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Communication

Modular Cyclopentenone Synthesis through the Catalytic Molecular Shuffling of Unsaturated Acid Chlorides and Alkynes

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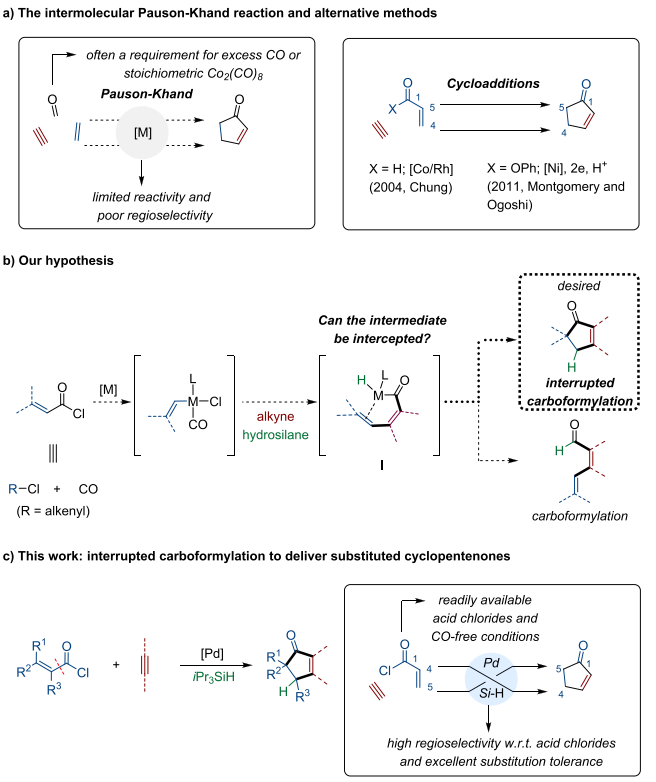
ABSTRACT: We describe a general strategy for the intermolecular synthesis of polysubstituted cyclopentenones using palladium catalysis. Overall, this reaction is achieved via a molecular shuffling process involving an alkyne, an α,β-unsaturated acid chloride, which serves as both the alkene and carbon monoxide source, and a hydrosilane to create three new C−C bonds. This new carbon monoxide-free pathway delivers the products with excellent yields. Furthermore, the regioselectivity is complementary to conventional methods for cyclopentenone synthesis. In addition, a set of regio- and chemodivergent reactions are presented to emphasize the synthetic potential of this novel strategy.

The construction of multiple C−C bonds in a single reaction allows for a dramatic increase in molecular complexity.[1,2] These reactions, when modular, allow for rapidly generating libraries of complex molecules.[3] As part of our investigation into palladium-catalyzed carbofunctionalizations, we recently reported such a modular process best described as an intermolecular carboformylation of alkynes.[4] A molecular shuffling strategy was key to orchestrate a sequential bond formation in a programmed order: (1) an aromatic acid chloride was first deconstructed to its aryl, CO, and Cl fragments by a Pd catalyst; (2) the individual fragments on the Pd center were then merged via consecutive carbometalation of an alkyne, CO reinsertion, and C−H reductive elimination, to provide the carboformylated compounds with excellent stereoselectivity.

We thus questioned whether this unique reactivity pattern could be further utilized in the construction of cyclopentenones.[5,6] These highly functionalized motifs, commonly found in natural products, bioactive compounds, and key synthetic building blocks, are often accessed intramolecularly via the Pauson−Khand reaction (PKR)[7,8] or Nazarov cyclization.[9,10] This strategy can be useful but often results in an inherent lack of flexibility given the need for the synthesis of the intermediate over several steps, undermining its potential. By contrast, the intermolecular PKR enables chemists to envision a simple one-step synthesis of the cyclopentenones, yet the feasibility is traditionally limited (Scheme 1a, left).[11,12] Specific challenges are (1) alkenes show low reactivity; (2) unreliable control of regioselectivity with respect to the alkene component, and (3) the requirement of excess hazardous chemicals (e.g., pressurized CO gas or stoichiometric cobalt−carbonyl complexes). While several creative solutions have been demonstrated to overcome specific challenges, such as the alkene scope being improved by the preinstallation of a cleavable directing group[13,14] and the use of CO surrogates[15] and less toxic metal catalysts/reagents,[16,17] these developments have not yet provided a general solution. Instead, approaches that are mechanistically distinct from the PKR introduce

Scheme 1. Context of the Work



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paradigms that are often complementary in nature. One such example is the development of cyclization reactions of unsaturated carbonyl compounds and alkynes to generate cyclopentenones using Co/Rh and Ni catalysts, respectively (Scheme 1a, right).[18,19]

We hypothesized that we could utilize the previously described carboformylation process as a distinct manifold for the intermolecular creation of carbocycles with a unique substitution pattern (Scheme 1b).[20,21] Specifically, we questioned if a proposed key intermediate of the carboformylation reaction, **I**, could be diverted to undergo an intramolecular cyclization. Such a framework for cyclopentenone synthesis could, in principle, offer several complementary features when compared to the state-of-the-art: (1) an alternative de novo reaction design where a wide range of alkene substrates can be tolerated; (2) safe and practical application due to the absence of pressurized CO as a reagent; (3) facile creation of a quaternary carbon center at the 5-position, a rare substitution pattern. Herein, we report the successful realization of an intermolecular PK-type reaction of internal alkynes using an α,β-unsaturated acid chloride as an alkenyl and CO source (Scheme 1c).

As a model reaction for our initial investigations, an α,β-unsaturated acid chloride (**1a**) and an alkyne (**2a**) were combined with a Pd precatalyst and a range of phosphine ligands that have been shown to mediate the reversible decarbonylation of acid chlorides.[4,22] Gratifyingly, we identified several suitable phosphine ligands for this reaction. Importantly, the carboformylation product was not observed to any detectable extent, effectively validating our hypothesis that the carboformylation process can indeed be interrupted to deliver cyclopentenones (see SI). A systematic investigation led to the best yields of **3a** being obtained with an electron-deficient monophosphine ligand, **MP1** (Table 1 and see SI). While triarylphosphines other than **MP1** resulted in moderated yields of **3a**, the results show a dependence on both the ratio of P to Pd and the electronics of the phosphine ligands (Table 1 and see SI). An increased P to Pd ratio, particularly with more basic or sterically less hindered phosphines, impeded the reaction. Presumably, this decreased reactivity is due to hampered alkenyl coordination to the Pd species, which is required for the intramolecular cyclization.[23]

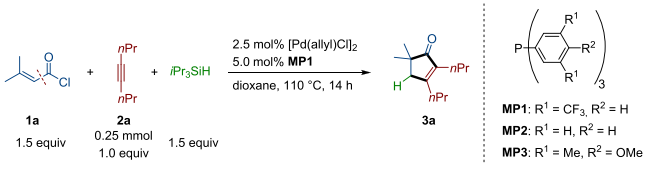
The yield of the desired product increased proportionally to the steric bulk of the trialkylsilane (Table 1, entry 5, and see SI). An inexpensive bulky silane, triisopropylsilane (iPr$_3$SiH), proved optimal. Alternative hydride sources, such as formate salts, failed to deliver the product (Table 1, entry 6). We performed an experiment using **1a** as a limiting reagent, as well as a separate experiment using equimolar amounts of all reagents, to demonstrate the reaction's efficiency. Both reactions afforded **3a** in good yields of 84% and 78%, respectively (Table 1, entries 7 and 8). This result highlights the high efficiency with respect to the CO surrogate.[24] The catalyst system was found to be highly active, with lower catalyst loadings of 1.0, 0.5, and 0.2 mol % giving the desired product in 95%, 82%, and 53% yield, respectively (see SI). In the absence of either the ligand or Pd precatalyst, the formation of **3a** was not observed (Table 1, entry 9). Other transition metal catalysts such as Ni(cod)$_2$, Co$_2$(CO)$_8$, [Rh(cod)Cl]$_2$, or [Ir(cod)Cl]$_2$ did not afford **3a** (Table 1, entry 11, and see SI for details).

We next explored the substrate scope of this transformation (Table 2). β-Dialkyl, β-diarylsubstituted and β-monosubstituted enoyl chlorides are well tolerated, giving a single regioisomer in each instance. We were able to confirm the structure of compound **3e** by X-ray crystallography. Notably, we could construct a variety of challenging quaternary carbon centers demonstrated by several novel examples (**3b**−**3f**), including spirocycles. Previously, this rare substitution pattern has only ever been formed in Pauson−Khand cycloaddition reactions as a minor regioisomer with highly strained alkenes.[25,26] Sterically hindered β-aryl enoyl chlorides (**3k**−**3o**) provided excellent yields, while other aryl-substituted acid chlorides resulted in moderate to good yields, regardless of electronic properties. A large variety of functional groups including ethers (**3b**, **3l**, **3q**, **3r**, **3ac**), alkenes (**3d**), carbamates (**3f**), nitriles (**3z**, **3an**), esters (**3m**, **3w**), aldehydes (**3x**), sulfones (**3y**), halogens (F: **3u**, **3ad**, **3af**, Cl: **3o**, **3s**, Br: **3t**, and even I: **3ab**), and nitro groups (**3aa**) were compatible under the reaction conditions. It is noteworthy that the reductively labile groups (e.g., esters, halides) survived the reductive reaction conditions. Acid chlorides bearing heterocycles such as thiophenes (**3ah**, **3aj**) and furans (**3ag**, **3ai**) are also effective reaction partners.

Conveniently, the reaction can be performed directly from the α,β-unsaturated carboxylic acid, when combined with Ghosez's reagent, for in situ formation of the acid chloride (**3d**, **3f**, **3x**).[27] In this manner, geranic acid was smoothly converted to the corresponding cyclopentenone (**3d**).

Remarkably, acryloyl chloride could be used as both an ethene and a CO surrogate (**3ak**), addressing a classical limitation of the conventional PKRs.[28] Further, the reaction also works with both α-substituted and α,β-disubstituted enoyl chlorides bearing methyl (**3al**), fluoro (**3am**),[29] cyano (**3an**), and phenyl (**3ao**) groups, to furnish a single diastereomer in these cases bearing an additional β-substituent in moderate to low yield. In the reaction of 2,3-diphenylacryloyl chloride, an additional product (**3ao-2**) arising from isomerization of the desired product was also observed. Likewise, the reaction with sorbic acid chloride bearing a conjugated diene functionality also resulted in isomerization of the distant alkene to give **3ar** (E/Z = 82:18, separable E/Z isomers).[17d] To further test

Table 1. Reaction Optimization



entry	variations from above conditions	**3a** (%)[a]
1	none	99
2	**MP2** (5.0 mol %) instead of **MP1**	79
3	**MP2** (10.0 mol %) instead of **MP1**	37
4	**MP3** (5.0 mol %) instead of **MP1**	68
5	Et$_3$SiH instead of iPr$_3$SiH	30
6	HCO$_2$M (M = K or Na) instead of iPr$_3$SiH	<3
7	**1a**/**2a**/iPr$_3$SiH equivalent ratio = 1.0/1.5/1.0	84
8	**1a**/**2a**/iPr$_3$SiH equivalent ratio = 1.0/1.0/1.0	78
9	no **MP1** or no [Pd(allyl)Cl]$_2$	n.d.
10	Pd(PPh$_3$)$_4$ (5.0 mol %) instead of [Pd(allyl)Cl]$_2$/**MP1**	8
11	*Ni, Co, Rh, or Ir* instead of [Pd(allyl)Cl]$_2$	n.d.

[a]The GC yields are based on the moles of a limiting reagent versus *n*-dodecane, an internal standard.

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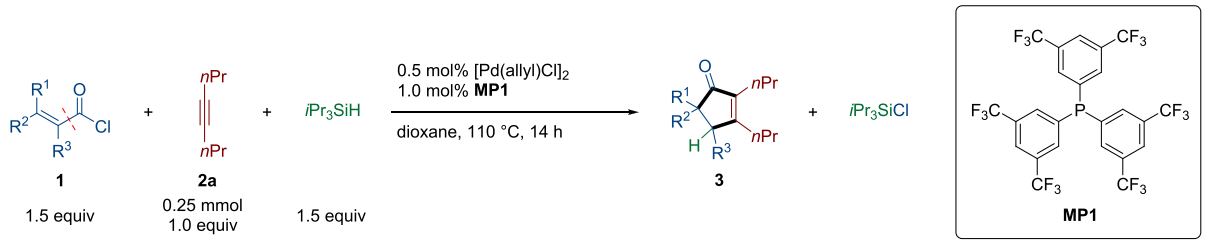
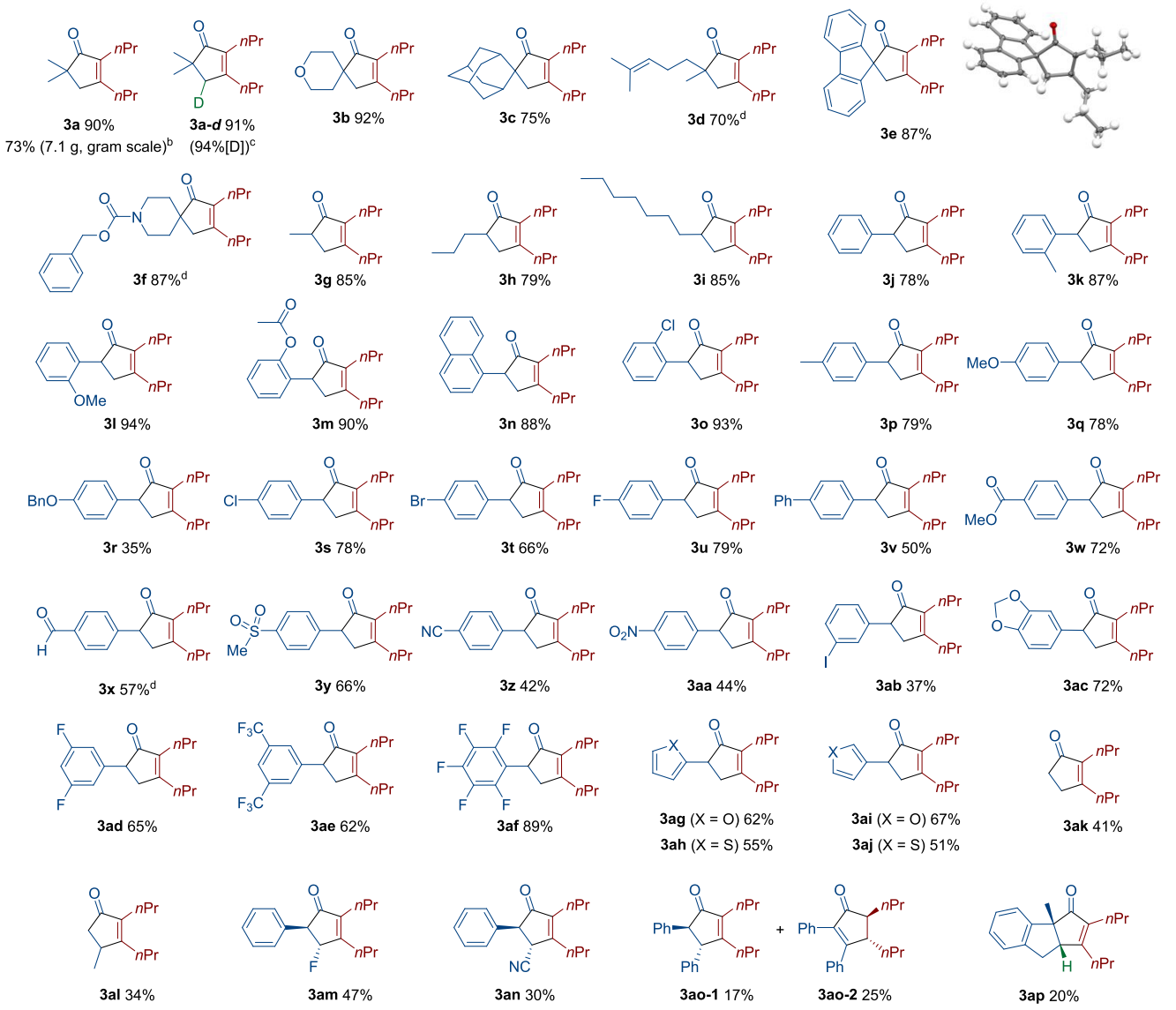
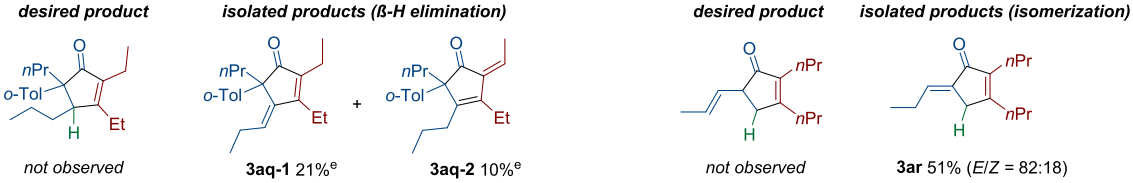
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Scope with Respect to α,β-Unsaturated Acid Chlorides[a]





Outliers



[a]All yields are isolated as a single regioisomer unless stated otherwise. [b]Open system, 50 mmol scale. [c]iPr$_3$SiD (1.5 equiv). [d]The corresponding carboxylic acid (1.5 equiv) and Ghosez's reagent (1.5 equiv) instead of **1**. [e]3-Hexyne (1.5 equiv) instead of **2a**. For details, see SI.

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

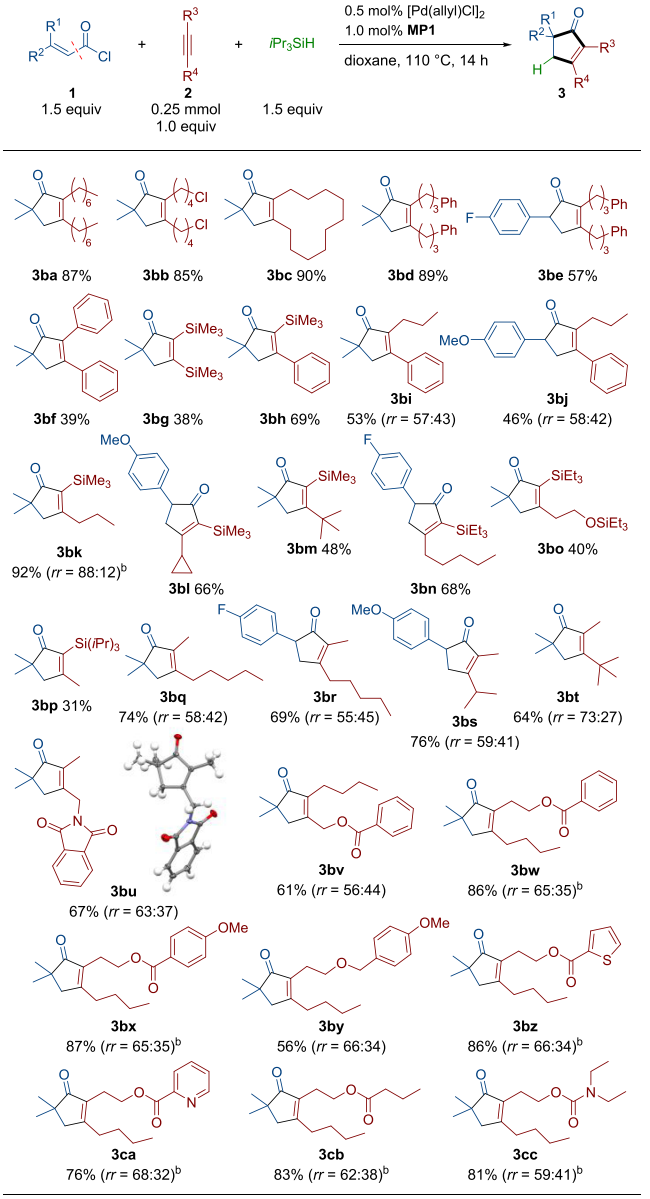
variation in the substitution pattern of the α,β-unsaturated acid chloride, fully substituted systems were examined. 3-Methyl-1*H*-indene-2-carbonyl chloride, a ring-fused tetrasubstituted enoyl chloride, affords the desired tricyclic compound (**3ap**) as a single diastereomer. When an acyclic tetrasubstituted enoyl chloride was subjected to the reaction conditions, two isomers (**3aq-1** and **3aq-2**) were produced, which may result from an acyl Mizoroki−Heck-type coupling followed by β-H elimination.[2,20] It is possible that the steric bulk installed into the substrate prevents the desired product formation. From these studies, it appears that the reaction is sensitive to steric encumbrance at the α-position of the acid chloride, presumably resulting from a less favorable carbometalation step of the alkenyl-Pd species into an alkyne due to increased steric bulk. Gratifyingly, the developed conditions were easily translated to multigram scale (50 mmol) experiments, affording compound **3a** in 73% yield (7.1 g).

A set of functionalized dialkyl alkynes reacted efficiently (Table 3). Additionally, a cyclic alkyne (**3bc**), diarylalkyne (**3bf**), and even a bis-trimethylsilyl alkyne (**3bg**) all undergo the reaction in moderate to excellent yields. The reaction is compatible with alkyl-silyl (**3bk**−**3bp**) and aryl-silyl (**3bh**) alkynes, furnishing the corresponding products with excellent regioselectivity, offering a versatile functional handle for further decoration.[30] It is worth noting that the extremely bulky triisopropylsilyl group (**3bp**) is also tolerated, without any erosion of regioselectivity. Additionally, several functionalities appended to the alkyne, such as alkyl chlorides (**3bb**), phthalimides (**3bu**), esters (**3bv**−**3bx**, **3cb**), carbamates (**3cc**), silyl ethers (**3bo**), and *S*- and *N*-heteroaryl groups (**3bz** and **3ca**), were well tolerated. While negligible regioselectivity was observed for unsymmetrical aryl-alkyl (**3bi**, **3bj**) and alkyl-alkyl (**3bq**−**3bv**) alkynes, a modest improvement resulted from using a sterically differentiated unsymmetrical alkyne (**3bt**), with a preference for alkenyl insertion at the more sterically encumbered position, presumably to minimize steric repulsion during carbopalladation. However, a polar functionality installed at the β-position relative to the alkyne (**3bw**−**3cc**) leads to a slight preference for the opposite regioisomer, resulting in the directing group tether being situated at the 2-position of the corresponding cyclopentenone. Terminal alkynes did not provide the corresponding cyclopentenones, while conversion of the alkyne was observed, suggesting other processes such as polyaddition are operative.

Four interesting products can in theory be obtained from the combination of our three starting materials and reagents. While **3a** was the only observed product under the standard reaction conditions (see SI), it was found that, in the absence of a phosphine ligand, its regioisomer (**4a**), from a formal reductive [3 + 2] cyclization, is formed,[19,20c] demonstrating ligand-controlled regioselectivity (Scheme 2a).[31] The modulated reactivity of the system in the presence of a phosphine ligand is thus crucial to allow the proposed fundamental steps of the reaction to occur in the right sequence. Further, Rh(I), a popular catalyst for carbonylation chemistry, showed a distinct reactivity with α,β-unsaturated acid chlorides, forming the hydroacylated product (**5a**) stereoselectively with an unoptimized yield of 59%.[32] Thus, this metal-based chemodivergence can also lead to useful substrates for subsequent Nazarov-type reactions (Scheme 2a).[9,10]

During our studies, we found that subjecting phenylacetyl chloride to the reaction conditions resulted in reductive

Table 3. Scope with Respect to Internal Alkynes[a]



[a]All yields are isolated as a single regioisomer unless otherwise stated. [b]Isolated as an inseparable mixture of regioisomers. For details, see SI.

decarbonylation of the acid chloride, resulting in the formation of toluene (see SI).[4,33] We thus hypothesized that this compound could serve as a novel CO surrogate in carbonylation reactions.[15,22g,24] Intriguingly, a four-component coupling was achieved when phenylacetyl chloride, acting as a CO equivalent, was coupled with a vinyl iodide, acting as an alkene partner, to deliver the cyclopentenone product (**3as**) in moderate yield with excellent regioselectivity (Scheme 2b).[20,34] Other vinyl (pseudo)halides required harsher reaction conditions and/or an exogenous chloride source to increase their conversion (**3at** and **3au**). This unique reactivity demonstrates that a variety of vinyl (pseudo)halides can also be used in a four-component coupling to deliver the desired cyclopentenone products.

Interestingly, the use of an aryl stannane as a carbon nucleophile, in place of the hydride nucleophile, led to the pentasubstituted product (**3av**) in 58% yield.[35] This is another

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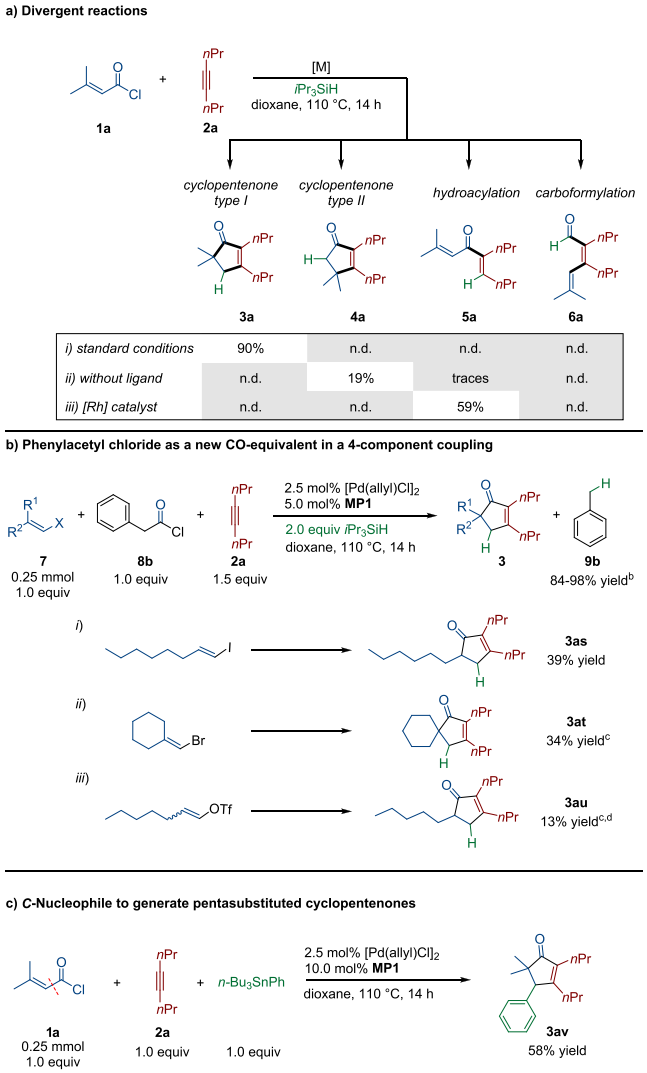
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 2. Synthetic Applications[a]



[a]All yields are isolated as a single isomer. [b]GC yields. [c]130 °C. [d]LiCl (2 equiv) was added. For details, see SI.

class of compound that is not directly accessible through PK-type reactions (Scheme 2c).

In conclusion, we have developed a CO-free intermolecular synthesis of cyclopentenones using alkynes, α,β-unsaturated acid chlorides, and a hydrosilane taking advantage of a molecular shuffling process. Further, we showcased the benefit of using a molecular shuffling strategy by extending the reactivity to divergent processes, building on the potential of this concept as a novel strategy to develop a vast array of CO-free carbonylation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10832.

Experimental details for all reactions and analytic details for all products (PDF)

Crystallographic data (CCDC 2035178, compound **3e**) (CIF)

Crystallographic data (CCDC 2045251, compound **3l**) (CIF)

Crystallographic data (CCDC 2045252, compound **3v**) (CIF)

Crystallographic data (CCDC 2035179, compound **3bu-1**, major) (CIF)

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Notes

The authors declare no competing financial interest.

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