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COMMUNICATION

Access to the *Syn* Diastereomers of Cryptophane Cages using HFIPOriane Della-Negra,^a Yoann Cirillo,^a Thierry Brotin,^b Jean-Pierre Dutasta,^b Pierre-Loïc Saïdi,^c Bastien Chatelet^{*a} and Alexandre Martinez^{*a}Received 00th January 20xx,
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Cryptophane cages can adopt either an *anti* or *syn* configuration that present different recognition properties. While the synthesis of *anti*-cryptophanes is well reported, the synthesis of *syn*-cryptophanes remains a challenge. Herein, we demonstrate that the use of HFIP as a co-solvent during the second ring closure reaction significantly affects the regioselectivity, providing an easier access to the *syn*-cryptophane stereomers.

Over the past few years, cryptophanes have been widely used as molecular receptors and as sensor devices.^{1,2} These supramolecular hosts are made of two cup-shaped [1.1.1]-orthocyclophane units, usually named cyclotrivenatrylene (CTV), but generally and more accurately described as cyclotribenzylene (CTB) moieties, connected by three linkers.^{1,3} Most cryptophanes can be obtained under two diastereomeric forms (*syn* and *anti*),^{1,4} that display different physicochemical properties and complexation affinity towards selected guests.^{5–10}

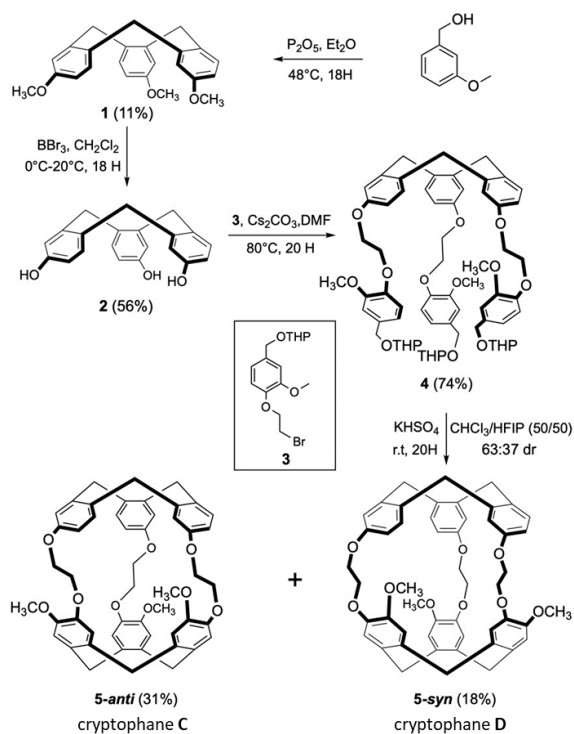
Cryptophanes can be synthesized following two main routes: the “direct method” and the “template method”. Briefly, the direct method consists in the synthesis of bis(vanillyl alcohol) derivatives, which are then treated with formic acid to give rise to the desired cryptophanes.¹ This approach usually affords cryptophanes in low yields.⁸ The “template method” involves the formation of the two CTB units at two different stages of the synthesis. To carry out the three Friedel-Crafts reactions, formic acid (HCOOH) and scandium triflate Sc(OTf)₃ have been widely used to promote the formation of the CTB units. These two reagents usually give rise to cryptophanes with moderate to good yields.^{4,8} Formic acid enables in some cases obtaining both diastereomers,⁸ but is not suitable for molecules

bearing specific protecting groups such as allyl or benzyl substituents. Furthermore, it can sometimes be difficult to separate the expected cryptophanes from polymeric materials. In contrary, the use of Sc(OTf)₃ in equimolar amount was found to provide, under mild conditions, good yields and more convenient purification steps for the synthesis of a wide range of *syn* and *anti*-cryptophanes.^{1,4–11} Nevertheless the access to *syn* isomers bearing ethylenedioxy linkers remains highly challenging. Whereas *anti*-cryptophane **A** (Fig. 1) was first synthesized in 1981 by Collet et al., only recently, around 40 years after the seminal work of Collet et al., the thirteen-step synthesis of the *syn*-diastereomer, cryptophane **B** (Fig. 1), was reported by Brotin et al..⁶ Thus, a faster and more convenient synthetic route to obtain the *syn*-diastereomers of cryptophanes could allow for a wider use of these compounds as the physical and the recognition properties of the two diastereomers of a cryptophane strongly differ, for instance in the recognition of halogenomethanes,^{12,13} or in the *in-out* exchange rate of the xenon guest, thus leading to the realization of unprecedented bio-probes based on *syn*-cryptophanes.

Quite recently, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) has become a popular solvent in chemistry.^{14,15} It exhibits specific features due to the presence of the trifluoromethyl groups and the formation of dimers and trimers of HFIP. Compared to isopropanol, its ionizing power, Brønsted acidity and H-bond acidity are enhanced.^{16,17} Furthermore, due to its low boiling point (58.2 °C) it can be easily separated from other solvents and products, and reused without any decrease of its activity.¹⁸ The use of this fluorinated solvent in Friedel-Crafts benzylation reactions has been reported in the last decade.^{16,18–21} Notably, it was first used alone for the benzylation of arenes with benzyl fluorides and benzyl chloride.^{18–20} Combined to catalytic Brønsted acids, it was applied on highly electronically deactivated benzylic alcohols.²¹ Finally, more recently Friedel-Crafts benzylation of arenes with benzylic alcohols has been reported in HFIP catalyzed by bisulfate salt. These conditions performed on a wide range of arenes and benzylic

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Scheme 1 General pathway for the synthesis of cryptophanes **C** (5-*anti*) and **D** (5-*syn*).

alcohols gave rise to unsymmetrical diarylmethanes in high yields with good to high regioselectivity.²⁰

Herein, we report the use of the HFIP/bisulfate salt combination to promote the synthesis of *syn* and *anti*-cryptophanes. We have been able to obtain both diastereomers in a single step for cryptophanes **A** (*anti*) and **B** (*syn*), **C** (*anti*) and **D** (*syn*), and **E** (*anti*) and **F** (*syn*) (Fig. 1), providing a convenient and fast access to the *syn* isomers. In each case, the ratio *anti*/*syn* was similar and estimated around 3/2 both by ^1H NMR analysis of the crude reaction mixtures and the isolated yields of the separated diastereomers.

We first attempted to perform the synthesis of cryptophanes **C** (5-*anti*) and **D** (5-*syn*). Indeed, the template method, using either formic acid or $\text{Sc}(\text{OTf})_3$ in the last cyclization step, led to mixture of **C** (5-*anti*) and **D** (5-*syn*) diastereomers with an *anti*/*syn* ratio of 83/17 or 86/14, respectively (Table 1).^{4,20} Thus, we decided to use this synthesis as benchmark in order to address both the ability of HFIP to provide the desired cryptophane cages and to modulate the regioselectivity of the last cyclization step. The precursor **4** was obtained in three steps (Scheme 1). CTB **1** was synthesized by trimerization of (3-methoxyphenyl)methanol using P_2O_5 .²² Then, removal of the three methyl groups were achieved using BBr_3 in CH_2Cl_2 to give CTV **2**,²³ which then reacted with protected benzyl alcohol **3** in presence of Cs_2CO_3 , in DMF to give precursor **4** in 74% yield.⁴ Finally, compound **4** was dissolved in a mixture of $\text{CHCl}_3/\text{HFIP}$ (1/1, v/v) in the presence of KHSO_4 (0.7 equiv.). After stirring overnight at room temperature, ^1H NMR analysis of the crude reaction mixture

(Fig. 1), showed the formation of cryptophanes **C** (5-*anti*) and **D** (5-*syn*) in 59/41 ratio (Table 1). Purification by chromatography gave yields of 31% and 18% for cryptophanes **C** (5-*anti*) and **D** (5-*syn*), respectively. Compared to the previous methods using HCOOH , the global yield was increased (49% compared to 30%),²⁴ and was somewhat lower than that obtained with $\text{Sc}(\text{OTf})_3$ (58%) (Table 1).⁴ More interesting, the yield of cryptophane **D** (5-*syn*) was enhanced (18% compared to 8% and 5% respectively). Thus, this confirms that HFIP, in the presence of KHSO_4 , acts as efficient medium to promote the Friedel-Crafts reactions leading to cryptophane cages in good yields, and more interestingly allows modulating the regioselectivity of the cyclization, providing much more *syn* isomer than the other known methods. To address the thermodynamic or kinetic control of the regioselectivity of this last cyclization step, the minor diastereomer, cryptophane **D**, was dissolved in a 1/1 mixture of $\text{CHCl}_3/\text{HFIP}$ and then KHSO_4 was added. After 20h at 20°C , no reaction occurred and cryptophane **D** was fully recovered, demonstrating that this cyclization step is not reversible and thus is under kinetic control. These cryptophanes could be used like cryptophane **A** for the encapsulation of xenon,²⁵ but they are most specifically known for their binding properties with chloroform.^{26–28} The improved yield in the synthesis *syn*-cryptophane **D** prompted us to test the HFIP/ KHSO_4 combination for the synthesis of other cryptophanes.

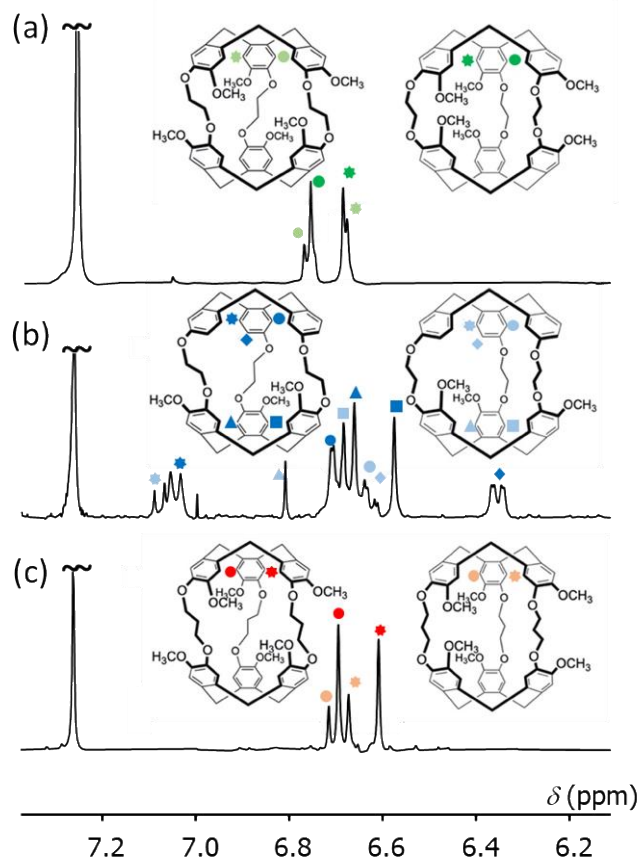


Fig. 1 ^1H NMR spectra (CDCl₃) of the crude reaction mixtures resulting from the synthesis of (a) Cryptophanes **A** and **B**, (b) Cryptophanes **C** and **D** and (c) Cryptophanes **E** and **F**.

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Table 1. Summary of the yields and ratios obtained for the synthesis of *anti* and *syn* cryptophanes with HFIP and KHSO₄, and comparison with Sc(OTf)₃ and HCOOH.

Cryptophanes	Sc(OTf) ₃ ^a		HCOOH ^a		KHSO ₄ , HFIP/CHCl ₃ ^b	
	Yield	Ratio <i>anti/syn</i> ^c	Yield	Ratio <i>anti/syn</i> ^c	Yield	Ratio <i>anti/syn</i> ^c
A (anti-10a)	51 % ⁴	100/0	80 % ⁸	100/0	60 %	75/25
B (syn-10a)	0 % ⁴		0 % ⁸		20 %	
C (anti-5)	50 % ⁴	86/14	25 % ²⁴	83/17	31 %	63/37
D (syn-5)	8 % ⁴		5 % ²⁴		18 %	
E (anti-10b)	28 % ⁴	100/0	27 % ⁸	35/65	40 %	62/38
F (syn-10b)	0 % ⁴		50 % ⁸		25 %	

^a Reported results are obtained from literature as indicated. In case of cryptophanes **A**, **B**, **C** and **D** synthesized using Sc(OTf)₃ we have also reproduced the experiments and obtained similar yields (for instance we were unable to isolate cryptophane **B** using these conditions).

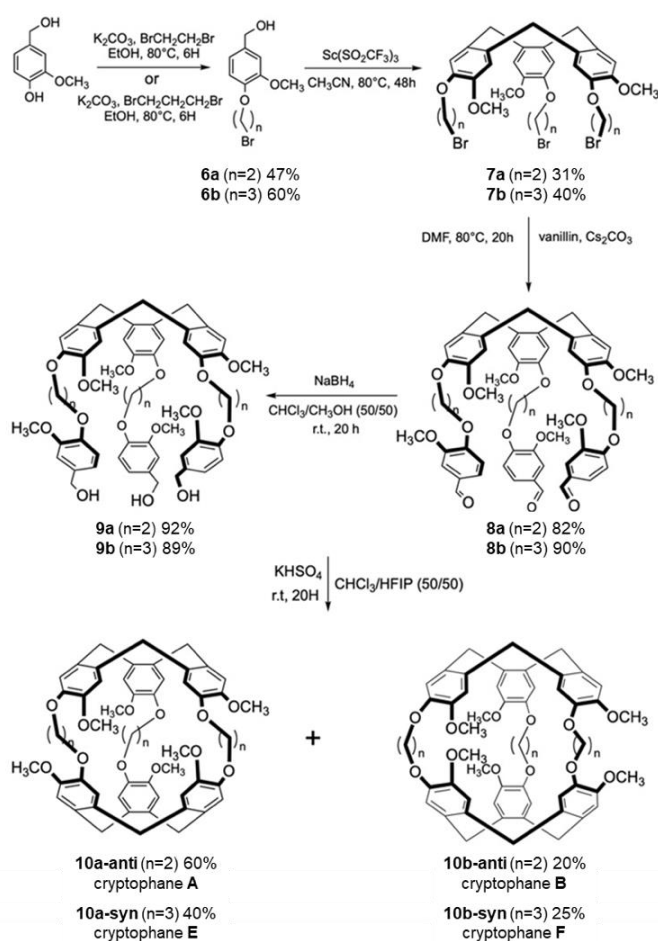
^b The results obtained using KHSO₄, HFIP/CHCl₃ have been obtained in the present study.

^c Ratios obtained from isolated products; in case of the use of HFIP/CHCl₃ mixture, they are similar to those obtained from NMR analysis of the crude reaction mixtures: (61/39), (59/41) and (64/36) for cryptophanes **A/B**, **C/D** and **E/F**, respectively.

Thus, we then focused on the synthesis of cryptophanes **A** and **B** (Scheme 2). The five-step synthesis first consisted in the nucleophilic substitution of vanillic alcohol by 1,2-dibromoethane to give compound **6a**. Then, a first Friedel-Crafts reaction was performed using Sc(OTf)₃ to give compound **7a**,²⁹ which reacted with vanillin in the presence of Cs₂CO₃ in DMF to afford the derivative **8a** that was then reduced using NaBH₄ to give precursor **9a** in 96% yield. Finally, this precursor reacted under the same conditions described above to give cryptophanes **A (anti-10a)** and **B (syn-10a)**.

Interestingly, the ¹H NMR analysis of the crude product revealed the presence of four signals in the aromatic part of the spectrum (Fig. 1), corresponding to cryptophanes **A (anti-10a)** and **B (syn-10a)**.⁶ The ratio between the two diastereomers was estimated to (61/39) for *anti*-10a and *syn*-10a respectively (Table 1), closed to the one obtained for cryptophanes **C** and **D**, but more importantly, it was the first time that both cryptophanes **A** and **B** were obtained in the same time using the "template method". Indeed, the use of HCOOH only afforded cryptophane **A** in 80% yield,⁸ whereas Sc(OTf)₃ enabled to obtain the *anti*-form in 51% yield.⁴ These last two conditions were also performed in this study and the absence of cryptophane **B** was confirmed. Nevertheless, cryptophane **B** was obtained quite recently using an alternative pathway, which consisted in thirteen steps for an overall yield of 0.15%.⁶ Here, after a simple purification by chromatography, we managed to isolate cryptophanes **A (anti-10a)** and **B (syn-10a)** in 60% and 20% yield, respectively. This five-step synthesis afforded cryptophane **B** with an overall yield of 3% from vanillic alcohol. This simplified pathway should be useful for further investigations on guest recognition with this *syn*-cryptophane.⁶

Finally, we applied the same reaction steps starting from 1,3-dibromopropane to study the formation of cryptophanes **E (anti-10b)** and **F (syn-10b)** (Scheme 2). As for the previous

**Scheme 2** General pathway for the synthesis of cryptophane **A (10a-*anti*)**, **B (10a-*syn*)**, **E (10b-*anti*)** and **F (10b-*syn*)**.

syntheses, the ^1H NMR analysis of the crude reaction mixture showed the formation of both *anti* (cryptophane **E**) and *syn* (cryptophane **F**) cryptophanes (Fig. 1) in a ratio estimated at 64/36 (Table 1). Finally, cryptophanes **E** (*anti*-**10b**) and **F** (*syn*-**10b**) were isolated with 40% and 25% yields, respectively. On one hand, compared to $\text{Sc}(\text{OTf})_3$, the global yield was increased (65% compared to 28%) and both diastereomeric forms were obtained (Table 1).⁴ On the other hand, regarding HCOOH , the *syn/anti* ratio was reversed (Table 1).⁸

Interestingly with the use of HFIP/ KHSO_4 , we noticed that in all three cases a ratio of around 3/2 was observed and maintained between *anti* and *syn* cryptophanes (Table 1). In most cases $\text{Sc}(\text{OTf})_3$ specifically afforded the *anti*-form,⁴ whereas with HCOOH the *anti/syn* ratio showed a dependence with the number of methylene units in the linkers. An odd number will mainly lead to *syn*-cryptophanes while an even number will favour *anti*-cryptophanes.⁸ The way HFIP modifies the stereoselectivity is not yet known. Different studies suggest that HFIP can establish different kind of interactions with arenes compounds^{15,30}. These interactions can affect the conformation of the linkers during the second ring-closure reaction and consequently the regioselectivity of the cyclization steps leading to cryptophane cages. In solution, HFIP is able to form helical hydrogen-bonding networks and its use can affect the conformation of peptides, proteins and polyenes, hence more compact structures can be adopted during the cyclisation of this latter.^{30–32} Thus, HFIP probably affects the conformation of the linkers during the second ring-closure reaction and consequently the regioselectivity of the cyclization steps leading to cryptophane cages. Titration experiments have been performed, supporting some interactions between the precursor of cyclisation **4** and HFIP (see Figures S25 and S26).³³

In summary, we have described the use of HFIP in the presence of KHSO_4 as a new system to synthesize cryptophane cages. Yields are comparable or even better than those obtained with the template approach using HCOOH or $\text{Sc}(\text{OTf})_3$. Interestingly, this new procedure allows for an easy access to the *syn*-diastereomers, in particular for the synthesis of cryptophane **B** obtained with an overall yield of 3%. Moreover, it opens new ways for a wider use of these molecular receptors. This work constitutes a new approach to *syn*-diastereomers of cryptophanes and for the synthesis of other cage compounds based on CTB units, and more generally the synthesis of host molecules involving Friedel-Crafts reactions in their cyclization steps.

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

There are no conflicts to declare.

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