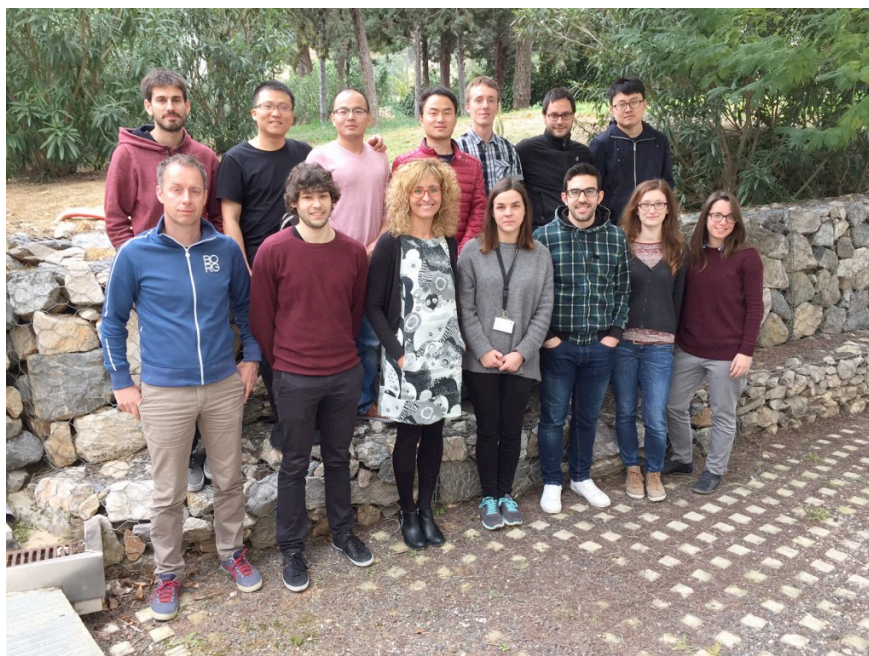


Kleij Research Group



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Abstract

Our research activities currently focus on the valorization/upgrading of carbon dioxide and renewable feedstocks into value-added organic molecules using rational organocatalytic and metal-mediated catalytic approaches. In order to achieve these goals we use highly functional organic cyclic carbonates as versatile and accessible synthetic precursors. A primary focus is on sustainable solutions thereby improving on (1) overall activity and chemo-selectivity, and (2) stereo-chemical features. Our targeted portfolio of organic structures include oxazolidinones,

CO₂-based (bio)polymers and more complex organic matter derived from stereo-selective or enantioselective coupling approaches; examples are substituted allylic compounds and chiral amino acid derivatives. An important part of our work puts attention to new catalyst design and efforts to reach a higher level of understanding concerning the observed reactivity/selectivity features by means of mechanistic and computational studies. Collaborations with the industrial sector having interest in bio-based polymers form also part of our work in order to be able to transfer technological advancements from bench to and beyond pilot scale.

CO₂ to Carbonates

In our ongoing quest towards the valorization of carbon dioxide towards the synthesis of derivatives useful from an organic chemistry context (*i.e.*, the valorization of CO₂), we have considered the use of both metal- as well as organocatalytic approaches to prepare heterocyclic compounds (cyclic carbonates/carbamates) from CO₂ and suitable epoxide precursors. One of these approaches is outlined in Figure 1 (novel organocatalytic potential), where cavitand based polyphenols are proposed as modular and easy to obtain catalytic materials for the formation of cyclic carbonates.

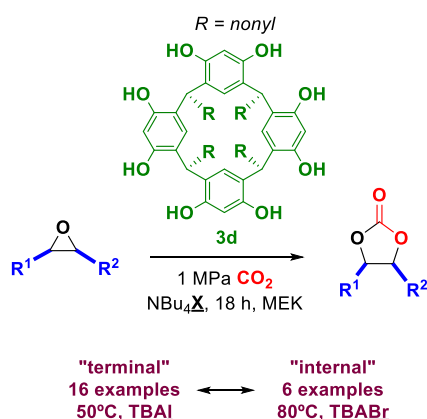


Fig. 1 – Cavitand based binary catalysts for the efficient formation of cyclic carbonates.

Most importantly, the cavitand based binary catalysts are among the first purely organic based systems that provide a solution for the coupling reaction of internal epoxides and CO₂ and thus help to provide more sustainable solution in this area of CO₂ catalysis (see: *ChemSusChem* **2016**, 9, 749).

In a separate project, we have focused on the implementation of a new approach towards CO₂ conversion by enabling an active role of the substrate in the activation of this small molecule. Epoxy alcohols/amines having a pendant OH/NH₂ group are able to activate CO₂ in a way reminiscent of the activation observed by the enzyme carbonic anhydrase, and in the presence of a simple, cheap and modular Al(III) complex the conversion of various "epoxy" substrates was carried out successfully. The principal results that were obtained relate to some unusual substitution patterns in the carbonate/carbamate structures (unprecedented tri-substitutions), but moreover, the approach could be extended to organic targets with a higher level of relevance including the use of a

diterpene scaffold (sclareol) and Toloxatone (Figure 2). The latter structure exemplifies that the catalytic strategy may be well suited towards the development of a wider series of oxazolidinones, pharmaceutically highly relevant scaffolds in modern drug discovery and development (see *ACIE* **2016**, 55, 3972).

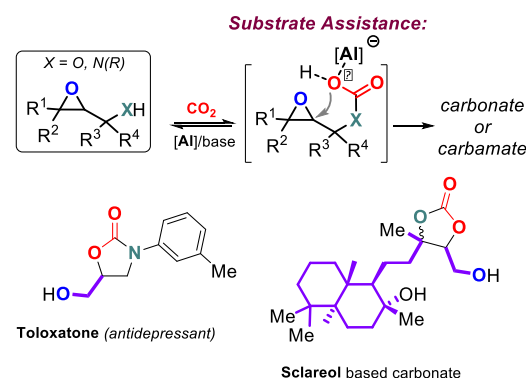


Fig. 2 – The use of a substrate-assisted CO₂ activation approach towards the synthesis of pharma-relevant synthons/compounds.

CO₂ to Fine Chemicals

The conversion of CO₂ into fine-chemicals that are of use in commercial settings is a clear example how to "upgrade" carbon dioxide. To this end, we have developed a novel approach that takes advantage over the wide experience we have attained over the years in the preparation of functional cyclic carbonates. In particular, vinyl-substituted cyclic carbonates are easy to prepare intermediates that can be activated by suitable Pd-catalysts. Upon activation, the cyclic carbonate is decarboxylated (–CO₂) thereby producing a highly reactive, ambivalent Pd-stabilized intermediate that can be intercepted by suitable electrophiles or nucleophiles.

We considered the formation of allylic amines as an interesting challenge using vinyl cyclic carbonates as their precursors. The stereo-selective preparation of such allylic amines, and specifically tri/tetra-substituted analogues remains elusive, and progress up to date has been limited in both scope and reactivity. However, we found that by appropriate tuning of the ligand (phosphine), metal precursor [Pd(II), Pd(0)] and reaction conditions (rt, DMF, *no* additive) we were able to selectively produce the (*Z*)-configured allylic amines (regio-selectivity towards the linear product >95% in all cases) with stereo-selectivities beyond 99% in >35 examples. More importantly, we found that tetra-

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substituted allylic amines (9 examples) were formed also exclusively as the (Z) isomers, which is unprecedented results compared to the state of the art in this area (see *JACS* **2016**, *138*, 11970).

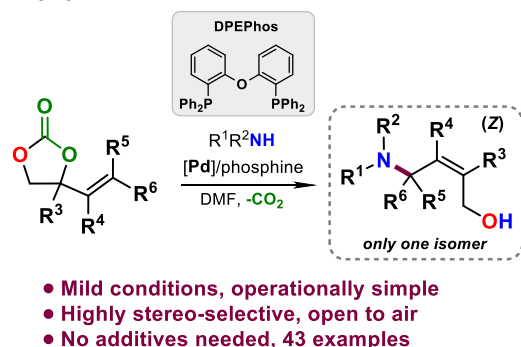


Fig. 3 – Stereo-selective formation of highly substituted (Z) configured linear allylic amines using Pd-catalysis.

Computationally, we found that a six-membered palladacycle is crucial towards the formation of the (Z) isomer, and possible interconversion between isomeric forms of Pd-based intermediates at a late stage of the catalytic cycle (i.e. pi-sigma-pi interconversion) is energetically less favored by at least 6 kcal/mol.

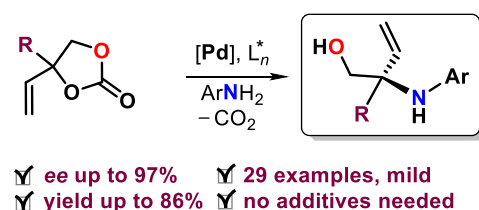


Fig. 4 – Asymmetric synthesis of branched α,α -disubstituted aryl-allylic amines featuring tertiary, tetra-substituted C-centers.

Apart from the formation of the linear allylic amine product, the nucleophilic attack of an amine onto a decarboxylated carbonate species can also occur with preference for the internal position of the allylic unit (i.e. formation of the branched compound); however, this is typically highly disfavored in Pd-catalysis and therefore seen as challenge without a suitable solution to date. We screened various ligands (mostly phosphoramidite based ones) to present a solution for this synthetic challenge and found that a proper choice of Pd-precursor, phosphoramidite ligand and reaction conditions (0°C, THF, open to air), a large series of branched α,α -disubstituted aryl-allylic amines could be prepared with high asymmetric induction up to 97% ee. It should be noted that these conversions (as for their linear analogues presented in Figure 3) do not require any (base)

additive nor special precautions therefore offering practical and attractive protocols for these pharma-relevant building blocks. Also, as far as we know this is the first general procedure for the preparation of chiral branched allylic amines based on Pd-catalysis, marking thus a significant step forward since the state of the art in the area utilizes more expensive Rh or Ir catalysis (see *JACS* **2016**, *138*, 14194).

CO₂/Renewables to Polymers

As a third major research line towards the valorization of renewables/CO₂, the ring-opening copolymerization (ROCOP) of epoxides with either (1) CO₂ or (2) cyclic anhydrides was evaluated. Limonene oxide (LO), being commercially available and cheap, is derived from the renewable and abundant terpene limonene. In order to provide copolymers from CO₂ with improved rigidity and thermal stability, terpolymerization of LO with cyclohexene oxide (CHO) and CO₂ was investigated. Various terpolymer grades could be prepared using Al(III) complexes combined with chloride nucleophiles as a binary catalyst. The incorporation kinetics of both epoxide monomers was followed to ensure the presence of both monomers throughout the polymer backbone. Up to 40% of LO could be incorporated by variation of the catalyst composition, reaction conditions and monomer ratio. Since LO has a double bond available for further manipulations, we induced cross-linking of the double bonds by thiol-ene click reactions triggered by radical initiation. The resultant cross-linked polycarbonate polymers were then evaluated and their thermal decomposition (T_d^{10}) and glass transitions (T_g) determined and compared against the parent polycarbonates. This comparison showed a marked increase in both T_d^{10} and T_g values (Figure 5). Thus, the incorporation of a functional, renewable monomer allows to fine-tune the properties of polycarbonates towards highly rigid structures useful in adhesives/coating applications (see *Macromolecules* **2016**, *49*, 6285).

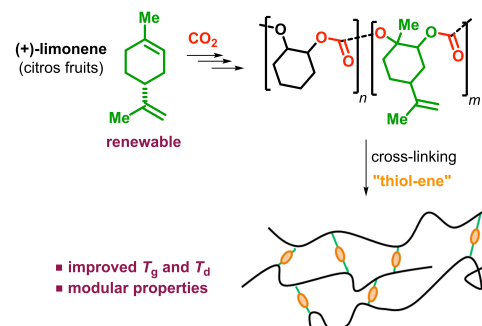


Fig. 5 – Cross-linking LO-based terpolymers to create thermally stable polycarbonate structures.

Polyesters with renewable content were prepared by combination of simple and accessible epoxides (propylene oxide, PO, and CHO) with various cyclic anhydrides (partially) derived from renewable, terpene-based resources. This afforded a wide series of polyesters with tunable glass transitions over a wide range from an unprecedented 66–184°C. Fe(III) and Al(III) catalysts were employed, with the Al(III) complexes typically giving slightly better results in terms of molecular weight, polydispersity and T_g values. The use of both systems allowed to control the ROCOP process with M_n values of up to XX. These combined data are the most promising ones in the context of aliphatic polyesters with potential in coatings and related applications. Some of the (partially) biobased polymers are currently under investigation in collaboration with industrial partners to exploit their full potential ((see *Macromolecules* **2016**, *49*, 6394)

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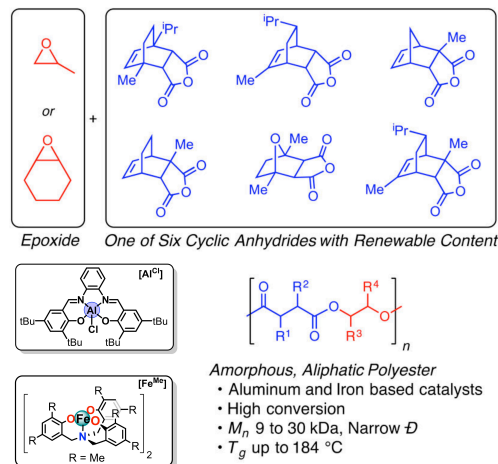


Fig. 6 – Partially renewable polyesters derived from cyclic anhydrides and aliphatic epoxides.

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