

## Research Group Kleij



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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 challenges. Our targeted portfolio of organic structures includes complex

organic carbonates, allylic derivatives, amino acids and propargylic compounds through innovative stereo-selective or enantioselective coupling approaches. An important part of our work puts attention to new catalyst design and efforts to reach a higher level of mechanistic understanding concerning the observed reactivity/selectivity features through experimental and computational studies. Interdisciplinary collaborations with the industrial in the area of biobased polymers also form part of our activities in order to be able to transfer technological advancements from bench to and beyond pilot scale.

## Cyclic Carbonates

The valorization of carbon dioxide towards the synthesis of derivatives useful from an organic point of view (*i.e.*, the valorization of CO<sub>2</sub>) continues to draw our attention. Our focus is on sustainable metal based and organocatalytic protocols that can deliver CO<sub>2</sub> transformations towards the creation of higher levels of complexity: highlights of these endeavors are described below. We have developed a new organocatalytic concept where a hydrogen-bonding (HB) catalyst (*i.e.*, squaramide) is not involved in the initial activation of the epoxide reagent but primarily stabilizes oxoanionic intermediates that result from nucleophilic ring-opening of the oxiranes and following its reaction with CO<sub>2</sub> to form a carbonate anion (Figure 1).

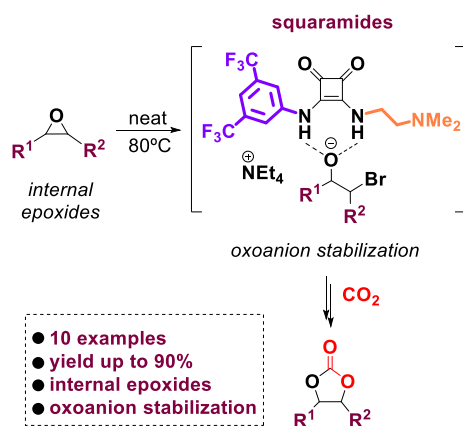


Fig. 1 – The use of a new organocatalytic concept in cyclic carbonate formations from epoxides and CO<sub>2</sub>.

This new concept demonstrates that novel types of organocatalysts can be designed for challenging substrates (internal epoxides) and provide reasonable alternatives to metal-based catalysts (*ACS Catal.* **2017**, *7*, 3532-3539).

Stereochemical conversions with carbon dioxide remain challenging though rewarding in the area of CO<sub>2</sub> catalysis. Based on our previous success using substrate-controlled reactivity, we have used cyclic epoxy alcohols and CO<sub>2</sub> to design new stereodivergent synthesis of bicyclic carbonates. While several manifolds have been reported to be operative in the [3+2] cycloaddition of epoxides and CO<sub>2</sub>, our work revealed a new, unprecedented approach towards stereocontrol in these conversions. The basis for this control is the presence of an Al(III) aminotriphenolate complex and a suitable

nucleophile/base to mediate the coupling process. Interestingly, control experiments revealed that first an oligomeric species is formed, from which the product is furnished by a controlled degradation of the oligomeric chain via a pendant pronucleophile (alcohol group) which is proposed to be activated by HB to an adjacent carbonate group. This organization sets up the system to provide *anti-cis* type isomers, which cannot be attained through any previously known mechanistic route. The discovery of new manifolds holds thus promise to design more general type of stereodivergent CO<sub>2</sub>-based transformations creating rather complex ring structures. A few examples of functional bicyclic carbonates are presented below with built-in groups useful towards post-synthetic transformation, an aspect that was successfully studied and demonstrated (*ACS Catal.* **2017**, *7*, 5478-5482)

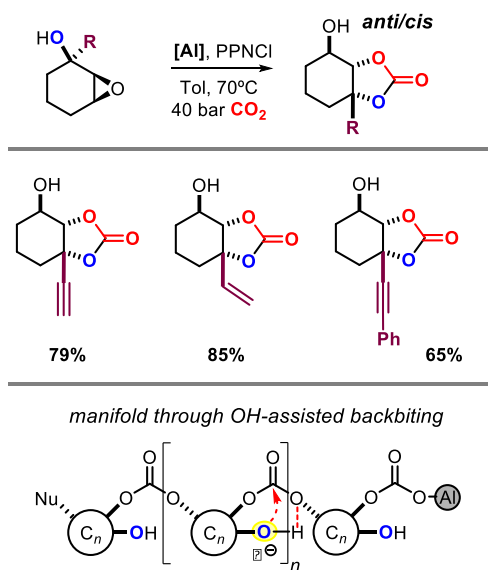


Fig. 2 – Substrate-controlled stereodivergent synthesis of bicyclic organic carbonates under Al-catalysis.

The last highlighted example of conversion of CO<sub>2</sub> into cyclic carbonates involves the use of renewable, long chain fatty acid precursors and their stereoretentive conversions into mono-, di- and tri-carbonate compounds under Al(III)/nucleophile binary catalysis. We developed the first general method towards such biocarbonates that serve as potential precursors of isocyanate-free polyhydroxyurethanes, generally abbreviated as PHUs. The Al-based catalyst delivers the fatty acid cyclic carbonates

in high yield and in a diastereospecific manner, and the first examples of such transformations providing either di- or tricarbonates were presented. A fatty acid epoxy alcohol substrate showed additional utility towards nucleophile-free conversions, and this substrate was proposed to involve a sequence or steps with the alcohol directing the initial formation of a six-membered carbonate, following isomerization to a thermodynamically more stable five-membered one under the experimental conditions (*Green Chem.* **2017**, *19*, 3535-3541)

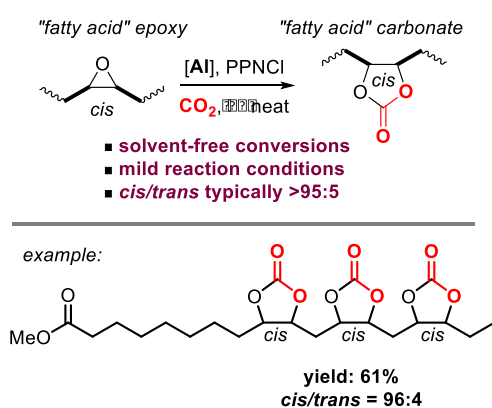


Fig. 3 – Stereospecific formation of fatty acid based biocarbonates under Al(III)/nucleophile binary catalysis.

## Fine Chemical Synthesis

The conversion of CO<sub>2</sub> into more complex fine-chemicals is a clear example of how to "upgrade" carbon dioxide. We have thus developed novel approaches that take advantage over specifically functionalized cyclic carbonates and related heterocycles/substrates. In particular, vinyl-substituted cyclic carbonates are easy to prepare synthetic intermediates that can be activated by suitable Pd(0) precursors towards decarboxylation, and subsequent attack by external electrophiles or nucleophiles. A highly reactive, "zwitterionic" (allyl)Pd intermediate is formed that can be intercepted and offers new ways for stereocontrolled annulation reactions and asymmetric allylic substitutions.

Two distinct highlights are discussed here: the asymmetric synthesis of aliphatic  $\alpha,\alpha$ -disubstituted allylic amines, and the formation of allylic ethers with chiral quaternary centers. The aliphatic allylic amines could not be prepared using vinyl cyclic carbonates since the more

nucleophilic amines easily ring open the carbonates affording linear carbamate products. Therefore, a new approach was warranted and we finally discovered that the use of linear carbonates (Boc protected allylic alcohols or similar; see Figure 4, top) allowed for the efficient and enantioselective synthesis of the targeted allylic amines. Importantly, this procedure represents the first Pd-catalyzed AAA (asymmetric allylic alkylation) able to generate these fine chemical building blocks while having appreciable scope in reaction partners (*Angew. Chem. Int. Ed.* **2017**, *56*, 11797-11801).

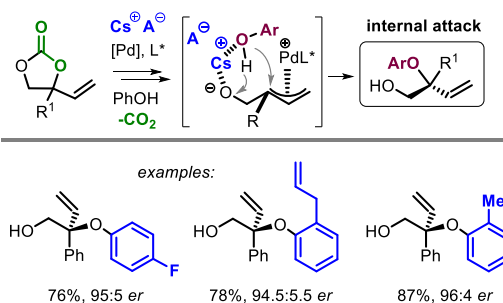
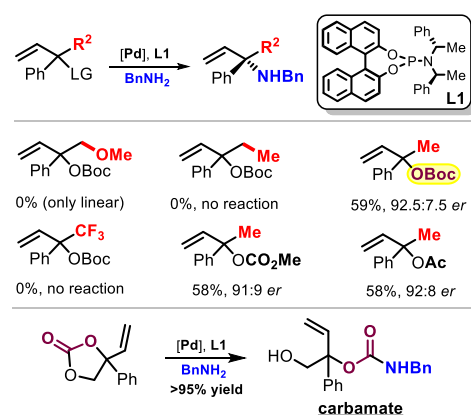


Fig. 4 – Small molecule catalysis leading to enantio-enriched building blocks for fine chemical synthesis: Top – chiral aliphatic allylic amine preparation; Bottom – synthesis of chiral allylic ethers.

The formation of the chiral allylic ethers (Figure 4, lower part) required the presence of a Cs additive to direct the attack of the phenolic nucleophile towards the sterically challenging "internal" position of the allyl-Pd intermediate, though eventually the asymmetric induction was satisfying leading to allylic ethers with elusive chiral quaternary stereocenters (*Org. Lett.* **2017**, *19*, 6388-6391). By using alkyne-functionalized lactones, a new protocol for the chiral synthesis of  $\gamma$ -amino acids was also successfully

developed. The approach is based on the asymmetric, challenging ring-opening aminolysis of the substrate in the presence of amine nucleophiles operative under Cu-catalysis (*Angew. Chem. Int. Ed.* **2017**, *56*, 15035-15038).

## Bio-Based Polymers

Further advancements in the area of biobased polymers have been made, and particularly in the area of polycarbonates with unusual modulation of the thermal resistance. Poly-(limonene)carbonates (**PLCs**) of different molecular weights ranging from 1500 to 16000 g/mol were prepared and first subjected to epoxidation affording their oxidized form (**PLCO**) without any noticeable degradation of the polycarbonate backbone. Interestingly, the glass transitions of these **PLCOs** increased markedly, and could be further influenced by rigidifying the pendent groups by conversion into cyclic carbonate units (**PLDCs**). This furnished several new polymers with increased CO<sub>2</sub> content and relatively high thermal resistance expressed in the highest *T<sub>g</sub>* values (up to 180 °C) reported to date for a polycarbonate polymer. Also for the smaller oligomers, high *T<sub>g</sub>* values of around 152 °C were note making these exceptionally suitable for use as monomers in block copolymer synthesis (*ACS Catal.* **2017**, *7*, 3860-3863).

Terpene building blocks like the ones used to assemble new **PLCs** with unusual thermal behavior could also be used to prepare semi-aromatic polyesters by alternate coupling of the

## Articles

“Pd-Catalyzed Enantio- and Regioselective Formation of Allylic Aryl Ethers “

*Org. Lett.* (**2017**) *19* - 6388-6391

J. Xie, W. Guo, A. Cai, E.C. Escudero-Adán, A.W. Kleij

“Copper-Mediated SN<sub>2</sub>' Allyl-Alkyl and Allyl-Boryl Couplings of Vinyl Cyclic Carbonates

*Org. Lett.* (**2017**) *19* - 6096-6099

N. Miralles, J.E. Gómez, A.W. Kleij, E. Fernández

“Polystyrene-supported bifunctional resorcinarenes as cheap, metal-free and recyclable catalysts for epoxide/CO<sub>2</sub> coupling reactions”

*Green Chem.* (**2017**) *19* - 5488-5493

terpene oxides with phthalic anhydride (**PA**). Among the developed bio-polyesters, the ones derived from PA and methene oxide (poly[**PA-alt-methene oxide**]) showed the highest thermal potential with *T<sub>g</sub>*'s amounting to 165 °C (*Macromolecules* **2017**, *50*, 5337-5345).

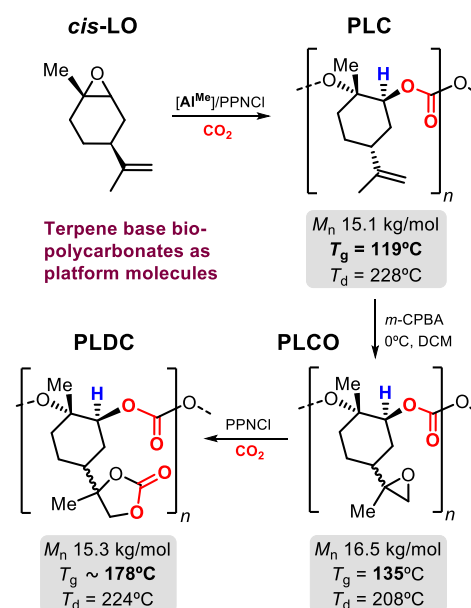


Fig. 5 – **PLC** polymers derived from limonene oxide and several functionalized congeners (**PLCO**, **PLDC**).

T. Jose, S. Cañellas, M.A. Pericàs, A.W. Kleij

“Copper-Catalyzed Synthesis of  $\gamma$ -Amino Acids Featuring Quaternary Stereocenters”

*Angew. Chem. Int. Ed.* (**2017**) *56* - 15035-15038

J.E. Gómez, W. Guo, S. Gaspa, A.W. Kleij

“Asymmetric Synthesis of  $\alpha,\alpha$ -Disubstituted Allylic Amines via Pd-Catalyzed Allylic Substitution”

*Angew. Chem. Int. Ed.* (**2017**) *56* - 11797-11801

W. Guo, A. Cai, J. Xie, A.W. Kleij

“Semiaromatic Polyesters Derived from Renewable Terpene Oxides with High Glass Transitions”

*Macromolecules* (**2017**) *50* - 5337-5345

L. Peña-Carrodeguas, C. Martín, A.W. Kleij

## 2017 Annual Scientific Report

“Substrate Triggered Stereoselective Preparation of Highly Substituted Organic Carbonates”

*ACS Catal.* (2017) 7 - 5478-5482

V. Laserna, E. Martín, E.C. Escudero-Adán, A.W. Kleij

“Fatty Acid Based Biocarbonates: Al-Mediated Stereoselective Preparation of Mono-, Di- and Tricarbonates under Mild and Solvent-less Conditions”

*Green Chem.* (2017) 19 - 3535-3541

L. Peña-Carrodeguas, A. Cristófol, J.M. Fraile, J.A. Mayoral, V. Dorado-Horrillo, C.I. Herrerías, A.W. Kleij

“Access to Biorenewable Polycarbonates with Unusual Glass-Transition Temperature ( $T_g$ ) Modulation”

*ACS Catal.* (2017) 7, 3860-3863

N. Kindermann, A. Cristófol, A.W. Kleij

“Pushing the Limits with Squaramide-based Organocatalysts in Cyclic Carbonate Synthesis”

*ACS Catal.* (2017) 7 - 3532-3539

S. Sopeña, E. Martín, E.C. Escudero-Adán, A.W. Kleij

“Metal-Free Synthesis of *N*-Aryl Amides using Organocatalytic Ring-Opening Aminolysis of Lactones”

*ChemSusChem* (2017) 10 - 1969-1975

W. Guo, J. Enrique Gómez, L. Martínez-Rodríguez, N.A.G. Bandeira, C. Bo, A.W. Kleij

“CO<sub>2</sub> Catalysis – Editorial”

*ChemSusChem* (2017) 10 - 1036-1038

A.W. Kleij, M. North, A. Urakawa

“Vanadium(V) Catalysts with High Activity for the Coupling of Epoxides and CO<sub>2</sub>: Characterization of a putative Catalytic Intermediate”

*ACS Catal.* (2017) 7 - 2367-2373

C. Miceli, J. Rintjema, E. Martín, E.C. Escudero-Adán, C. Zonta, G. Licini, A. W. Kleij

“Synthesis of Carbonates from Alcohols and CO<sub>2</sub>”

*Top. Curr. Chem.* (2017), 375 - 1-28

N. Kindermann, T. Jose, A. W. Kleij

“Mechanistic Insights into the Carbon Dioxide-Cyclohexene Oxide Copolymerization reaction: Is one Metal Center enough?”

*ChemSusChem* (2017) 10 - 1233-1240

J. González-Fabra, F. Castro-Gómez, A. W. Kleij, C. Bo

“Aluminum-Mediated Formation of Cyclic Carbonates: Benchmarking Catalytic Performance Metrics”

*ChemSusChem* (2017) 10 - 1274-1282

J. Rintjema, A. W. Kleij

“Recent Progress in Stereoselective Synthesis of Cyclic Organic Carbonates and Beyond”

*Curr. Opin. Green Sust. Chem.* (2017) 3 - 55-60

J. E. Gómez, A. W. Kleij