72.7, 71.3, 70.3, 63.3, 60.8, 59.7–58.7, 50.0, 31.1. MS: *m*/*z* (%) = 1570.06 (4.1) (calcd. for $[C_{62}H_{106}N_4O_{40}+Na]^+$: 1569.63), 1584.09 (25.5) (calcd. for $[C_{63}H_{108}N_4O_{40}+Na]^+$: 1583.64), 1593.11 (62.0) (calcd. for $[C_{64}H_{110}N_4O_{40}+Na]^+$: 1597.66), 1612.12 (8.3) (calcd. for $[C_{65}H_{112}N_4O_{40}+Na]^+$: 1611.68).

Palladium-Catalyzed Tsuji–Trost Reaction

The TPPTS water-soluble phosphane (0.32 mmol) was dissolved in water (2.56 g) in a Schlenk tube under a nitrogen atmosphere. This solution was then transferred into another Schlenk tube containing $Pd(OAc)_2$ (0.036 mmol). After stirring with a magnetic bar for 15 h at room temperature, the obtained solution was transferred into a mixture of alkyl allyl carbonate (1.80 mmol), diethylamine (3.60 mmol), dodecane (0.75 mmol – GC internal standard) and heptane (3.2 g). The medium was vigorously stirred (1000 rpm) at room temperature and the reaction was monitored by quantitative gas chromatographic analysis of the organic layer.

Supporting Information

Supporting Information ia available and contains experimental details – NMR spectra, Tsuji–Trost reaction: impact of **4** on the cleavage reaction of **8**, **9**, **10** and **11**.

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could be determined as these compounds are neither volatile for headspace determination nor sufficiently soluble in water for NMR or ITC measurements.

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