https://doi.org/10.17952/37EPS.2024.YIF02

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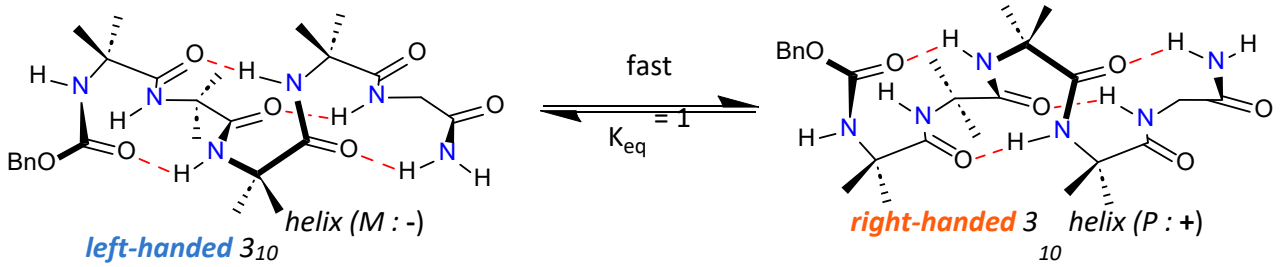
Bimodal Use of Chiral α-Trifluoromethylalanine in Aib Foldamers: Study of the Position Impact Towards the Helical Screw-Sense Preference

Young Investigators Mini Symposium flash communications – *29th August 2024*

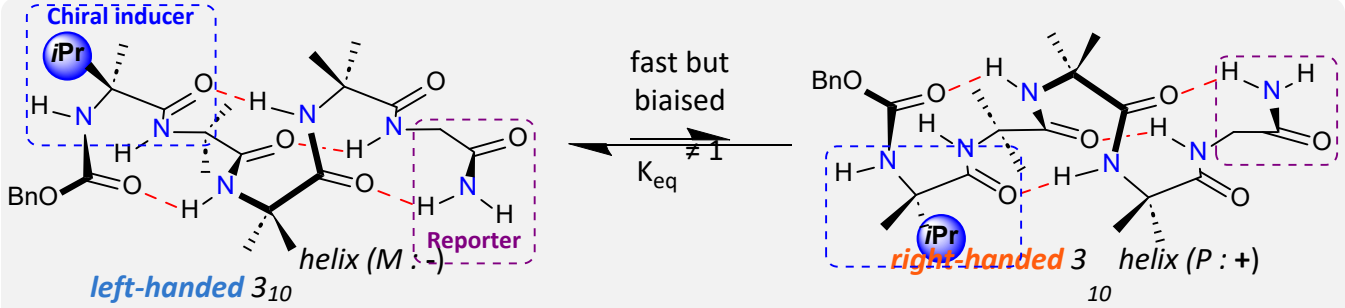
37th EPS European Peptide Symposium
14th IPS International Peptide Symposium
25 - 29 August 2024
Satellite Workshop 30 - 31 August 2024
Florence, Italy- 2024

α-Aminoisobutyric acid (Aib) oligomers

- Formation of stable right- (***P***) or left-handed (***M***) $\mathbf{3_{10}}$ helices



Nature **2022**, *607*, 387-392.

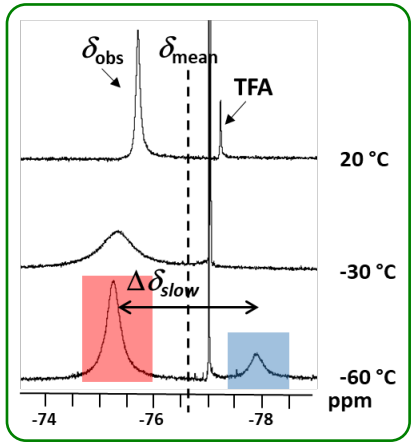


helical excess = **+95%** *(h.e.)*

J. Org. Chem. **2014**, *79*, 10, 4659–4675.

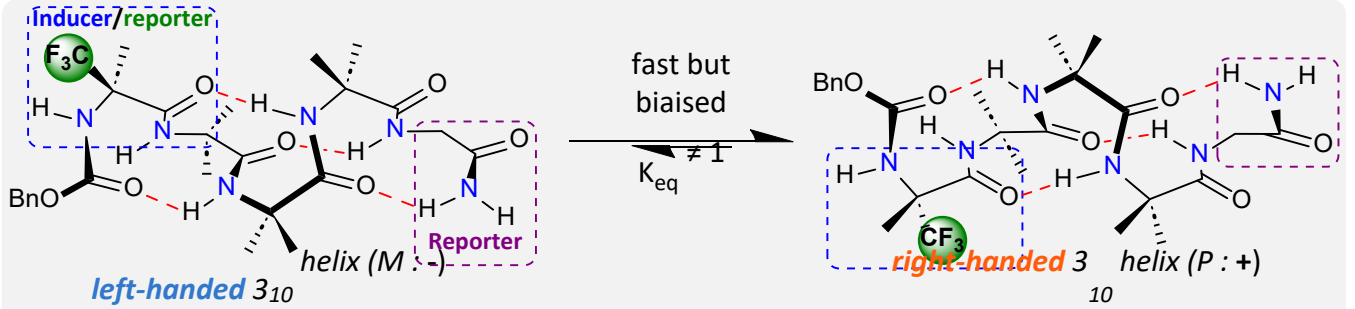
The chiral inducer promotes a screw-sense preference

X These systems need independently a **chiral inducer** along with an NMR **reporter**



h.e. by **^{19}F NMR** fits with results obtained through **^{1}H** NMR **reporter**

✓ **α-TfmAla** as a **chiral inducer** and **^{19}F** NMR **reporter**

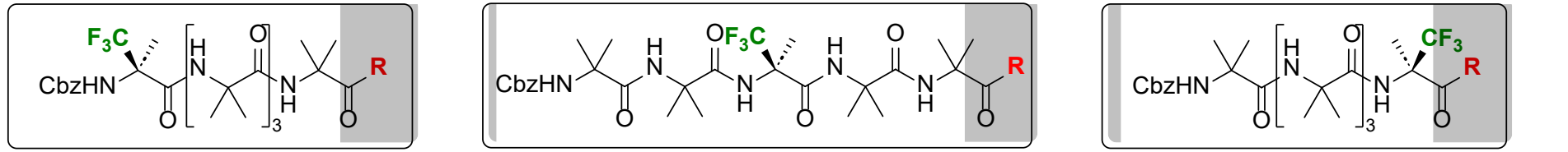


helical excess = **-80/-83%** *(h.e.)*

Chem. Eur. J. **2022** e202103887.

Bimodal use of α-TfmAla : study of the position impact

***N*-terminal** | **Middle** | ***C*-terminal**



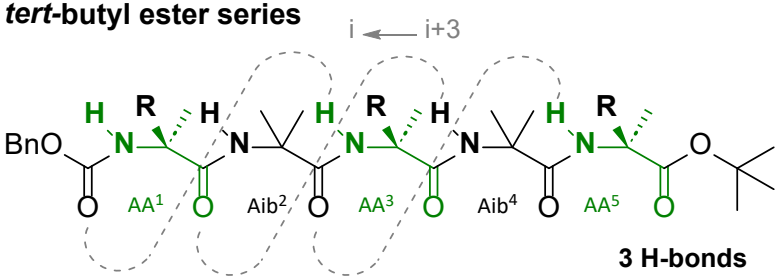
R = -O*t*Bu
R = -NH*t*Bu

88% ← ↗ ***h.e*** & $n_{H\text{-bond}}$ → **50%**

R = -CF_3 or Me

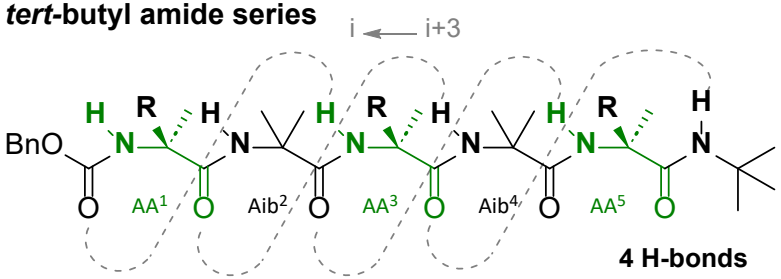
AA = Aib or α-TfmAla

***tert*-butyl ester series**

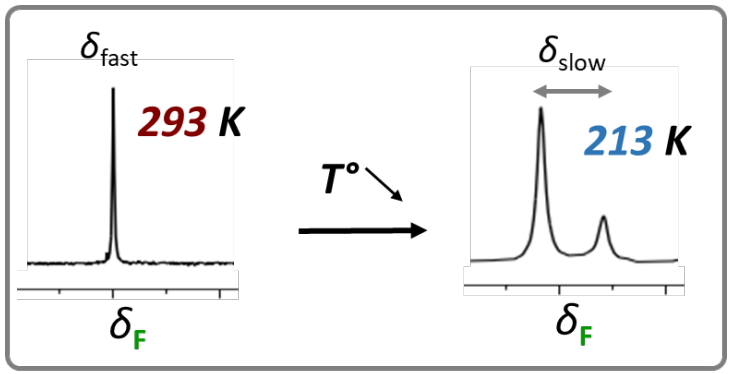


3 H-bonds

***tert*-butyl amide series**

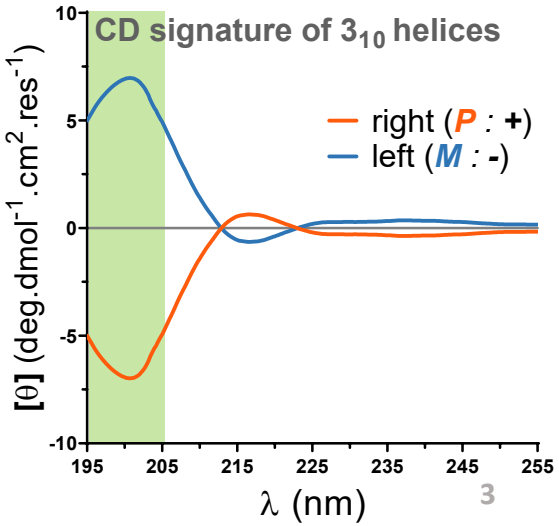


4 H-bonds



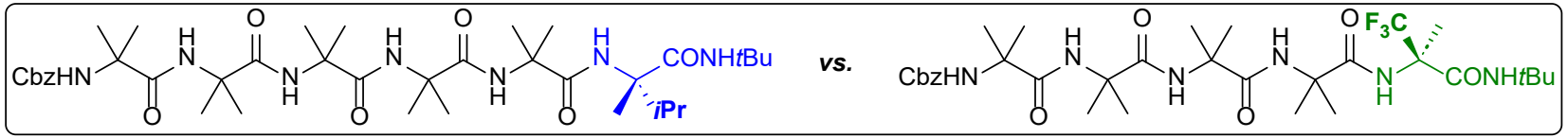
^{19}F NMR allows **helical excess determination at low T°**

CD allows **screw-sense preference determination**

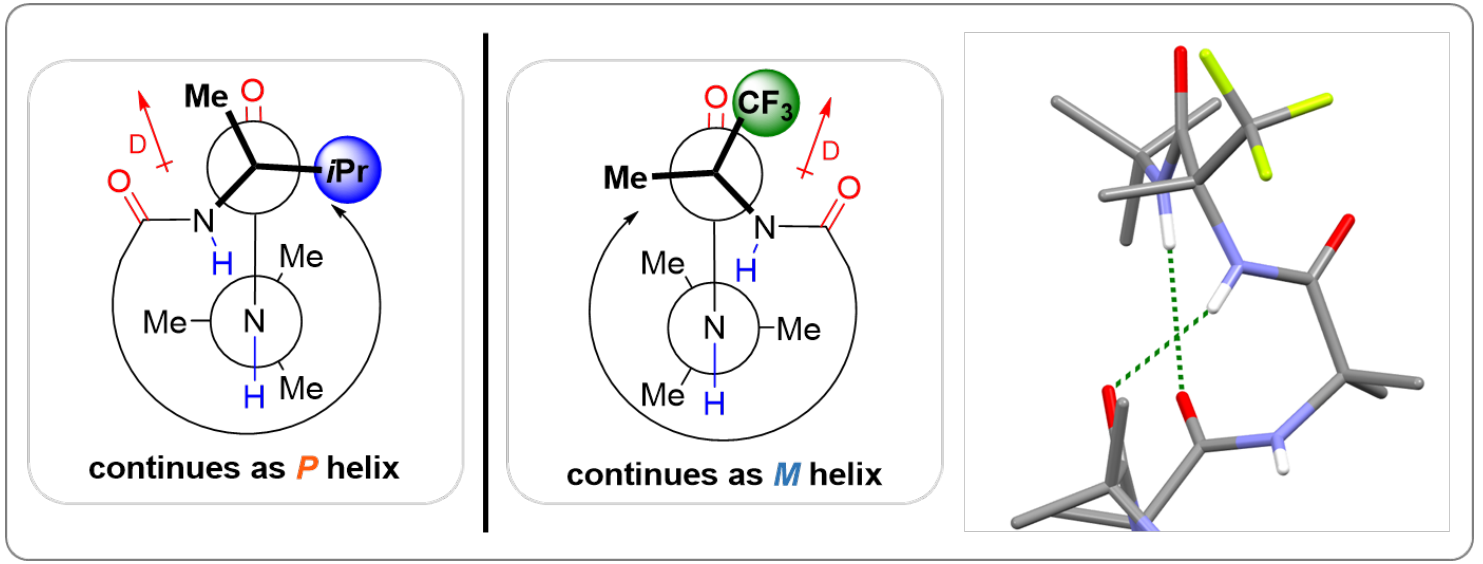


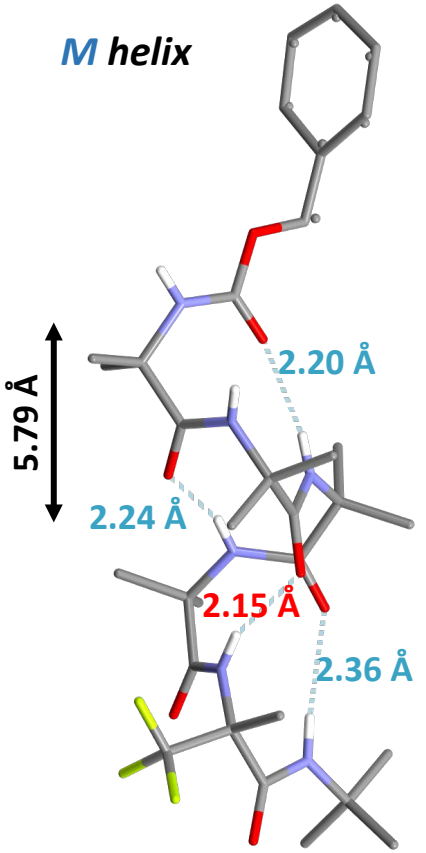
Chem. Eur. J. **2024**, *30*, e202400540.

Helical screw-sense inversion : dipole alignment of the –CF_3 group



Chem. Commun. **2014**, *50*, 7949-7952





- Stereo-electronic effect of **-CF_3** group seems to be the principal contribution
- Dipole alignment observed in the solid state
- ✓ Versatility of **α-TfmAla** residue to induce and determine helical excess in Aib oligomers

Want to learn more ?

Chem. Eur. J. **2024**, *30*, e202400540.