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Intermediate Control: Unlocking Hitherto Unknown Reactivity and Selectivity in N-Conjugated Allenes and Alkynes

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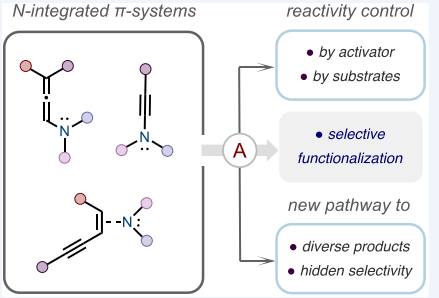
CONSPECTUS: Controlling selectivity through manipulation of reaction intermediates remains one of the most enduring challenges in organic chemistry, providing novel solutions for selective C−C π-bond functionalization. This approach, guided by activation principles, provides an effective method for selective functional group installation, enabling direct synthesis of organic molecules that are inaccessible through conventional pathways. In particular, the selective functionalization of N-conjugated allenes and alkynes has emerged as a promising research focus, driven by advances in controlling reactive intermediates and activation strategies. In this regard, our group, alongside others, has established some new approaches that have emerged as a suitable platform for the synthesis of functionalized enamides. This Account reviews recent developments in the field, highlighting new modes of reactivity and selectivity, atom-economical functionalizations, and strategies for regio- and stereocontrol, while providing mechanistic insights into related transformations.



Our study is systematically organized into two sections based on substrate type and chronological research progression. In the first section, we establish a platform by controlling allenamide-derived intermediates, enabling both allenamide-alkyne (AA) cross-coupling and a few novel electrophile-promoted hydrofunctionalization reactions. The unprecedented selectivity in Pd-catalyzed allenamide-alkyne cross-coupling is achieved through neighboring group chelation, with phosphine ligand selection controlling the reaction outcome. In parallel, the electrophile-promoted functionalizations—including haloalkynylation, hydrooxycarbonylation, hydrodifluoroalkylation, and intermolecular hydroamination—are achieved through strategic selection of electrophiles or their precursors.

Additionally, our findings demonstrate how ynamides' reactivity toward both electrophiles and nucleophiles, controlled through activator modulation, expands the scope of accessible transformations. Key findings include: (1) chemoselective [2 + 2 + 2] annulation through efficient trapping of N-arylated nitrilium electrophiles by ynamides, (2) divergent C−H annulation of indole-derived vinylogous ynamides controlled by metal and ligand selection via intramolecular hydroarylation, (3) bromoalkynylation-enabled functional group migration through a novel 1,3-alkynyl shift.

The final section explores how N-electron polarization in 1,3-enynes enables new chemoselectivity in metal-free inter- and intramolecular couplings with indole substrates. Our findings demonstrate that modulating N-electron conjugation within the enyne skeleton—through both linear and cross conjugation—can direct activation pathways and control product selectivity.

This Account aims to stimulate broader research into the intermediate-controlled functionalization of activated π-systems. Future research directions include advanced activator design, novel functional group migration strategies, and deeper mechanistic studies to enable rational reaction development.

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- Pradhan, T. R.; Paudel, M.; Feoktistova, T.; Cheong, P. H.-Y.; Park, J. K. Silaborative Assembly of Allenamides

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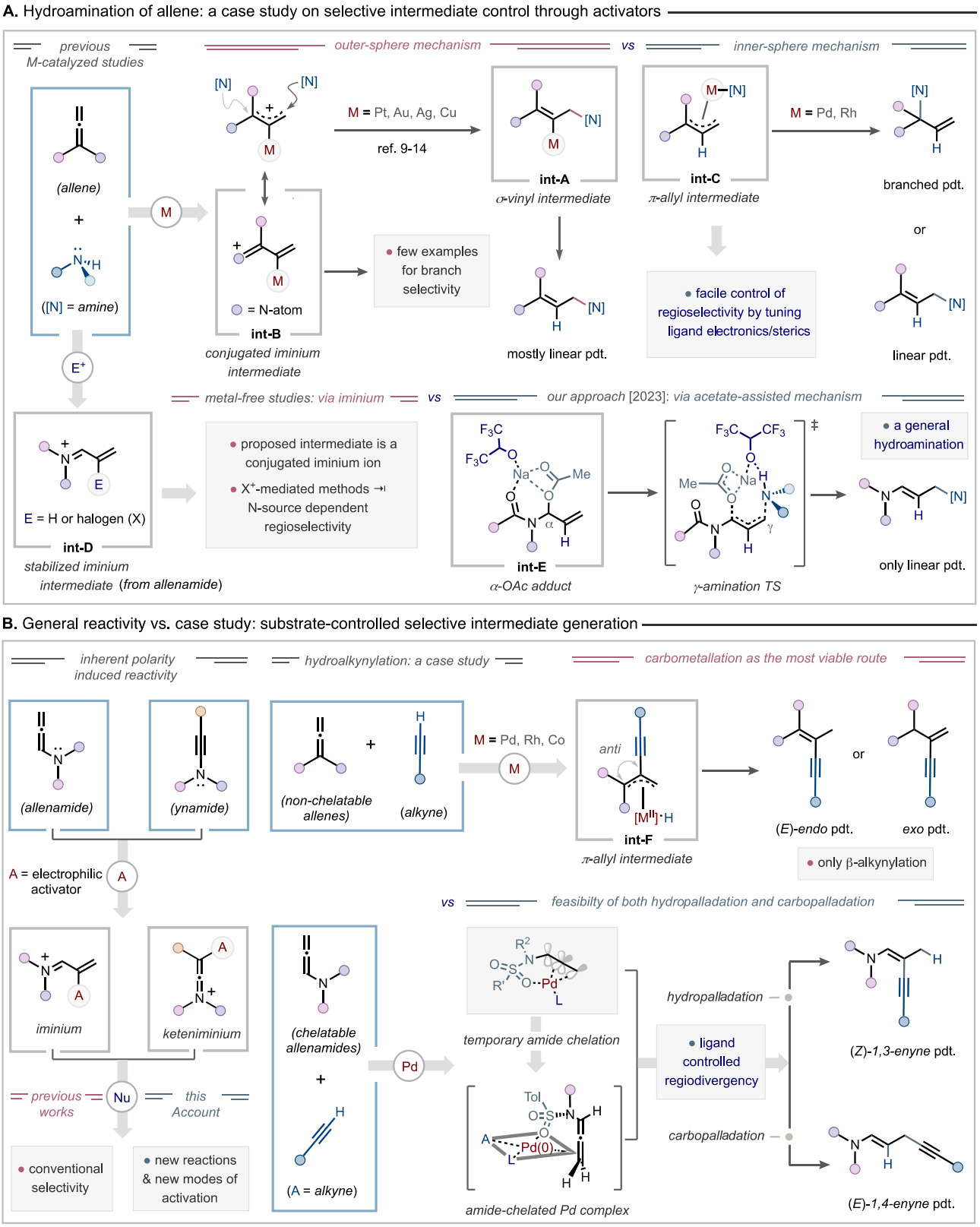
Scheme 1. (A) Case Study for Activator Controlled Allene Hydroamination; (B) Case Study for Substrate Controlled Allene Hydroalkynylation



and Alkynes: Highly Regio- and Stereocontrolled Access to Bi- or Trimetallic Skipped Dienes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e2021161.[2] Achieving interelementation with Si—B reagents in the assembly of two distinct π-systems has remained challenging, particularly in intermolecular reactions. A phosphine-free Pd(0) catalyst elegantly facilitates this tricomponent transformation.

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- Alam, K.; Hong, S. W.; Oh, K. H.; Park, J. K. Divergent C−H Annulation for Multifused N-Heterocycles: Regio- and Stereospecific Cyclizations of N-Alkynylindoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 13387−13391.[3] This study demonstrates regiodivergent intramolecular C−H annulation through metal- and ligand-controlled hydroarylation.
- Sagar, K.; Pradhan, T. R.; Farah, A. O.; Wise, H. R.; Merja, B. C.; Srimannarayana, M.; Cheong, P. H.-Y.; Park, J. K. General Hydroamination of Allenamides: Mechanistic Insights with an Acetate Adduct and 1,1,1,3,3,3-Hexafluoro-2-propanol. *Org. Lett.* **2023**, *25*, 5574−5578.[4] The first H^+-mediated intermolecular hydroamination of allenamides was achieved through strategic acetate additive incorporation.

1. INTRODUCTION

The greater the contrast, the greater the potential. Great energy only comes from a correspondingly great tension of opposites.

- Carl Gustav Jung

In this Account, we examine how contrasting reaction pathways and reactive intermediates give rise to distinct selectivity patterns in organic synthesis.[5] This principle is particularly evident in the retrosynthetic analysis of C−C π-systems,[6] where systematic comparison of reactive intermediates reveals the underlying control elements of chemical transformations. Structural variations of π-carbogenic fragments dictate coupling selectivity,[7,8] while the interplay between reactive intermediates, coupling partners, and activators enables precise control over reaction outcomes. However, to understand the significance of a new reactivity platform and its contrasting selectivity, it is crucial to identify the specific role of reactive intermediates involved in the transformation.

1.1. Defining the Significance of Intermediate Control via Activators: An Illustrative Example

Scheme 1A illustrates this principle through a fundamental allene hydroamination reaction that enables regiodivergent formation of branched or linear products. Panunzi's pioneering 1978 report described a platinum-mediated linear-selective hydroamination of neutral allenes with amines.[9] This noncatalytic C−N bond formation via π-philic activation established the foundation for subsequent catalytic methods.[10−16] π-Philic metal activators including Pt,[10] Au,[11,12] Ag,[13] and Cu[14] facilitate amine interception through an outer-sphere mechanism, generating metal-bound σ-alkenyl complex **int-A** to yield linear amination products (with rare exceptions via **int-B**[10b]). Conversely, Pd[15] and Rh[16] catalysts—controlled by ligand selection—enable selective formation of either regioisomer through an amine-ligated metal-bound π-allyl intermediate (**int-C**). While the regiochemistry of both pathways depends on the choice of metal and ligand, inner-sphere mechanisms typically provide superior selectivity control, enabling the formation of either α- or γ-amination products.

In transition metal-free systems, electrophile-bound intermediates (**Int-D**) direct C−N bond formation with functionalized partners in both inter- and intramolecular reactions.[17,18] In such cases, the regiochemical outcome depends on both the electrophilic activator (H^+ or X^+) and amine nucleophilicity. To constitute a general approach, our laboratory recently developed a distinct approach to this transformation through H^+ activation of N-conjugated allenes (allenamides).[4] HFIP-mediated allenamide protonation generates a reactive electrophilic intermediate (**int-E**) stabilized by NaOAc, enabling a general allenamide-amine coupling. While mechanistically related to other metal and metal-free couplings, this intermediate-guided strategy achieves unique regioselectivity through γ-amination. This approach demonstrates how precise control of reaction intermediates—that is, amination of **int-E** through γ-amination TS—can unlock novel transformation pathways.

1.2. Controlling Selectivity through Substrate Chelation and Ligand Coordination

Electron-biased π-systems (allenamides and ynamides) enable efficient exploration of chemical selectivity while maintaining modularity and atom economy, offering strategic advantages through intermediate control.[19−21] These π-systems exhibit two fundamental reactivity modes: N-lone pair electron delocalization and N-neighboring group chelation with activators. N-Electron delocalization generates polar intermediates (conjugated iminium[17,18] or keteniminium species[22]) for subsequent electrophilic and nucleophilic additions (left, Scheme 1B). For instance, the hydroamination reaction proceeds through electrophilic activation,[4] as illustrated in Section 1.1. Alternatively, the keteniminium reactivity of ynamides can be manipulated to reveal an unconventional phenomenon, unlocking new avenues for skeletal diversity (vide infra, not discussed here in detail).[22]

In chelation-controlled functionalization, stereo- and regiochemical outcomes are directed through temporary chelation between a metal activator, neighboring group, and coordinating ligand. This interaction leads to selectivity patterns distinct from nonchelatable substrates (Scheme 1B). Traditional hydroalkynylation of electron-deficient and neutral allenes proceeds through carbopalladation, generating π-allyl intermediates that yield β-selective products as two (*E*)-1,3-enyne regioisomers with electron-rich phosphine ligands.[23] While (*Z*)-stereo- and γ-regioselectivity appeared beyond conventional allene-alkyne coupling due to $\pi-\sigma-\pi$ equilibrium constraints, we discovered that chelation control of σ-vinyl intermediates enables two novel atom-economical coupling reactions when paired with sterically appropriate electron-rich ligands.

In this Account, we highlight recent transformations and research findings from our groups that demonstrate how reaction outcomes can be controlled through strategically activated substrates and carefully chosen activators. We assert that this compilation provides valuable retrosynthetic relationships that complement conventional reactivity patterns.

2. ELEVATING NEW SELECTIVITY WITH ALLENAMIDE AS A SUBSTRATE

2.1. Regiodivergent Hydroalkynylation

Hydroalkynylation has emerged as a powerful strategy for the atom-economical synthesis of (*cis*- or *trans*)-1,3- and 1,4-enynes from diverse allenic substrates.[8,23] Our research group recently achieved the first synthesis of *cis*-1,3- and 1,4-enynes using allenamides as substrates, opening new mechanistic pathways for exploration.[1]

Previous reports of allene hydroalkynylation under various metal catalysts follow a carbometalation mechanism (with few

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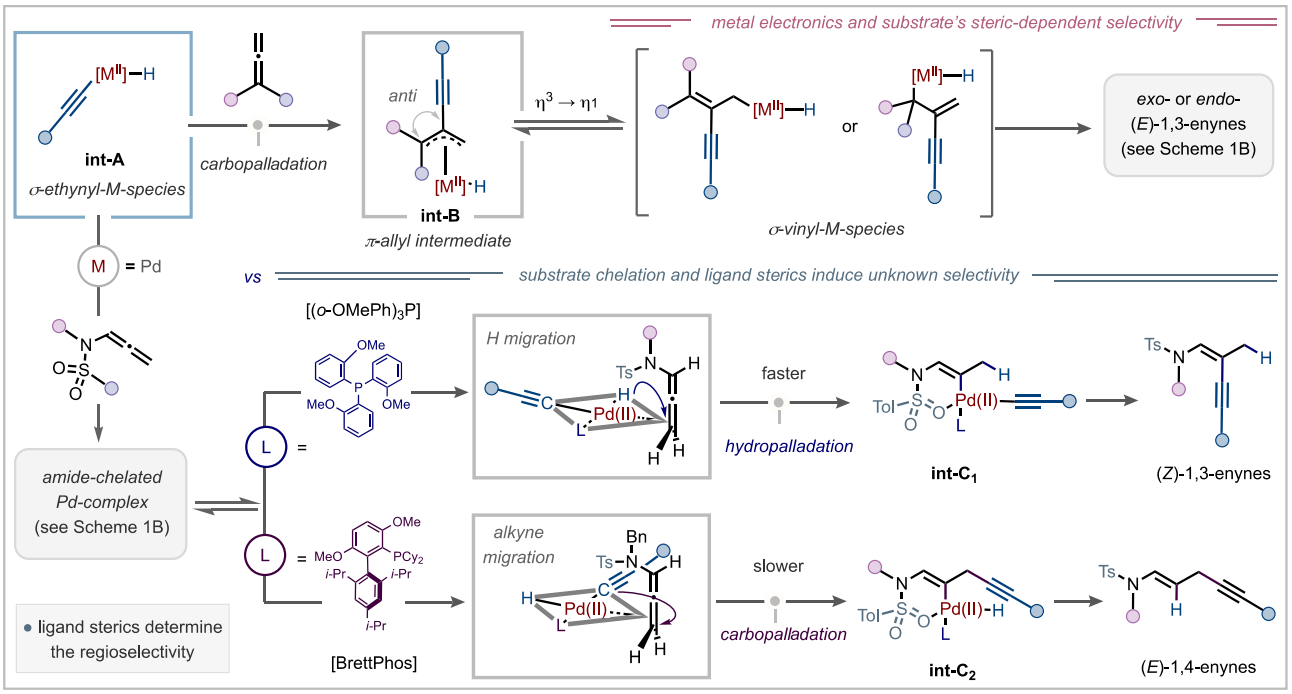
Scheme 2. Comparison of Our Regiodivergent Hydroalkynylation with Other Methods



exceptions[24]), yielding exclusively *trans*-1,3-enynes. Mechanistically, a σ-ethynylmetal species (**int-A**) intercepts the allene component at the β-position, forming an η^3-complex through carbopalladation. While *endo*/*exo*-product selectivity is governed by metal-catalyst electrophilicity through $\eta^3 \rightarrow \eta^1$ equilibrium, steric effects of (α) allenic substituents determine *E*-selectivity for *endo* enynes.

Whereas our methodology leverages neighboring group chelation and phosphine ligand effects to control intermediate reactivity, enabling divergent synthesis of *cis*-1,3-enynes and *trans*-1,4-enynes (Scheme 2). We hypothesized that these unprecedented selectivities could arise by redirecting π-allyl-Pd intermediates toward σ-vinyl-Pd species (**int-C$_1$** and **int-C$_2$**). Using $Pd(OAc)_2$, the electron-rich phosphine [(*o*-OMePh)$_3$P] promotes β-alkynylation via hydropalladation and H-migration, while the sterically bulky phosphine (BrettPhos) facilitates γ-alkynylation through carbopalladation through alkyne migration. The exceptional stereo- and regiocontrol achieved highlights the unique reactivity of allenamides compared to other allenic substrates.

2.2. Silaborative Coupling of Allenamides and Alkynes

Our approach leverages chelation assistance to regulate σ-Pd intermediates, aiming to develop atom-economical AA coupling through multicomponent reactions and synthesize novel π-carbogenic scaffolds. The interelemental reagent ($Me_2PhSiBpin$) emerged as an ideal candidate for diversification. We recognized that sulfonyl-chelation, combined with slow reductive elimination, could orchestrate a new category of bond-forming processes (Scheme 3).[2] Scheme 3 illustrates how substrate chelation directs the assembly of silaborated 1,4-skipped dienes via an η^1 complex. The mechanism begins with allenamide borylation to form intermediate **int-A**, which is intercepted by alkyne from a sterically accessible site. Notably, the two-component allene-silaboration adduct—a major side product with phosphine ligands (bottom, Scheme 3) or without suitable chelating groups—was previously achieved using phosphine ligands and neutral allenes.[25] This demonstrates that **int-A** must react with alkyne before reductive elimination to yield the silaborated coupling product. In collaboration with Cheong, density functional theory (DFT) calculations revealed that contraselective alkyne silylation (versus alkyne allylation) determines the regioselectivity of final C−Si bond formation, proceeding through an η^1 complex → **int-B**. This chelation-assisted, ligand-controlled pathway is particularly significant as its chemoselective reactivity in three-component coupling surpasses potential two-component pathways involving allene-hydroalkynylation, allene-silaboration, and alkyne-silaboration.

This ligand-free strategy could be extended to other π-systems—including alkenes, enynes, and ynamides—as alkyne replacements. Additionally, alternative bimetallic reagents such as B_2Pin_2 could enable efficient synthesis of versatile borylated analogue.

2.3. Alkynylation via Electrophilic Activation

While Pd-catalyzed alkynylative functionalization of allenamides efficiently accesses valuable chemical space, transition-metal-free alkynylation offers complementary tactical advantages. Our research group discovered that allenamides, when converted to β-halo N,O-aminals under halonium activation conditions,[26] become competent electrophilic partners.[27] In the presence of Lewis acids such as $BF_3{\bullet}OEt_2$, these N,O-aminals generate iminium ions that readily intercept nucleophilic alkynes (Scheme 4). Other groups have reported complementary alkynylation methodologies using premetalated alkyne nucleophiles in 1,2-addition processes.[28] The preformed conjugated iminium electrophile (**int-A**) enables unprecedented 1,4-selective alkynylation reactions, offering advantages in both stereo- and regioselectivity while accessing elusive carbon skeletons (bottom, Scheme 4). Under base-mediated conditions, the method accommodates diverse π-

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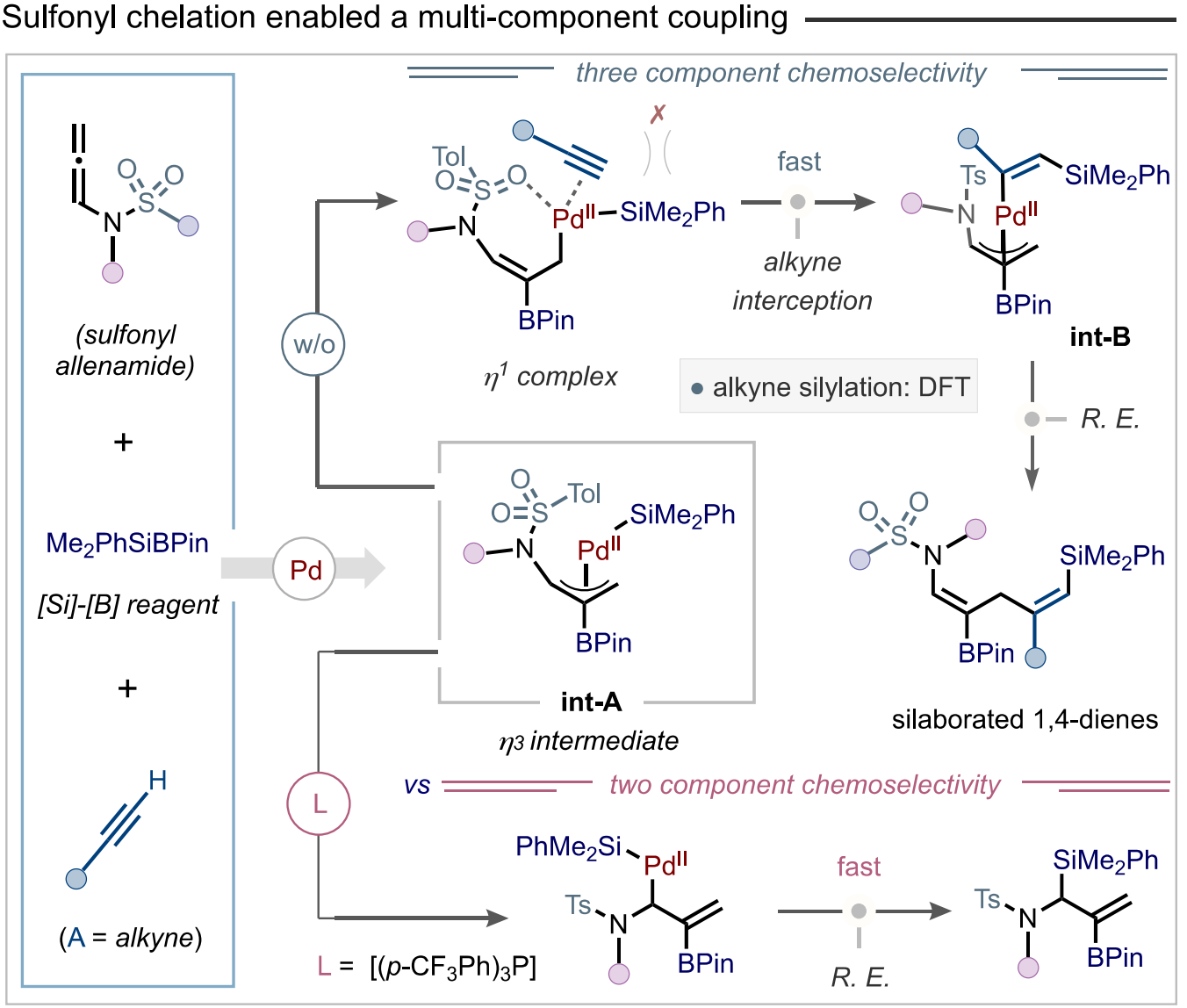
Scheme 3. Chelation-Assisted Phosphine-Ligand-Free Silaborative Assembly



systems and even enables cyclobutene ring formation. This approach enables synthesis of functionalized 1,4-enynes through Pd-catalyzed C−Br bond transformation. The nucleophilic addition's regioselectivity stems from the stability of iminium intermediate (**int-A**), as revealed through computational analysis and control experiments with electron-rich allenes. Notably, regioselectivity diminishes with nonelectron-withdrawing N-substituents, highlighting the crucial electronic cooperation between N-substituents and adjacent halogens in stabilizing the electrophilic vinyl halide species. In situ ^{1}H NMR and ESI-HRMS studies (showing isotopic molecular ion peaks) confirmed the existence of sulfonyl iminium intermediates. This identification of viable electrophilic species for nucleophilic addition—for example, Csp- or Csp^{2}-based nucleophiles—provides a powerful strategy for incorporating halogen atoms into valuable synthetic intermediates.

2.4. Allenamide Hydrofunctionalization via H+ Activation

We next focused on developing concise hydrofunctionalization routes that could offer unique reactivity profiles and enable selective enamide synthesis, distinct from established metal-catalyzed methods. This approach required careful consideration of activation parameters to generate desired intermediates while optimizing efficiency and selectivity.

2.4.1. Hydrooxycarbonylation. Hydrooxycarbonylation—the atom-economical coupling of carboxylic acids with terminal allenes—provides distinct advantages over traditional esterification methods. With neutral allenes, conventional metal catalysts (Pd, Rh, Ir, or Ag) operate through metal hydride activation to generate π-allyl metal intermediate **int-A** (Scheme 5).[12] While precious metal catalysts and ligands present practical challenges, the regioselectivity for electron-rich allenes (allenamides) is governed by electronic interactions between catalyst and substrate. Monnier demonstrated a strategic ligand-free Cu-catalyzed approach controlling alkenyl-copper intermediate (**int-B**) through cationic copper species.[29] However, this method faces limitations in complex molecular settings where multiple heteroatoms (N, S, O) can diminish Cu-catalytic activity and compromise chemoselectivity (bottom left, Scheme 5). Our research group developed a metal- and exogenous reagent-free method using H^{+}-activation

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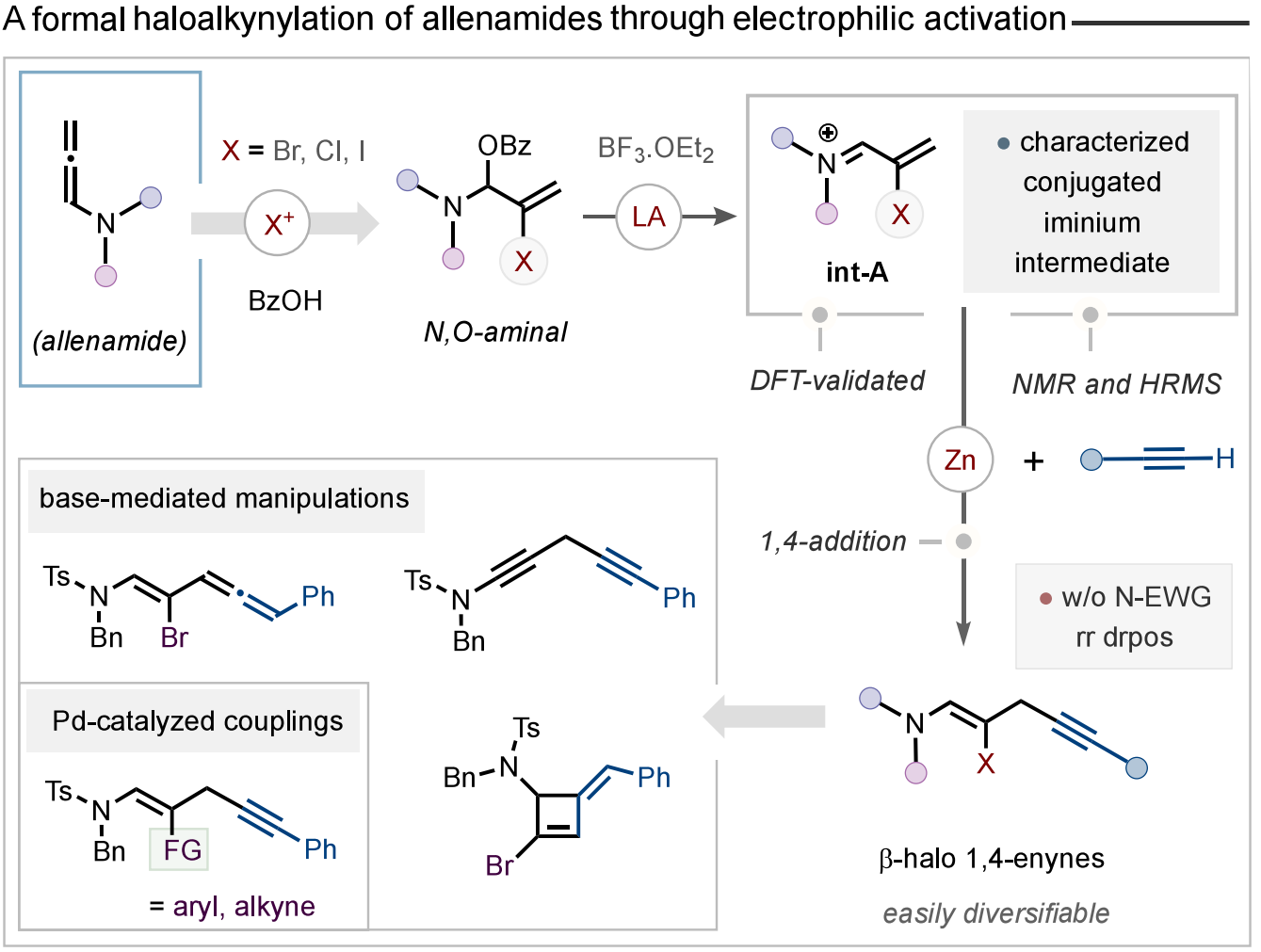
Scheme 4. Lewis-Acid-Mediated Iminium Formation for Alkyne Interception



to overcome these challenges (Scheme 5).[30] Notably, complex molecules that proved unreactive or low-yielding under Cu-catalysis underwent successful transformation using our method. DFT computations revealed a two-step electrophilic activation mechanism: carboxylic acid protonates the allenamide to form iminium-carboxylate complex **int-C**, followed by carboxylate interception of the vinylogous iminium terminus via 1,4-addition.

In collaboration with Kim's group, we extended this metal-free strategy to polymeric carboxylic acids (bottom right, Scheme 5) for postpolymerization modification (PPM).[31] Under modified conditions [100 °C in 1,4-dioxane/DME], diverse polymeric carboxylic acids—including sterically hindered methacrylic and acrylic acid copolymers—underwent efficient PPM to generate functional acrylate polymers with excellent conversion.

2.4.2. Hydroamination. While H^+ activation enables intramolecular allene-amine coupling through Brønsted-acid-activated π-allylic carbocation intermediates **int-A** (top, Scheme 6),[17] its limited amine scope restricts broader application. We hypothesized that H^+-mediated allene hydroamination could overcome these limitations by generating novel transient electrophilic intermediates (bottom, Scheme 6).[4] In collaboration with Cheong, we developed a new metal-free hydroamination protocol that achieves consistent chemo- and regioselectivity across diverse amine substrates.[32] Reaction optimization revealed that 1 equiv of NaOAc with 5 equiv of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) significantly enhanced efficiency, while DFT calculations elucidated the mechanistic role of NaOAc.

Mechanistic studies demonstrated that HFIP-mediated allenamide protonation generates an electrophilic intermediate enabling γ-selective attack by N-nucleophiles. Theoretical studies confirmed this pathway—ruling out an iminium intermediate—and revealed barrierless formation of the α-OAc adduct leading to the major hydroamination product. Acetate proves crucial by stabilizing the intermediate and directing γ-regioselectivity. Without NaOAc, both α- and γ-intermediates form, but neither generates the γ-adduct (via TS-1 or TS-2) due to high energy barriers and unfavorable reaction thermodynamics (bottom, Scheme 6). This aligns with experimental observations of 1:1 HFIP-adduct to product ratio. The preferred mechanism involves an acetate-associated intermediate enabling γ-selective nucleophilic addition to the α-OAc adduct. This differs from previous studies by Colmer[33] and Baidya,[34] where aryl amines preferentially undergo C-*para*-selective addition via a carbocationic intermediate in the rate-determining step.

2.4.3. Hydrodifluoroalkylation. While electrophilic activation of allenamides typically employs direct H^+ activators, hidden Brønsted acids (HBAs) offer distinct advantages through gradual H^+ release. Recently, Yu and Zhou

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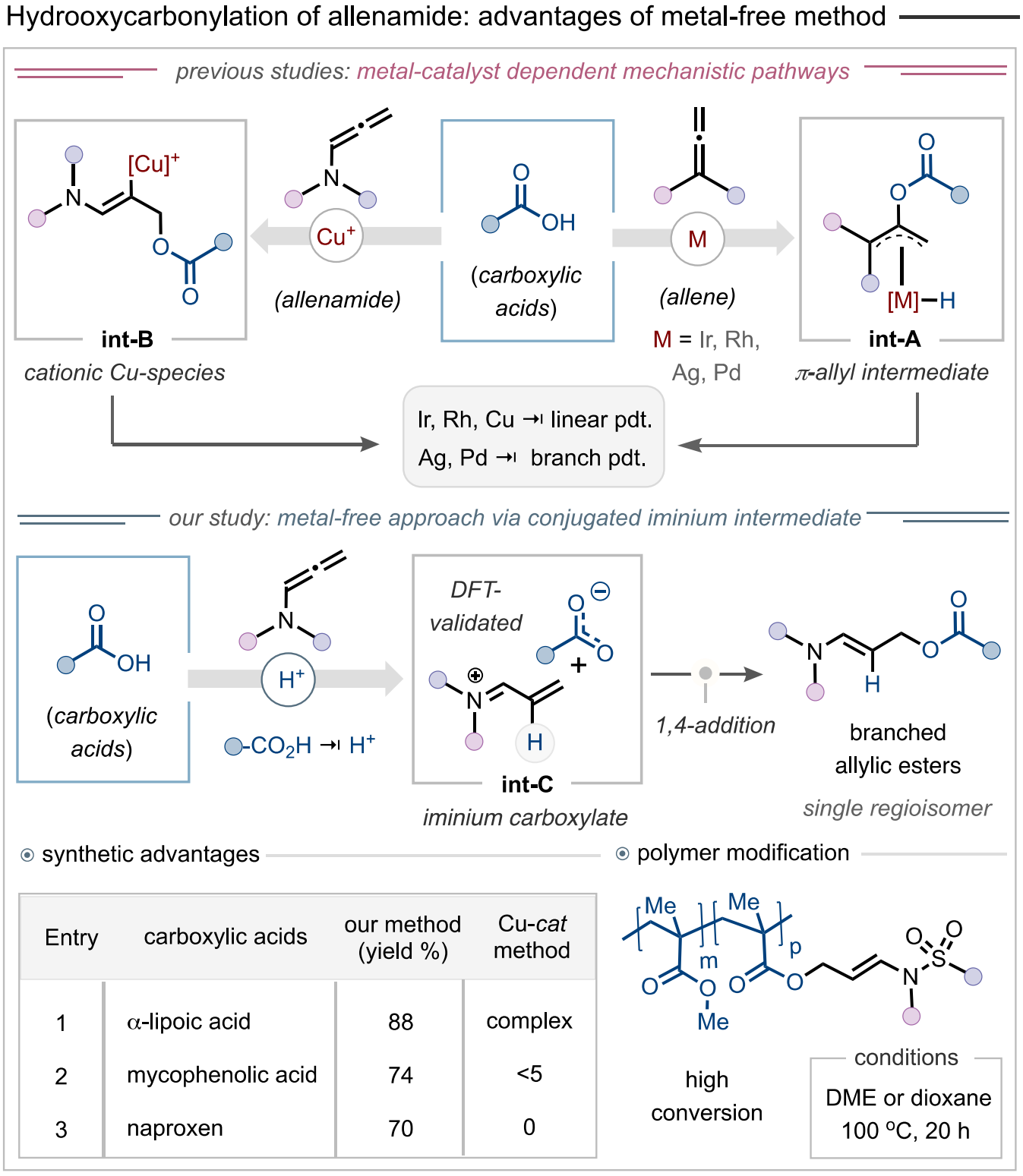
Scheme 5. Intermediate-Controlled Hydrooxycarbonylation



demonstrated that α,α-difluoroenoxysilanes (DFES) with hydrated $Mg(ClO_4)_2$ enable gentle carbocation formation from alkenes in hydrodifluoroalkylation (HDFA) reactions, achieving Markovnikov selectivity.[35] However, achieving high regio- and chemoselectivity with conjugated and cumulated π-systems like enones remains challenging.[36b] We proposed a difluoroenolate transfer to allenamides using HBA catalysis to enable selective α,α-difluoroketone synthesis. This approach addresses two key challenges (top, Scheme 7):[36b] (1) dehydroxylative and deacyloxylative difluoroalkylation typically produces regioisomer mixtures through S_N1/S_N1' and S_N2/S_N2' pathways, (2) catalytic decarboxylative allylation requires introduction of the α,α-difluoroketone group as an allylic carboxylate ester.

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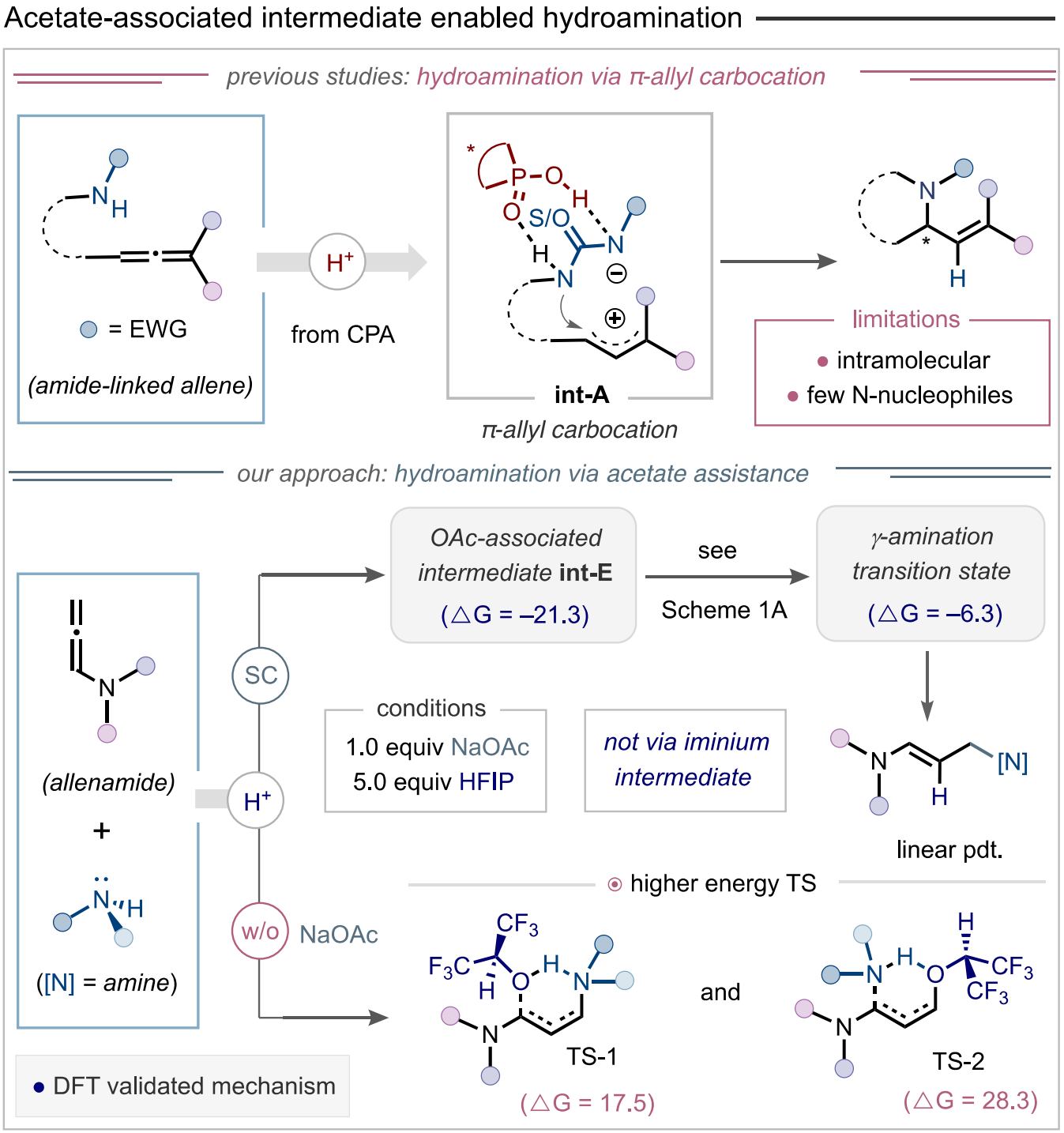
Scheme 6. H^+-Mediated and Acetate-Assisted Allene Hydroamination Reactions



Our lab recently developed the first HBA-catalyzed hydrodifluoroalkylation of allenamides using $Mg(ClO_4)_2{\cdot}6H_2O$ (bottom, Scheme 7).[36a] This catalyst serves dual functions in forming conjugated iminium intermediate (**int-A**): proton donation and perchlorate-mediated iminium stabilization, which effectively captures DFES while suppressing hydrolysis. Mechanistic studies, including in situ ^1H NMR detection of intermediates, confirmed H^+ transfer from residual solvent water and crystal water of $Mg(ClO_4)_2{\cdot}6H_2O$. Substoichiometric $Mg(ClO_4)_2{\cdot}6H_2O$ (without adding $HClO_4$) led to hydrolysis products due to longer reaction time, confirming the importance of adequate acidity.

This mild, selective method exhibits broad functional group tolerance and γ-selective chemoselectivity for mono- and disubstituted allenamides. The resulting γ-HDFA products serve as versatile intermediates, enabling stereocontrolled access to valuable halogenated enamides, multifunctional enamides, and pyran derivatives through electrophilic halogenation and carbonyl functionalization. The development of this HBA catalyst establishes a new paradigm for allenamide activation.

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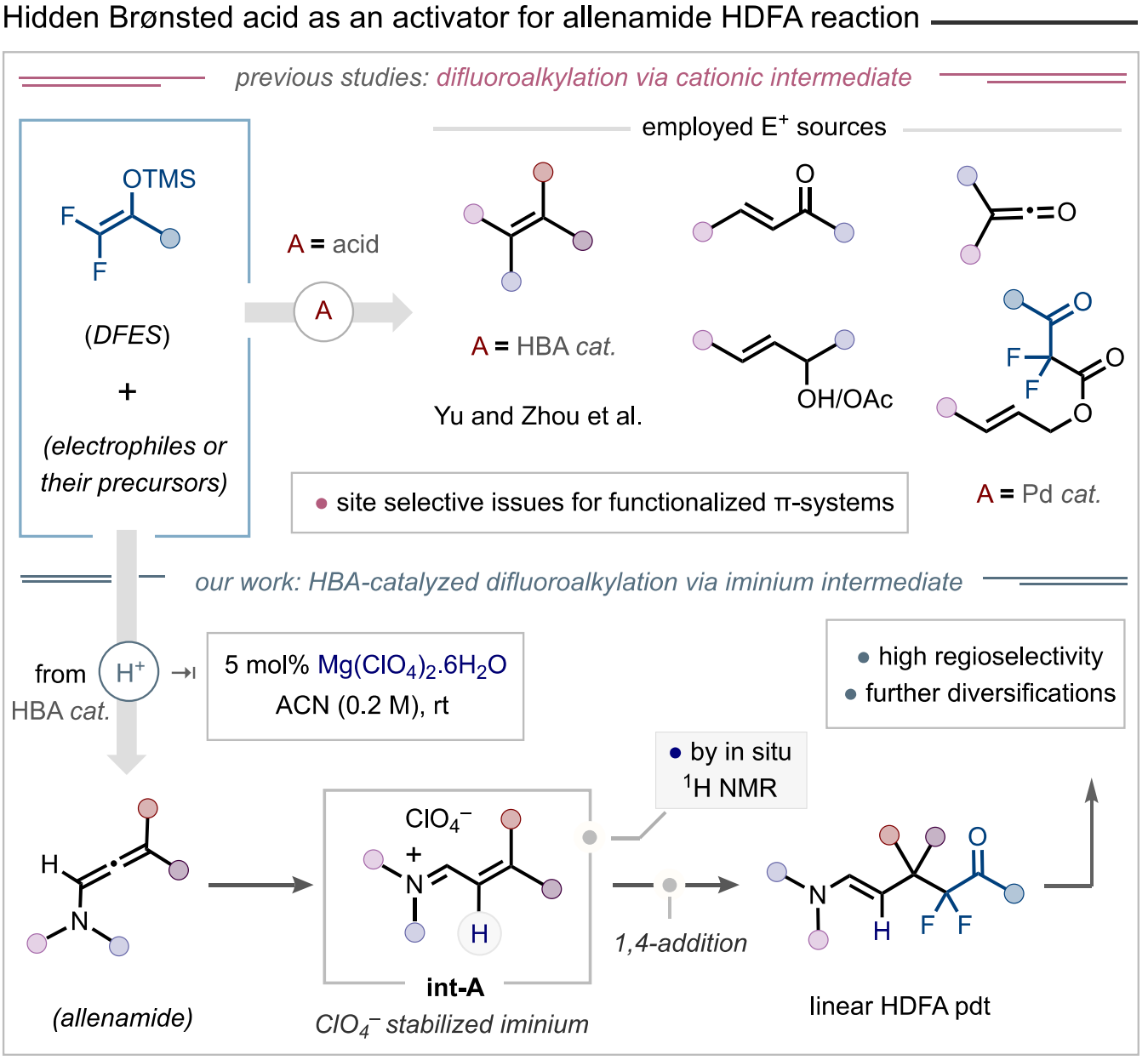
Scheme 7. HBA Catalysis for Selective Hydrodifluoroalkylation of Allenamides



3. ELEVATING NEW SELECTIVITY WITH N-CONJUGATED ALKYNE AS A SUBSTRATE

Recent advances in catalysis and activation mechanisms have expanded functionalization possibilities for N-conjugated alkynes, particularly ynamides. While these substrates traditionally exhibit α-nucleophilic and β-electrophilic selectivity, emerging strategies achieve reverse regioselectivity through neighboring group chelation and ring strain control.[22,37] These developments have broadened both inter- and intramolecular transformation scope, notably through 1,3-aryl migration-enabled ynamide difunctionalization for selective aryl and alkenyl group introduction.[22d,38] Though powerful, many approaches rely on prefunctionalized substrates, compromising atom economy. Our research group addresses this limitation through functional group migration strategies to access extended π-conjugated molecules. This Account describes our studies of yn(amine)amides, focusing on: (a) annulation reactions—(1) intermolecular multicomponent synthesis of 4-aminoquinolines[39] and (2) activator-controlled divergent, regiospecific, and stereospecific intramolecular hydroarylation[3]—and (b) intermolecular ynamide difunctionalization via 1,3-alkynyl-shift-enabled regioselective bromoalkynylation.[40]

3.1. Three-Component Assembly for the Synthesis of 4-Aminoquinolines

Our group harnessed ynamide amphoteric reactivity to achieve highly chemo- and regioselective [2 + 2 + 2] cycloaddition for modular synthesis (middle, Scheme 8).[39] This strategy enables diverse 4-aminoquinoline synthesis using nitriles, diaryliodoniums, and ynamides. The key electrophile forms through N-arylation of nitriles by arylcopper species, generated from Ar(Mes)IOTf and copper catalyst. This Cu-catalyzed rapid N-arylation under mild conditions contrasts with previous two-component (2A + B)[41] and (A + 2B)[42] [2 + 2 + 2] annulations

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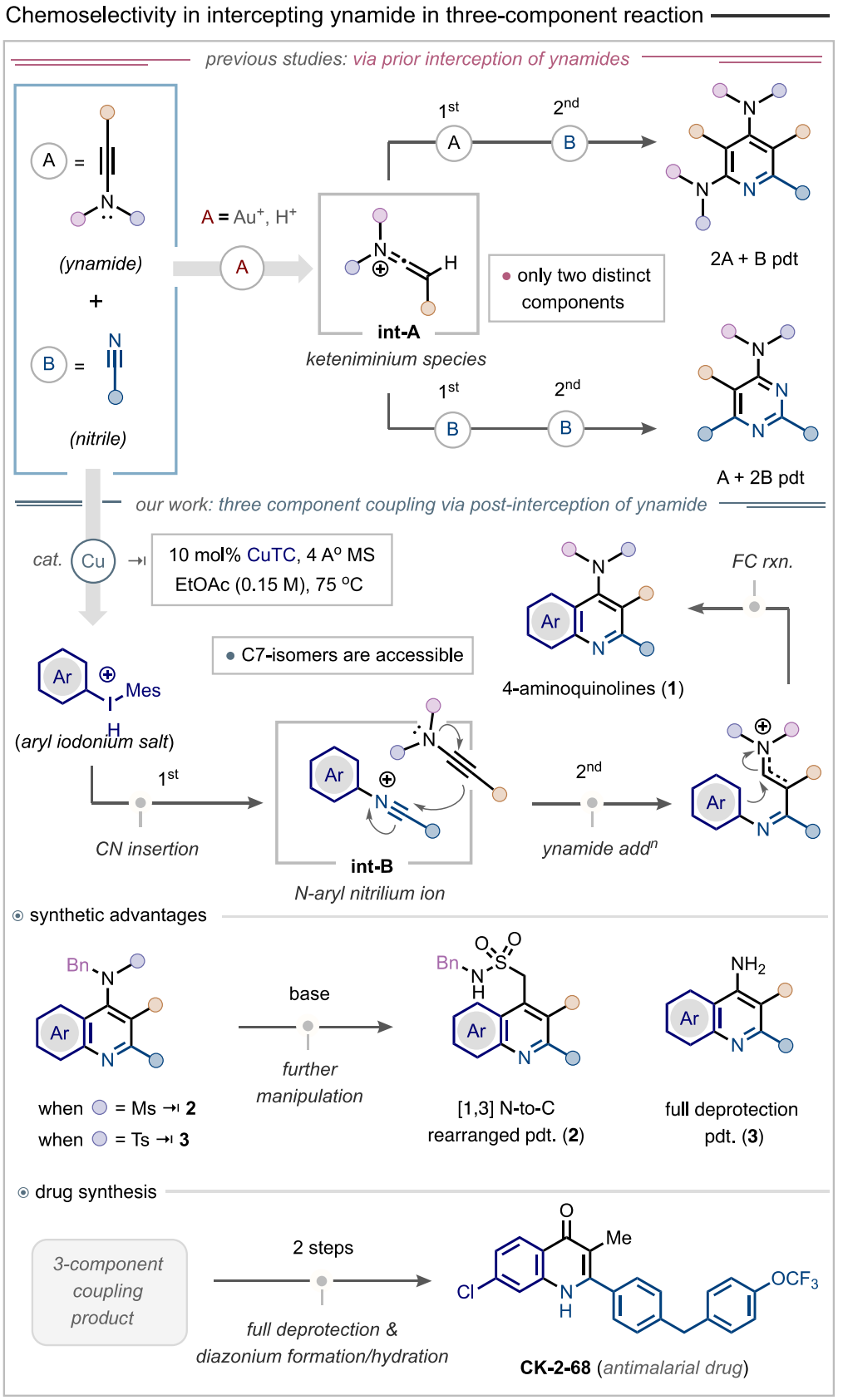
Scheme 8. Post-Interception of Ynamide Leading to a Three-Component Coupling



of nitriles and ynamides for N-heterocycle synthesis (top, Scheme 8). Beyond conventional nitrile-ynamide coupling, this method employs diverse aryl iodonium salts as electrophiles for efficient three-component assembly. This versatility enables prior nitrile activation to form nitrilium ion (**int-B**) with tunable N-aryl substituents.

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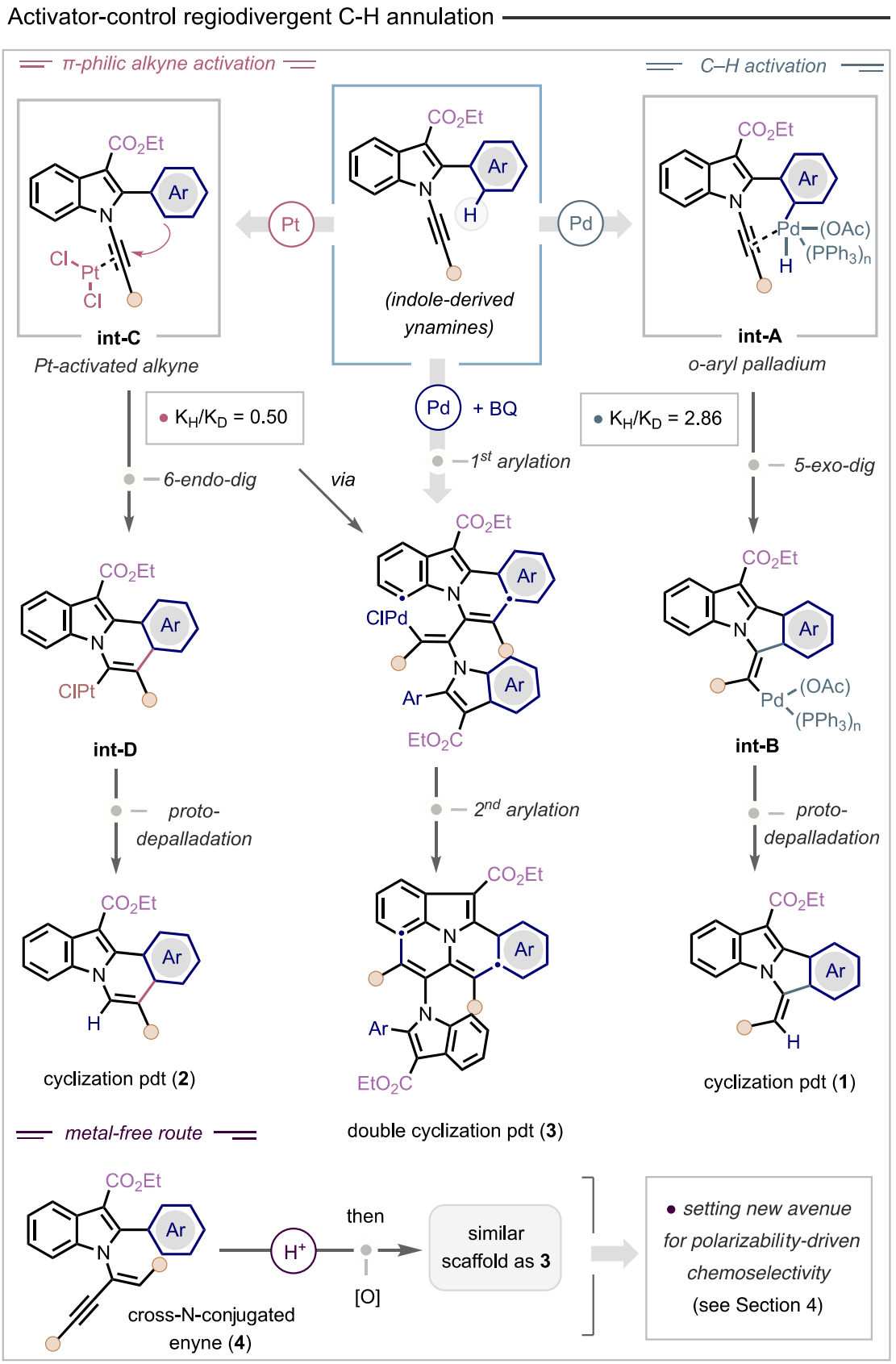
Scheme 9. Activator-Guided Control of Divergent C−H Annulation Pathways



These sp-electrophiles exhibit kinetic competency—demonstrated through competition experiments—condensing to keteniminium intermediates that undergo intramolecular Friedel−Crafts (FC)-type annulation. This selectivity enables regioselective synthesis of single C7-substituted isomers, providing systematic access to diverse 4-aminoquinolines (**1**).

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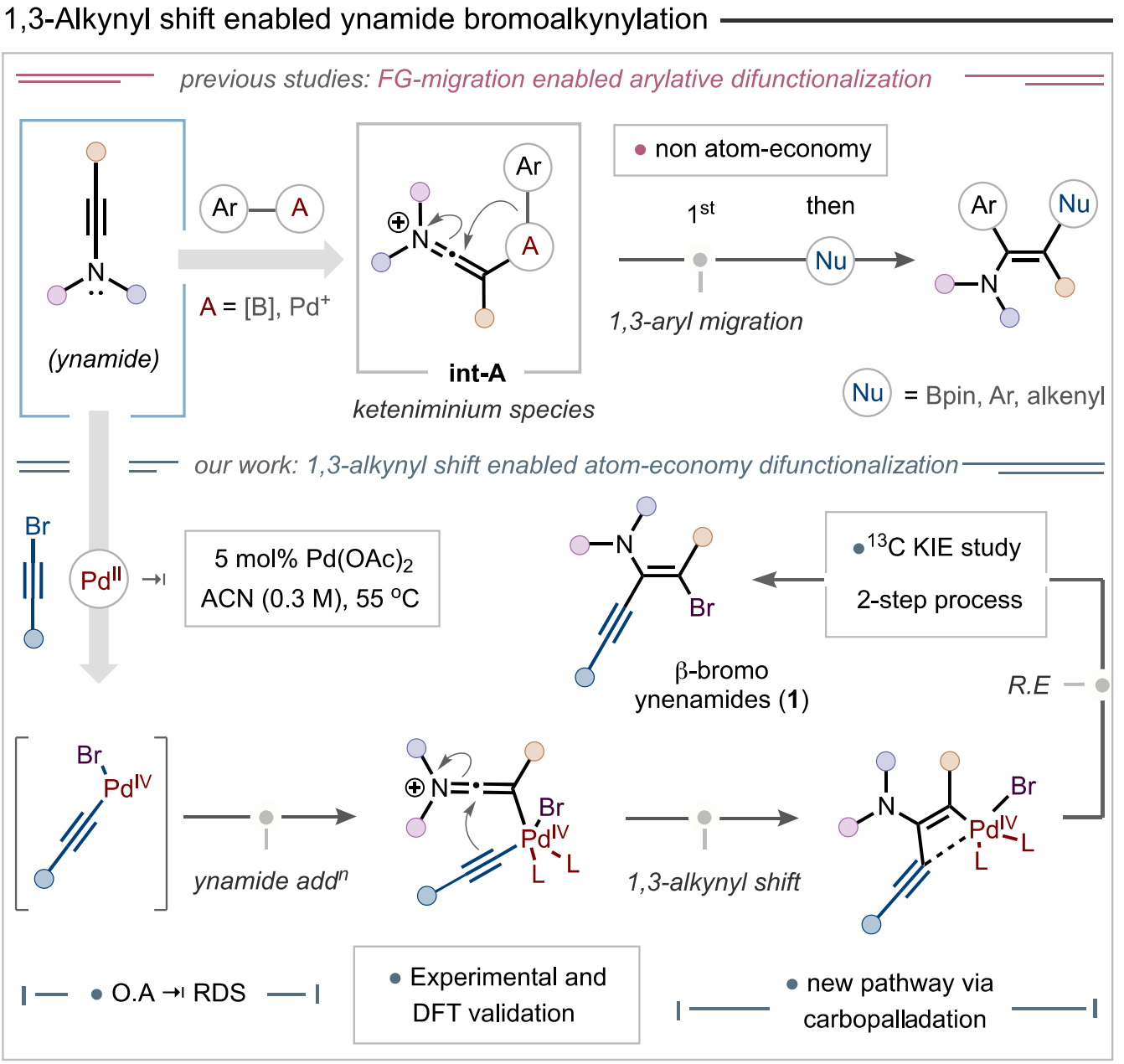
Scheme 10. 1,3-Alkynyl Shift Unveils a New Pathway for Ynamide Difunctionalization



Our Cu-catalyzed approach achieves superior regioselectivity compared to the metal-free methods of Movassaghi[43a] and Bräse[43b] groups, which yielded moderate results and limited meta-substituted products. N-sulfonylated aminoquinolines serve as versatile precursors that, under basic conditions, provide access to two biologically active compounds: quinolin-4-ylmethanesulfonamides (**2**) via a [1,3] N-to-C Truce-Smiles rearrangement, and aminoquinolines (**3**) through full deprotection via an imine intermediate (bottom, Scheme 8). This methodology's utility in medicinal chemistry is demonstrated by the efficient synthesis of antimalarial compound CK-2-68 using [2 + 2 + 2] annulation as the key step (bottom, Scheme 8).

3.2. Activator-Guided Divergent C−H Annulation for the Synthesis of Multi-Fused N-Heterocycles

Our group investigated vinylogous ynamide derived from indole in intermolecular annulations, demonstrating their first reported divergent C−H annulation using three distinct metal activators.[3] These intramolecular hydroarylations proceed through different activation mechanisms in Pd- and Pt-catalyzed reactions, contrasting with the typical α-nucleofunctionalization of ynamides (Scheme 9). The Pd-catalyzed reaction proceeds through alkyne-directed C−H activation, leading to 5-membered ring products (**1**) via 5-*exo-dig* cycloisomerization. In contrast, the Pt-catalyzed process employs π-activation of the alkyne, forming 6-membered ring products (**2**) through β-nucleofunctionalization in a 6-*endo-dig* cycloisomerization. Mechanistic studies using kinetic isotope effects (KIE) revealed distinct pathways: the Pd-catalyzed reaction showed a significant hydrogen/deuterium KIE (k_H/k_D

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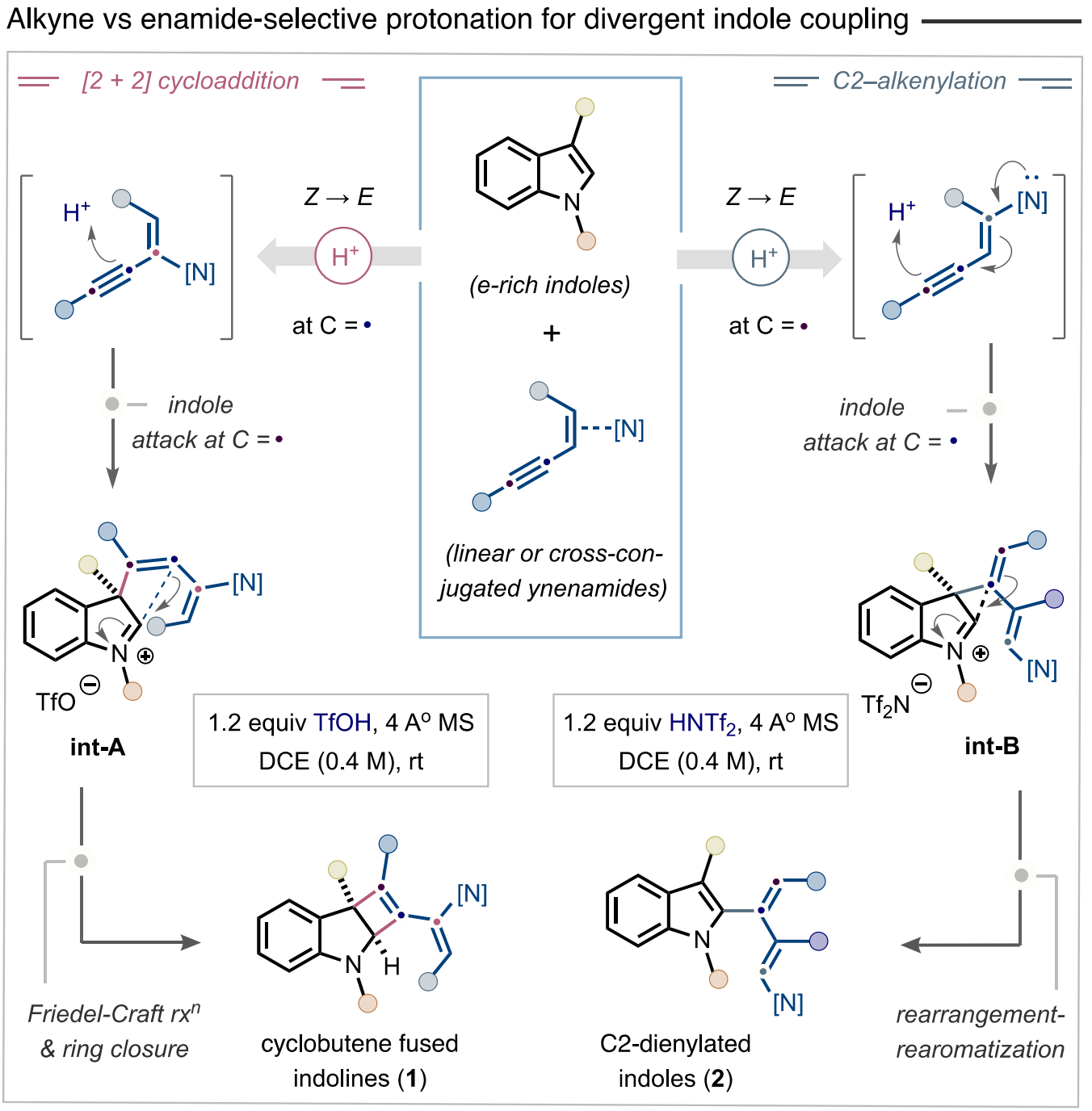
Scheme 11. Chemoselective Intermolecular Coupling via N-Electronic Conjugation



= 2.86), characteristic of aromatic C−H activation, while the Pt-catalyzed process exhibited an inverse KIE (k_H/k_D = 0.50), consistent with an electrophilic aromatic substitution mechanism. The Pd-catalyzed reaction mechanism proceeds through alkyne-directed ortho-palladation to form an *ortho*-aryl Pd-species (**int-A**), followed by *cis*-migratory insertion into the triple bond. Protodepalladation of the vinyl-Pd intermediate (**int-B**) then produces (*Z*)-6-alkylidene/benzylidene-6*H*-isoindolo[2,1-*a*]indoles (**1**), while regenerating $Pd(OAc)_2$ (right, Scheme 9). In contrast, the $PtCl_2$-catalyzed process involves intramolecular attack on the Pt-activated alkyne (**int-C**), generating a 6-membered Pt-bound vinyl intermediate (**int-D**). Subsequent protodeplatination yields indolo[2,1-*a*]isoquinolines **2** (left, Scheme 9).

When combined with an oxidant, the $PdCl_2$ catalyst enables construction of benzo[7,8]indolizino[2,3,4,5-*ija*]quinolines through double oxidative cyclization, proceeding via π-philic alkyne activation and tandem arylations (middle, Scheme 9). We further developed a metal-free approach to similar N-fused pentacyclic scaffolds using cross-N-conjugated enynes through double intramolecular arylation (bottom, Scheme 9). This enyne-based method demonstrates how chemo- and regioselectivity can be controlled by modulating electron density through N-electron conjugation under Brønsted acid conditions.

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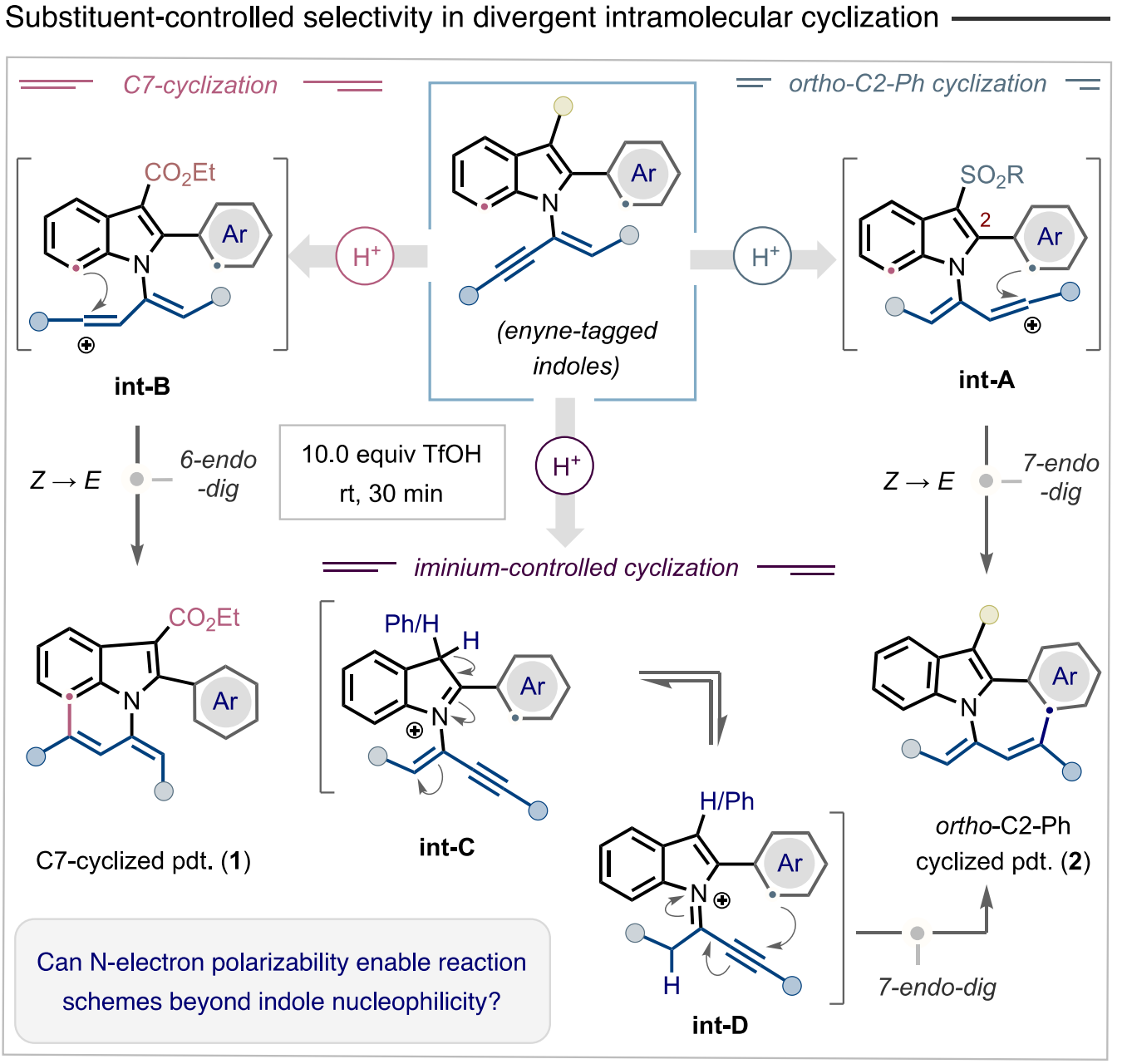
Scheme 12. Substituent-Dependent Nucleophilic Site Control for Divergent Intramolecular Cyclization



3.3. 1,3-Alkynyl-Shift-Enabled Atom-Economy Difunctionalization of Ynamides

One of the most challenging aspects of ynamides' difunctionalization is achieving their conversion to tetrasubstituted enamides in an intermolecular fashion. Recently, 1,3-functional group migration-assisted difunctionalization has gained attention due to its unique reactivity and selectivity compared to traditional ynamide chemistry. The research groups of Yamaguchi, Studer, and Sahoo have pioneered several arylative difunctionalization methods, including carboboration,[38a] diarylation,[22d] and aryl alkenylation,[38b] achieving precise regio- and stereocontrol (top, Scheme 10). The key to the success relies on the keteniminium-driven reactivity of ynamides caused by 1,3-aryl migration via **int-A**.

With this design strategy and our intention in developing atom economy alkynylative functionalization, very recently our laboratory successfully developed the bromoalkynylation of ynamides using alkynyl bromides and a Pd(II)-catalyst (bottom, Scheme 10).[40] By leveraging the dual functionality of alkynyl bromides, we achieved the formation of highly modifiable β-bromo ynenamides (**1**). This method builds upon previous work by the Jiang group, who demonstrated the Pd(II)-catalyzed haloalkynylation of internal alkynes.[44] Although other methods showed promise in stereocontrol, they struggled with regioselectivity issues. Our approach resolved this by observing that PdX_2 species tend to undergo oxidative addition with alkynyl halides, a process distinct from the direct halogenopalladation of alkynes by palladium salts. This observation allowed us to capitalize on the keteniminium reactivity of ynamides, facilitating a successful 1,3-alkynyl migration event.

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Employing a 5 mol % $Pd(OAc)_2$ catalyst, we were able to overcome the multifaceted selectivity of cross-coupling of two internal alkynes, leading to the formation of β-bromoynenamides (**1**) with excellent chemo- and regioselectivity. Via several experimental studies and DFT computation, we proposed that the reaction mechanism involves an atypical 1,3-alkynyl shift, with the initial oxidative addition between the Br-alkyne and Pd(II) catalyst acting as the rate-determining step. The Pd(II)/Pd(IV) catalytic cycle was confirmed as central to the process, supported by X-ray Photoelectron Spectroscopy (XPS) analysis identifying Pd(II) as the active catalyst.

To further explore the origins of the facile [1,3]-alkynyl shift, additional DFT computations were performed, indicating that the carbopalladation pathway is energetically favorable than halopalladation, which involves a [1,3]-halogen shift. Evaluating the experimental ^{13}C kinetic isotope effect (KIE) through DFT Onyx isotope effect studies revealed an inverse KIE, suggesting a stepwise reductive elimination mechanism. This mechanistic insight provides a valuable foundation for further developing extended conjugated π-systems through diverse functionalization of bromoynenamides.

4. MISCELLANEOUS FINDINGS: REACTIVITY STUDIES OF N-CONJUGATED ENYNES

Functional groups that modulate enyne skeleton polarizability can address selectivity challenges by inducing optimal polarity patterns, often enabling novel reactivity modes. This section will highlight the research findings from our group in this area and for a more in-depth review of enyne functionalization, we refer readers to Huang's detailed review.[45]

4.1. Intermolecular Indole Functionalization

Building on our preliminary studies[3] of N-electronic conjugation through electronic polarization, we investigated the fundamental reactivity of cross- and linear-conjugated ynenamides. In Brønsted-acid-mediated intermolecular coupling with electron-rich indoles, we observed divergent chemoselectivity, leading to dearomative [2 + 2] cycloaddition and alkenylation products (Scheme 11).[46] These pathways provide modular access to cyclobutene-fused indolines (**1**) and C2-substituted dienylation products (**2**), respectively. The cycloaddition approach addresses the challenge of coupling two electron-rich partners and complements previous metal-catalyzed alkene-enyne [2 + 2] cycloadditions, while the dienylation proceeds without requiring a directing group. Both processes involve *cis*−*trans* isomerization of the enamide unit, with the Brønsted acid serving dual roles in alkyne activation and enamide isomerization to the more stable *E* isomer. The dearomative cycloaddition proceeds through chemoselective protonation at the alkyne unit's proximal carbon, forming a vinyl cation intermediate (**int-A**) that controls the regioselectivity of subsequent Friedel−Crafts reaction and ring closure. Conversely, dienylation involves protonation at the alkyne unit's distal position—likely facilitated by a continuous electron flow sequence—enabling nucleophilic addition and rearrangement-rearomatization via **int-B**.

4.2. Intramolecular Indole Functionalization

Recognizing N-electron polarization effects on enyne carbon skeletons in indole chemistry, we explored how electronic modulation influences selectivity in intramolecular reactions.[47] While the polarity induction by indole N-electrons appears multidirectional, strategic placement of electronically distinct functional groups at C3 provides specific advantages: (i) strongly electron-withdrawing sulfonyl groups decrease indole electron density, promoting nucleophilic ortho attack at the C2 phenyl substituent via **int-A**; (ii) moderately electron-withdrawing esters direct cyclization to C7 through **int-B**; and (iii) neutral substituents (H or Ph) enable C3 protonation to form an iminium intermediate (**int-C** → **int-D**), shifting selectivity from C7 cyclization to C2 phenyl attack (Scheme 12). As observed in our previous study, the exocyclic double bond geometry in products **1** and **2** inverts from the starting material configuration due to acid-catalyzed isomerization to the thermodynamically favored isomer. These polarization-controlled transformations suggest broader applications beyond indole nucleophiles in future synthetic strategies.

5. CONCLUSION AND OUTLOOK

Controlling reaction intermediates is essential for directing chemical synthesis outcomes. Strategic substrate design through electronic activation enables precise control over these intermediates, guiding reactivity toward desired products. This Account describes our recent advances in functionalizing N-conjugated systems—allenes, alkynes, and 1,3-enynes—through selective activation strategies. By combining neighboring group chelation with targeted activators, we developed a versatile platform that led to several key discoveries: (1) innovative AA coupling approaches to novel multifunctional π-systems, (2) new activation modes enabling diverse hydrofunctionalization of N-conjugated allenes (allenamides), (3) mechanistic insights into unconventional reactivity of N-conjugated alkynes, and (4) chemoselective activation-functionalization methods for 1,3-enynes through electronic polarization control.

Significant opportunities remain in allen(yn- and ynen-)amide functionalization: (1) developing selective α-functionalization of allenamides through novel metal−ligand systems and activators, (2) expanding the scope to include diene and alkene coupling partners for enhanced synthetic and stereochemical diversity, and (3) developing radical-based transformations—a promising yet unexplored direction for those N-integrated π-systems highlighted in this Account.

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Author Contributions

This Account was written through the contributions of both authors.

Notes

The authors declare no competing financial interest.

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Jin Kyoon Park is a Professor in the Department of Chemistry at Pusan National University. He received his B.Sc. (1996), M.Sc. (1998), and Ph.D. (2003) from Seoul National University. Following six-month postdoctoral research at Korea Institute of Science and Technology, he joined LG Chem Ltd. as a senior research scientist (2004−2009). He then conducted research at Florida State University as a visiting scholar and postdoctoral researcher (2008−2012) before establishing his independent academic career at Pusan National University in 2012.

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