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Emergence of homochiral benzene-1,3,5-tricarboxamide helical assemblies and catalysts upon addition of an achiral monomer

Yan Li, Ahmad Hammoud, Laurent Bouteiller and Matthieu Raynal*

Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, Equipe Chimie des Polymères, 4 Place Jussieu, 75005 Paris (France) e-mail: matthieu.raynal@upmc.fr.

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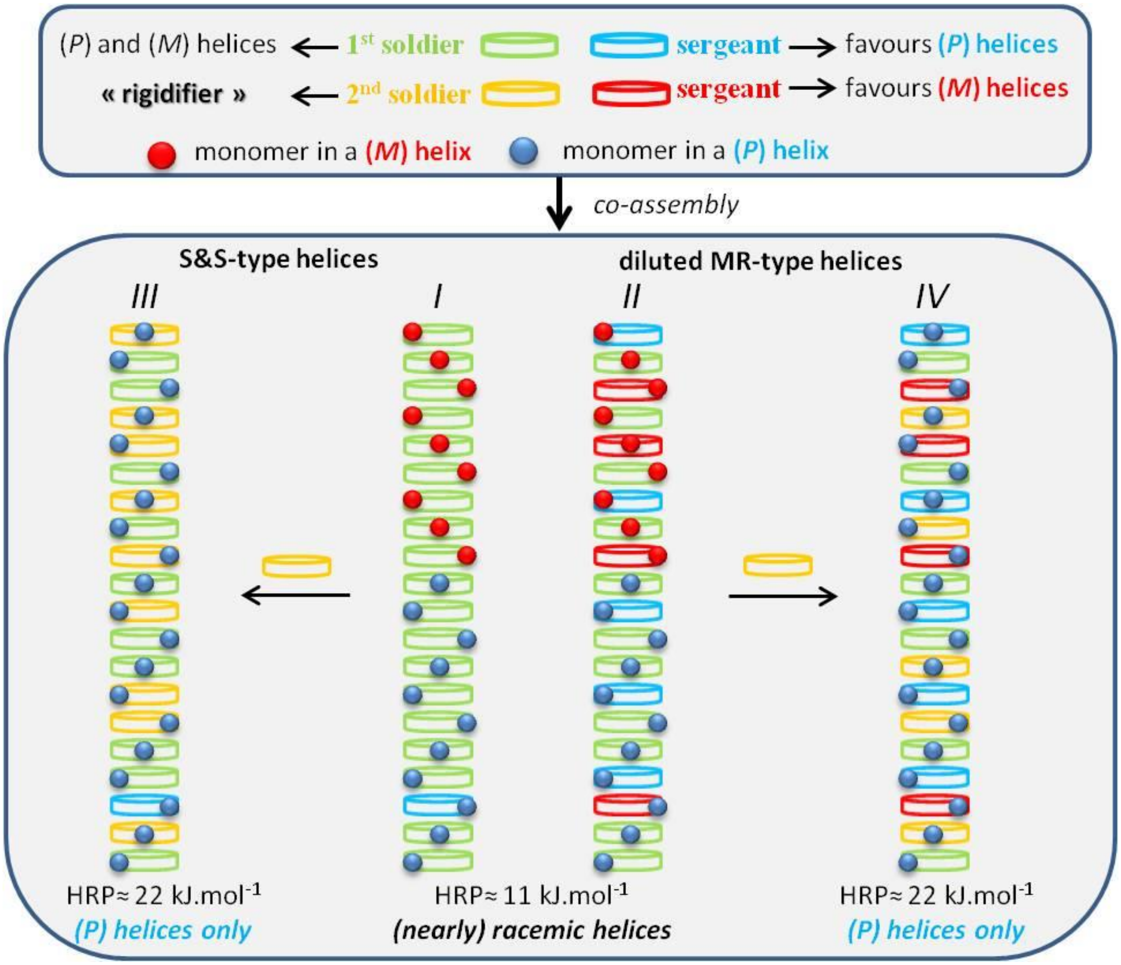
ABSTRACT: Chirality amplification refers to the ability of a small chiral bias to fully control the main chain helicity of polymers and assemblies. Further implementation of functional chirally-amplified helices as switchable asymmetric catalysts, chiral sensors and circularly-polarized light emitters will require a greater control of the energetics governing these chirality amplification effects. In this work, we report on the counterintuitive ability of an achiral molecule to suppress conformational defects in supramolecular helices thus leading to the emergence of homochirality in a system containing a very small chiral bias. We focus our investigation on supramolecular helices composed of an achiral benzene-1,3,5-tricarboxamide (BTA) ligand, coordinated to copper, and an enantiopure BTA co-monomer. Amplification of chirality as probed by varying the amount (sergeants-and-soldiers effect) or the optical purity (diluted majority-rules effect) of the enantiopure co-monomer, are modest in this initial system. However, both effects are hugely enhanced upon addition of a second achiral BTA monomer leading to a perfect control of the helicity either by means of a remarkably low amount of sergeants (0.5%) or a small bias from a racemic mixture of enantiopure co-monomers (10% *e.e.*). Such an enhancement in the amplification of chirality is only achieved by mixing the three components, *i.e.* the two achiral and the enantiopure co-monomers, highlighting a synergistic effect upon co-assembly of the three monomers. Investigation of the role of the achiral additive by multifarious analytical techniques supports its ability to stabilize the helical co-assemblies and suppress helix reversals *i.e.* conformational defects. Implementation of these helical copper precatalysts in the hydrosilylation of 1-(4-nitrophenyl)ethanone confirms that the effect of the achiral BTA additive is also operative under the conditions of the catalytic experiment. A highly enantioenriched product (90% *e.e.*) is produced by a supramolecular catalyst operating with ppm levels of chiral species.

Introduction

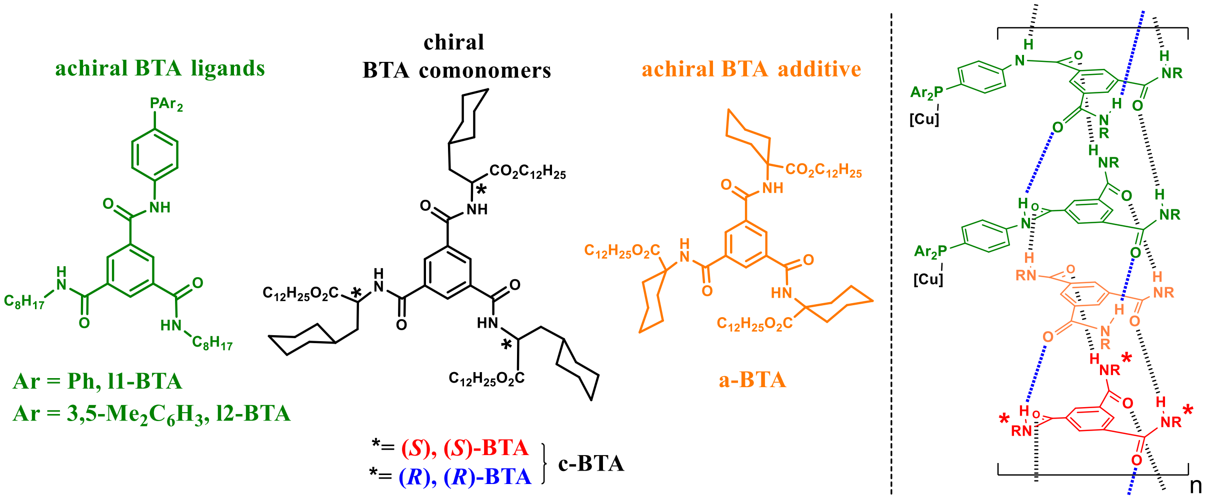
Asymmetric amplification refers to a quite large variety of topics in chemical sciences such as non-linear effects in asymmetric catalysis,[1] racemization/deracemization[2] processes and chiral replicators[3] that may ultimately constitute a basis to understand the elusive omnipresence of homochirality on Earth. In addition, amplification of chirality in helical covalent molecules[4] and supramolecular aggregates[5] deals with controlling helicity, expressed at the macromolecular or supramolecular level, but triggered by a small chiral bias at the molecular level. This minute conformational preference is usually too small to be directly measured (with extreme values as low as a few J.mol^{-1} per repeat unit in the case of chiral isotopic substitution)[6] but induces a conformational bias that is amplified through the whole nanostructure and may eventually lead to the formation of homochiral structures. Dynamic helical covalent and supramolecular polymers are particularly prone to chirality amplification as demonstrated by the diversity of scaffolds in which these phenomena have been expressed.[4c] The ultra high sensitivity to a variety of chiral inducers (*e.g.* monomers, additives, solvents, physical fields) has motivated the implementation of functional helical nanostructures as switchable asymmetric catalysts,[7] chiral stationary phases[8] and as optical devices able to emit[9] or selectively reflect[10] circularly-polarized light.

Green, Selinger and co-workers provided the experimental and theoretical basis of amplification of chirality in covalent poly(isocyanate)s, *i.e.* a class of stiff polymers in which the backbone adopts a stable but dynamic helical conformation in solution.[4a] These authors notably reported the possibility of controlling the backbone helicity by: (i) introducing a small amount of chiral monomers (sergeants) to copolymers mainly constituted of achiral monomers (soldiers) through the so-called sergeants-and-soldiers (S&S) effect,[11] (ii) mixing enantiopure co-monomers in a non-equimolar ratio through the majority-rules (MR) effect[12] and (iii) combining both effects, *i.e.* adding a non-equimolar ratio of enantiopure monomers to achiral monomers thus forming a terpolymer (diluted MR effect).[13] For all these cases, the chiral bias imparted by the sergeant or by the majority enantiopure monomer is transferred to soldiers (S&S), the minority enantiomer (MR) or both (diluted MR) which remain under its influence in between two helix reversals. Following these pioneering studies, similar effects have been observed for other covalent helical polymers[4b,14] and for supramolecular polymers.[4c,5b]

Extremely high levels of chirality amplification, by means of a small amount of sergeants (≤ 1%),[15] by a mixture of enantiopure monomers only moderately biased from the racemic mixture (≤10% *e.e.*),[15i,16] by chiral physical fields[17] or through spontaneous mirror-symmetry breaking phenomena[9,15i,17b,18] have been reported for a limited number of helical assemblies in solution or in the gel state. *N*,*N*′,*N*′′-trialkylbenzene-1,3,5-tricarboxamides (alkyl BTA) and their functional derivatives are ubiquitous synthons in supramolecular chemistry as a result of their robust assembly into dynamic helices stabilized by a threefold hydrogen-bond network and aromatic interactions.[19] S&S and MR



Scheme 1 Schematic representation of the concept. Supramolecular stacks are composed of a first soldier (green) and a low amount of sergeants (blue) (I) or a mixture of enantiopure monomers slightly biased from the racemic mixture (II). The stacks consist of a nearly equal amount of left and right-handed helical parts. Upon addition of a second soldier (orange), these helices become homochiral (III and IV). This soldier acts as a "rigidifier" by stabilizing the helical co-assemblies and removing helix reversals as indicated by the helix reversal penalty (HRP) values. This concept also applies for the construction of helical catalysts in which the first soldier bears a catalytic site.



Scheme 2 Left: chemical structures of the BTA monomers used in this study. Right: representation of the helical co-assemblies, preferentially right-handed, formed by mixing **l1-BTA**, [Cu(OAc)$_2$·H$_2$O], **(*S*)-BTA** and **a-BTA** (S&S type mixture). For a tentative molecular representation of the concept shown in Scheme 1 with BTA co-assemblies, see Chart S1b.

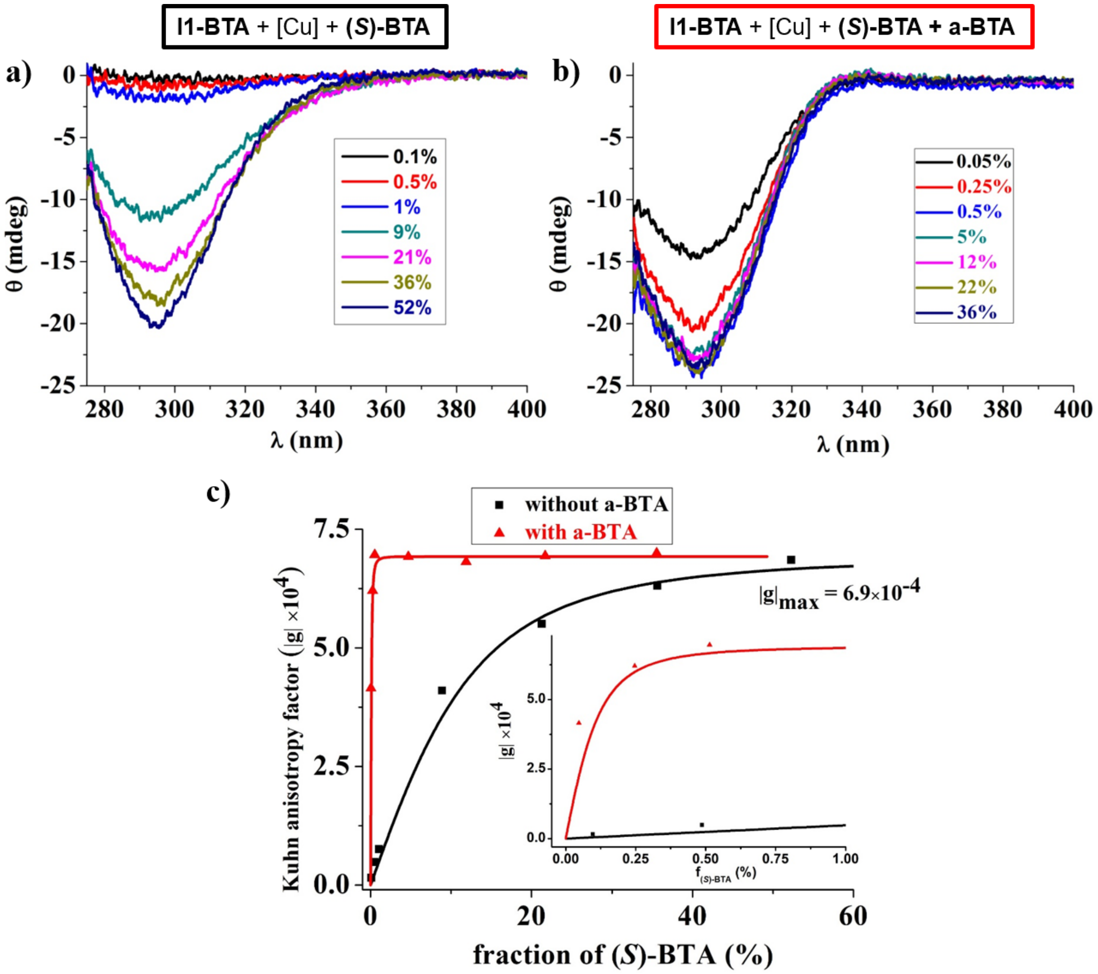


Figure 1 Chirality amplification through the S&S effect as probed by CD spectroscopy (293K, toluene), [Cu]= [Cu(OAc)$_2$·H$_2$O]. a) CD spectra of mixtures without **a-BTA** ([**l1-BTA**]/[Cu]= 4, [**l1-BTA**]= 5.80±0.04 mM, 0.006≤ [**(*S*)-BTA**]≤ 6.35 mM). b) CD spectra of mixtures with **a-BTA** ([**l1-BTA**]/[Cu]= 4, [**l1-BTA**]= 5.82±0.06 mM, [**a-BTA**]= 5.80±0.06 mM, 0.006≤ [**(*S*)-BTA**]≤ 6.39 mM). The superior maximal ellipticity reached for S&S mixtures with **a-BTA** is related to an increase of the intensity of the main UV-Vis absorption band (*vide infra*). c) Kuhn anisotropy factor (g) measured at λ= 295 nm as a function of the fraction of **(*S*)-BTA** in the mixtures. $g^{295} = \theta^{295}/(32980 \times Abs^{295})$ where θ and Abs are the ellipticity and UV absorbance measured at λ= 295 nm, respectively. $f_{c\text{-}BTA}$= [**c-BTA**]/([**c-BTA**]+[**l1-BTA**]+[**a-BTA]**). The data have been fitted for the mixtures with and without **a-BTA** (red and black solid lines, respectively) according to Smulders et al.[20] (see text).

effects exist in BTA helices[20-21] but are not exceptional and their enhancement would clearly be beneficial for a range of chirality-driven applications. Meijer and co-workers probed the limits of chirality amplification in BTA helical assemblies and their studies revealed that optimization by subtle variation in the structure of the monomer will improve the extent of amplification but solely up to the limits fixed by the number of reversals present in the helix.[20] As this latter parameter is intrinsically related to the stability of the BTA assemblies, the authors suggested that further improvement would require changing the chemical structure of the monomers (and thus the nature of the helix). We report herein that, albeit counterintuitive at first sight, the addition of an *achiral* BTA monomer switches the configurational state of BTA co-assemblies from poorly helically biased to single handed, thus leading to the emergence of homochirality in supramolecular systems embedding a very small chiral bias. The S&S and diluted MR effects are improved by two orders and one order of magnitude, respectively, which is attributed to the stabilization of the co-assemblies and the suppression of the helix reversals in presence of the achiral additive (see a representation of the present concept in Scheme 1). Furthermore, the copper atoms supported by these BTA helical assemblies serve as catalytic sites providing a highly enantio-enriched alcohol (>90% *e.e.*) despite catalytic loading in chiral species being at ppm levels.

Results

Chirality amplification probed by CD spectroscopy. We previously found that the mixture composed of the BTA ligand, **l1-BTA**, and the chiral BTA co-monomer, **c-BTA** (Scheme 2) yields very long one-dimensional co-assemblies in solution (DP$_n$ ≈250) with a radius corresponding to a single molecule of BTA in the cross-section.[22] **c-BTA** belongs to the family of BTAs derived from amino-esters (ester BTAs)[15g,23] which were shown to be efficient chiral inducers for asymmetric reactions performed with helical BTA catalysts.[22,24] In order to induce a sufficient bias in the handedness of these co-assemblies, an excess of **c-BTA** was employed relatively to **l1-BTA**.[22,24b] We have now investigated the possibility of generating homochiral helices with a lower amount of enantiopure co-monomer. Firstly, mixtures of **l1-BTA** and **(*S*)-BTA** in toluene are analyzed by CD spectroscopy with the presence of copper coordinated to the BTA ligand in order to be as close as possible to the catalytic conditions we established previously.[26]

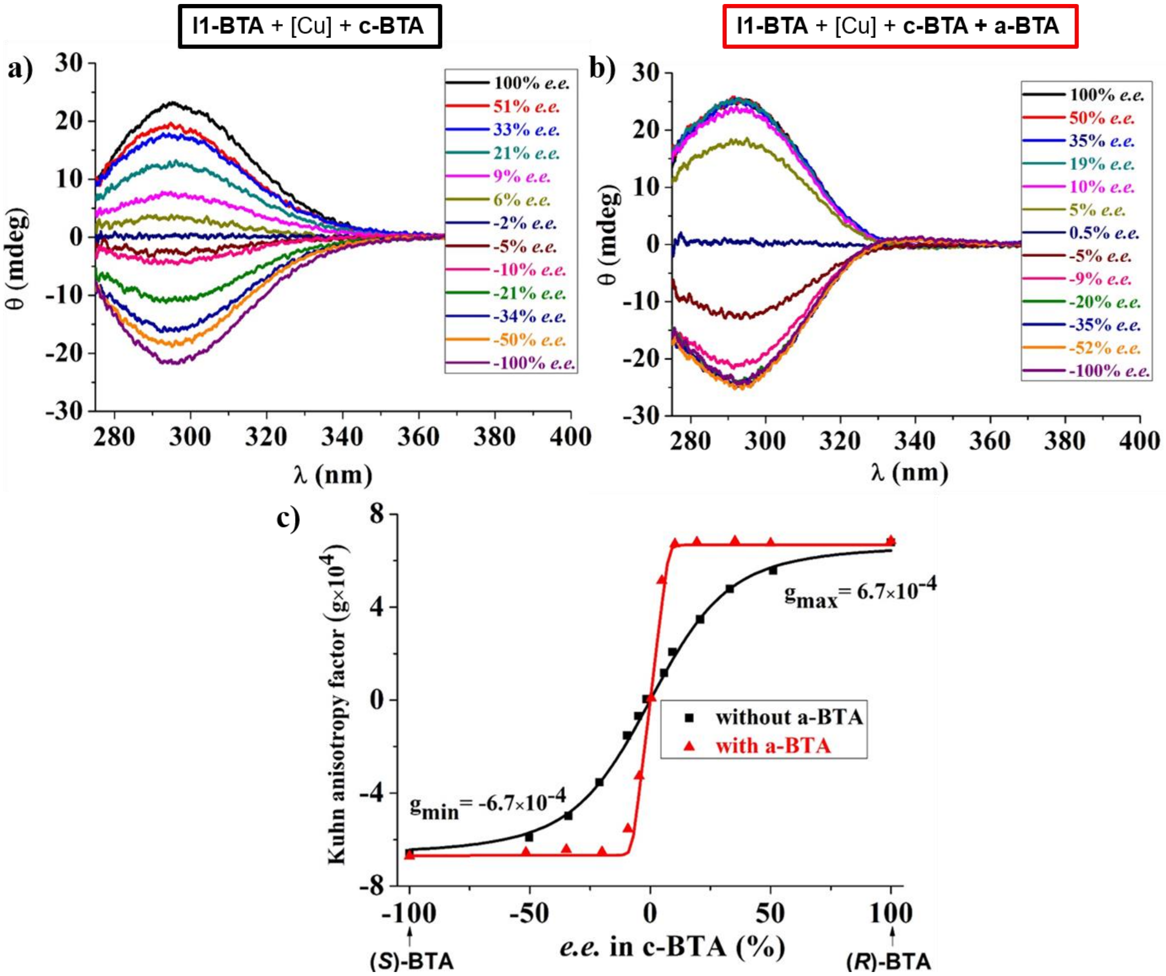


Figure 2 Chirality amplification through the diluted MR effect as probed by CD spectroscopy (293 K, toluene), [Cu]= [Cu(OAc)$_2$·H$_2$O]. a) CD spectra of mixtures <u>without</u> **a-BTA** ([**l1-BTA**]/[Cu]= 4, [**l1-BTA**]= 5.78±0.07 mM, -100% *e.e.*≤ **c-BTA**.≤ 100% *e.e.*, f$_{\text{c-BTA}}$= 0.53±0.02). b) CD spectra of mixtures <u>with</u> **a-BTA** ([**l1-BTA**]/[Cu]= 4, [**l1-BTA**]= 5.80±0.04 mM, [**a-BTA**]= 6.40±0.40 mM, -100% *e.e.*≤ **c-BTA**.≤ 100% *e.e.*, f$_{\text{c-BTA}}$= 0.34±0.02). The superior maximal ellipticity reached for diluted MR mixtures with **a-BTA** is related to an increase of the intensity of the main UV-Vis absorption band (*vide infra*). c) Kuhn anisotropy factor (g) measured at λ= 295 nm as a function of the optical purity of **c-BTA** in the mixtures. The data have been fitted for the mixtures with and without **a-BTA** (red and black solid lines, respectively) according to van Gestel[25] (see text).

CD analyses of sergeants-and-soldiers (S&S) type mixtures, in which **l1-BTA** coordinated to Cu and **(*S*)-BTA** are the soldiers and the sergeants, respectively, are shown in Figure 1a ([**l1-BTA**] and [Cu(OAc)$_2$·H$_2$O] are set constant at 5.80±0.04 mM and 1.46±0.02 mM, respectively). Mixtures with more than 0.5% of sergeants exhibit a Cotton effect with a maximum at $\lambda \approx$ 295 nm while no CD signal is detected for mixtures containing a lower amount of sergeant. The observed Cotton effect constitutes a direct probe of the extent of chirality induction in the co-assemblies since only the soldier is UV active in this region (induced CD).[22,24b,27] Accordingly, plotting the Kuhn anisotropy values (g) at λ= 295 nm as a function of the fraction of **(*S*)-BTA** in these mixtures (f$_{\text{(S)-BTA}}$) provides the amplitude of the S&S effect operating in this system (Figure 1c). Even though the plot deviates from linearity, no obvious plateau of the g value is reached meaning that a sizable fraction of enantiopure co-monomers (f$_{\text{(S)-BTA}}$≥ 52%) is required to get fully biased co-assemblies.

We previously reported that incorporating 1% of an ester BTA was enough to fully bias the handedness of (otherwise racemic) helical assemblies formed by *N*,*N*′,*N*′′-tris(octyl)benzene-1,3,5-tricarboxamide.[15g] We therefore hypothesize that the limited amplification of chirality observed in the present system is related to defects induced by **l1-BTA** coordinated to Cu, *i.e.* this monomer behaves as a "poor soldier". We thus test the possibility of inducing a conformational change in the co-assemblies upon addition of a second achiral BTA. We selected **a-BTA** (Scheme 2) since the cyclohexyl group attached on the amino-ester α-carbon is expected to reduce the conformational freedom of the amide functions and thus to rigidify the hydrogen-bonded network between the complementary monomers in the co-assemblies.[28] A new set of mixtures has been analyzed by CD which differs from the initial one only by the fact that the mixtures now contain two soldiers: **l1-BTA** coordinated to Cu and **a-BTA** ([**l1-BTA**]/[**a-BTA**]= 1). The influence of **a-BTA** on the amplitude of the S&S effect is dramatic (Figure 1b). The CD spectrum of the mixture with only 0.5% of sergeant is virtually identical to that of the mixtures containing higher fractions of enantiopure co-monomers. The S&S mixture with only 0.25% of **(*S*)-BTA** displays a g value which is equal to 90% of the maximal g value ($|g_{max}| = 6.9 \times 10^{-4}$). A similar g$_{max}$ value is reached for S&S mixtures with and without **a-BTA** corroborating the formation of similar homochiral, preferentially right-handed,[24b] co-assemblies but for drastically different fractions of sergeants, f$_{\text{(S)-BTA}}$= 0.5% and 52% respectively. The S&S effect is thus enhanced by two orders of magnitude in the presence of **a-BTA**.

We have investigated whether a similar effect is operative on co-assemblies obtained by mixing soldiers and non-equimolar amounts of enantiopure sergeants, *i.e.* for amplification of chirality through the diluted majority-rules effect. Mixtures containing **l1-BTA** coordinated to Cu and **c-BTA** of various optical purities (-100% *e.e.*→100% *e.e.*) have been analyzed in absence and presence of **a-BTA** (Figures 2a and 2b, respectively). Without additive, a nonlinear increase of the g value is observed as a function of the optical purity in **c-BTA** but no plateau is reached indicating that the amplification of chirality is modest (Figure 2c). Again, the addition of **a-BTA** has a huge effect on the extent of amplification of chirality since homochiral co-assemblies are obtained for scalemic mixtures only slightly biased from the racemic mixture (10% *e.e.*). The diluted MR effect is thus increased by one order of magnitude in the presence of **a-BTA**. A modulation in the relative proportion of the enantiomers of only 10% around the racemic composition produces homochiral helices with opposite handedness.

In the previous experiments, the addition of **a-BTA** induces an increase of the total BTA concentration. To demonstrate the robustness of our data and discard a possible influence of the concentration, we have performed similar S&S and diluted MR type experiments in which the total concentration in BTA monomers has been kept constant to 5.84±0.2 mM (Figure S1). Even in these conditions, upon partial substitution of **l1-BTA** by **a-BTA,** a plateau of g values is obtained for mixtures containing 0.5% of sergeants (S&S mixtures) or a 10% *e.e.* scalemic mixture (diluted MR mixtures) inferring a similar enhancement of the amplification of chirality in the helical co-assemblies. It is remarkable that this simple strategy allows to reach extremely high levels of chirality amplification for both the S&S and diluted MR effects with the same sergeant, which outperforms those obtained for helical assemblies of BTA monomers reported to date.[20-21]

Assembly behavior of the BTA partners. In order to unravel the role of **a-BTA**, we started by determining whether the presence of the three monomers was necessary to observe high amplification of chirality in our above-mentioned helical BTA systems. We have thus firstly characterized the self-assembly of the different BTA monomers. We previously reported that **l1-BTA** monomers aggregate through a cooperative pathway to form hydrogen bonded stacks, similar to the ones described for *N*,*N*′,*N*′′-tris(methoxyethyl)benzene-1,3,5-tricarboxamide[29] and other BTAs in the literature,[19] above a critical concentration of *ca.* 0.5×10^{-3} M in toluene (see the FT-IR and SANS signatures in Figure 3a and 3d respectively).[24b] In the same solvent, **c-BTA** assembles under the form of dimers only, the structure of which was unambiguously determined[23d] and revealed by the presence of hydrogen bonds between amide N-H and ester (instead of amide) carbonyls (see the FT-IR and SANS signatures in Figure 3b and 3d respectively). We have now studied the structure of the self-assemblies formed by **a-BTA** by means of FT-IR and SANS analyses. The FT-IR spectrum recorded in toluene at 1.0 mM, shows the presence of three broad bands in the N−H region with maxima at $\nu\approx 3448$ cm^{-1}, $\nu= 3402$ cm^{-1} and $\nu= 3293$ cm^{-1} which are attributed to free N−H, N−H bonded to ester C=O, and N−H (weakly) bonded to amide C=O, respectively (Figure S2a). A similar pattern is observed at 5.8 mM (Figures 3a and 3b), except that the free N−H band has decreased in intensity and the two others have become more intense meaning that a transition occurs between two species. However, the low intensity of the scattered intensity observed in SANS analyses of **a-BTA** at both 5.4 mM and 9.0 mM indicates that small assemblies are the dominant species in C_7D_8 (Figures 3d and S2b).

After determining the self-assembly behavior of **l1-BTA** (stacks), **c-BTA** (dimers) and **a-BTA** (small objects), we have investigated their co-assembly capability by analyzing their respective binary mixtures. A 1:1 mixture of **l1-BTA** coordinated to Cu and **a-BTA** analyzed by FT-IR (Figure 3a) reveals the presence of hydrogen-bonded stacks as the exclusively detected species thus indicating that both monomers co-assemble into the same helical assemblies. Conversely, the FT-IR spectrum of the 1:1 mixture between **a-BTA** and **(*S*)-BTA** is virtually identical to the weighted average of the spectra of the individual components (Figure 3b). Also, CD analyses of their binary mixtures in various molar ratios (Figure S3) reveal a CD signal which is closely proportional to the amount of **(*S*)-BTA** in the sample, thus indicating that no amplification of chirality occurs. These observations strongly suggest that **a-BTA** and **(*S*)-BTA**, when mixed together, preferentially tend to self-sort into their own self-assemblies (self-segregation) rather than mix into the same aggregates (co-aggregation).

Finally, the nature of the co-assembly formed by mixing **l1-BTA** coordinated to Cu, **(*S*)-BTA** and **a-BTA** has been precisely determined. The FT-IR spectrum of the three-component mixture totally differs from the FT-IR spectra of its individual components since it mainly consists of single band in the N−H and C=O regions (Figure 3c). These bands with a maxima at $\nu= 3239$ cm^{-1} and $\nu= 1640$ cm^{-1} are the signature of hydrogen-bonded amide functions in well-defined helical BTA stacks. The experimental spectrum is virtually identical to the one simulated in case of full co-assembly of the 3 BTA partners meaning that, a large fraction (≥ 90%) of **(*S*)-BTA** and **a-BTA** monomers are incorporated into the stacks formed by **l1-BTA**. This is further supported by SANS analysis of a similar mixture which shows a q^{-1} dependence of the scattered intensity at low q values which is indicative of the presence of cylindrical and rigid objects in C_7D_8 (Figure 3d). The SANS data can be fitted by making the assumption of a full incorporation of **(*S*)-BTA** and **a-BTA** into the stacks of **l1-BTA**. The excellent fit of the SANS data with the form factor for rigid rods of infinite length[30] confirms that the self-assemblies contain a single BTA molecule in the cross-section (r= 12.1 Å, n= 0.81) and that, indeed, stacks are the main contributor of the SANS intensity with only a low content (if any) of **(*S*)-BTA** and **a-BTA** self-assemblies. This full set of analyses offers a precise picture of the assembly behavior of the different BTA monomers: the small assemblies formed by **(*S*)-BTA** and **a-BTA** in which there is no or little implication of the amide carbonyls rearrange in the presence of amide-bonded stacks of **l1-BTA** to generate long helical co-assemblies, while they self-segregate in its absence. The presence of the three BTA partners thus appears to be crucial to generate rigid helical assemblies whose handedness can be fully biased by the enantiopure co-monomer.

Rationalization of the role of the achiral BTA additive. CD analyses have revealed the ability of **a-BTA** to promote the formation of homochiral helical assemblies when the fraction of sergeant is ≥ 0.5% (or its optical purity is ≥ 10% *e.e.*). We first compare the FT-IR analyses of the mixtures with and without **a-BTA** (Figure S4b). Both spectra are very similar indicating that the helical assemblies display a similar hydrogen bond network. Importantly, in both cases the incorporation of **(*S*)-BTA** into the stacks can be estimated to be superior to 90% which discards a potential bias in the **l1-BTA**/**(*S*)-BTA** ratio in the helical co-assemblies as a result of the presence of **a-BTA** (Figure S4a). Also, structural parameters determined above for the assemblies with **a-BTA** (r= 12.1 Å, n= 0.81, l> 120 nm) are similar to those determined previously for assemblies without **a-BTA** (r= 11.4 Å, n = 0.6, l> 100 nm) confirming that the achiral BTA additive does not significantly alter the geometry of

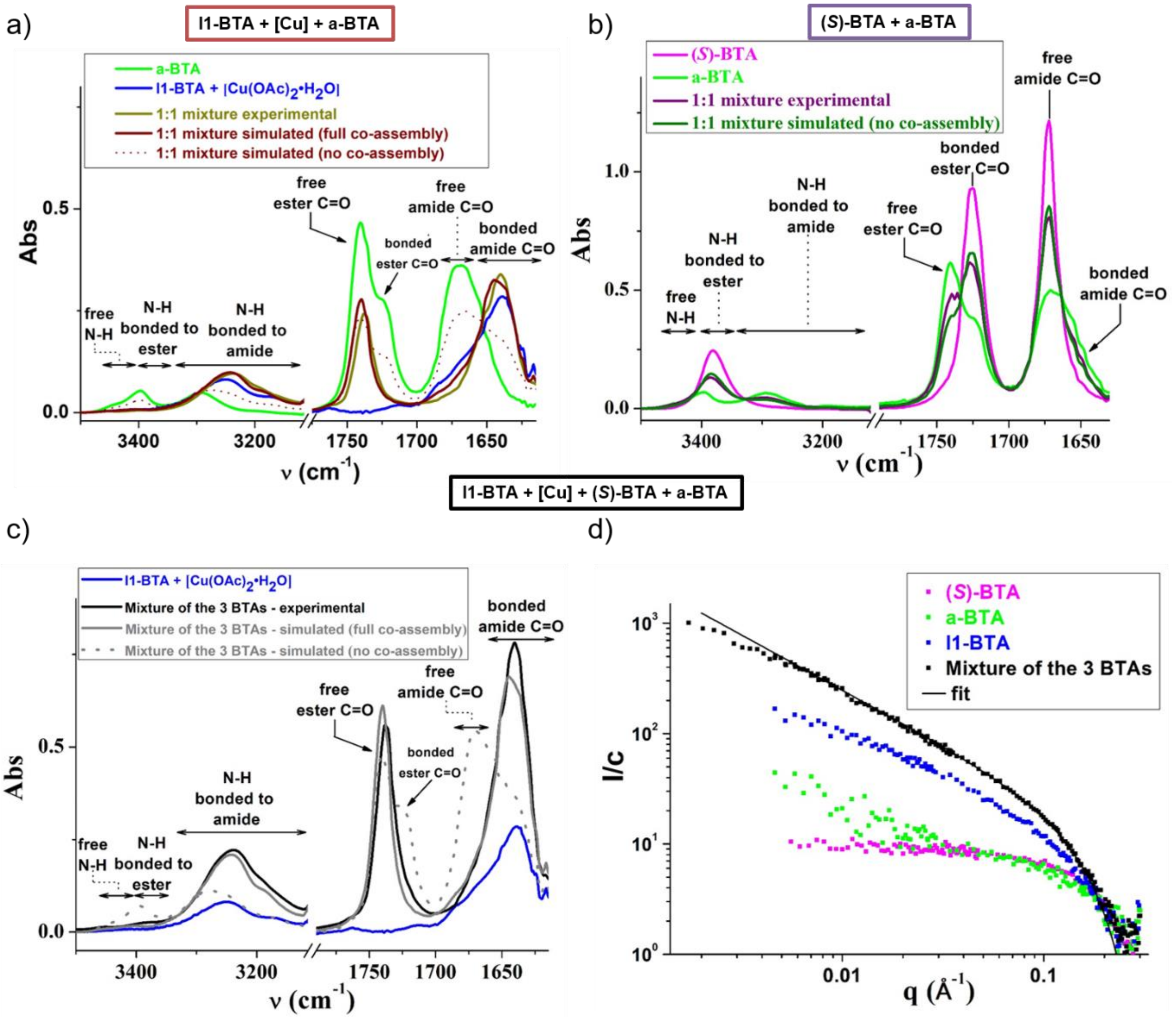


Figure 3 Characterization of the assemblies (293 K, [Cu]= [Cu(OAc)$_2$·H$_2$O]). For FT-IR spectra: Zoom on the N─H and C=O regions. Assignment of the N−H and C=O bands according to literature.[15g,23c] a) FT-IR spectra of **a-BTA** (5.8 mM), {**l1-BTA** (5.8 mM) + [Cu] (1.45 mM)} and their 1:1 mixture in toluene. Simulated spectra for no and full co-assembly. The simulated spectrum for full co-assembly was obtained by considering that all **a-BTA** monomers adopt the conformation of **BTA Aib** monomers[23c] in the co-assembled helical stacks (*i.e.* that they have the same IR spectrum). The good agreement of this simulation with the experimental spectrum means that most of the BTA monomers stack into helical co-assemblies (fraction≥ 90% by considering the measurement uncertainty). b) FT-IR spectra of **(*S*)-BTA** (5.8 mM), **a-BTA** (5.8 mM) and their 1:1 mixture in toluene. Simulated spectrum for no co-assembly. The good agreement of this simulation with the experimental spectrum means that **a-BTA** and **(*S*)-BTA** self-sort into their own co-assemblies. c) FT-IR spectra of the mixtures {**l1-BTA** (5.8 mM) + [Cu] (1.45 mM)} and {**l1-BTA** (5.8 mM) + [Cu] (1.45 mM) + **(*S*)-BTA** (0.58 mM, $f_{(S)\text{-BTA}}$= 0.048) + **a-BTA** (5.8 mM)} in toluene. Simulated spectra for no and full co-assembly. The good agreement of the former simulation with the experimental spectrum means that most of the BTA monomers stack into helical co-assemblies (fraction≥ 90% by considering the measurement uncertainty). d) SANS analyses: scattered intensity (cm^{-1}) normalized by the total BTA concentration (g.L^{-1}) for **(*S*)-BTA**[22] (19.9 g.L^{-1}, 17.0 mM), **a-BTA** (9.83 g.L^{-1}, 9.0 mM), **l1-BTA** (5.98 g.L^{-1}, 8.6 mM) and of the mixture {**l1-BTA** (3.94 g.L^{-1}, 5.7 mM) + [Cu] (0.29 g.L^{-1}, 1.45 mM) + **(*S*)-BTA** (0.68 g.L^{-1}, 0.58 mM, $f_{(S)\text{-BTA}}$= 0.062) + **a-BTA** (3.26 g.L^{-1}, 2.99 mM)} in C_7D_8. The SANS data of the mixture is fitted by the form factor for rigid rods of infinite length, assuming that all BTA monomers are co-assembled into the rods.

the supramolecular helices.[22] We thus attribute the synergistic effect observed upon co-assembly of the three partners to a conformational change induced by **a-BTA** upon its incorporation into the helical co-assemblies. Closer examination of the FT-IR spectra of the mixtures with and without **a-BTA** (Figure S4b) reveals the following differences: i) the maximum of the N─H band is shifted from 3248 to 3239 cm^{-1} and ii) the amide I band is narrower. Notable differences are also observed in the CD and UV-Vis absorption spectra of the same mixtures (Figure S5). The main UV absorption band is narrower and its intensity is significantly increased when **a-BTA** monomers are incorporated into the stacks despite the fact that **a-BTA** self-assemblies barely absorb in that region. A similar change in the intensity and shape of the corresponding Cotton effect is also seen. These observations infer the formation of a stronger and more regular intermolecular hydrogen bond network when **a-BTA** is present in the helical BTA co-assemblies. One can thus expect a difference in the stability of the respective co-

Table 1 Helix reversal penalty (HRP) and mismatch penalty (MMP) (both in kJ.mol^{-1}) determined by simultaneously fitting CD data of Figures 1 and 2 following procedures described by Smulders et al.[20] (for S&S) and by van Gestel[25] (for diluted MR). Comparison with the values obtained for selected helical systems in the literature (293 K).

Helical systems		Opt. S&S$^{(a)}$	Opt. diluted MR$^{(b)}$	HRP	MMP
l1-BTA·Cu + (***S***)**-BTA** (*this work*)	without **a-BTA**	≥52%	≥50% *e.e.*	11.0±2.5	0.4±0.4
	with **a-BTA**	0.5%	10% *e.e.*	**22.1±0.5**	**0.3±0.2**
Alkyl BTA (reference[21e])		5%	≥30% *e.e.*	12.6±2.0$^{(c)}$	1.9±0.2$^{(c)}$
Triphenylamine trisamide (reference[15h])		0.3%	*nr*	20.5$^{(d)}$	1.0$^{(d)}$
Bisurea (references[16a,34])		*nr*	10% *e.e.*	19.5$^{(e)}$	0.05$^{(e)}$

(a) Minimum amount of sergeants required to get homochiral helices in S&S experiments. (b) Minimal optical purity in sergeant required to get homochiral helices in diluted MR experiments. (c) Obtained by fitting independently S&S and MR experiments yielding a precise value for the HRP and MMP, respectively [conditions: 2×10^{-5} M in MCH]. (d) Obtained by fitting the S&S experiment [conditions: 3×10^{-5} M in MCH]. (e) Obtained by fitting simultaneously the helicity and stability data [conditions: 10^{-3} M in cyclohexane]. *nr*: not reported.

assemblies. Indeed, precisely probing the assembly process by VT-CD spectroscopy shows that helical assemblies with **a-BTA** are more stable (by *ca.* 20 K) than those lacking **a-BTA** (Figure S6).

Additional support towards the stabilization of the helical co-assemblies when **a-BTA** is present comes from the quantification of the conformational defects in the supramolecular helices. Amplification of chirality in dynamic supramolecular systems has been consistently modelled by statistical mechanics.[25,31] The statistical model developed by van Gestel and its adaptation by Smulders et al.[20,21e] were successfully applied to quantify energetic parameters governing chirality amplification in S&S,[31a] MR[31b] and diluted MR effects.[25] Its robustness was demonstrated for various BTA monomers[6b,20,21c,21e,32] as well as other types of aggregating disk-like molecules.[15h,32-33] In order to allow a comparison of the present system with those described in the literature, we have fitted the CD data of Figures 1 and 2 simultaneously by following procedures described by Smulders et al.[20] (for S&S) and by van Gestel[25] (for diluted MR). It allows extracting two energetic parameters: the helix reversal penalty (HRP) that corresponds to the energy needed to reverse the handedness of the supramolecular helix and the mismatch penalty (MMP) which is the energy paid for incorporating a monomer in a helix of its nonpreferred helicity. The quality of the fits for the CD data allows us to obtain a precise set of values for helical co-assemblies with and without **a-BTA** and to compare them with the data published in the literature for other helical systems (Table 1). Strikingly, the value of HRP doubles in the presence of **a-BTA** (from 11.0 to 22.1 kJ.mol^{-1}) while the MMP value is not impacted. The energetic values determined from the fit are actually "effective HRP and MMP values"[25] which likely reflects the average of the values of each BTA partner in the co-assemblies. Even though an achiral monomer may be anticipated to lower the helicity as it exhibits no chiral preference,[25] our data show that the effective HRP value in the presence of **a-BTA** is actually very high and this is possibly due to (i) a high conformational rigidity and (ii) the formation of strong intermolecular interactions with the other BTA monomers. Compared to previously reported BTA mixtures, the better chirality amplification properties observed in the present system is likely related to its higher HRP value (Table 1).[20,21e] BTA helices embedding **a-BTA** exhibit a similar extent of amplification of chirality than triphenylamine trisamide[15h] and bisurea[16a,34] based assemblies which is well substantiated by their remarkably close energetic parameters.

Asymmetric catalysts built on an extremely chirally-amplified helical backbone. We previously found that helical co-assemblies with an excess of **(*S*)-BTA** relatively to **l1-BTA** provided 1-(4-nitrophenyl)ethanol (NPnol) with 54±2% *e.e.* when applied in the copper-catalysed hydrosilylation of 1-(4-nitrophenyl)ethanone (NPnone) at 293 K (reaction scheme in Figure 4).[22,24b] We now probe whether the generation of homochiral helices in the presence of **a-BTA** as determined by CD spectroscopy also holds for catalytic mixtures. Except otherwise stated, catalytic experiments are implemented at a concentration in [**l1-BTA**] of 16.1 mM, a catalytic loading of 3.0 mol% in [$Cu(OAc)_2{\cdot}H_2O$], with $PhSiH_3$ acting both as an activator of the copper precatalyst and as a reducing agent.[35] For S&S-type catalytic mixtures without **a-BTA**, the optical purity in NPnol increases non linearly with the fraction of **(*S*)-BTA** present in the catalytic mixture (16 µM≤ [**(*S*)-BTA**]≤ 18.4 mM), but no plateau is reached (|*e.e.*$_{max}$|= 57.6%, Figure 4a, black curve). Conversely, in presence of **a-BTA** ([**l1-BTA**]/[**a-BTA**]= 1), a plateau is reached with a concentration in **(*S*)-BTA** of 160 µM ($f_{(S)\text{-BTA}}$= 0.50%, |*e.e.*$_{max}$|= 51.4%), and 98% of the plateau value is achieved with only 80 µM of sergeant ($f_{(S)\text{-BTA}}$= 0.25%, |*e.e.*|= 50.4% Figure 4a, red curve). This is in good agreement with the minimal fraction of **(*S*)-BTA** required to get homochiral helices as probed by CD spectroscopy. This drastic effect of **a-BTA** on the selectivity is not related to a change in the total BTA concentration since doubling the concentration in **l1-BTA** (without additive) has no significant influence (compare blue and black curves in Figure 4a). In fact, a remarkable correlation is found between the selectivity and the optical purity of the supramolecular helices as shown by the similarity of their curves as a function of $f_{(S)\text{-BTA}}$ (Figures 4b). It demonstrates that the enhancement of the enantioselectivity observed at low $f_{(S)\text{-BTA}}$ values in presence of **a-BTA** is related to its ability to promote the formation of homochiral helices. The only discrepancy arises for mixtures containing a higher fraction of **(*S*)-BTA** since the optimal selectivities with and without additive slightly differ, 51.4% and 57.6% *e.e.*, respectively, despite the respective helices being homochiral. We assume that this gap is related to a slight difference in the conformation of the PPh_2 moiety and the related copper catalyst that modifies the energetics of the enantiodiscriminating event without affecting the optical purity of the helical main chain.

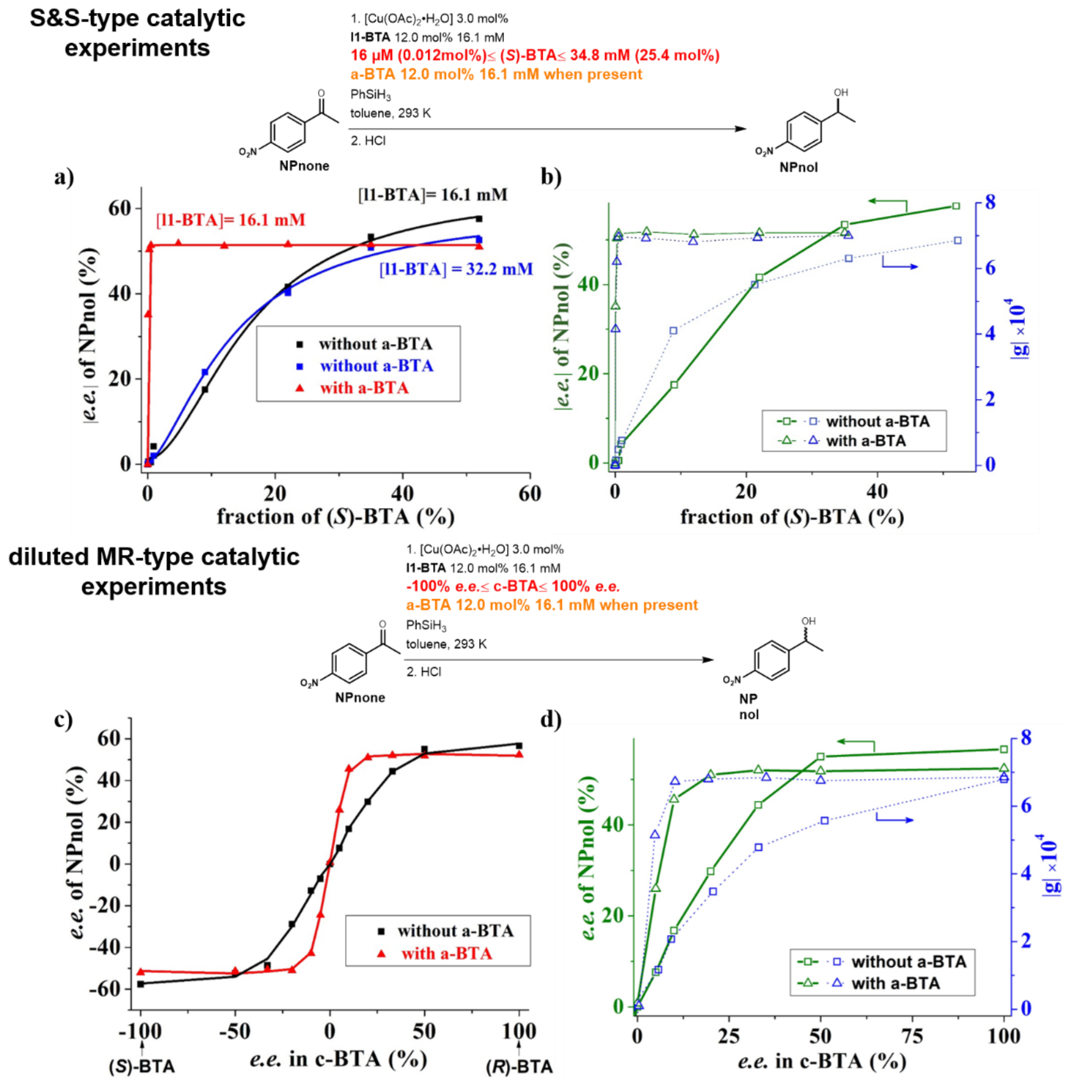
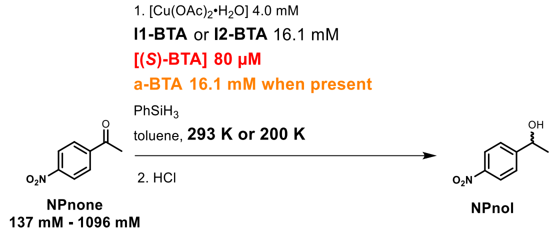


Figure 4 Asymmetric catalysis with S&S- and diluted MR-type helical catalysts (293K). a) Enantioselectivity in NPnol (±1%) versus the fraction of **(*S*)-BTA** in the catalytic mixtures with and without **a-BTA**. Conditions: see the reaction scheme and SI. b) Plot of the enantioselectivity in NPnol and of the Kuhn anisotropy factor versus the fraction of **(*S*)-BTA** in the catalytic mixtures. c) Enantioselectivity in NPnol (±1%) versus the optical purity in **c-BTA** in the catalytic mixtures with and without **a-BTA**. Conditions: see the reaction scheme and SI. d) Plot of the enantioselectivity in NPnol and of the Kuhn anisotropy factor versus the optical purity in **c-BTA** in the catalytic mixtures. Zoom on the scalemic mixtures biased in **(*R*)-BTA**. Conversion >99% was obtained for all catalytic experiments as determined by GC and ^{1}H NMR analyses. The optical purity was determined by GC analysis, *e.e.* are set as positive and negative when (*S*)-NPnol and (*R*)-NPnol are the major enantiomers, respectively. Lines are guides for the eye.

The effect of the achiral BTA additive on the selectivity was also probed for diluted MR-type catalytic mixtures ([**c-BTA**]= 18.4 mM). Whilst reaching the optimal selectivity requires a significantly optically-enriched mixture of BTA enantiomers in absence of **a-BTA** (*e.e.* in **c-BTA**≥ 50% *e.e.*, black curve in Figure 4c), a plateau is reached with a 20% *e.e.* scalemic mixture in presence of **a-BTA** ($|e.e._{max}|$= 51.7%, red curve). A mixture in **c-BTA** slightly biased from the racemic mixture (10% *e.e.*) yields (*S*)-NPnol (+44.0% *e.e.*) and (*R*)-NPnol (-42.4% *e.e.*) when **(*R*)-BTA** and **(*S*)-BTA** are the major enantiomers, respectively. The degree of selectivity provided by the catalyst is directly related to the optical purity of the supramolecular helices probed by CD spectroscopy, excepting that, again, homochiral helices with and without **a-BTA** provide slightly different selectivities (51.6% and 57.0% *e.e.* respectively, Figure 4d).

The results obtained with S&S-type helical catalysts have been further investigated (Table 2). Significant selectivities are found for catalytic mixtures containing very low amounts of **(*S*)-BTA** monomers. More specifically, the addition of **a-BTA** to the mixture with as low as 80 μM of sergeant ($f_{(S)\text{-BTA}}$= 0.25%) switches the state of the helical catalyst from non selective (*e.e.*< 1%) to significantly selective (−50.4% *e.e.,* entries 1 and 2). The fraction of **(*S*)-BTA** (relatively to **l1-BTA**, 0.5%) and its catalytic loading (relatively to NPnone, 0.06 mol% *i.e.* 600 ppm) are *ca.* fifty times and equal, respectively, to the higher chirally-amplified helical catalysts reported in the literature.[24a,36] Optimization of the catalytic system was pursued by changing the nature of the BTA ligand and the reaction temperature. A BTA ligand with methyl groups at the *meta* positions of the aromatic rings attached to the phosphorus atom, **l2-BTA** (Scheme 2), displays higher selectivity than **l1-BTA** (entry 3) at 293 K. Upon lowering the temperature to 200 K, the effect of **a-BTA** on the selectivity provided by **l2-BTA** is remarkable. Indeed, the selectivity rises from <3% *e.e.* to −90%

Table 2 Optimization of S&S-type helical catalysts.



Entry	BTA ligand	T	[a-BTA] (mM)	[NPnone] (mM)	(S)-BTA loading in ppm	e.e.±1% in NPnol (%)
1	I1-BTA	293 K	-	137	600	0.5
2	I1-BTA	293 K	16.1	137	600	−50.4
3	I2-BTA	293 K	16.1	137	600	−66.5
4	I2-BTA	200 K	-	137	600	−2.5
5	I2-BTA	200 K	16.1	137	600	**−89.5**
6	I2-BTA	200 K	16.1	137	600(a)	**90.6**
7	I2-BTA	200 K	16.1	1096	75(a)	73.8

Catalytic loading in **(*S*)-BTA**= [**(*S*)-BTA**]/[NPnone]. Conversion >99% was obtained for all catalytic experiments. The optical purity of NPnol was determined by GC analysis, *e.e.* are set as positive and negative when (*S*)-NPnol and (*R*)-NPnol are the major enantiomers, respectively. (a) **(*R*)-BTA** was used instead of **(*S*)-BTA**.

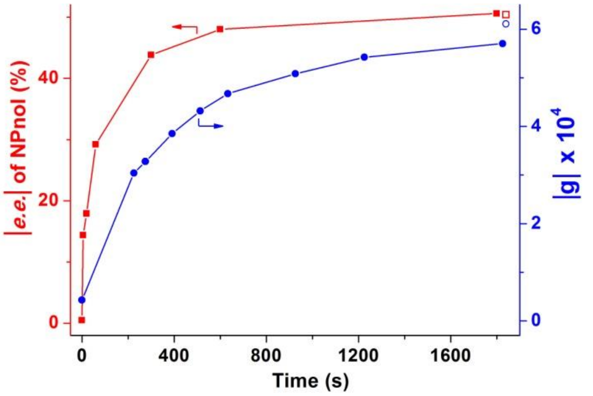


Figure 5 Kinetics related to the emergence of selectivity and homochirality. Plot of the enantioselectivity in NPnol (red curve) and of the g^{295} values (blue curve) versus aging time for the mixture with $f_{(S)\text{-BTA}}$= 0.25%. Conditions for catalysis: see Table S9. Conditions for CD analyses: see Table S5. The empty red square and the empty blue circle correspond to the enantioselectivity and the g^{295}.value, respectively, of a solution of identical composition but heated to reflux prior to analysis.

e.e. allowing both enantiomers of NPnol to be obtained with high levels of enantiopurity (entries 4-6). The extent of selectivity that emerges from this system (Δ*e.e.*= 87%) is higher than that observed for the reference ligand **I1-BTA** (Δ*e.e.*= 69%) under the same conditions (Table S8). The system remains active at remarkably low loadings in Cu and **BTA (*S*)-Cha** (0.38 mol% and 75 ppm, respectively) at the cost of a limited drop in enantioselectivity (−74% *e.e.*, entry 7). Further data on this optimization study are compiled in Table S8.

Probing the dynamics of the formation of chirally-amplified helices. It might be questioned whether the amplification of chirality that emerges after the addition of the achiral BTA is dynamic in nature *i.e.* whether it simply occurs upon mixing the different partners or whether it results from a complex kinetically frozen state. The kinetics involved in the formation of the selective helical catalysts were probed by performing a set of catalytic experiments as follows: NPnone, toluene, **I1-BTA**, $[Cu(OAc)_2]\cdot H_2O$, **(*S*)-BTA** (80 µM, $f_{(S)\text{-BTA}}$= 0.25%) and **a-BTA** which acts as a "rigidifier" of the assembly were mixed at 293 K followed by, after a given aging time, $PhSiH_3$ which triggers the catalytic reaction. No selectivity is observed without the achiral additive under these conditions. A significant level of selectivity (−29% *e.e.*) is achieved when the components are aged for 1 minute prior to the catalytic event (Figure 5, red curve). From then, the selectivity increases slowly but steadily until reaching −50.6% *e.e.* when the components are aged for 30 minutes before $PhSiH_3$ addition. This selectivity is almost identical (−50.4% *e.e)* to the one obtained when a solution of the same partners is heated prior to catalysis indicating that the same thermodynamic state is reached from molecularly dissolved BTAs (heated solution) or from assembled BTAs (room temperature solution). The dramatic effect of the additive on the selectivity is efficiently probed by these experiments since it occurs on a much longer time scale (30 minutes) than the catalytic reaction (< 2s).[24b] This effect can also be probed by means of CD and UV-Vis spectroscopy. **a-BTA** was added to a mixture of **I1-BTA**, $[Cu(OAc)_2]\cdot H_2O$ and **(*S*)-BTA** ($f_{(S)\text{-BTA}}$= 0.25%) in toluene, the solution was stirred for 20 seconds and full CD (Figure S7a) and UV-Vis (Figure S7b) spectra were recorded at regular times (0−1825 s). The evolution of the g^{295} values extracted from these spectra (Figure 5, blue curve) as a function of the time of mixing is similar to that of the catalyst selectivity indicating that emergence of chirality and selectivity are concomitant phenomena. Conversely, all recorded UV-Vis absorption spectra are virtually identical and similar to the one of the heated solution with the same composition (Figure S7b). This might be explained by a fast incorporation of **a-BTA** into the stacks followed by a slower disappearance of the helix reversals. Previously, exchange rate between sergeants and soldiers from their individual helical BTA assemblies was reported to occur on the time scale of seconds.[21d,24b] The slower kinetics associated with the formation of highly chirally-amplified helices likely originates from the fact that in the present system the additive triggers a set of conformational changes including the removal of the helix reversal(s) which requires an important reorganization of the monomers within the co-assemblies.

Discussion

The importance of helix reversals in controlling the optical purity of poly(isocyanate)s in dilute solutions had been recognized from the seminal work of Green and co-workers.[6a] A steep increase in the optical activity of an alkane solution of a S&S-type poly(isocyanate) copolymer upon lowering the temperature was attributed to a reduction of the helix reversal population.[6a,37] Not surprisingly, helix reversals also play a key role in determining the extent of amplification of chirality in dynamic supramolecular helices.[16a,20,21c,21e,25,31,33a] Extremely high levels of amplification have been reported for molecular helices in gels[15b,15e,15f,15i,16b,17f,18b,18c] and in liquid crystalline states[38] or for one-dimensional assembly of covalent helices.[14f] It was surmised that defects present in isolated helical chains would be excluded upon interactions of the chains.[6a] Chirality amplification is expected to be greater when both the HRP and the length of the helices are large.[33] However, few studies have addressed the possibility of tuning the number of helix reversals in supramolecular systems,[15h,20,21e,32,33d,39] mostly because a significant alteration would require changing the nature of the interactions governing the assemblies.[20]

In the present system, amplification of chirality occurs in isolated BTA helices for which the helix reversals are excluded upon incorporation of the achiral BTA monomer. Comparison of spectroscopic and scattering analyses with and without this BTA additive are consistent with no or limited modification of the geometry of the helices at the nm scale but subtle changes in the conformation of the amide functions and the PPh_2 group are detected which can be attributed to a more regular organization of the monomers within the stacks in presence of the additive. Previous rheological[40] and spectroscopic[21d] studies demonstrated that homochiral BTA helical assemblies possess increased correlation lengths (*i.e.* distance between defects/helix reversals) and increased stability relatively to racemic mixtures of BTAs. The stabilization of the helices incorporating **a-BTA** as determined by VT-CD experiments (Figure S6) goes along this line except that here the decreased number of defects is triggered by an achiral monomer, not an enantiopure one. The relatively slow kinetics associated with the emergence of homochirality can thus be attributed to a series of conformational changes and monomer reorganization within the stacks that are necessary for this exclusion of the helix reversals. Compared to other amino acids, quaternary amino acids (such as Aib, aminoisobutyric acid) severely restrict the possible rotation about the N-C$^\alpha$ and C$^\alpha$-C' bonds and, as a consequence, promote helical conformation in relatively short peptide sequences.[41] We hypothesize that **a-BTA** which also possesses an α,α-dialkylated Aib type moiety has a similar effect in restricting the conformation of the hydrogen-bonded amide functions thus preventing the formation of the defects in the supramolecular helical assemblies.

Introducing intrinsically achiral catalytic monomers into the preferred-handed helical scaffold of covalent or supramolecular polymers enables the formation of an enantio-enriched product whose configuration is determined solely by the handedness of the helices.[7,24,36,42] A particularly remarkable advantage of such a catalytic system is that catalytic activity and selectivity arise from different chemical species and, consequently, the amount of chiral inducers relatively to the catalytically active species (S&S ratio) and to the substrate (catalytic loading in mol%) can be drastically reduced. Ultimately, asymmetric helical catalysts which get rid of chiral inducers have been reported with the limitations that degree of enantioinduction is low (*e.e.*≤ 46%) and that the configuration of the major enantiomer is left to chance.[43,44] In the present system, the enantioselectivity provided by the copper centres is greatly affected by the incorporation of the achiral additive into the S&S-type and diluted MR-type helical assemblies. For mixtures with 0.5% of sergeant, **a-BTA** switches the state of the copper catalysts from non selective (< 3% *e.e.*) to selective (up to 90% *e.e.*) and this can be directly related to the generation of homochiral helices in which all copper centres are positioned in a similar chirally biased environment. The co-assembly process leading to the formation of the helical catalysts is under thermodynamic control leading to excellent reproducibility of the catalytic results and control of the configuration of the enantio-enriched product by the nature of the sergeant. Both enantiomers are accessed in highly enantio-enriched form (90% *e.e.*) with 600 ppm of sergeants (relatively to NPnone) and significant enantioselectivity (74% *e.e.*) is still obtained with only 75 ppm of sergeants. Long-range chiral information transfer in these helical catalysts allows chirality inducers to be employed at drastically lower amount than the catalytic sites thus offering a strategy that circumvent the selectivity – activity paradigm, *i.e.* it paves the way towards a new class of active asymmetric catalysts which operate at ppm levels of chiral species.[3b,45]

Conclusion

In conclusion, we disclose the ability of an achiral BTA monomer to fully bias the helicity of co-assemblies that are otherwise almost racemic in its absence, and which contain as little as 0.5% of sergeants (S&S effect) or a 10% *e.e.* scalemic mixture of enantiopure co-monomers (diluted MR effect). This strategy, albeit counterintuitive at first sight, improves both the S&S and the diluted MR effect by two orders and one order of magnitude, respectively, thus reaching levels of chirality amplification that have been achieved by the best supramolecular single helices reported to date. Precise investigation of the assembly behavior of the different BTA partners by multifarious analytical techniques reveals that each monomer plays a precise role towards the generation of homochiral co-assembly: the BTA ligand forms long but racemic and disordered stacks that favor the co-assembly of the other BTA monomers, the enantiopure co-monomer imposes a preferred-helical conformation to the BTA assemblies and finally the achiral BTA additive reduces the number of defects in the co-assembly. The last point is reflected by the higher stability of the helices incorporating the achiral additive. The helical catalysts generated from these homochiral co-assemblies display significant selectivities (up to 90% *e.e.*) despite the limited amount of sergeant (ppm levels relatively to the substrate) or low optical purity of the sergeant (10–20% *e.e.*) present in the catalytic mixture. Further work is directed towards further control of the microstructure of supramolecular co-assemblies in order to get structurally-complex multicomponent systems with increased dynamicity and emerging functionalities.[46]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Chart S1, Figures S1-S7, Tables S1-S9, General procedures, Chiral GC analyses, Synthetic procedures and NMR spectra. (PDF)

AUTHOR INFORMATION

Corresponding Author

*matthieu.raynal@upmc.fr.

Author Contributions

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

Notes

The authors declare no competing financial interests.

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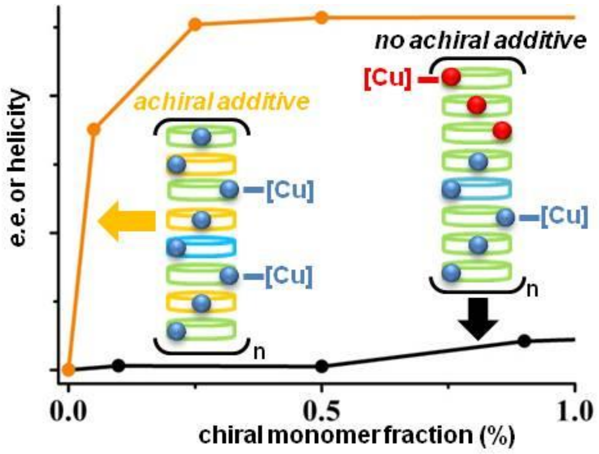
e.e. or helicity
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