Article

Highly Modular Synthesis of 1,2-Diketones via Multicomponent Coupling Reactions of Isocyanides as CO Equivalents

Anne-Marie Dechert-Schmitt, Michelle Garnsey, Hanna Wisniewska, James Murray, Taegyo Lee, Daniel W. Kung, Neal Sach, and Donna G Blackmond

ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 11 Apr 2019

Highly Modular Synthesis of 1,2-Diketones *via* Multicomponent Coupling Reactions of Isocyanides as CO Equivalents

Anne-Marie Dechert-Schmitt,[1]* Michelle R. Garnsey,[1] Hanna M. Wisniewska,[1] James I. Murray,[2] Taegyo Lee,[1] Daniel W. Kung,[1] Neal Sach,[1] Donna G. Blackmond[2]*

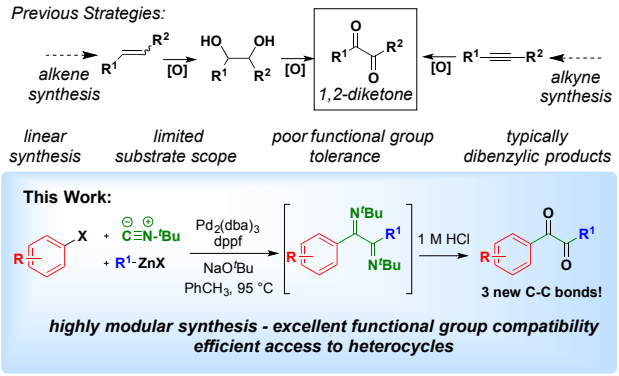
[1]Pfizer Worldwide Research and Development, Groton CT, 06340 USA; [2]Department of Chemistry, Scripps Research, La Jolla, CA 92037 USA

ABSTRACT: A one pot four-component Pd-catalyzed coupling has been developed for the synthesis of unsymmetrical 1,2-diketones from aryl halides and alkyl zincs employing t-butyl isocyanide as a CO source. The intermediate 1,2-diketones have been elaborated to quinoxalines. Mechanistic studies help to rationalize the high selectivity for the bis- vs. mono-insertion product. Keywords: isocyanides, Pd catalysis, reaction progress kinetics, multicomponent reactions, heterocycles

Introduction

Multicomponent one-pot reactions offer efficiency and sustainability in organic synthesis and are increasingly being employed to build complexity in pharmaceutical and fine chemical synthesis.[1–3] Of particular value are highly modular unions of widely available building blocks to access novel structural motifs. 1,2-Diketones are useful intermediates in synthetic organic chemistry; often used in the synthesis of medicinally relevant heterocycles, such as imidazoles, pyrazines, and quinoxalines as well as natural products.[4-12] They are also used in materials chemistry[13-14] and as ligands for various metal complexes.[15-18] Despite their widespread synthetic utility, 1,2-diketone synthesis is typically achieved *via* lengthy linear sequences and oxidative protocols.[19-32] These approaches are often limited to (symmetrical) dibenzylic 1,2-diketones and suffer poor compatibility with heteroaryl substrates; preventing efficient access to large libraries of these highly versatile derivatives (Scheme 1).

Scheme 1. 1,2-Diketone Syntheses



Carbonylation of aryl halides in the formation of ketones is well established; however, such reactions however, such reactions typically require high pressure CO, which can pose a safety risk in typical batch pharmaceutical manufacturing. While the development of stable CO-releasing molecules has addressed safety challenges and present an attractive approach to isotope labeling studies,[33] their use in large scale manufacturing would be problematic from cost and environmental perspectives. The use of isocyanide as a stoichiometric CO equivalent[33,34] has emerged as a powerful alternative to other CO sources,[35] as demonstrated in a variety of reactions, including carbonylative Sonogashira coupling and aryl halide formylation[36,37]. Herein, we report a novel method for the preparation of unsymmetrical 1,2-diketones utilizing (heteroaryl) aryl halides, organozinc reagents and *t*-butyl isocyanide as a CO equivalent. This work is the first example of a modular approach allowing formation of three new C-C bonds from three independent compounds in a one-pot protocol. Detailed kinetic and mechanistic studies help to rationalize both the high selectivity to double cyanide addition and the success of the final intramolecular C-C bond formation. In addition to providing a modular approach and broad scope in a straightforward synthesis of diketones using isocyanides as CO surrogates, the reaction can also provide 1,2-diimines or be further elaborated without purification to other molecules important in medicinal chemistry including heterocycles, such as quinoxaline derivatives.

Background

Isocyanides have emerged as an advantageous building block in synthetic organic chemistry, utilized extensively in the multicomponent Passerini and Ugi reactions.[38] *t*-Butyl isocyanide has been utilized as a C1 reactant in transition metal catalyzed carbonylation-type reactions to form aryl aldehydes,[39] diaryl ketones,[40] carboxylic acids,[41] amides,[42] amidines,[43] (thio)imidates,[44] thiocarbamates,[45] as well as various heterocycles.[46] Interestingly, most transition metal catalyzed isocyanide coupling methodologies produce mono insertion products. The first notable example of double isocyanide insertion utilized in the context of synthesis was reported by

Yamamoto and coworkers[47] in the Co-mediated formation of diiminofuran derivatives. Whitby and coworkers[48] demonstrated the Pd-catalyzed synthesis of α-iminoimidates via double insertion of isocyanides into aryl halides followed by trapping with metal alkoxides, a multi-component reaction that forms two C-C and one C-O bond. Kobiki and coworkers developed a Pd-catalyzed double insertion of isocyanides with $BiAr_3$ reagents, generating a third new C-C bond in an intramolecular step, to produce symmetrical α-diimines, with good scope with respect to the isocyanide but limited to formation of symmetrical diimine systems from the few Bi reagents commercially available.[49] Shen and coworkers[50] demonstrated further substrate scope in the double cyanide insertion and suggested the versatility of the α-iminonitriles formed for conversion to a variety of products. However, such conversions generally require strong nucleophilic bases and are limited in scope.

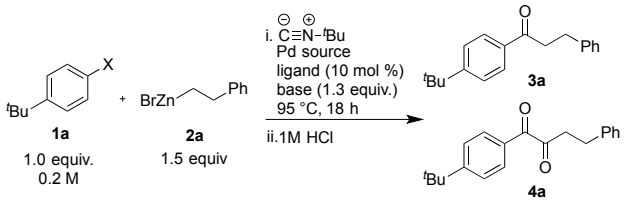
These and most approaches to double isocyanide insertion involve intramolecular formation of the final C-C bond. Several recent reports take advantage of the transition metal catalyzed double isocyanide insertion to form various heterocycles such as pyrrolo[2,3-b]indoles, 5-iminopyrrolones, 3-Iminoindol-2-amines, maleimides, pyrrole derivatives, phthalimides, benzofurans, and thiazolidines.[51] In addition, the selectivity for double insertion is not well understood and has not been probed mechanistically. The work we report here offers a modular approach to the intermolecular formation of three carbon-carbon bonds *via* double isocyanide insertion into aryl halides and alkyl zinc reagents to produce 1,2- diketones, as well as a mechanistic study to rationalize the formation of the bis isocyanide insertion product relative to the mono isocyanide insertion product.

Results and Discussion

Table 1 shows initial studies of the reaction coupling aryl halides with isocyanides and alkylzinc reagents. Initial studies of the coupling of 1-bromo-4-(*tert*-butyl)benzene with *t*-butyl isocyanide and phenethyl zinc bromide were undertaken with a desire to produce the monoketone **3a**. Analysis of the reaction mixture indicated that ketone **3a** was formed along with byproduct diketone **4a** in a 1:1 ratio (Table 1, entry 1). Notably, the use of other isocyanides resulted in little to no conversion to either the mono or bis ketone (see SI for more details).

Recognizing the value of such a modular approach to 1,2-diketones, we shifted our efforts to optimize for the diketone **4a**. Switching from the ligand Johnphos to dppf resulted in the formation of diketone **4a** in 25% yield, with no detected monoketone **3a** (entry 2, Table 1). Addition of an extra equivalent of the *t*-butyl isocyanide with triethylamine as a more soluble base in toluene afforded the diketone product **4a** in 61% yield (entry 3, Table 1). Encouraged by these results, a high-throughput screen of 76 bases was conducted to find improved conditions (See SI for full details). NaO^{t}Bu was selected as the optimal base. Scaling the conditions identified in high-throughput reaction optimization afforded the desired product in 83% (Entry 4, Table 1). Reduction in concentration further improved the yield to 90% (83% isolated). The reaction could also be performed on a gram scale, albeit in diminished yield of 52%. We found that while both aryl bromide and iodide were competent electrophiles in the transformation, aryl chlorides were unreactive (Table 1, entries 6-7).

Table 1. Optimization of the 1,2-Diketone Synthesis.



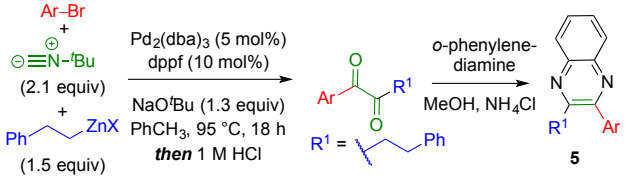
	X	Base	Solvent	Equiv. ^{t}BuNC	Yield[a,f] %**4a** (%**3a**)
1	Br	Na_2CO_3	DMF	1.1	15 (13)[b]
2	Br	Na_2CO_3	DMF	1.1	25 (0)[c]
3	Br	Et_3N	Toluene	2.1	61 (0)[c]
4	Br	NaO^{t}Bu	Toluene	2.1	83 (0)[c]
5	Br	NaO^{t}Bu	Toluene[d]	2.1	90 (0)[c,e]
6	I	NaO^{t}Bu	Toluene[d]	2.1	82 (0)[c]
7	Cl	NaO^{t}Bu	Toluene[d]	2.1	0 (0)[c]

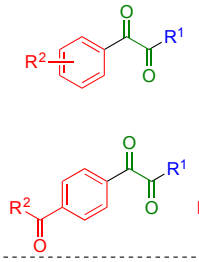
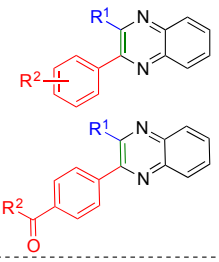
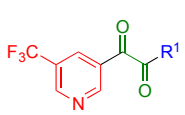
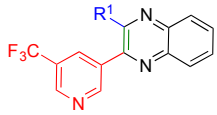
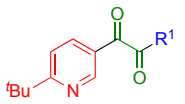
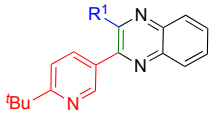
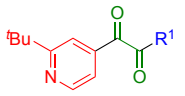
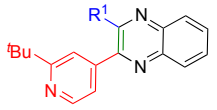
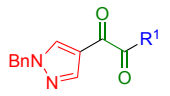
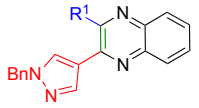
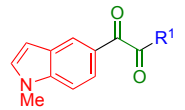
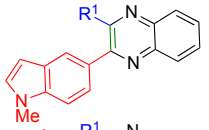
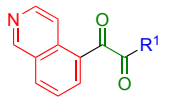
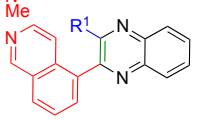
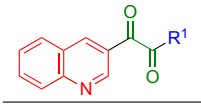
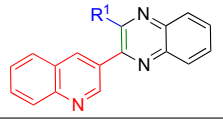
[a]NMR yield relative to 2,6-dimethoxytoluene internal standard. [b]$Pd(OAc)_2$ (5 mol%), Johnphos. [c]$Pd_2(dba)_3$ (5 mol%), dppf. [d]**1a** at 0.086 M. [e]83% isolated yield. [f]All reactions performed on a 0.5 mmol scale with respect to reactant **1a**. See Table S1 in the supporting information.

We next sought to investigate substrate scope with respect to aryl halide (Table 2). The diketone products showed traces of decomposition upon standing at room temperature, but could be stored for long periods of time in the freezer. Isolated yields were obtained by conversion to quinoxaline derivatives. A wide variety of functional groups were well tolerated, including *tert*-Bu esters, amides and nitriles, as well as electron deficient and electron rich aryl halides. Importantly, heteroaryl derivatives were efficient coupling partners in the process, demonstrating a significant advantage over oxidative 1,2-diketone synthesis.[19,26,30,31,52,53]

Next we turned our attention to reaction scope determination with respect to the organozinc coupling partner (Table 3). Primary zinc reagents, including methyl zinc chloride and *n*-Pr zinc bromide coupled efficiently to form the desired product, while phenethyl magnesium bromide gave no desired product. Various secondary zinc reagents, including cycloalkyl derivatives were also competent coupling partners in this process. Attempts to couple aryl zinc halides were unsuccessful, presumably dye to the decreased ability of these species to undergo transmetallation. Similarly the more reactive diarlyzinc reagents gave no desired product.

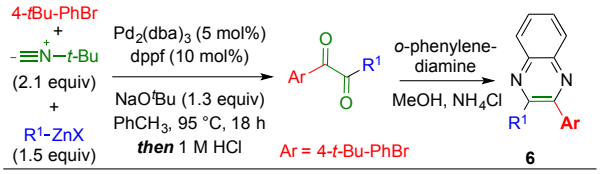
Table 2. Substrate Scope for 1,2-diketone synthesis.

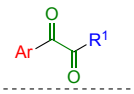
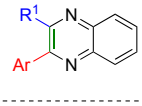
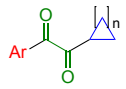
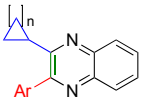
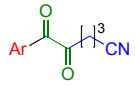
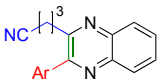
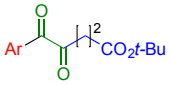
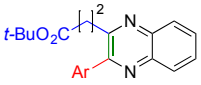
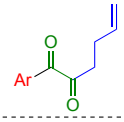
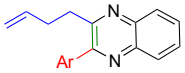
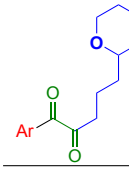
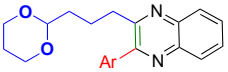


1,2-dicarbonyl product	quinoxaline product	isolated yield[a]
		R^2 = ^{t}Bu **5a** 69% R^2 = 4-Cl **5b** 66% R^2 = 4-OMe **5c** 71% R^2 = 4-NMe_2 **5d** 55% R^2 = 4-CN **5e** 76% R^2 = 3-CF_3 **5f** 67% R^2 = 2-Me **5g** 83%
		R^2 = O^{t}Bu **5h** 76% R^2 = NHMe **5i** 44% R^2 = NMe_2 **5j** 75%
		**5k** 70%
		**5l** 69%
		**5m** 51%
		**5n** 62%
		**5o** 70%
		**5p** 54%
		**5q** 78%

[a] Reactions conducted on 0.5 mmol Ar-Br. Isolated yield is of the quinoxaline.

Table 3. Zinc Scope for 1,2-diketone synthesis.



1,2-dicarbonyl product	quinoxaline product	isolated yield[a]
		R^1 = Me **6a** 56% R^1 = *n*-Pr **6b** 78% R^1 = *i*-Pr **6c** 38%
		n = 1 **6d** 61% n = 2 **6e** 83% n = 3 **6f** 36%
		**6g** 68%
		**6h** 79%
		**6i** 54%
		**6j** 70%

[a] Reactions conducted on 0.5 mmol Ar-Br. Isolated yield is of the quinoxaline.

To investigate the mechanism of this reaction, with particular focus on the high selectivity for *bis vs. mono* addition, methods of monitoring reaction progress for use of the Reaction Progress Kinetic Analysis methodology[54] were investigated. Reaction monitoring using ReactIR spectroscopy combined with sample analysis demonstrated that the isocyanide stretching vibration at 2134 cm^{-1} provides an accurate measure of reaction progress. The temporal concentration profiles (Figure 1) for the aryl halide **1a** and product **4a** may be calculated from that of isocyanide using the reaction stoichiometry and the concept of "excess" ([*xs*]) as shown in eqs. 1–3. Figure 1 shows excellent agreement between analytical measurement of [**1a**], [isocyanide], and [**4a**] and the ReactIR profile measured for [isocyanide] and calculated for [**1a**] and [**4a**]. This ensures that further studies may be carried out by monitoring the profile of isocyanide.

$$[xs]^{\mathbf{1a}} = [isocyanide]_0 - 2\cdot[\mathbf{1a}]_0 \quad (1)$$

$$[\mathbf{1a}]_0 = \frac{[isocyanide]_0 - [xs]^{\mathbf{1a}}}{2} \quad (2)$$

$$[\mathbf{4a}]_t = [\mathbf{1a}]_0 - [\mathbf{1a}]_t \quad (3)$$

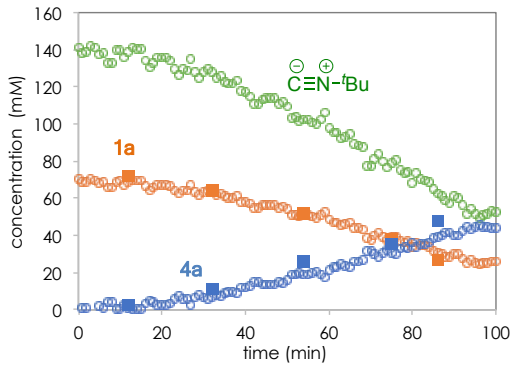


Figure 1. Concentration profiles for the reaction of Scheme 1 monitored by ReactIR spectroscopy (open circles) and HPLC analysis of discrete samples (filled squares). The ReactIR profile for isocyanide is used to calculate those for **1a** and 4a from eqs. 1–3. HPLC samples are obtained for **4a** after workup. Reaction conditions: $[\mathbf{1a}]_0$ = 70 mM; $[\mathbf{2a}]_0$ = 105 mM (in THF); $[\text{isocyanide}]_0$ = 150 mM; $[\text{NaO}^t\text{Bu}]_0$ = 90 mM (in THF); $[\text{Pd}_2(\text{dba})_3]$ = 3.5 mM; [dppf] = 7 mM; toluene 95 °C.

The kinetic profile shows a slight sigmoidal shape indicative of an induction period at the outset of the reaction. In experiments varying the initial concentrations of the various reaction components, we noted that higher concentrations of NaO^tBu helped to eliminate this induction period, as shown in Figure 2, where a time shift of the profile exhibiting an induction period gives excellent overlay on that from the reaction carried out under identical conditions except with higher $[\text{NaO}^t\text{Bu}]$.

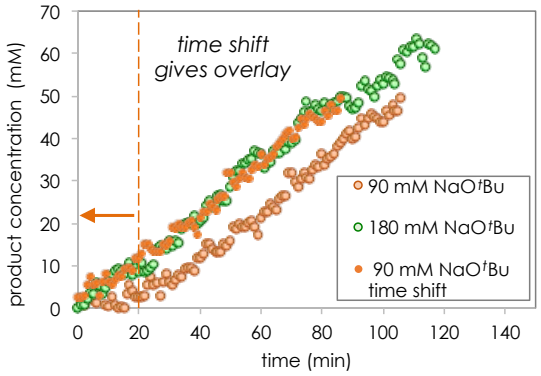


Figure 2. Concentration profiles for the reaction of Scheme 1 monitored by ReactIR spectroscopy. Reaction conditions: $[\mathbf{1a}]_0$ = 70 mM; $[\mathbf{2a}]_0$ = 105 mM (in THF); $[\text{isocyanide}]_0$ = 150 mM; $[\text{Pd}_2(\text{dba})_3]$ = 3.5 mM; [dppf] = 7 mM; toluene 95 °C. $[\text{NaO}^t\text{Bu}]_0$ as shown in legend. A time shift of 20 min for the reaction profile at lower $[\text{NaO}^t\text{Bu}]_0$ is shown.

The role of the base in catalyst activation was explored further using ^{31}P-NMR studies of the dppf ligand, as shown in Figure 3. The species formed from $\text{Pd}_2(\text{dba})_3$ addition to dppf (Figure 3b) exhibits two peaks, as previously noted,[55] and is unaffected by addition of the aryl bromide substrate **1a** (Figure 3c). Addition of NaO^tBu to $\text{Pd}_2(\text{dba})_3$/dppf results in a shift in the two peaks. Under reaction conditions, the addition of substrates causes a further shift (Figures 3d, 3e). This demonstrates that addition of base is necessary to enter the catalytic cycle.

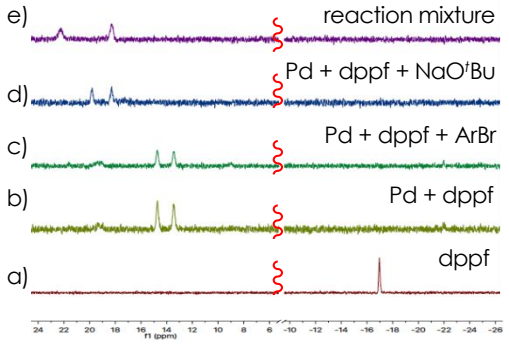


Figure 3. ^{31}P-NMR spectra of various reaction components in toluene. a) dppf ligand (20 mM); b) $\text{Pd}_2(\text{dba})_3$ (10 mM) plus dppf ligand (20 mM); c) $\text{Pd}_2(\text{dba})_3$ (10 mM) plus dppf ligand (20 mM) plus **1a** (70 mM); d) $\text{Pd}_2(\text{dba})_3$ (10 mM) plus dppf ligand (20 mM) plus NaO^tBu (90 mM); e) under the standard reaction conditions of Figure 1 at ca. 14% conversion of **1a**.

The results in Fig. 3 suggest that a palladium species formed after interaction of the catalyst precursor with base serves as the active entry into the catalytic cycle. This proposal is supported by previous work by Amatore and Jutand,[55] who documented multiple roles for the base in Suzuki-Miyaura reactions catalyzed by Pd phosphine complexes. In the present case, the similarity of spectra d) and e) in Figure 3 suggest that the role of the base appears to occur prior to oxidative addition of the aryl halide and may be related to accelerating removal of dba ligands to produce the active catalytic species. Precatalyst activation and inhibition processes have been investigated in detail recently for other transition metal-catalyzed reactions.[56]

"Same excess" experiments[54] showed that the reaction system is robust, showing little if any catalyst deactivation, as evidenced by the time and concentration shift overlay in Figure 4, top. Carrying out Variable Time Normalization Analysis (VTNA)[57] for reactions at different catalyst concentrations showed that the reaction is first order in [Pd] (Figure 4, bottom). These data demonstrate the robustness of the catalyst system.

Further "different excess" kinetic studies[44] were carried out varying the initial concentration of each of the reactants in turn. Strikingly, Figure 5 shows that identical profiles are observed in reactions higher $[\mathbf{1a}]_0$, $[\mathbf{2a}]_0$, or $[\text{isocyanide}]_0$, indicating that the reaction exhibits zero order kinetics in all three substrate concentrations. These results suggest the resting state within the cycle is a Pd species containing all three substrates and that reductive elimination is a likely candidate for the rate-determining step.

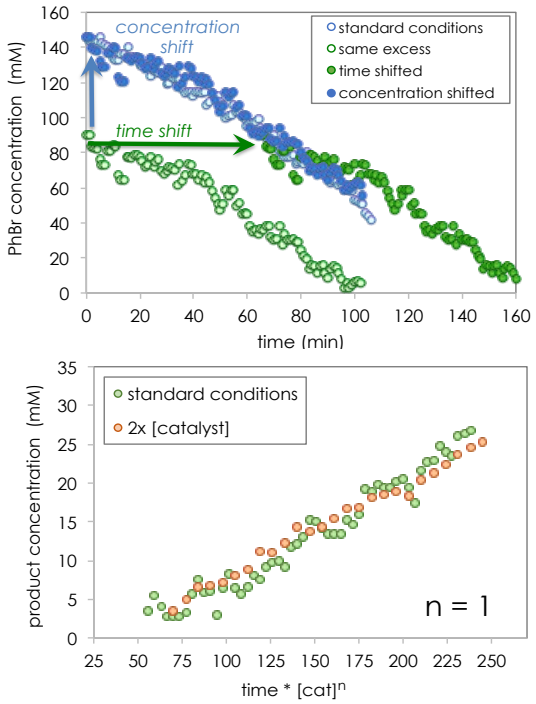


Figure 4. "Same excess" protocol (top) showing overlay for time and concentration shifted profiles. Variable Time Normalization Analysis[57] (VTNA, bottom) for reaction profiles of the reaction of Scheme 1 carried out under the conditions of Figure 1 and at twice the Pd and ligand concentrations.

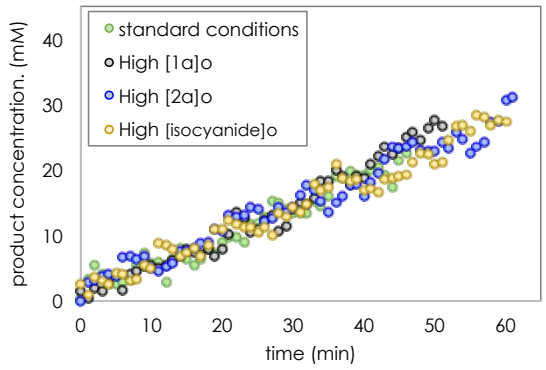


Figure 5. Concentration profiles for the reaction of Scheme 1 monitored by ReactIR spectroscopy. Standard conditions are those of the reaction in Figure 1. Only one component is altered in each of the other experiments. High $[\mathbf{1a}]_0$ = 100 mM; High $[\mathbf{2a}]_0$ = 175 mM (in THF); High [isocyanide]$_0$ = 210 mM. Curves are time-shifted to account for the induction period at the outset of the reaction.

Examining the influence of ligand bite angle on reactivity for Pd catalysts with selected phosphine ligands.[58] (Figure 6) showed that increasing ligand bite-angle resulted in increased rates of reaction. Since larger bite angles should increase the rate of reductive elimination, these results are consistent with the suggestion that this step is rate-determining. These studies allow us to propose the mechanism shown in Scheme 2, in accordance with precedent from previous literature on Pd-catalyzed carbonylation reactions.[59,60]

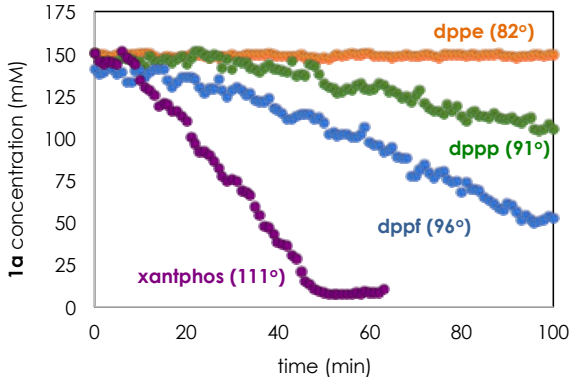
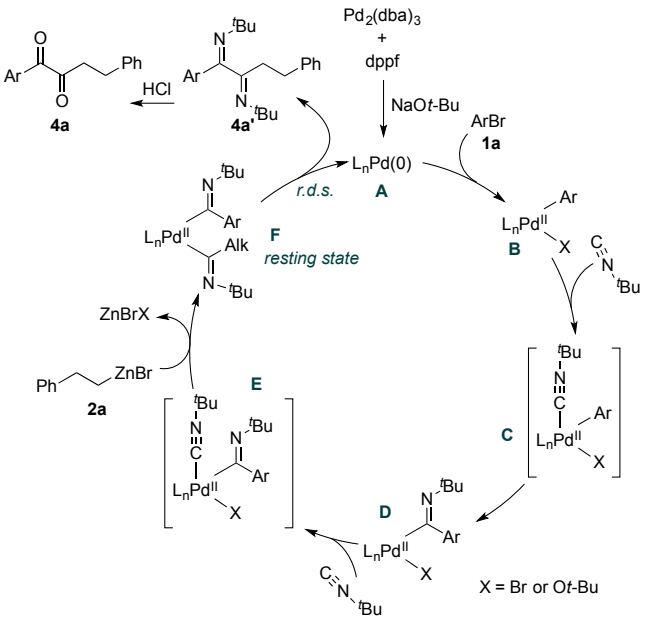


Figure 6. Concentration profiles for the reaction of Table 1 monitored by ReactIR spectroscopy under the standard conditions in Figure 1 using ligands with different bite angles as shown.

Scheme 2. Proposed Reaction Mechanism for the Multicomponent Reaction of Scheme 1.

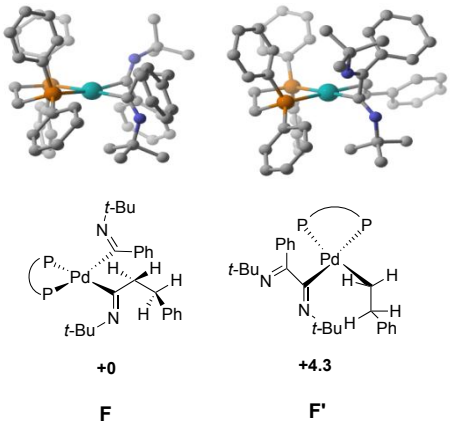


Kinetic studies of the induction behavior couple with NMR studies of the catalyst interaction with various reaction components suggests that NaO^{t}Bu assists in converting $Pd_2(dba)_3$ and the dppf ligand into the active catalyst **A**, which is likely to be a zerovalent Pd with the chelating phosphine. In similar systems Pd-alkoxide intermediates have been proposed as the active catalyst[61,62] and this remains a possibility in our case. Oxidative addition of **1a** to Pd/dppf only occurs after formation of this active catalyst, giving species **B**. Subsequent coordination of isocyanide and subsequent migratory insertion to form **D**. Coordination of a second equivalent of isocyanide affords complex **E**, which upon transmetallation and subsequent migratory insertion of

the alkyl ligand into the metal isocyanide bond furnishes **F**. This complex is the resting state of the catalyst and undergoes rate-determining reductive elimination to produce diimine product **4a'** and regenerate the active catalyst **A**.

The catalyst resting state **F** contains all four reactant components. We carried out DFT calculations to probe the nature of the species, as shown in Scheme 3. The lowest energy conformation for two potential candidates **F** and **F'** revealed that a Pd-iminoacyl species **F** similar to that proposed by Whitby[48] and analogous to the acyl species proposed by Yamamoto[47] is significantly lower in energy than a putative bis-insertion intermediate **F'**. Reductive elimination from a bis-iminoyl complex **F** as compared to **F'** has been shown experimentally in related carbonylation studies.[63,64]

Scheme 3. Proposed Catalyst Resting States.

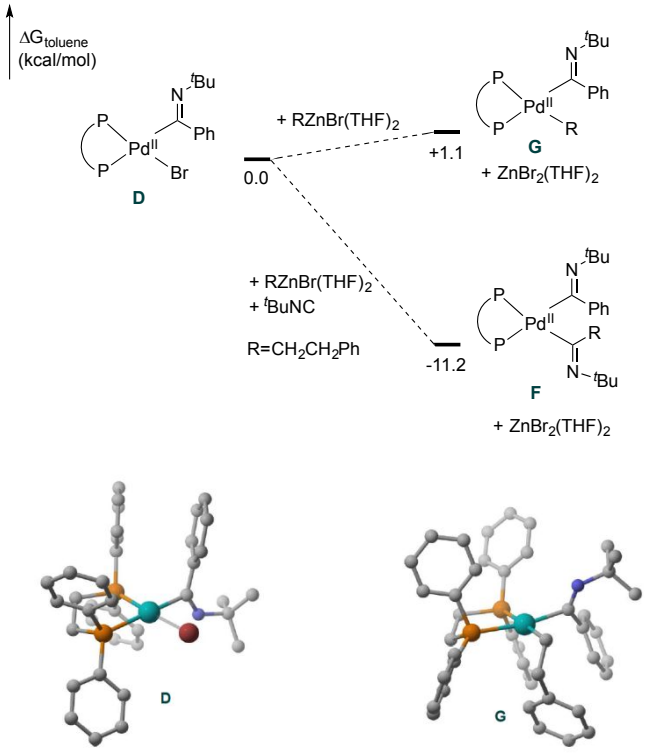


Calculations also allow us to rationalize why double insertion of isocyanide dominates over the possible mono-insertion product in this system. Scheme 4 compares the calculated reaction coordinate from species **D** in Scheme 2 to the resting state **F** to the analogous species **G** for a mono-insertion product, which lies at significantly higher energy. Strong and rapid coordination of the isocyanide to the catalytic Pd center may rationalize preference for double addition.[59]

Conclusions

We report development of the first highly modular synthesis of unsymmetrical 1,2-diketones employing Pd catalysis and *t*-butyl isocyanide as CO equivalents. The highly modular transformation forges three new C-C bonds in one synthetic operation from readily available building blocks. Kinetic and mechanistic studies have revealed reductive elimination to be rate-determining, which rationalized the high selectivity for bis *vs.* mono isocyanide addition in this process. Further studies investigating alternate nucleophilic coupling partners and controlling for mono isocyanide addition are ongoing in our laboratory.

Scheme 4. Reaction Coordinate from Species D to a Putative Mono-Insertion Product, G, Compared to the Observed Bis-Insertion Product, F.



Supporting Information. Reaction procedures, compound characterization data, and kinetic and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Anne-Marie.DechertSchmitt@pfizer.com,

Blackmond@scripps.edu

ACKNOWLEDGMENT

DGB acknowledges funding from Scripps Research. Jason Chen and the Scripps Automated Synthesis Facility are acknowledged for helpful discussions. AMDS acknowledges helpful discussions with Rob Singer, Kevin Hesp and Daniel Schmitt.

REFERENCES

((1) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. Self-Consistent Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C via Controlled Oligomerization. *J. Am. Chem. Soc.* **2008,** *130*, 17281-17283.

(2) Tian, M.; Yan, M.; Baran, P. S. 11-Step Total Synthesis of Araiosamines. *J. Am. Chem. Soc.* **2016**, *138*, 14234-14237.
(3) Touré, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.* **2009**, *109*, 4439-4486.
(4) Hoyos, P.; Sinisterra, J.-V.; Molinari, F.; Alcántara, A. R.; Domínguez de María, P. Biocatalytic Strategies for the Asymmetric Synthesis of α-Hydroxy Ketones. *Acc. Chem. Res.* **2010**, *43*, 288-299.
(5) Irannejad, H.; Nadri, H.; Naderi, N.; Rezaeian, S. N.; Zafari, N.; Foroumadi, A.; Amini, M.; Khoobi, M. Anticonvulsant Activity Of 1,2,4-Triazine Derivatives With Pyridyl Side Chain: Synthesis, Biological, and Computational Study. *Med. Chem. Res.* **2015**, *24*, 2505-2153.
(6) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. Allosteric Akt (PKB) Inhibitors: Discovery and SAR of Isozyme Selective Inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 761-764.
(7) McKenna, J. M.; Halley, F.; Souness, J. E.; McLay, I. M.; Pickett, S. D.; Collis, A. J.; Page, K.; Ahmed, I. An Algorithm-Directed Two-Component Library Synthesized Via Solid-Phase Methodology Yielding Potent and Orally Bioavailable p38 MAP Kinase Inhibitors. *J. Med. Chem.* **2002**, *45*, 2173-2184.
(8) Samanta, S.; Roy, D.; Khamarui, S.; Maiti, D. K. Ni(II)–Salt Catalyzed Activation of Primary Amine-sp^3 Cα–H and Cyclization With 1,2-Diketone to Tetrasubstituted Imidazoles. *Chem. Commun.* **2014**, *50*, 2477-2480.
(9) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. Efficient Synthesis of Imidazoles from Aldehydes and 1,2-Diketones Using Microwave Irradiation. *Org. Lett.* **2004**, *6*, 1453-1456.
(10) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. Broadening the Scope of 1,2,4-Triazine Synthesis by the Application Of Microwave Technology. *Tetrahedron Lett.* **2003**, *44*, 1123-1127.
(11) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. General Microwave-Assisted Protocols for the Expedient Synthesis Of Quinoxalines and Heterocyclic Pyrazines. *Tetrahedron Lett.* **2004**, *45*, 4873-4876.
(12) Schmitt, D. C.; Lam, L.; Johnson, J. S. Three-Component Coupling Approach to Trachyspic Acid. *Org. Lett.* **2011**, *13*, 5136-5139.
(13) Hernández-Cruz, O.; Zolotukhin, M. G.; Fomine, S.; Alexandrova, L.; Aguilar-Lugo, C.; Ruiz-Treviño, F. A.; Ramos-Ortíz, G.; Maldonado, J. L.; Cadenas-Pliego, G. High-Tg Functional Aromatic Polymers. *Macromolecules* **2015**, *48*, 1026-1037.
(14) Mosnáček, J.; Weiss, R. G.; Lukáč, I. Photochemical Transformation of Benzil Carbonyl Pendant Groups in Polystyrene Copolymers to Benzoyl Peroxide Carbonyl Moieties and the Consequences of Their Thermal and Photochemical Decomposition. *Macromolecules* **2002**, *35*, 3870-3875.
(15) Erker, G.; Czisch, P.; Schlund, R.; Angermund, K.; Krüger, C. Reductive Coupling of CO: Formation of a 1:1 Adduct of η2-Ketone- and Enediolato-Complex upon Carbonylation of Bis(cyclopentadienyl)hafnacyclobutane. *Angew. Chem. Int. Ed.* **1986**, *25*, 364-365.
(16) Hofmann, P.; Frede, M.; Stauffert, P.; Lasser, W.; Thewalt, U. Monomeric, Mononuclear Enediolate Complexes of Zirconium: Molecular Geometry and Electronic Structure of the Products of Reductive CO Coupling on the Metal. *Angew. Chem. Int. Ed.* **1985**, *24*, 712-713.
(17) Song, L.-C.; Liu, P.-C.; Han, C.; Hu, Q.-M. Synthesis and Characterization of Cp2Ti-Containing Organometallics Via In Situ Oxidative-Addition of 'Cp2Ti' Intermediate: Crystal Structures of (1-C10H7S)2TiCp2, [(η5-C5H5)Fe(η5-C5H4CH2S)]2TiCp2 and [η2-OC(Ph) C(Ph)O]TiCp2. *J. Organomet. Chem.* **2002**, *648*, 119-125.
(18) Spikes, G. H.; Sproules, S.; Bill, E.; Weyhermüller, T.; Wieghardt, K. One- and Two-Electron Reduced 1,2-Diketone Ligands in $[CrIII(L\bullet)_3]$ (S = 0) and $Na_2(Et_2O)2[VIV(LRed)_3]$ (S = 1/2). *Inorg. Chem.* **2008**, *47*, 10935-10944.
(19) Chen, S.; Liu, Z.; Shi, E.; Chen, L.; Wei, W.; Li, H.; Cheng, Y.; Wan, X. Ruthenium-Catalyzed Oxidation of Alkenes at Room Temperature: A Practical and Concise Approach to α-Diketones. *Org. Lett.* **2011**, *13*, 2274-2277.
(20) He, Z.; Qi, X.; She, Z.; Zhao, Y.; Li, S.; Tang, J.; Gao, G.; Lan, Y.; You, J. Room-Temperature Coupling/Decarboxylation Reaction of α-Oxocarboxylates with α-Bromoketones: Solvent-Controlled Regioselectivity for 1,2- and 1,3-Diketones. *J. Org. Chem.* **2017**, *82*, 1403-1411.
(21) Kashiwabara, T.; Tanaka, M. Synthesis of 1,2-Diketones by the Transition Metal-Catalyst-Free Reaction of α-Oxo Acid Chlorides or Oxalyl Chloride with Organostannanes. *J. Org. Chem.* **2009**, *74*, 3958-3961.
(22) Liu, X.; Cong, T.; Liu, P.; Sun, P. Synthesis of 1,2-Diketones via a Metal-Free, Visible-Light-Induced Aerobic Photooxidation of Alkynes. *J. Org. Chem.* **2016**, *81*, 7256-7261.
(23) Lv, W.-X.; Zeng, Y.-F.; Zhang, S.-S.; Li, Q.; Wang, H. Mild $Mn(OAc)_3$-Mediated Aerobic Oxidative Decarboxylative Coupling of Arylboronic Acids and Arylpropiolic Acids: Direct Access to Diaryl 1,2-Diketones. *Org. Lett.* **2015**, *17*, 2972-2975.
(24) Min, H.; Palani, T.; Park, K.; Hwang, J.; Lee, S. Copper-Catalyzed Direct Synthesis of Diaryl 1,2-Diketones from Aryl Iodides and Propiolic Acid. *J. Org. Chem.* **2014**, *79*, 6279-6285.
(25) Qi, C.; Jiang, H.; Huang, L.; Chen, Z.; Chen, H. DABCO-Catalyzed Oxidation of Deoxybenzoins to Benzils with Air and One-Pot Synthesis of Quinoxalines. *Synthesis* **2011**, *3*, 387-396.
(26) Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. Wacker-Type Oxidation of Alkynes into 1,2-Diketones Using Molecular Oxygen. *Org. Lett.* **2009**, *11*, 1841-1844.
(27) Saberi, D.; Hashemi, H.; Niknam, K. One-Pot Solvent-Free Synthesis of Diaryl 1,2-Diketones by the Sequential Heck Oxidation Reaction of Aryl Halides with Styrenes. *Asian J. Org. Chem.* **2017**, *6*, 169-173.
(28) Wang, C.; Lei, S.; Cao, H.; Qiu, S.; Liu, J.; Deng, H.; Yan, C. Regioselective Copper-Catalyzed Dicarbonylation of Imidazo[1,2-a]pyridines with N,N-Disubstituted Acetamide or Acetone: An Approach to 1,2-Diketones Using Molecular Oxygen. *J. Org. Chem.* **2015**, *80*, 12725-12732.
(29) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. Gold-Catalyzed Synthesis of Benzil Derivatives and α-Keto Imides via Oxidation of Alkynes. *Org. Lett.* **2011**, *13*, 1556-1559.
(30) Zhao, X.-F.; Zhang, C. Iodobenzene Dichloride as a Stoichiometric Oxidant for the Conversion of Alcohols into Carbonyl Compounds; Two Facile Methods for Its Preparation. *Synthesis* **2007**, *4*, 551-553.
(31) Jung, M. E.; Deng, G. Synthesis of α-Diketones from Alkylaryl- and Diarylalkynes Using Mercuric Salts. *Org. Lett.* **2014**, *16*, 2142-2145.
(32) Palmieri, A.; Gabrielli, S.; Sampaolesi, S.; Ballini, R., Nitroaldol (Henry) Reaction Of 2-Oxoaldehydes With Nitroalkanes As A Strategic Step For A Useful, One-Pot Synthesis Of 1,2-Diketones. *RSC Adv.* **2015**, *5*, 36652-36655.
(33) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. Palladium-Catalyzed Migratory Insertion of Isocyanides: An Emerging Platform in Cross-Coupling Chemistry. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084-7097.
(34) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. Metal-Mediated and Metal-Catalyzed Reactions of Isocyanides. *Chem. Rev.* **2015**, *115*, 2698-2779.
(35) For general reviews of reactions with CO surrogates, see: a) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. Carbonylations of Alkenes with CO Surrogates. *Angew. Chem. Int. Ed.* 2014, *53,* 6310-6320. b) Gautam, P.; Bhange B. M. Recent Advances In The Transition Metal Catalyzed Carbonylation of Alkynes, Arenes and Aryl

Halides Using CO Surrogates. *Catal. Sci. Technol.* **2015**, *5*, 4663-4702.
(36) Tang, T.; Fei, X.-D.; Ge, Z.-Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Bromides via tert-Butyl Isocyanide Insertion. *J. Org. Chem.* **2013**, *78*, 3170-3175.
(37) Jiang, X.; Wang, J.-M.; Zhang, Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed Formylation of Aryl Halides with tert-Butyl Isocyanide. *Org. Lett.* **2014**, *16*, 3492-3495.
(38) a) Dömling, A.; Ugi, I. Multi Component Reactions of Isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210. (b) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev*. **2006**, *106*, 17-89. (c) Lygin, A. V.; de Meijere, A.; Isocyanides in the Synthesis of Nitrogen Heterocycles. *Angew. Chem., Int. Ed*. **2010**, *49*, 9094-9124. (d) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. Isocyanoacetate Derivatives: Synthesis, Reactivity, and Application. *Chem. Rev*. **2010**, *110*, 5235-5331.
(39) Zhang, Y.; Jiang, X.; Wang, J. M.;Chen, J. L.; Zhu, Y. M. Palladium-Catalyzed Synthesis of Aldehydes From Aryl Halides and Tert-Butyl Isocyanide Using Formate Salts as Hydride Donors. *RSC Adv*. **2015**, *5*, 17060-17063.
(40) Chen, Z.; Duan, H. Q.; Jiang, X.; Wang, J. M.; Zhu, Y. M.; Yang, S. L. Palladium-Catalyzed Synthesis of Biaryl Ketones via tert-Butyl Isocyanide Insertion. *Synlett* **2014**, *25*, 1425-1430.
(41) Chen, Z.B.; Liu, K.; Zhang, F.-L.; Yuan, Q.; Zhu, Y.-M. Palladium-Catalyzed Oxidative Coupling of Arylboronic Acid With Isocyanide to Form Aromatic Carboxylic Acids. *Org. Biomol. Chem*., **2017**, *15*, 8078-8083.
(42) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. Synthesis of Amides via Palladium-Catalyzed Amidation of Aryl Halides. *Org. Lett.* **2011**, *13*, 1028-1031.
(43) (a)Zhu, F.; Li, Y.; Wang, Z.; Orru, R. V.A.; Maes, B.U. W.; Wu, X.-F. Palladium-Catalyzed Construction of Amidines from Arylboronic Acids under Oxidative Conditions. *Chem. Eur. J.* **2016**, *22*, 7743-7746. (b) Saluste, C. G.; Whitby, R. J.; Furber, M. A Palladium-Catalyzed Synthesis of Amidines from Aryl Halides." Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156-4158.
(44) Saluste, C. G.; Whitby, R. J.; Furber, M. Palladium-Catalysed Synthesis of Imidates, Thioimidates and Amidines from Aryl Halides. *Tetrahedron Lett.* **2001**, *42*, 6191-6194.
(45) Vlaar, T.; Mampuys, P.; Helliwell, M.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. Multicomponent Synthesis of 4-Aminophthalazin-1(2*H*)-ones by Palladium-Catalyzed Isocyanide Insertion *J. Org. Chem.* **2013**, *78*, 6735–6745.
(46) (a) Xu, P.; Wang, F.; Wei, T.-Q. Yin, L.; Wang, S.-Y. Palladium-Catalyzed Incorporation of Two C1 Building Blocks: The Reaction of Atmospheric CO_2 and Isocyanides with 2-Iodoanilines Leading to the Synthesis of Quinazoline-2,4(1*H*,3*H*)-diones**.** *Org. Lett.*, **2017**, *19*, 4484-4487. (b) Tang, T.; Jiang, X.; Wang, J.-M.; Sun, Y.-X.; Zhu, Y.-M. Divergent Synthesis Of 6H-Isoindolo[2,1-A]Indol-6-Ones and Indenoindolones: An Investigation of Pd-Catalyzed Isocyanide Insertion. *Tetrahedron* **2014**, *70*, 2999-3004. (c) Fan, X.-Y.; Jiang, X.; Zhang, Y.; Chen, Z.B.; Zhu, Y.-M. Palladium-Catalyzed One-Pot Synthesis of Diazoles via Tert-Butyl Isocyanide. *Org. Biomol. Chem*. **2015**, *13*, 10402-10408. (d) Liu, B.; Yin, M.; Gao, H.; Wu, W.; Jiang, H. Synthesis of 2-Aminobenzoxazoles and 3-Aminobenzoxazines via Palladium-Catalyzed Aerobic Oxidation of *o*-Aminophenols with Isocyanides. *J. Org. Chem.*, **2013**, *78*, 3009-3020. (e) Geden, J. V.; Pancholi, A. K.; Shipman, M. Palladium-Catalyzed Multi-component Synthesis of 2-Aryl-2-imidazolines from Aryl Halides and Diamines. *J. Org. Chem.* **2013**, *78*, 4158-4164. (f) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. Overcoming the Limitations of Directed C–H Functionalizations of Heterocycles. *Nature* **2014**, *515*, 389-393. (g) Jiang, X.; Tang, T.; Wang, J.-M.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed One-Pot Synthesis of Quinazolinones via *tert*-Butyl Isocyanide Insertion. *J. Org. Chem.* **2014**, *79,* 5082-5087.
(47) Sugano, L.; Tanese, T.; Kobayashi, K.l Yamamoto, Y. Cobalt-catalyzed Preparation of Diiminofuran Derivatives through Double Insertion of Isocyanide into a Metal-Carbon σ-Bonds. *Chem. Lett.* **1991**, *20*, 921-924.
(48) Whitby, R.J.; Saluste, C.G.; Furber, M. Synthesis of α-Iminoimidates by Palladium Catalysed Double Isonitrile Insertion. *Org. Biomol. Chem.* **2004**, *2*, 1974-1976
(49) Kobiki, Y.; Kawaguchi, S.-I.; Ogawa, A. Palladium-Catalyzed Synthesis of α-Diimines from Triarylbismuthines and Isocyanides. *Org. Lett.* **2015**, *17*, 3490-3493.
(50) Chen, Z. B.; Zhang, Y.; Yuan, Q.; Zhang, F. L.; Zhu, Y. M.; Shen, J. K. Pd-Catalyzed Synthesis of α-Iminonitriles from Aryl Halides via Isocyanide Double Insertion Reaction. *J. Org. Chem.* **2016**, *81*, 1610-1616.
(51) (a) Gao, Q.; Zhou, P.; Liu, F.; Hao, W.-J.; Yao, C.-S.; Jiang, B.; Tu, S.-J. Cobalt(II)/Silver Relay Catalytic Isocyanide Insertion/Cycloaddition Cascades: A New Access to Pyrrolo[2,3-B]Indoles. *Chem. Commun*. **2015**, *51*, 9519-9522. (b)Pan, Y. Y.; Wu, Y. N.; Chen, Z. Z.; Hao, W. J.; Li, G. G.; Tu, S. J.; Jiang, B. Synthesis of 3-Iminoindol-2-amines and Cyclic Enaminones via Palladium-Catalyzed Isocyanide Insertion-Cyclization *J. Org. Chem*. **2015**, *80*, 5764-5770. (c)He, Y.; Wang, Y.-C.; Hu, K.; Xu, X.-L.; Wang, H.-S.; Pan, Y.-M. Palladium-Catalyzed Synthesis of 5-Iminopyrrolones through Isocyanide Double Insertion Reaction with Terminal Alkynes and Water. *J. Org. Chem.* **2016**, *81,* 11813-11818. (d)Hu, W.; Zheng, J.; Li, J.; Liu, B.; Wu, W.; Liu, H.; Jiang, H. Assembly of Polysubstituted Maleimides via Palladium-Catalyzed Cyclization Reaction of Alkynes with Isocyanides. *J. Org. Chem.* **2016**, *81*, 12451-12458. (e) Hu, W.; Li, J.; Xu, Y.; Li, J.; Wu, W.; Liu, H.; Jiang, H. Palladium-Catalyzed Redox-Neutral N–O/C(sp3)–H Functionalization of Aryl Oximes with Isocyanides. *Org. Lett.* **2017**, *19*, 678-681. (f) Senadi, G. C.; Lu, T.-Y.; Dhandabani, G. K.; Wang, J.-J. Palladium-Catalyzed Double-Isocyanide Insertion via Oxidative N–O Cleavage of Acetyl Oximes: Syntheses of 2H-Pyrrol-2-imines. *Org. Lett.* **2017**, *19*, 1172-1175. (g) Wang, X.; Xiong, W.; Huang, Y.; Zhu, J.; Hu, Q.; Wu, W.; Jiang, H. Palladium-Catalyzed Synthesis of 1H-Indenes and Phthalimides via Isocyanide Insertion. *Org. Lett***.** **2017**, *19*, 5818-5821. (h) Hu, W.; Li, M.; Jiang, G.; Wu, W.; Jiang, H. Synthesis of 2,3-Difunctionalized Benzofuran Derivatives through Palladium-Catalyzed Double Isocyanide Insertion Reaction. *Org. Lett.* **2018**, *20*, 3500–3503. (i) Yuan, W.-K.; Liu, Y. F.; Lan, Z.; Wen, L-R.; Li, M. Nickel Catalysis Enables Access to Thiazolidines from Thioureas via Oxidative Double Isocyanide Insertion Reactions. *Org. Lett.* **2018**, *20*, 7158-7162. (j) Hongwei, S.; Tang, S.; Li, D.; Zhou, Y.; Huang, J.; Zhu, Q. Cascade Double Isocyanide Insertion and C–N Coupling of 2-iodo-2'-isocyano-1,1'-biphenyls. *Org. Biomol. Chem*. **2018**, *16*, 3893-3896.
(51) Su, Y.; Zhang, L.; Jiao, N. Utilization of Natural Sunlight and Air in the Aerobic Oxidation of Benzyl Halides. *Org. Lett.* **2011**, *13*, 2168-2171.
(52) Su, Y.; Zhang, L.; Jiao, N. Utilization of Natural Sunlight and Air in the Aerobic Oxidation of Benzyl Halides. *Org. Lett.* **2011**, *13*, 2168-2171.
(53) Khurana, J. M.; Kandpal, B. M. A Novel Method of Synthesis of 1,2-Diketones from 1,2-Diols using N-Bromosuccinimide. *Tetrahedron Lett.* **2003**, *44*, 4909-4912.
(54) a) Blackmond, D.G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chemie Int. Ed*. **2005**, *44*, 4032-4320; b) Mathew, J.S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E.A.C.; Blackmond, D.G. Investigations of Pd-Catalyzed ArX Coupling Reactions Informed by Reaction Progress Kinetic Analysis. *J. Org. Chem.* **2006**, *71*, 4711-4722; c) Blackmond, D.G. Kinetic Profiling of Organic Catalytic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852-10866.

(55) a) Amatore, C. Gamez, S.; Jutand, A. Rate and Mechanism of the Reversible Formation of Cationic (η^3-Allyl)- palladium Complexes in the Oxidative Addition of Allylic Acetate to Palladium(0) Complexes Ligated by Diphosphanes, *Chemistry: Eur. J.* **2001**, *7*, 1273-1280; b) Amatore, C.; Jutand, A.; Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination of Pd-Catalyzed Suzuki-Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. *Chemistry: Eur. J.* **2011**, *17*, 2492-2503.

(56) Keske, E.C.; West, T.H.; Lloyd-Jones, G.C. Analysis of Autoinduction,Inhibition, and Autoinhibition in a Rh-Catalyzed C-C Cleavage: Mechanism of Decyanative Aryl Silylation. *J. Am. Chem. Soc.* **2018**, *8*, 8932-8940.

(57) Bures, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem. Int. Ed*. **2016**, *55*, 16084-16087.

(58) a) Marcone, J.E.; Moloy, K.G. Kinetic Study of Reductive Elimination from the Complexes (Diphosphine)Pd(R)(CN). *J. Am. Chem. Soc.* **1998**, *120*, 8527-8528; b) Guiry, P.; Brown, J.M. Bite Angle Dependence of the Rate of Reductive Elimination From Diphosphine Palladium Complexes, **1994**, *220*, 249-259; c) Dierkes, P.; van Leeuwen, P.W.N.M.; The Bite Angle Makes the Difference: A Practical Ligand Parameter For Diphosphine Ligands. JCS *Dalton Trans.* **1999**, 1519-1529.

(59) Fernandez-Alvarex, V.M.; de la Fuente, V.; Godard, C.; Castillon, S.; Claver, C.; Maseras, F.; Carbo, J.J. Pd-Catalysed Mono- and Dicarbonylation of Aryl Iodides: Insights into the Mechanism and the Selectvity. *Chem. Eur. J.* **2014**, *20*, 10982-10989.

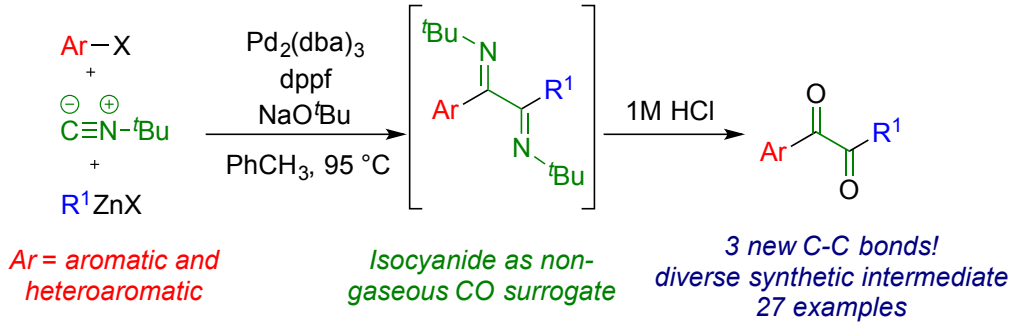
(60) Bartand, C. F. J. Palladium-Catalyzed Carbonylations—A Reaction Come of Age. *Organometallics* **2008**, *27*, 5402-5422.

(61) Amatore, C.; Jutand, A. Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions. *Acc. Chem. Res.* **2000**, *33*, 314-321.

(62) Mann, G.; Hartwig, J. F. Palladium Alkoxides: Potential Intermediacy in Catalytic Amination, Reductive Elimination of Ethers, and Catalytic Etheration. Comments on Alcohol Elimination from Ir(III) *J. Am. Chem. Soc.* **1996**, *118*, 13109-13110.

(63) Ozawa, F.; Sugimoto, T.; Yamamoto, T.; Yamamoto, A. Preparation of *trans*-Pd(COCOR)CI($PMePh_2$)$_2$ Complexes (R = Ph and Me) and Their Reactivities Related to Double Carbonylation Promoted by Palladium. *Organometallics* **1984**, *3*, 692-697.

(64) Chen, J.-T.; Sen. A. Mechanism of Transition-Metal-Catalyzed "Double Carbonylation" Reactions. Synthesis and Reactivity of Benzoylformyl Complexes of Palladium(II) and Platinum(II). *J. Am. Chem. Soc.* **1984**, *106*, 1506-1507.



Ar = aromatic and heteroaromatic

Isocyanide as non-gaseous CO surrogate

3 new C-C bonds!
diverse synthetic intermediate
27 examples