Diastereoselective Synthesis of Open-Chain Secondary Alkyllithium Compounds and Trapping Reactions with Electrophiles

G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, P. Knochel,
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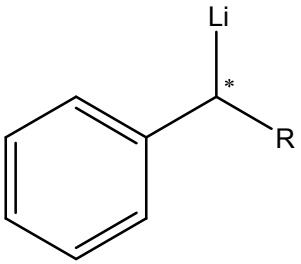
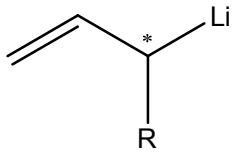
David PIERROT, STeRéO group meeting, 20.01.14

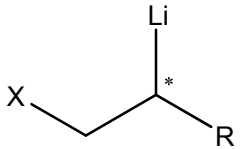
Stereoselective generation of secondary alkyl lithium compounds



benzylic



allylic



α-heteroatom-substituted

R = alk
X = S, N, O

Stabilized alkyl lithium compounds have been widely studied

The behaviour of the unstabilized ones remains a challenge.

To learn more about the stereochemical behaviour of alkyl lithium compounds:
A. Basu, S. Thayumanavan, *Angew. Chem.* **2002**, *114*, 716-738
W. K. Lee, Y. S. Park, P. Beak, *Acc. Chem. Res.* **2009**, *42*, 224-234

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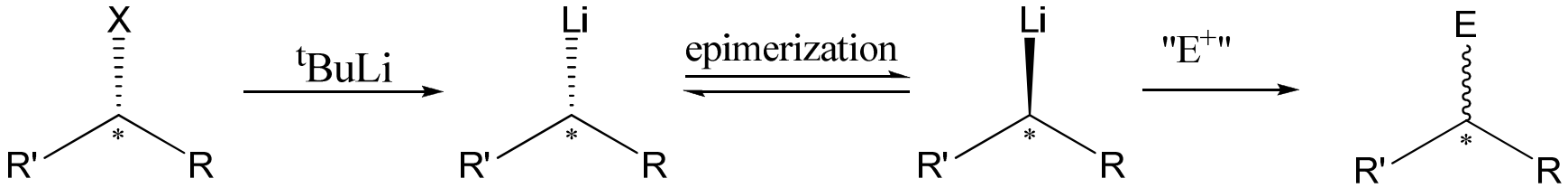
Preparation of unstabilized secondary alkyl lithiated compounds



Unstabilized alkyl lithium compounds have been less studied

How can these compounds be stereoselectively generated ?
How do they behave ?
How long do they live ?

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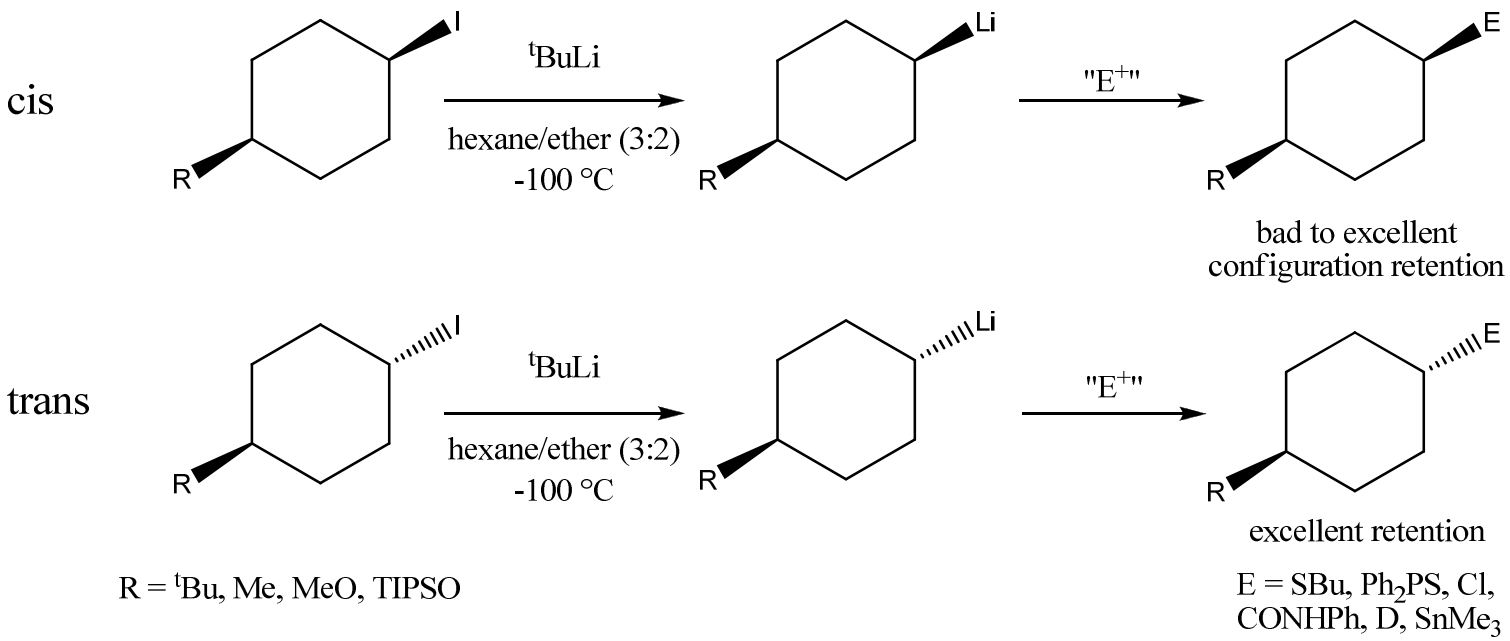
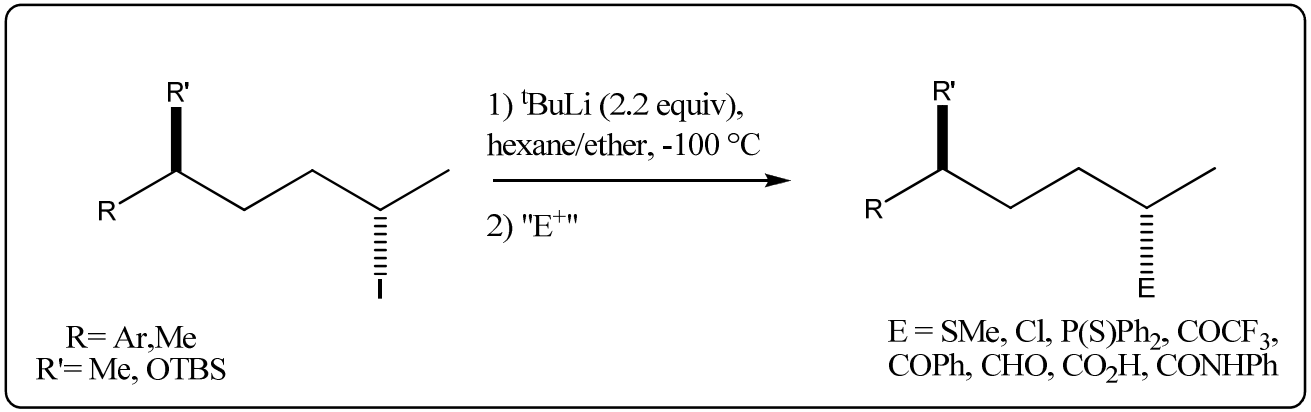
Previously, in the Knochel group

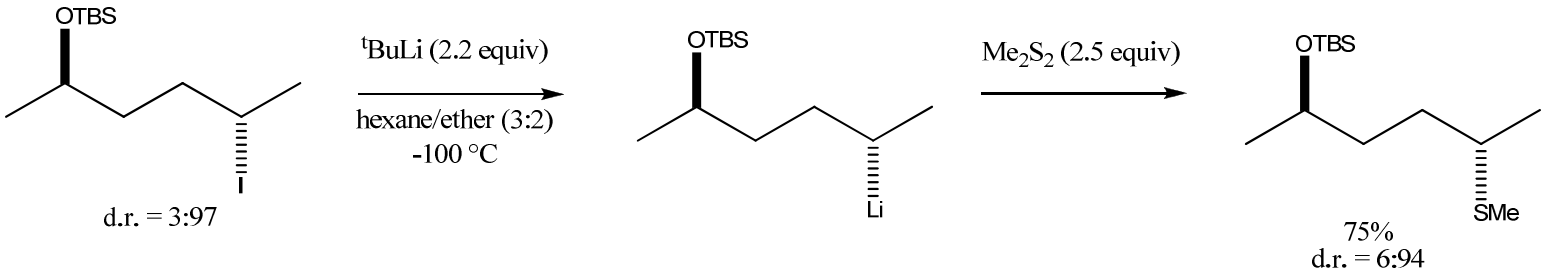


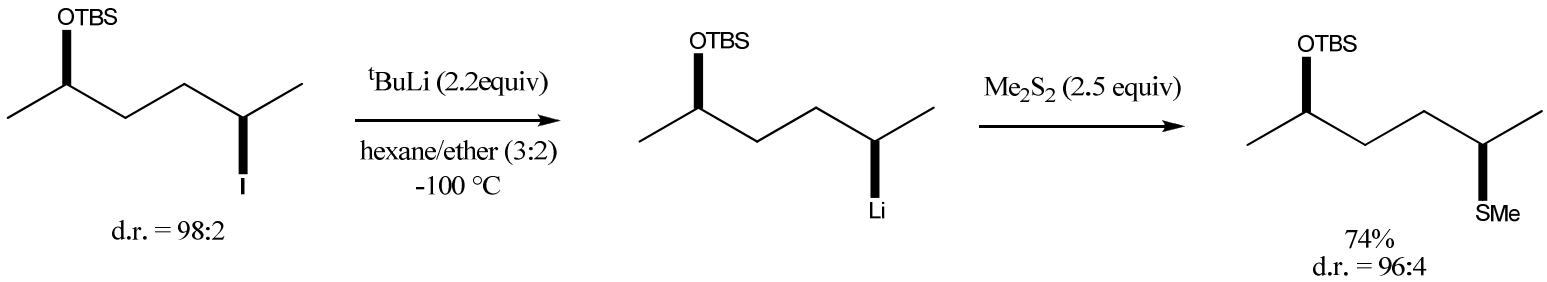
Poorest retention results were obtained with a methoxy (stabilizing) group.

S. Seel, G. Dagousset, T. Thaler, A. Frischmuth, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 4614-4622

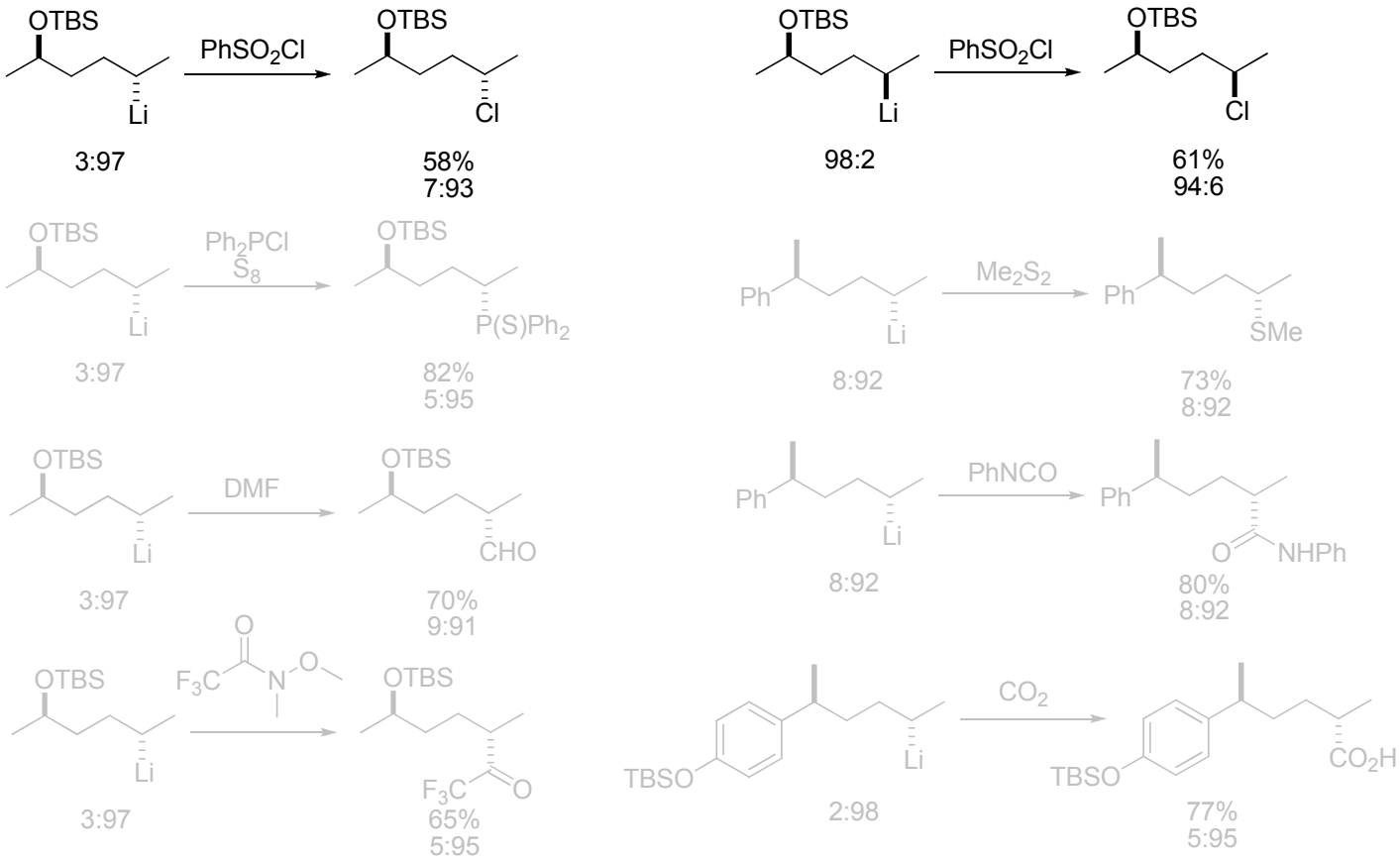
Experiment design







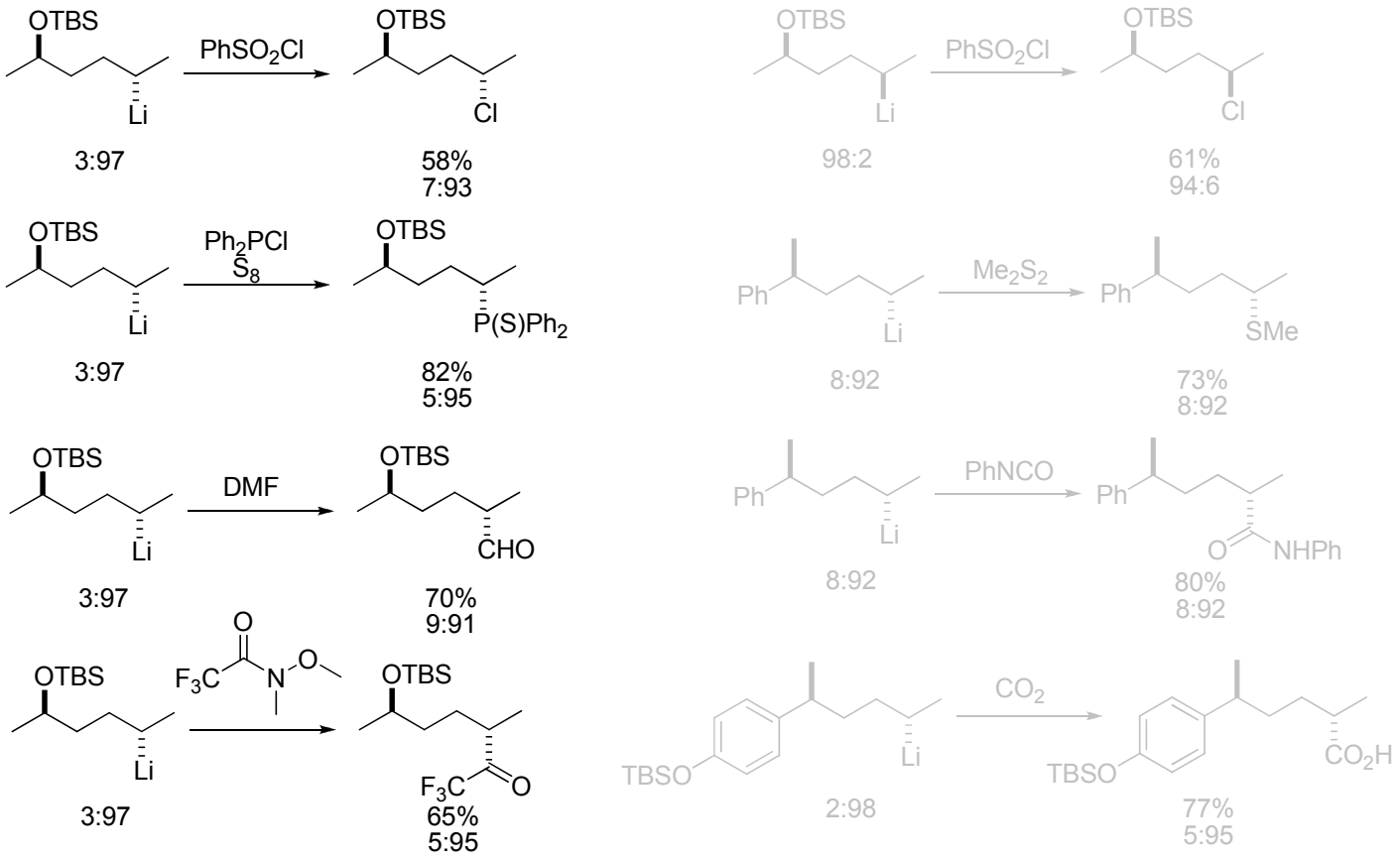
Selected examples



Reaction conditions: hexane/ether, -100 °C, 5 min

Stereoretention and reaction yields are slightly better starting from the syn compound.

Selected examples



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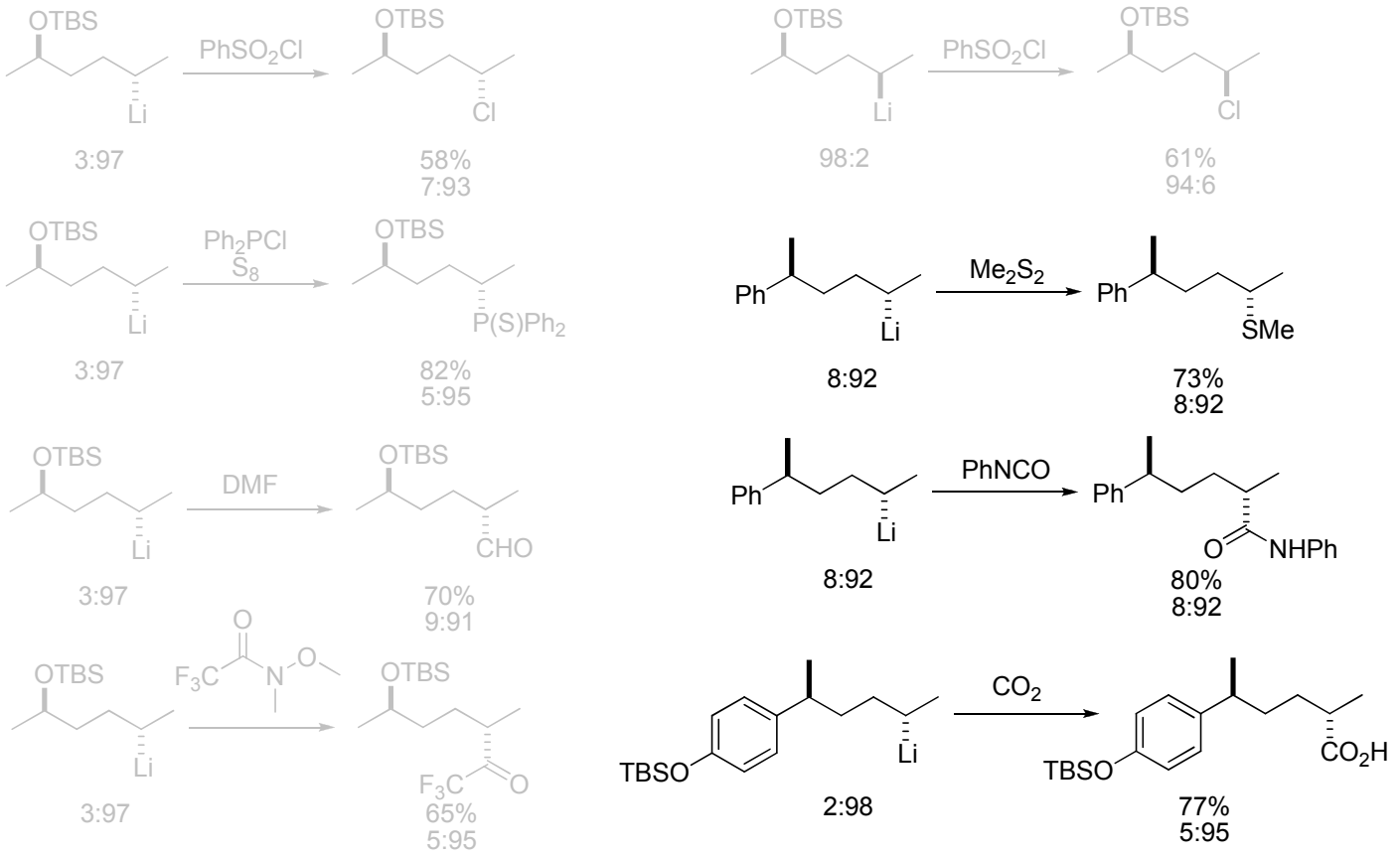

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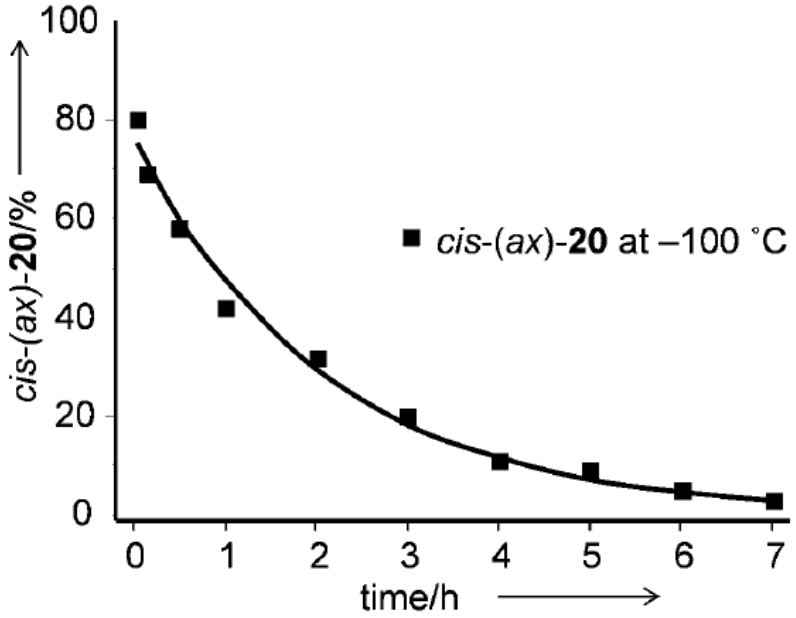
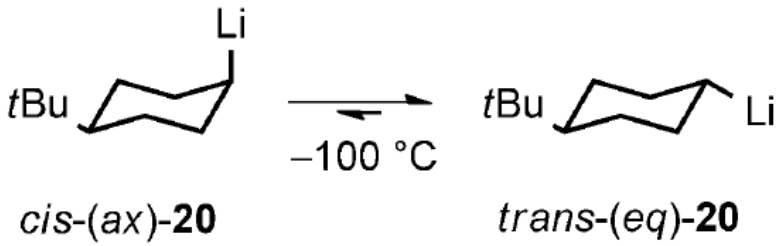
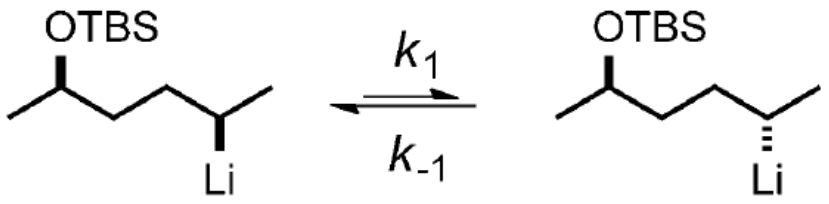
Thermodynamical study





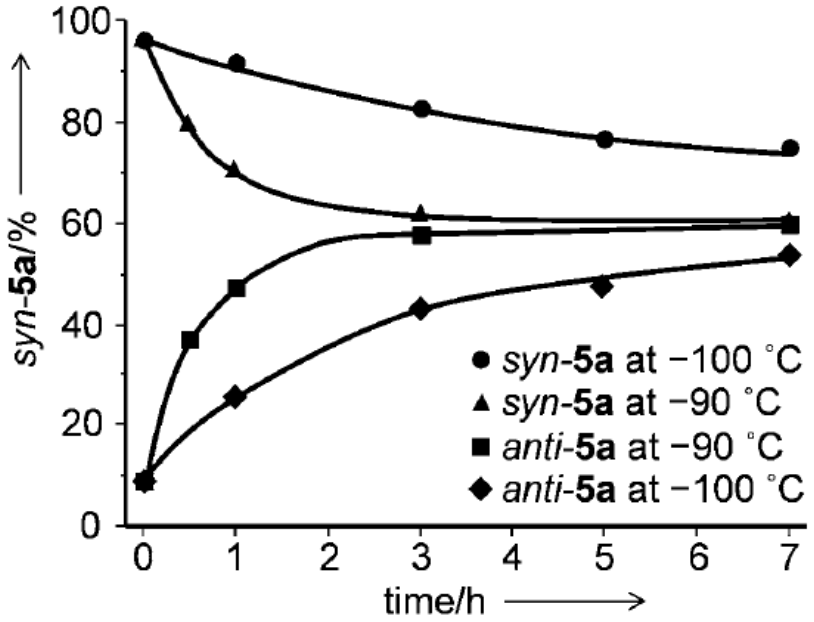
Thermodynamical study

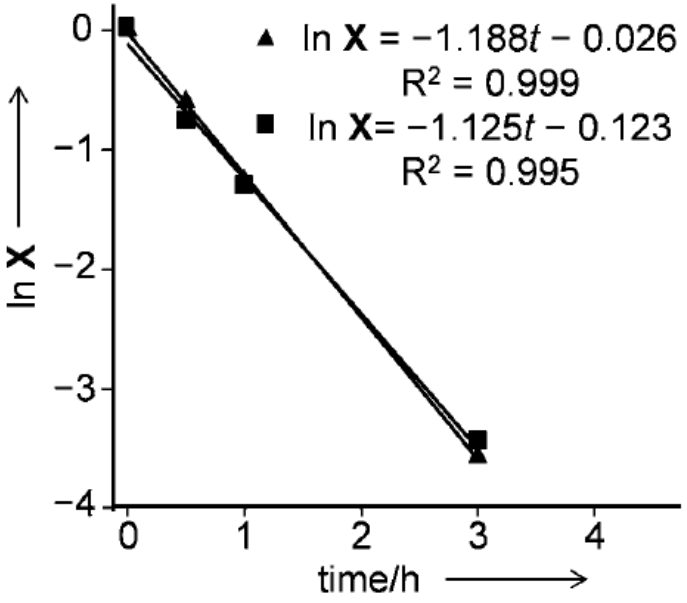


syn-**5a** *anti*-**5a**

$$\frac{d[syn]}{dt} = k_{-1}[anti] - k_1[syn]$$

$$\ln \frac{[\boldsymbol{syn}] - [\boldsymbol{syn}]^{\mathbf{eq}}}{[\boldsymbol{syn}]^{\circ} - [\boldsymbol{syn}]^{\mathbf{eq}}} = -(k_1 + k_{-1})\,t \quad (1)$$





$$\Delta G^{\circ}\,(T = -90\ ^{\circ}\mathrm{C}) = -RT\ln\frac{[anti]^{eq}}{[syn]^{eq}} = 0.62\ \mathrm{kJ.mol^{-1}}$$

Conclusion

- a wide and complete study
- synthetic application example ?
- why this test substrate design ?
- scope design


That's all Folks!