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Vinyl and Alkynyl Substituted Heterocycles as Privileged Scaffolds in Transition Metal Promoted Stereoselective Synthesis

Debasish Ghorai, Balázs L. Tóth, Matteo Lanzi, and Arjan W. Kleij*

Cite This: *Acc. Chem. Res.* 2024, 57, 726−738
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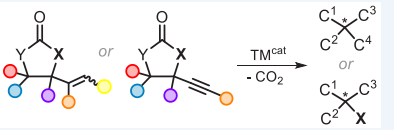
CONSPECTUS: Biologically active compounds and pharmaceutically relevant intermediates often feature sterically congested stereogenic centers, in particular, carbon stereocenters that are either tertiary tetrasubstituted ones or quaternary in nature. Synthons that comprise such bulky and often structurally complex core units are of high synthetic value and represent important incentives for communities connected to drug discovery and development. Streamlined approaches that give access to a diverse set of compounds incorporating acyclic bulky stereocenters are relatively limited, though vital. They enable further exploration of three-dimensional entities that can be designed and implemented in discovery programs, thereby extending the pool of molecular properties that is inaccessible for flat molecules. However, the lack of modular substrates in particular areas of chemical space inspired us to consider functionalized heterocycles known as cyclic carbonates and carbamates as a productive way to create sterically crowded alkenes and stereocenters.



In this Account, we describe the major approximations we followed over the course of 8 years using transition metal (TM) catalysis as an instrument to control the stereochemical course of various allylic and propargylic substitution processes and related transformations. Allylic substitution reactions empowered by Pd-catalysis utilizing a variety of nucleophiles are discussed, with amination being the seed of all of this combined work. These procedures build on vinyl-substituted cyclic carbonates (VCCs) that are simple and easy-to-access precursors and highly modular in nature compared to synthetically limited vinyl oxiranes. Overall these decarboxylative conversions take place with either "linear" or "branched" regioselectivities that are ligand controlled and offer access to a wide scope of functional allylic scaffolds. Alternative approaches, including dual TM/photocatalyzed transformations, allowed us to expand the repertoire of challenging stereoselective conversions. This was achieved through key single-electron pathways and via formal umpolung of intermediates, resulting in new types of carbon−carbon bond formation reactions significantly expanding the scope of allylic substitution reactions.

Heterocyclic substrate variants that have triple bond functional groups were also designed by us to enable difficult-to-promote stereoselective propargylic substitution reactions through TM catalysis. In these processes, inspired by the Nishibayashi laboratory and their seminal findings in the area, we discovered various new reactivity patterns. This provided access to a range of different stereodefined building blocks such as 1,2-diborylated 1,3-dienes and tetrasubstituted α-allenols under Cu- or Ni-catalysis. In this realm, the use of lactone-derived substrates gives access to elusive chiral γ-amino acids and lactams with high stereofidelity and good structural diversity.

Apart from the synthetic efforts, we have elucidated some of the pertinent mechanistic manifolds operative in these transformations to better understand the limitations and opportunities with these specifically functionalized heterocycles that allowed us to create complex synthons. We combined both theoretical and experimental investigations that lead to several unexpected outcomes in terms of enantioinduction models, catalyst preactivation, and intermediates that are intimately connected to rationales for the observed selectivity profiles. The combined work we have communicated over the years offers insight into the unique reactivity of cyclic carbonates/carbamates acting as privileged precursors. It may inspire other members of the synthetic communities to widen the scope of precursors toward novel stereoselective transformations with added value in drug discovery and development in both academic and commercial settings.

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Received: December 2, 2023
Revised: January 19, 2024
Accepted: January 22, 2024
Published: February 22, 2024

ACS Publications
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https://doi.org/10.1021/acs.accounts.3c00760
Acc. Chem. Res. 2024, 57, 726−738

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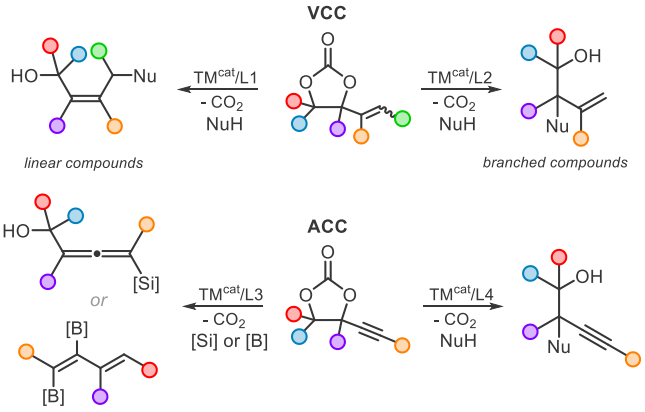
INTRODUCTION

The quality of life in modern society is heavily built on progressive technology allowed by scientific research and development. The alliance of academically triggered findings and their translation to a business-oriented focus has greatly advanced the use of knowledge and economically driven activities in areas ranging from smart materials, renewable energy production, and information technology to drug discovery. In the latter category, it is pivotal to be able to access and test a large and structurally diverse series of compounds to better understand structure−activity relationships (SARs). Furthermore, such an approach allows optimization of their ability to address some of the most challenging and ongoing health problems (long COVID, Alzheimer's disease, cancer, malaria, diabetes, among others) that we face globally. For a number of commercial pharmaceutical and agrochemical compounds, the presence of (a)cyclic quaternary stereocenters marks an important advantage in terms of the chemical space that can be accessed. Synthetic methodologies that can help to expand the presence of acyclic quaternary carbons (i.e., sp^3-hybridized stereogenic centers) in drug candidates increase the 3D character of the molecule and its potential to interact with target proteins.[5,6] This structural requisite poses the intrinsic challenge of forging such conformationally flexible and sterically encumbered stereocenters in an efficient way while preserving synthetic diversity and practicality useful toward natural product synthesis.[7]

Therefore, in order for synthetic drug protocols to become widely implemented, one needs to consider not only the catalyst but also the reagents used to create such stereogenic centers. Our laboratory has been active for over a decade in the area of carbon dioxide valorization into heterocyclic compounds known as cyclic carbonates and carbamates.[8,9] More recently, we started a dedicated research program in which particular members of a large pool of accessible heterocycles (Chart 1, vinyl-substituted cyclic carbonates (VCCs) and

Chart 1. Main Types of Heterocycles Used over the Years and Their Utilization in Catalytic Decarboxylative Transformations based on Allylic and Propargylic Substitution Chemistry



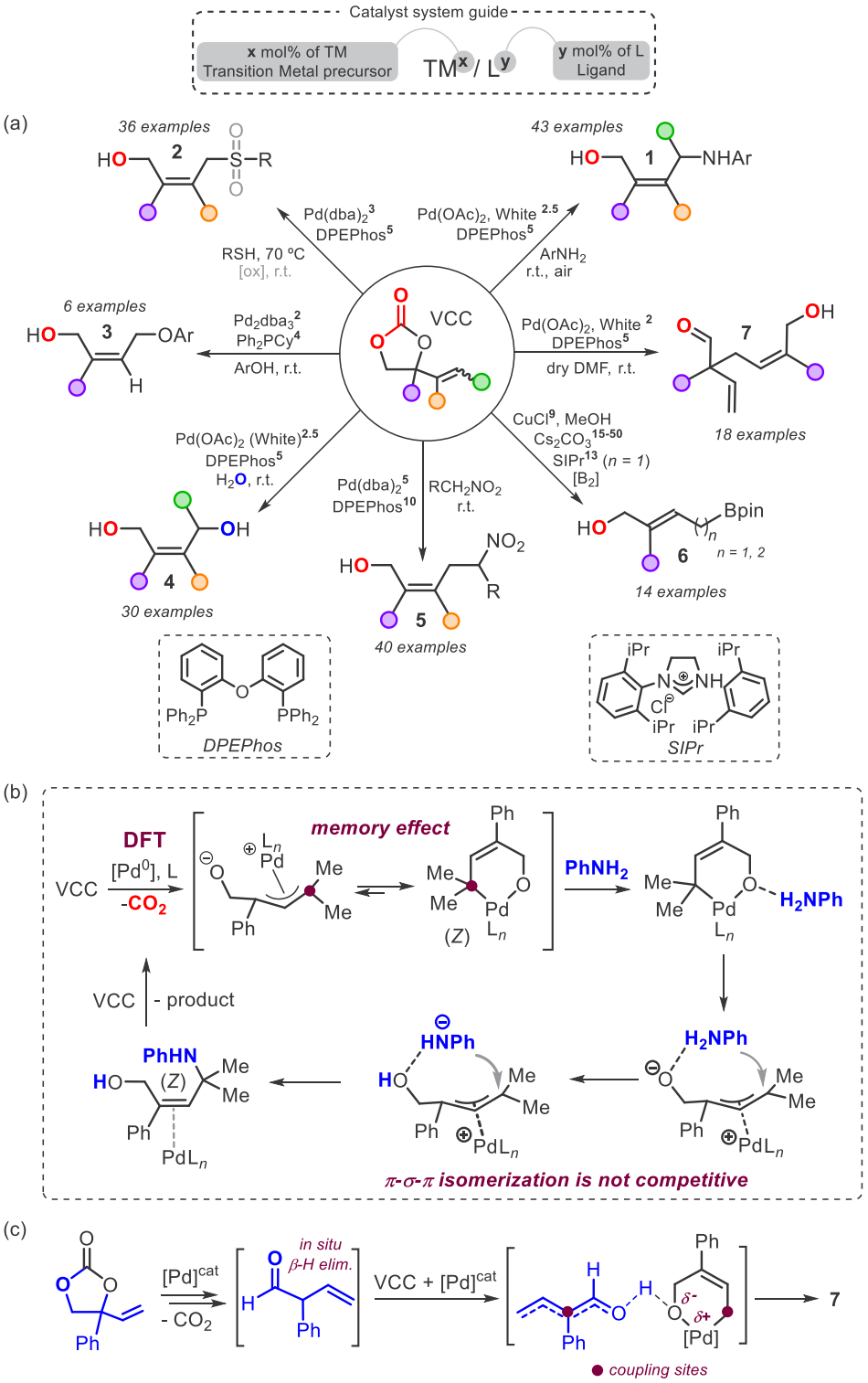
alkynyl-functionalized cyclic carbonates (ACCs)) were chosen to serve as either allylic or propargylic surrogates giving *in situ* access to reactive metal−allyl or metal−allenyl species.[10] These intermediates can be productively advanced to complex scaffolds that encompass either highly substituted C=C bonds or sterically crowded tertiary/quaternary stereogenic centers. Apart from these classical approaches that involve allylic and propargylic substitution chemistry, we have also investigated alternative concepts such as photocatalysis to induce the diastereo/enantioselective formation of quaternary stereocenters.[11] The difference is that these protocols are usually based on key single-electron-transfer (SET) mechanistic steps and may involve the formal umpolung of intermediates, thereby providing a wider range of reactivity patterns and coupling partners. As a consequence, this can cover a larger area of the chemical space. The successful development of various catalytic processes that involve the utilization of cyclic carbonates/carbamates as precursors further inspired us to design similar/related substrates. In particular, we used substrates that retain all of the original atoms upon activation and ring-opening, offering straightforward access to chiral amino acid synthons and a wide scope of functionalized caprolactones. Our combined efforts (Chart 1) show that the heterocyclic derivatives play a crucial role and can be regarded as privileged substrates. These in turn serve to motivate further research on larger-ring congeners, the use of alternative and more sustainable (transition) metals, and the presence of other types of functional groups such as allenes.[12]

CLASSICAL ALLYLIC SUBSTITUTION REACTIONS USING VCCs

At the onset of our stereoselective synthesis program, we became inspired by the prospect of vinyl-substituted cyclic carbonates (VCCs) as allylic precursors through *in situ* activation and decarboxylation in the presence of a suitable Pd(0) complex.[13] At the same time, we saw an opportunity to tackle a long-standing challenge at the time to develop generic stereocontrolled protocols for both (a) linear allylic amines with fully substituted double bonds (Scheme 1a) and (b) enantio-enriched tertiary, tetrasubstituted branched allylic amines (Scheme 2). It is important to emphasize here that in comparison to vinyl epoxides (that were previously frequently utilized as allylic surrogates),[14] the use of bench-

https://doi.org/10.1021/acs.accounts.3c00760
Acc. Chem. Res. 2024, 57, 726−738

Scheme 1. Developed Linear Allylic Derivatives from VCCs under Pd or Cu Catalysis[a]



[a]The superscripts refer to the loadings in mol %.

stable and modular VCCs has several advantages as they are easily accessible from β-hydroxy ketones in two steps and allow for various reactivity patterns as will be discussed below. The first transition metal (TM)-catalyzed decarboxylative transformation of VCCs was reported by the Yoshida group in 1987 and they demonstrated an efficient Pd-promoted decarboxylative carbonylation process leading to vinyl lactones as products.[15] It was not until the first decade of this century that more groups picked up on the versatile reactivity of these VCCs in various TM-catalyzed transformations. Prominent examples of such conversions include CH-bond allylations, cycloadditions reactions and various types of enantioselective transformations.[16−18] The first contribution from our laboratory in this area originates from 2016, showing that VCCs

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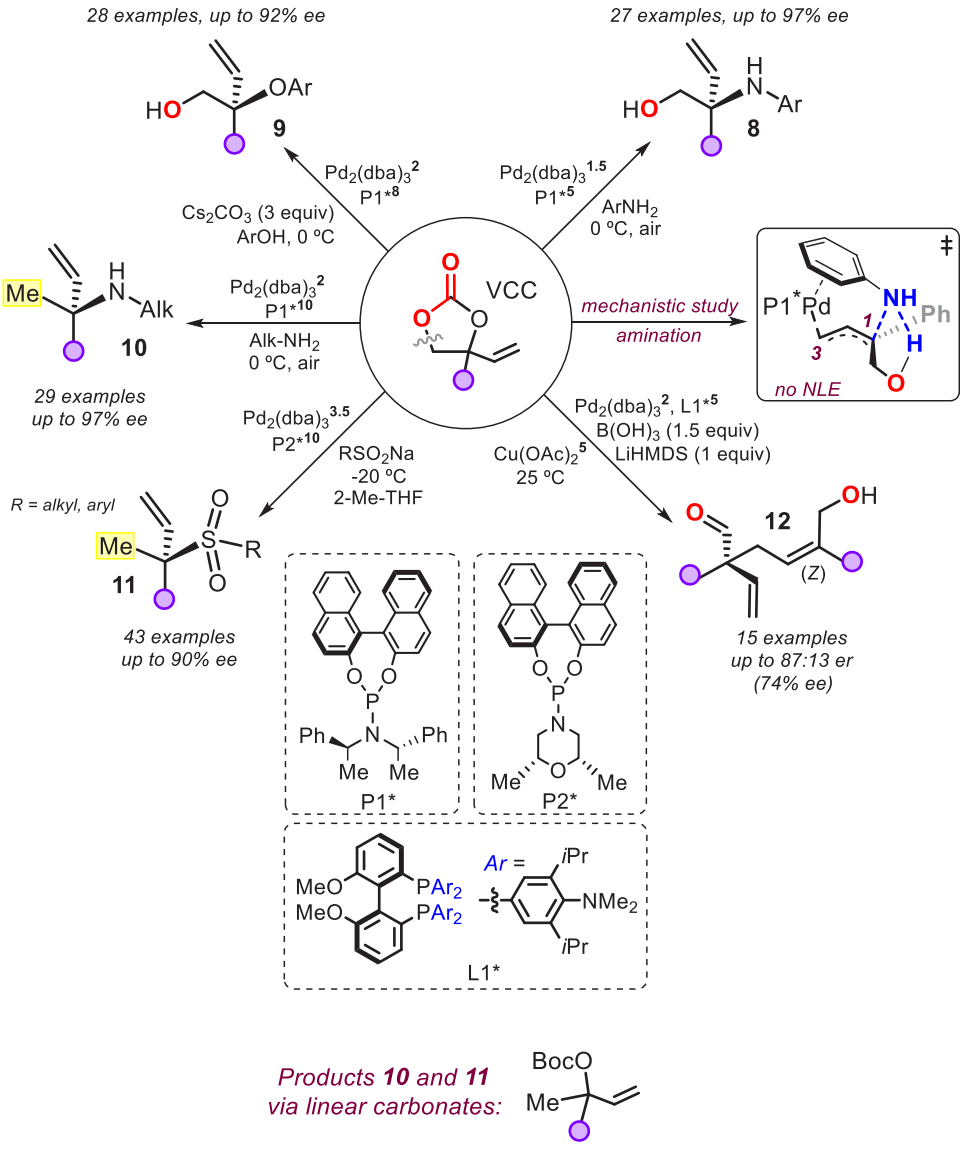
Scheme 2. Developed Branched Allylic Derivatives from VCCs under Pd and/or Cu Catalysis[a]



[a]The superscripts refer to the loadings in mol %.

are modular substrates in the generation of a wide scope (43 examples) of highly substituted (*Z*)-configured linear allylic amines under Pd catalysis (Scheme 1a: compounds **1**; using 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate, known as the White catalyst).[2] Key to the high stereoselectivity (typically *Z*/*E* > 99:1) is the intermediacy of a (*Z*)-arranged palladacyclic intermediate after decarboxylation, as suggested by extensive density functional theory (DFT) based computations (Scheme 1b) and with ESI-MS support for the molecular formula. Activation of the less reactive aromatic amine (NuH) is believed to occur via formal proton transfer to the basic oxygen in this palladacyclic derivative (and not as often suggested via a zwitterionic structure after decarboxylation). This evolves into an acyclic Pd(allyl) species and a formal amide acting as an activated nucleophile (Nu) that subsequently attacks the C-terminus of the allyl group, providing the final product (Scheme 1). The choice of the ligand is important, and DPEPhos (bis[(2-diphenylphosphino)phenyl]ether), a chelating diphosphine, was highly beneficial toward the formation of the (*Z*) linear allylic amine product. Of further note here is that a comparative study was carried out with a vinyl epoxide substrate, but its use led to only a trace amount of product.[2] At this stage, we believe that the manifold using such substrates, despite leading to similar kinds of Pd(allyl) intermediates after ring-opening, likely involves a different and more energy-demanding preactivation.

In order to further explain the high level of stereocontrol, a DFT analysis of potential $\pi-\sigma-\pi$ isomerization processes of all acyclic Pd(allyl) intermediates was performed. In all of these cases, the energy requirement was at least 5 kcal/mol larger than that for the desired C−N coupling process. This observation thus rationalizes the experimental results and preferred formation of the allylic amine target. Interestingly, a subset of tetrasubstituted allylic amines could be prepared stereoselectively with up to 4 different "carbon" substituents, which is known to be quite challenging.[19]

These 1,4-amino-alcohols were shown to be of value in the generation of stereodefined 2-butene-1,4-diamines. Soon after, we investigated other types of pronucleophiles (NuH) including thiols, phenolic compounds, water, nitroalkanes,

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and diboron reagents (Scheme 1a, compounds **2**−**6**). The use of thiols, compared to aromatic amines, was more challenging and a higher reaction temperature (70 °C) was needed for effective turnover, and lower *Z*/*E* ratios (typically 80:20 up to 99:1) were observed.[20] A reasonable scope of allylic thioethers **2** could be accomplished, and we also extended the protocol to a one-pot allylic substitution/oxidation sequence affording linear allylic sulfones (8 examples; *Z*/*E* values from 84:16 to 94:6) under high stereocontrol. Apart from *S*-based pronucleophiles, *O*-based ones also proved to be productive. The presence of phenols allowed again for room temperature conversions leading to allylic ethers of type **3** (*Z*/*E* > 99:1), but in these cases the utilization of a different ligand (Ph_2PCy) proved to be more productive.[21] Taking advantage of the key outcomes of the DFT studies, we envisioned that even a poor nucleophile like water could be activated providing *in situ* a "hydroxide" species advancing decarboxylated VCCs toward the formation of synthetically versatile 2-buten-1,4-diols (Scheme 1a, **4**).[22] Isotope-labeling studies ($H_2{}^{18}O$) supported that the origin of the introduced O atom in the decarboxylated diol product is from water, and the scope of 30 examples (*Z*/*E* in most cases >99:1) included various examples of products featuring tetrasubstituted C═C fragments. This kind of substrate activation could be further extended to the use of nitroalkanes.[23] Their use led to *in situ* prepared nitronates acting as carbon-based nucleophiles promoting highly selective C−C bond formations culminating in homoallylic nitroalkanes **5** showing in the majority of the cases exclusive formation of the *Z*-isomer (*Z*/*E* > 99:1). The synthetic value of these compounds was later demonstrated by devising straightforward protocols for the synthesis of various indolizidine and quinolizidine alkaloids with (*Z*)-homoallylic nitroalkanes playing a key role.[24]

The last two examples in Scheme 1 deviate from the others by virtue of the catalyst used (derivatives **6**) and the process outcome (compounds **7**). Formal borylation of VCCs can be conveniently done in the presence of the diboron reagents diborylmethane and B_2pin_2 (pin = pinacol) leading to *E*-configured allylic or homoallylic boranes **6**, respectively.[25] These reactions are empowered by Cu-catalysis and follow a regioselective S_N2'-type pathway with the reactions that involve B_2pin_2 requiring the presence of the carbene ligand 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) to push the yield of the product (**6**, *n* = 1). The different stereochemistry (*E*) here is explained by a regioselective *syn*-addition of a Cu-Bpin intermediate to the double bond of the VCC following an *anti*-S_N2' release of the product (**6**) while extruding CO_2.

The last example in Scheme 1a is the cascade redox-neutral cross-coupling of two VCCs via *in situ* umpolung, furnishing unusual compounds **7** that comprise a quaternary center with a rare combination of a vinyl, allyl, aldehyde, and aromatic substituents.[26] In the mechanistic scenario leading to products of type **7**, one VCC is activated by Pd(0), followed by decarboxylation (Scheme 1c). In the absence of a suitable nucleophile, the Pd(allyl) species advances to a β-unsaturated aldehyde. The latter then engages with a second activated VCC (cf., palladacyclic intermediate in Scheme 1b) undergoing proton-transfer thereby generating a dienolate nucleophile (i.e., formal umpolung of the VCC occurred).[27] The latter subsequently attacks the Pd(allyl) intermediate to form the cross-coupled product **7** with a highly functionalized stereogenic center. This proposal was supported by detailed DFT and microkinetic studies being in line with some of the experimental observations.

From the subtle variations and similarities in the experimental conditions, ligands, and Pd precursors reported in Scheme 1, it is clear that delicate process optimization is required to maximize the chemo- and stereoselectivity. Furthermore, the overall manifold giving rise to the formation of these linear allylic derivatives builds strongly on the intermediacy of a palladacyclic intermediate that is able to activate rather weak (pro)nucleophiles such as anilines and H_2O. In most of the developed transformations, a diverse set of stereo- and electronic modulations were tolerated.

Given the success with the allylic substitution reactions using VCCs as allylic surrogates, we considered the possibility to promote the more challenging formation of branched products by ligand-induced regio- and enantio-control through a dynamic kinetic asymmetric transformation (DYKAT).[1] We opted for allylic amination, inspired by the lack of generic Pd-mediated protocols leading to α,α-disubstituted, branched allylic amines. Combining the VCCs with unactivated aromatic amines in the presence of a Pd(0) precursor and an optimized phosphoramidite ligand (P1*, Scheme 2) at 0 °C afforded a series of chiral allylic amines **8** with excellent enantiomeric excess (ee values up to 97%).

Mechanistic studies (possible nonlinear effect; NLE), control experiments, and DFT analysis revealed that the regio- and enantio-control is guided by an unanticipated η^2-aryl interaction between the Pd center and the aryl group of the amine nucleophile. This inner-sphere process is devoid of any significant NLE in line with the proposed presence of only one chiral ligand in the selectivity-determining transition state (Scheme 2).[28] As for the linear allylic derivatives summarized in Scheme 1, extending the asymmetric synthesis to the use of other nucleophiles was possible. Branched allylic ethers of type **9** (Scheme 2) could be readily prepared from VCCs in the presence of various phenols and Cs_2CO_3 as an additive with enantioselectivities of up to 92% ee. The base additive requirement is mechanistically explained through an interaction with the phenol substrate thereby increasing its nucleophilic character in a metal-tethered nucleophilic attack.[21]

The use of aliphatic amines as reaction partners for VCCs was hampered as these reagents are nucleophilic enough to spontaneously ring-open the cyclic carbonate thereby leading to linear carbamates.[29] In order to enable the formation of α,α-disubstituted branched aliphatic amines **10** (Scheme 2), tertiary allylic carbonates/acetates had to be used as reaction partners to avoid undesired aminolysis.[30] At the time, the development of this methodology marked an important milestone in the area, as it represents one of the few TM-mediated generic protocols for chiral branched allylic aliphatic amines featuring a tertiary tetrasubstituted stereogenic center. Interestingly, the asymmetric formation of both aromatic as well as aliphatic allylic amines **8** and **10** is promoted by the same phosphoramidite ligand P1*.

This requirement changed when tertiary allylic carbonates and sodium alkyl/aryl sulfonates were combined to produce branched allylic sulfone **11** (Scheme 2). In this case, further ligand engineering was crucial to optimize the regio- and enantio-control of the substitution process,[31] and the new phosphoramidite ligand P2* was developed. The successful exploitation of P2* in the Pd-catalyzed formation of the allylic sulfones was demonstrated (43 examples) though the enantio-

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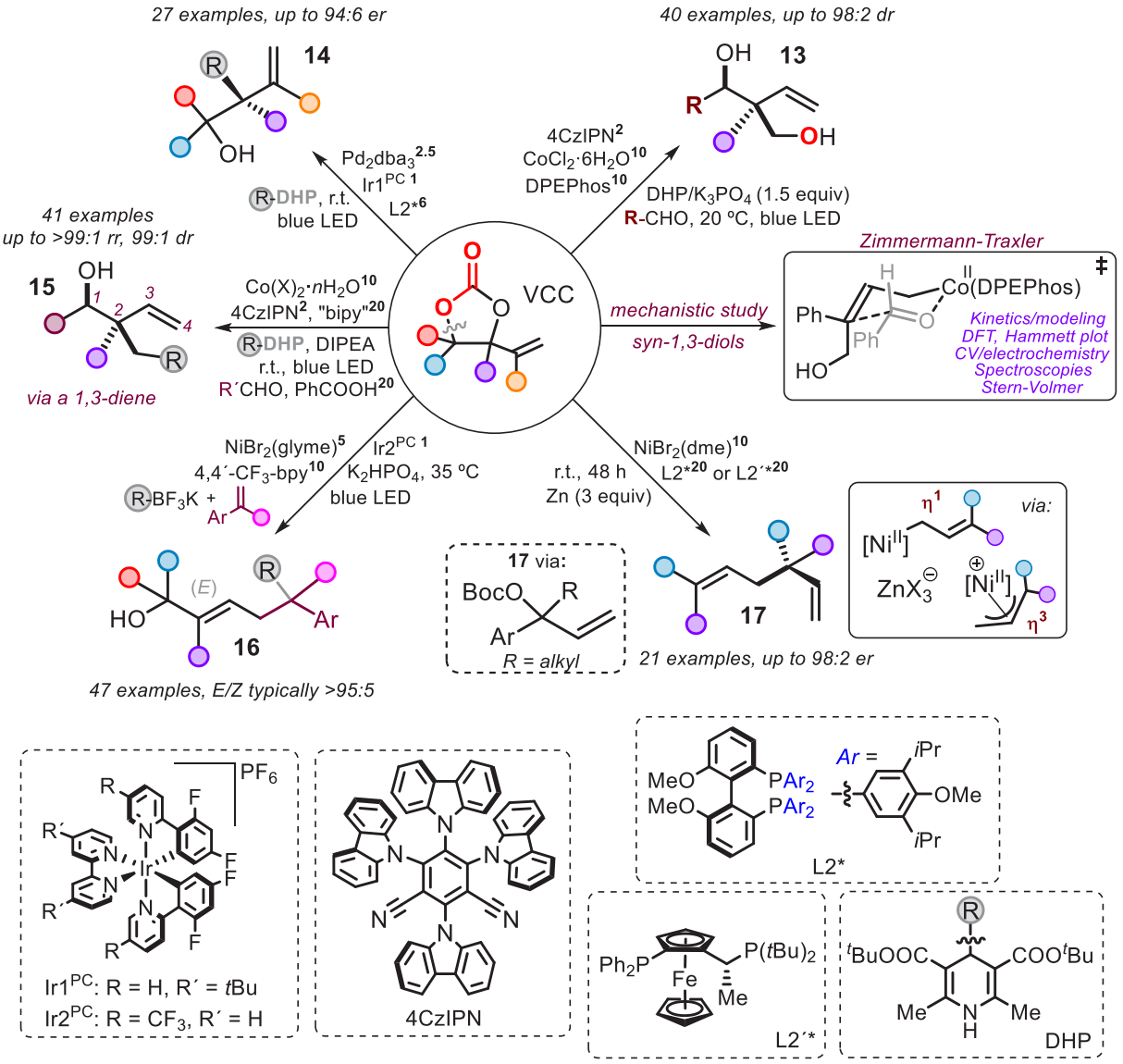
Scheme 3. Dual Catalysis Approaches in Allylic Alkylation[a]



[a]The superscripts refer to the loadings in mol %.

control compared to the synthesis of compounds **8** and **10** was slightly inferior with values around 94:6 er. The protocol could be applied to the formal synthesis of (−)-agelasidine A (a natural sesquiterpene), whose preparation involves the intermediacy of a tertiary allylic sulfone.

Finally, the enantioselective version of the VCC-cross-coupling process of Scheme 1a (compounds **7**) was studied.[32] The presence of sterically demanding chiral ligands such as the optimized L* (Scheme 2, a BIPHEP (6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) based one) further challenged efficient cross-coupling. Therefore, additives (boric acid: $B(OH)_3$, and lithium hexamethylenedisilane: LiHMDS) were needed to increase the potential of the reaction intermediates to be converted into products **12**. A more limited scope of 15 examples was achieved with fair levels of enantioinduction (er values up to 87:13). In the mechanistic rationale for this $C(sp^3)-C(sp^3)$ bond formation process, the boric acid helps to activate the VCC with the formation of an intermediate borate species that undergoes transmetalation involving the Cu additive. A Cu-stabilized dienolate then combines with the electrophilic Pd(allyl) intermediate to produce compounds of type **12** in a formal dual-metal catalysis protocol.

RELATED ALLYLIC SUBSTITUTION PROCESSES

So far, the formation of linear or branched allylic compounds from VCCs has been discussed using classical two-electron processes and empowered by Pd-catalysis. In this section, we delineate other efforts that build on single-electron-transfer (SET) events using Pd and alternative metals. In addition, some prospects are presented on how to vary the structure of the VCC heterocycle to accommodate other types of allylic alkylations that are not based on decarboxylative couplings.

In 2021, we reported the use of Co/photoredox dual catalysis as an efficient approach for the decarboxylative formation of *syn*-configured 1,3-diols featuring quaternary carbon centers from VCCs.[33] The key to success in this transformation is the *in situ* SET reduction of a Co(II)-DPEPhos complex enabled by 4CzIPN (2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitriles) as a photocatalyst using DHPs

https://doi.org/10.1021/acs.accounts.3c00760
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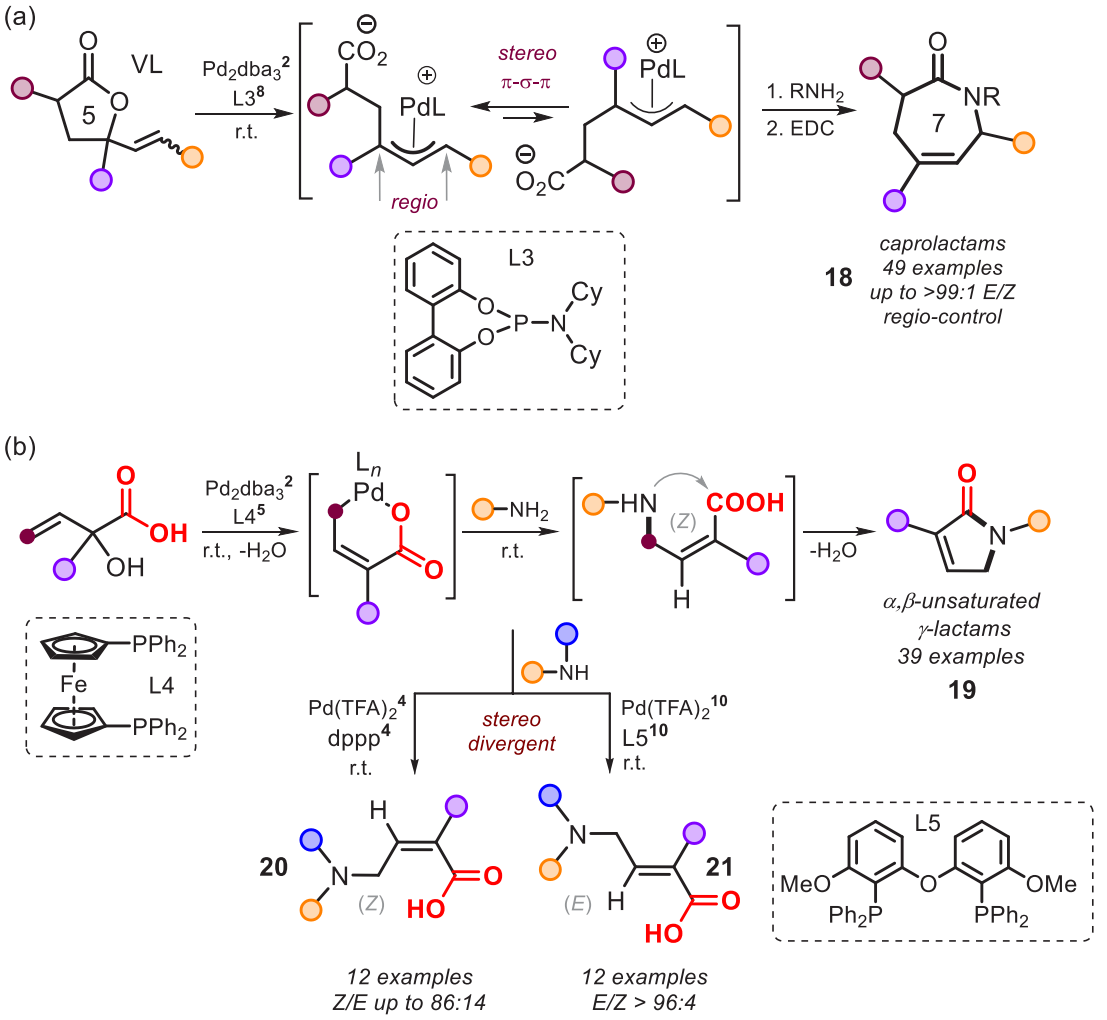
Scheme 4. Vinyl Substituted Lactones and Carboxyl-Derived Allylic Alcohols in Allylic Substitutions[a]



[a]The superscripts refer to the loadings in mol %.

(dihydropyridines) as a source of electrons (Scheme 3). In their presence, a low-valent Co(I) species is generated that promotes oxidative addition of the VCC to furnish a Co(III)allyl derivative. The latter undergoes a second SET yielding a nucleophilic Co(II)allyl complex that can engage with electrophiles such as aldehydes via a Zimmermann−Traxler-type transition state to mediate C−C bond formation in a diastereoselective way. These dual-catalyzed reactions have a wide scope in VCCs and aldehydes (aliphatic aldehydes are less reactive, giving rise to lower yield of product) producing a total of 40 examples of *syn*-1,3-diols with typically high levels of diastereocontrol (dr ≥ 9:1, Scheme 3; derivatives **13**). Mechanistically, this process was studied in detail by a variety of spectroscopic techniques (transient absorption, UV−vis, IR, quantum yield experiments, Stern−Volmer quenching studies), DFT analysis, cyclic voltammetry and spectroelectrochemistry, and control experiments including a Hammett plot.[3,33] The key outcome of these studies showed that the diastereoselectivity is determined in the Zimmermann−Traxler transition state (Scheme 3), with a larger amount of the *syn*-diol being formed through a Curtin−Hammett scenario.

The predicted dr (96:4) via microkinetic modeling aligns well with the experimental value (95:5), and the stereocontrol is a function of various parameters including the nature of the ligand, the base, and the solvent.[3] Apart from these findings, another crucial observation was that the excited-state photocatalyst requires a catalytic base to produce turnover and is counter-productively quenched by the precatalyst Co(II)-Cl_2(DPEPhos). These intercatalyst interactions therefore play a decisive role in the overall catalytic efficiency of the system. A dual Pd/Ir-based photoredox catalyst system (Scheme 3, compounds **14**) was developed leading to enantio-enriched homoallylic alcohols with either a combination of contiguous tri/tetrasubstituted or tetra/tetrasubstituted carbon centers.[34] Despite the sterically challenging synthesis of these homoallylic alcohols **14**, appreciable enantiocontrol could be achieved up to 94:6 er, although in most cases lower enantioselectivity was observed. In this protocol, various dihydropyridines (DHPs) could be used as radical precursors providing a means to vary the nature of the quaternary stereogenic centers in the product. The most likely mechanistic scenario here is that upon formation of a chiral Pd(II)allyl intermediate, the organic radical that is formed by SET via the photocatalyst $Ir1^{PC}$ combines with the Pd(II) species (i.e., radical-metal crossover takes place). Consequently a Pd(III) complex is generated following reductive elimination (C−C bond formation) of the product and SET reduction of the resultant Pd(I) derivative to initiate the next turnover.[35]

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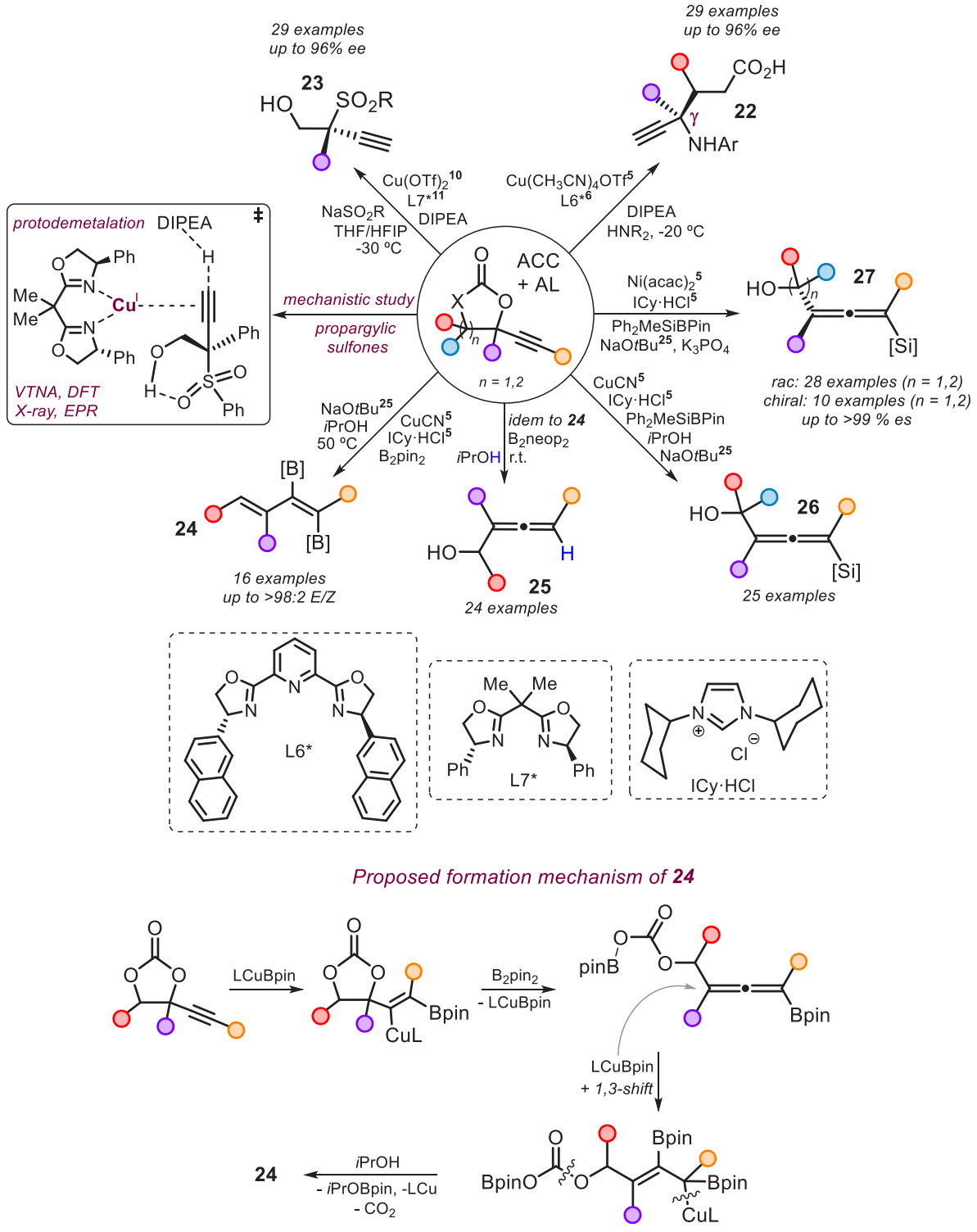
Scheme 5. Transformation of ACCs by Metal Catalysis[a]



[a]The superscripts refer to the loadings in mol %.

A different way to produce homoallylic alcohols is the combination of VCCs with radical precursors in a formal catalytic Co/photoredox process (Scheme 3, **15**).[36] While the process resembles greatly the one developed for compounds **12**, the key differences are the use of different catalyst components (i.e., $Co(X)_2{\cdot}nH_2O$ and the "bipy" ligand; here either 2,2′-bipyridine (bpy) or 6,6′-dimethyl-2,2′-bipyridine, (dmbpy)). In addition, some distinct reaction conditions were also needed to facilitate after initial decarboxylation of the VCC a β-hydroxy elimination step, affording 2-substituted 1,3-dienes as synthetic intermediates. This protocol thus creates new potential for VCCs as 1,3-diene surrogates under Co-catalysis. More specifically, they were shown to undergo highly regio- and stereoselective conversion (rr and dr values up to ≥99:1) into 1,2-dicarbofunctionalized homoallylic alcohols **15** with a wide scope of aldehydes and DHPs as reaction partners.

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More recently, we developed a three-component strategy for the coupling between VCCs, disubstituted olefins, and various radical precursors (DHPs and RBF_3K) under Ni/photoredox catalysis. This gave access to a wide range of (*E*)-configured allylic alcohols (Scheme 3, **16**).[37] The process is promoted by a Ni(II)bpy complex in combination with $Ir2^{PC}$ as a photocatalyst under basic conditions. All three components can be modulated allowing one to devise an ample scope of products **16** with good levels of steric and electronic modulation. The scope could be further widened by changing the VCC for other types of allylic precursors (vinyl epoxides and linear carbonates) and interestingly the use of 4CzIPN instead of the $Ir2^{PC}$. These variations gave rise to the other stereoisomer (*Z*) as the major reaction component. Such stereodivergent approaches have gained recent momentum in organic synthesis and offer exciting possibilities to access either stereoisomer by a simple switch in photocatalyst.[38,39]

In the last example of Scheme 3, a reductive, Ni-mediated coupling between two linear carbonates is shown, representing an unusual cross-coupling event.[40] This is a rather unusual coupling process leading to a "head-to-tail" connection between two allyl fragments, furnishing 1,5-dienes **17** with a quaternary stereogenic center. The enantio-induction level for these products **17** reached 98:2 er (using either L2* or L2′*) accompanied by high levels of regio-, stereo-, and chemocontrol. The mechanism of this cross-electrophile coupling (XEC) process was investigated by kinetic studies, EPR, NMR, isolation and crystallographic analysis of Ni-based intermediates, and various control reactions. The combined data are in line with both electrophilic and nucleophilic Ni^{II}(allyl) species being present, with divalent Zn playing an imperative role in mediating a bimetallic coupling pathway.

All results gathered in Scheme 3 (compounds **13**−**16**) demonstrate that the use of photoreductive conditions allows access to different kinds of metal−allyl species through SET processes and as a consequence novel reactivity patterns. The application of photocatalysis to enable cross-couplings such as those illustrated for the synthesis of **17** can be seen as a new way to create sterically dense stereocenters.

A different embodiment of our work also focused on related heterocyclic substrates and their use in formal allylic substitution processes (Scheme 4a). In this regard, changing one of the O atoms in the VCC precursor by a carbon one results into vinyl lactones (VLs), which thus far have been rarely investigated in the area.[41] Vinyl lactones can be activated by Pd(0) and after ring-opening, amination of the Pd(allyl) species occurs with *E* or *Z* stereochemistry. Apart from the stereochemistry, also the regioselectivity (linear vs branched) and chemocontrol (mono- vs diallylation) need to be controlled to favor the formation of the linear, *E*-configured ε-amino acid. In the latter case, the allylic amination can be combined with dehydrative ring-closure to form a caprolactam derivative of type **18**.[42] This catalytic methodology is one of the very few generic ones for functionalized lactones with a ring size of ≥7. Such lactones are of widespread interest to the field of polymer chemistry and may offer alternative monomers for the preparation of functionalized polyesters via catalytic ring-opening polymerization (ROP).[43]

Scheme 4b depicts a special type of an allylic alcohol precursor with a built-in carboxylic acid group, which likely activates the OH group toward oxidative addition to Pd(0) releasing H_2O and culminating in a palladacyclic intermediate through *C*,*O*-chelation.[44] The latter then activates the incoming pronucleophile (primary amine, RNH_2) for proton transfer resulting in the formation of a (*Z*)-configured γ-amino acid. The latter spontaneously cyclizes, forming an α,β-unsaturated γ-lactam of type **19**. This procedure is operationally simple, can be carried out at rt and delivers interesting building blocks for pharmaceutical development from accessible precursors. When the procedure involves secondary amines (R_2NH), an interesting stereodivergent synthesis of γ-amino acids can be realized.[45] Reoptimization of the initial procedure using diphosphine ligand L4 provided conditions that maximize the yield and stereocontrol toward (*Z*) configured products **20** with good levels of stereoselectivities and appreciable yields; both stereoisomers are separable by column purification. The synthesis of compound **20** is facilitated by a combination of $Pd(TFA)_2$ (TFA = trifluoroacetate) and the diphosphine dppp (1,3-diphenylphosphinopropane, bite angle 91.6°). In order to access the (*E*) products **21**, a higher amount of precatalyst $Pd(TFA)_2$ was needed (10 mol %) together with the presence of substituted DPEPhos L5 having a larger bite angle (∼101°).

The collective results in this section further exemplify that VCCs and related precursors, such as VLs and acyclic allylic alcohols with activating carboxylic acid groups, offer synthetic versatility to create compounds with higher levels of structural complexity. Such synthons are of potential value for follow-up chemistry in fine chemical and pharmaceutical discovery/development campaigns.

TRANSFORMATIONS INVOLVING ACCs AS SUBSTRATES

In the previous section, VCCs were discussed as modular allylic surrogates. As a logical extension, we surmised that alkynyl-functionalized cyclic carbonates (ACCs, see Chart 1) could serve as multipurpose precursors toward decarboxylative propargylic substitution reactions and allene formation reactions. We first scrutinized the use of ACCs with terminal alkyne groups in formal asymmetric propargylic substitution reactions under Cu-catalysis. Inspired by the seminal work of Nishibayashi in this area,[46,47] and the lack of generic protocols for the formation of γ-amino acids incorporating tertiary tetrasubstituted carbon stereocenters, we designed new types of alkyne-substituted lactones (Scheme 5, X = C, *n* = 1; ALs) to serve as suitable substrates in ring-opening amination.[48] The process takes advantage of the irreversible nature of the C−N bond formation reaction, as initial ring-opening of the five-membered lactone is thermodynamically disfavored. A structurally diverse family of γ-amino acid building blocks (29 examples) could be prepared under Cu-catalysis with high stereofidelity (er values up to 98:2, ee values up to 96%, Scheme 5, **22**). In some cases, spontaneous cyclization to the γ-lactams occurred which themselves are useful pharmaceutical synthons.[49] The presence of alkyne groups allows for further diversification, for instance via semi-hydrogenation to vinyl lactams and reduction to pyrrolidines.[48]

While for the preparation of chiral γ-amino acids **22** the utilization of PYBOX ligand L6* proved to be highly efficient, the enantioselective synthesis of elusive propargylic sulfones **23** (Scheme 5, X = O, *n* = 1) not only required a different ligand (BOX ligand L7*) but also revealed a crucial role for the base (DIPEA) in this manifold to attain high stereocontrol.[50] Products **23** were formed with up to 96% ee, with good variation levels of both the ACC and sodium sulfonate substrates. Remarkably, various other propargylic precursors

https://doi.org/10.1021/acs.accounts.3c00760
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(alkynyl epoxides and linear versions of the ACC) were tested under similar reaction conditions, but this showed either nonproductive catalysis (alkynyl epoxide) or significantly lower ee values of the products (linear substrates; ee up to 70%). As opposed to the use of alkynyl lactones (ALs), the conversion of ACCs into products **23** allows for increased potential for postsynthetic operation by virtue of the OH group and a wider exploration of chemical space. Initially, we believed that the enantio-discriminating step is a *re* facial attack of the sulfonate nucleophile onto a Cu(allenylidene) intermediate with product release controlled via protodemetalation following previous mechanistic hypotheses.[46,47] In addition, we observed a positive nonlinear effect (NLE), and this prompted us to investigate the reaction mechanism of this propargylic sulfonylation in detail.[4]

Variable Time Normalization Analysis (VTNA − using ReactIR) provided kinetic data from which a first-order dependence on [Cu] was determined. Furthermore, EPR analysis of the initial stage of the sulfonylation reaction supported the presence of a Cu(I) species in the productive cycle. This was further corroborated by isolation and crystallographic analysis of various Cu complexes during the preactivation stage. The combined experimental data served as valuable input for comprehensive DFT studies revealing that, unexpectedly, enantio-control is exerted during the proto-demetalation stage (Scheme 5) with a crucial role for the base. The developed computational model predicts an er of 99.5:0.5 while experimentally an er of 96.5:3.5 was achieved for a benchmark conversion. While it was clear from the isolation of various Cu(II) and Cu(I) complexes that only one ligand is involved in the productive cycle, calculations on the relative stability of homo- and heterochiral $Cu(L7^*)_2$ demonstrated that at the Cu(I) oxidation state, the heterochiral diligand Cu complex is significantly more stable than the homochiral ones thus explaining the experimentally observed NLE.

Apart from heterocyclic substrates possessing terminal alkyne substituents, ACCs decorated with internal alkyne groups as novel and modular precursors were also studied using both Cu- and Ni-catalysis (Scheme 5, compounds **24**−**27**). The change to Ni-catalysis altered the reactivity pattern typically encountered in propargylic substitution chemistry. Treatment of ACCs having internal alkyne groups (C≡C−R) with the diborane B_2pin_2 in the presence of catalytic Cu(ICy)CN formed *in situ* from CuCN, ICy·HCl, and NaO*t*Bu, delivered an easy entry for (*E*)-1,2-diborylated-1,3-dienes under high stereocontrol (*E*/*Z* up to 33:1).[51] Upon expanding the scope of diboranes, we encountered an interesting dichotomic effect. The presence of $B_2(neop)_2$ [short for bis(neopentyl glycolato)diboron] gave rise to a rather distinct product (**25**), viz., a 2,3-allenol under nearly the exact same reaction conditions applied in the preparation of compounds **24**. A rationale for this divergent reactivity is that after initial *syn*-addition of *in situ* formed Cu(Bpin) or Cu(Bneop), the introduction of a second Bpin is sterically more facile, leading to a diborylated product. Contrary to this, in the case of Bneop a *β*-oxygen elimination step occurs. This sets up the intermediate for deborylation and 2,3-allenol formation (cf., **25**), with *i*PrOH acting as a promotor for proto-demetalation as supported by deuterium labeling studies.

In a similar approach, when the diborane reagent is replaced by the silylborane $Ph_2MeSiBpin$, silylated 2,3-allenols are produced (Scheme 5, **26**) with ample structural variation.[52] In this protocol, allenes with four different substituents are generated under attractive conditions (rt, accessible reagents). Preliminary results indicated that other silylboranes such as $Et_3SiBpin$ also productively participate in giving silylated allene derivatives, and iodination of these 2,3-allenols creates access to tetrasubstituted dihydrofurans. In order to expand these silylations, two further variations were considered: (a) using larger-ring congeners of the ACC ($n = 2$) and (b) replacing Cu with Ni in the catalytic protocol. The use of Ni-catalysis holds promise as a relatively unexplored approximation, but if successful it may allow for enantiospecific point-to-axial chirality transfer taking advantage of the known potential of Ni catalysts in stereospecific cross-coupling reactions.[53] The activation of a Ni(II) precursor takes place under virtually the same conditions as in the Cu-mediated methodologies and starts with its reduction to Ni(0). Oxidative addition of the ACC to Ni(0) is followed by the formation of an intermediate silyl-Ni(allenyl) species after decarboxylation, and finally reductive elimination occurs to afford the products **27** (Scheme 5).[54] The diversity of racemic silylated 2,3- and 3,4-allenols is quite broad (28 examples), whereas the initial hypothesis of enantiospecific conversion of chiral ACCs into chiral 2,3- and 3,4-allenols by Ni-catalysis could be substantiated by a modest scope of products with the enantiospecificity reaching >99%.[54]

■ OUTLOOK AND OPPORTUNITIES

In this Account, we present various heterocyclic substrates that have become rather privileged scaffolds in TM-mediated stereoselective synthesis. Their modular nature in terms of ring size, variation of the type of heterocycle, stereoelectronic features, and functionality have enabled a wide range of synthetic transformations based on unusual reactivity patterns empowered by transition metal catalysis. Two-electron based catalytic conversions offer a way to expand known methods for the synthesis of stereodefined linear/branched allylic derivatives and propargylic compounds. Moreover, SET-based processes have allowed widening of the scope via unprecedented manifolds and reaction (radical) intermediates. Despite the progress achieved in the area by our group and others, the range of applications still remain limited. There is a clear need to further diversify the heterocyclic (and related) substrates by introducing other types of functional groups (such as allenes). Also, it would be useful to generate reactive intermediates akin to the 1,3-diene derived from VCCs (for instance, 1,3-enynes). Lastly, examination of larger congeners (six- and seven-membered analogues of VCCs and ACCs) may create additional potential. Combined, such potential developments will create new opportunities for stereoselective substitutions, cycloaddition reactions, and radical-based functionalization approaches based on metal catalysis. In this context, we believe that conventional metals such as Pd, Ir, Rh, and Ru may be replaced by less commonly used Fe, Co, Mn, and Ni harnessing their large potential for SET and rich redox chemistry. However, in order to enable such a transition, a profound knowledge of how to control the reactivity of alternative base metal complexes and catalysts is required. Such a shift of the conventional reactivity paradigm necessitates a strong alliance between different disciplines leading to an extended toolbox for catalytic transformations of complex small molecules with challenging stereoelements. In this respect, a thorough and detailed mechanistic understanding of these processes will be key to advancing the field, and the use of computational and AI-based approaches will likely gain

https://doi.org/10.1021/acs.accounts.3c00760
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importance. Another crucial aspect will be to increase the efficiency of the synthetic methodologies leading to tertiary and quaternary stereocenters in terms of reaction times, selectivity profiles, and scalability, which are frequently affected by the sterically demanding nature of the (cross-)coupling processes. Further to this, there is little current potential to control processes that furnish compounds with contiguous stereogenic centers and, combined with the aforementioned challenges, remain important topics to be studied and resolved.

AUTHOR INFORMATION

Corresponding Author

Arjan W. Kleij − *Institute of Chemical Research of Catalonia (ICIQ), the Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain; Catalan Institute of Research and Advanced Studies (ICREA), 08010 Barcelona, Spain;* orcid.org/0000-0002-7402-4764; Email: akleij@iciq.es

Authors

Debasish Ghorai − *Institute of Chemical Research of Catalonia (ICIQ), the Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain;* orcid.org/0000-0001-7051-1613

Balázs L. Tóth − *Institute of Chemical Research of Catalonia (ICIQ), the Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain*

Matteo Lanzi − *Institute of Chemical Research of Catalonia (ICIQ), the Barcelona Institute of Science and Technology (BIST), 43007 Tarragona, Spain*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.3c00760

Author Contributions

CRediT: **Debasish Ghorai** conceptualization, investigation, writing-review & editing; **Balázs L. Tóth** conceptualization, investigation, writing-review & editing; **Matteo Lanzi** conceptualization, investigation, writing-review & editing; **Arjan W. Kleij** conceptualization, investigation, writing-review & editing.

Notes

The authors declare no competing financial interest.

Biographies

Debasish Ghorai received his B.Sc. in Science from Vidyasagar University (India) and M.Sc. in Chemistry from IIEST. After completing his Ph.D. degree (2014) at IIT Kharagpur under the supervision of Prof. Ganesan Mani, he carried out postdoctoral work at IISER Bhopal with Prof. Joyanta Choudhury, at the Georg-August Universität, Göttingen (Germany) with Prof. Lutz Ackermann, and at NC State University (Raleigh, USA) with Prof. Stefano Menegatti. At present, he is a postdoctoral fellow at ICIQ (Tarragona, Spain) in the group of Prof. Arjan W. Kleij working on novel Ni-mediated regio- and enantioselective allylic transformations.

Balázs L. Tóth obtained his Ph.D. in 2020 with Zoltán Novák at Eötvös Loránd University (ELTE), Budapest, Hungary. During his Ph.D. he did a half-year internship in the laboratory of Burkhard König at the University of Regensburg, Germany. In 2021, he started to work as a postdoctoral researcher with Martin Fañanás Mastral at CiQUS, Santiago de Compostela, Spain. He joined the team of Arjan W. Kleij at ICIQ in 2022 as a Marie Curie Fellow. Recently, he started investigating novel Co/photoredox dual catalytic transformations using cyclic carbonate precursors.

Matteo Lanzi obtained his M.Sc. in 2017 at the University of Parma (Italy) with Prof. Giovanni Maestri. Later on, he joined the same research group as a Ph.D. student, working on transition metal catalyzed and photoredox polycyclization of unsaturated substrates. After postdoctoral appointments in the groups of Ryan Gilmour (Münster, Germany) and Joanna Wencel-Delord (Strasbourg, France), he joined the Kleij research group at ICIQ where he holds a Marie Curie Fellowship. His current research is focused on the development of new enantioselective metal-catalyzed transformations to assemble functionalized allylic and propargylic compounds.

Arjan W. Kleij is an ICREA professor and ICIQ Group Leader at the Institute of Chemical Research of Catalonia (Tarragona, Spain). After his Ph.D. with Gerard van Koten at the University of Utrecht (The Netherlands), he completed two postdoctoral positions at the Autonomous University of Madrid (with Javier de Mendoza) and the University of Amsterdam (with Joost Reek) and two industrial appointments in The Netherlands at Avantium Technologies (Amsterdam) and Hexion Specialty Chemicals (Rotterdam). Since October 2006, he is based at ICIQ and focuses on the use of metal-promoted stereoselective transformations empowered by modular and easy-to-assemble heterocyclic precursors.

ACKNOWLEDGMENTS

The authors thank the Cerca program/Generalitat de Catalunya, ICREA, MICINN (PID2020-112684GB-I00 and Severo Ochoa Excellence Accreditation 2020−2023 CEX2019-000925-S), and AGAUR (2017-SGR-232) for support. D.G. appreciates postdoctoral funding from AGAUR (2018-BP-00243) and AEI (PCI2021-122021-2B), and B.L.T. and M.L. received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreements 101026029 and 101105057.

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