

HARNESSING THE CHEMISTRY OF CO₂

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ABSTRACT

Our research program is broadly focused on activating CO₂ through the use of organic and organometallic based catalysts. Some of our methods have centered on annulation reactions of unsaturated hydrocarbons (and carbonyl substrates) to provide a diverse array of carbocycles and heterocycles. We use a combination of catalyst discovery and optimization in conjunction with classical physical organic chemistry to elucidate the key mechanistic features of the cycloaddition reactions such that the next big advances in catalyst development can be made. Key to all of our cycloaddition reactions is the use of a sterically hindered, electron donating *N*-heterocyclic carbene (NHC) ligand, namely IPr (or SIPr), in conjunction with a low valent nickel pre-catalyst. The efficacy of this ligand is two-fold: (1) the high σ -donating ability of the NHC increases the nucleophilicity of the metal center which thereby facilitates interaction with the electrophilic carbonyl and (2) the steric hindrance prevents an otherwise competitive side reaction involving only the alkyne substrate. Such a system has allowed for the facile cycloaddition to prepare highly functionalized pyrones, pyridones, pyrans, as well as novel carbocycles. Importantly, all reactions proceed under extremely mild conditions (room temperature, atmospheric pressures, and short reaction times), require only catalytic amounts of Ni/NHC and readily available starting materials, and afford annulated products in excellent yields. Our current focus revolves around understanding the fundamental processes that govern these cycloadditions such that the next big advance in the cyclization chemistry of CO₂ can be made. Concurrent to our annulation chemistry is our investigation of the potential for imidazolylidenes to function as thermally-actuated CO₂ sequestering and delivery agents.

PERSONNEL**PI:** Janis Louie**Post-docs:** Dr. Rodrigo Cella**Graduate Students:** Bret Van Ausdall, Christopher Kareis, Jorge De Freitas, Puneet Kumar**PUBLICATIONS**

- (1) H. A. Duong, J. Louie "Regioselectivity in Ni/Phosphine Catalyzed Cycloadditions of Alkynes and Isocyanates" *J. Organomet. Chem.* **2005**, *690*, 5098-5104; *Invited Contribution to a Special Issue (Organometallic Chemistry - The Next Generation)*.
- (2) H. A. Duong, J. Louie "A Nickel-Catalyzed Cycloaddition of Alkynes and Isocyanates that Affords Pyrimidine-diones" *Tetrahedron* **2006**, *62*, 7547-7551; *Invited Contribution to a Special Edition on Recent Advances in Organonickel Chemistry*.
- (3) T. N. Tekavec, G. Zuo, K. Simon,[†] J. Louie "An In Situ Ni Catalyst for Cycloaddition Reactions" *J. Org. Chem.* **2006**, *71*, 5834-5836.
- (4) P. R. Chopade, J. Louie "[2+2+2] Cycloaddition Reactions Catalyzed by Transition Metal Complexes" *Adv. Synth. Catal.* **2006**, *348*, 2307-2327.
- (5) T. N. Tekavec, J. Louie "Nickel-Catalyzed Cycloaddition of Enynes and Carbonyls" *J. Org. Chem.* **2008**, *73*, 2641-2648.
- (6) T. N. Tekavec, J. Louie "Nickel-Catalyzed Cycloisomerization of Enynes: Mechanistic Evidence for Catalyst Generation via C-H Activation of Carbene Ligands" *Tetrahedron* **2008**, *64*, 6870-6875; *Invited Contribution to a Special Edition Honoring Professor John F. Hartwig's Young Investigator Prize*.
- (7) K. Zhang, P. R. Chopade, J. Louie "Coupling of Vinyl Aziridines and Isocyanates" *Tetrahedron Lett.* **2008**, *49*, 4306-4309.
- (8) G. Zuo, K. Zhang, J. Louie "Nickel Catalyzed Reactions of Vinyl Aziridines and Aziridinyl-enynes" *Tetrahedron Lett.* **2008**, *49*, 6797-6799.
- (9) S. Wang, D. M. Troast, M. Conda-Sheridan, G. Zuo, D. LaGarde, J. Louie, D. Tantillo "On the Mechanism of the Ni(0)-Catalyzed Vinylcyclopropane-Cyclopentene Rearrangement" *J. Org. Chem.* **2009**, *20*, 7822-7833.
- (10) B. R. D'Souza, J. Louie "Nickel Catalyzed Cycloadditive Couplings of Enynes and Isocyanates" *Org. Lett.* **2009**, *11*, 4168-4171.
- (11) B. R. Van Ausdall, J. L. Glass,[†] K. M. Wiggins,[†] A. M. Arif, J. Louie "A Systematic Investigation of Factors Influencing the Decarboxylation of Imidazolium Carboxylates" *J. Org. Chem.* **2009**, *20*, 7935-7942.

PROGRESS REPORT (8/15/2005 – 7/31/2009)

RESEARCH GOALS AND SPECIFIC OBJECTIVES

Our research program seeks to harness the chemical potential of CO₂ by accomplishing a progressive set of objectives. We have discovered a series of Ni based catalysts for annulating CO₂ with diynes to afford 2-pyrones. We have also been successful in expanding the cycloaddition chemistry to include other substrates to provide value added heterocycles and carbocycles. In addition, we continue our efforts to understand the mechanism of Ni-catalyzed cycloadditions of diynes and CO₂. We have evaluated model reactions, performed detailed kinetic analyses, and have isolated and characterized intermediates. Our kinetic analysis has led to the isolation of a well-defined, eta-2 bound nitrile Ni-imidazolylidene complex suggesting that initial binding between the metal and the heterocumulene may be important for cyclization. Importantly, this complex was found to react with alkynes to ultimately afford pyridines.

In an effort to substantiate the last step of the cycloaddition mechanism, C-O bond-forming reductive elimination, we attempted to prepare well-defined Ni-alkoxide complexes. During the course of these syntheses, we found interesting and novel reactivity between Ni-imidazolylidene complexes and aryl halides. Given the importance of oxidative addition of aryl halides not only in our chemistry but in cross coupling chemistry, we have embarked on a detailed analysis of the scope of this reactivity. In addition, to address our initial goal, new methods for the synthesis of Ni-alkoxides are being developed.

Parallel efforts have focused on developing imidazolylidenes to function as thermally-actuated CO₂ sequestering and delivery agents. We have recently developed a universal and direct method for the carboxylation of imidazolium salts and have successfully prepared a series of imidazolylium carboxylates. We continue to study the physical properties of these imidazolylium carboxylates and, more importantly, how their structural features affect their ability to act as carboxylating agents.

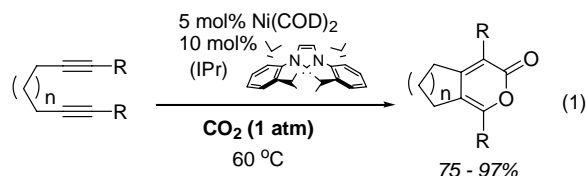
POTENTIAL IMPACT IN SCIENCE & TECHNOLOGIES OF INTEREST TO DOE

Pollution prevention and waste management continue to be profound challenges for modern society. One potential solution to this problem is the development and utilization of ideal reactions for the production of valuable commodities. In an ideal synthetic reaction, raw materials are converted to the desired product with complete selectivity and without any waste products. Only heat, light, and/or a catalyst are necessary to facilitate the reaction. For example, annulations of unsaturated hydrocarbons with CO₂ could efficiently provide oxygen-containing heterocycles, an important structural motif found in numerous economically important and biologically relevant systems. As added benefits, CO₂ is relatively non-toxic, non-flammable, and abundant and a wide range of unsaturated hydrocarbons are already used chemical feed stocks on an industrial scale. Although considerable effort has been directed toward the discovery of new and efficient protocols, activation of CO₂ has yet to reach its full potential.

Our research presents several strategies for addressing the challenges of activating CO₂. In addition, our cycloaddition chemistry addresses several fundamental issues pertaining to catalysis as it applies to energy conservation. We have been fortunate to be honored by the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation (Teacher-Scholar Award), and the American Chemical Society (Cope Scholar Award) for our efforts in these fields.

DEVELOPMENT OF A CYCLOADDITION CATALYST^{1,2}

In an effort to increase the number of methods available to synthetic chemists for the utilization of CO₂ as a feedstock, we have developed a Ni based catalyst that mediates the cycloaddition of diynes and CO₂ to afford 2-pyrones. We found the combination of catalytic amounts both Ni(COD)₂ and IPr successfully converted a wide variety of diynes to their corresponding pyrones in excellent yields (Equation 1). The reaction tolerated both acid- and base-sensitive functional groups such as esters, ethers, and silyl ethers; and fused five- and six-membered rings were prepared in excellent yields. Unsubstituted diynes afforded their respective pyrone products as well. Importantly, reaction conditions were exceptionally mild (i.e., atmospheric pressure of CO₂, 60 °C). In addition, IPrBF₄ and KO-*t*-Bu could be used in lieu of the air sensitive IPr without any loss in catalytic activity.



The regioselectivity of Ni(0)-catalyzed cycloadditions of CO₂ (1 atm) with various asymmetrical diynes was also explored (Equation 2). A series of asymmetrically substituted diynes, containing one terminal methyl group and another terminal group of varying size (Et, *i*-Pr, *t*-Bu, and TMS) were prepared. As shown in Table 1, even in cases when the difference between the terminal diyne substituents was small (Me vs. Et, Entry 1 and Me vs. *i*-Pr, Entry 2), a considerable excess of one regioisomer was observed. Complete regioselectivity was observed when the bulky substituent was *t*-Bu (Entry 3) or larger (TMS, Entry 4).

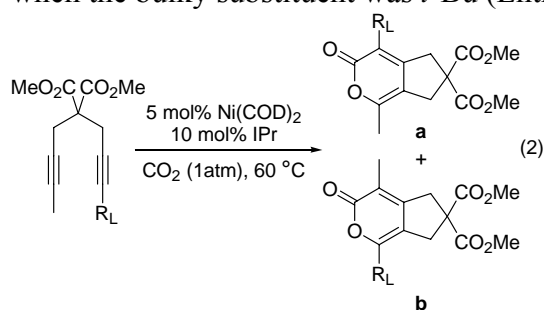


Table 1. Nickel-catalyzed cycloaddition of CO₂ and asymmetrical diynes

Entry	Substrate	Product a:b	% Yield
1	R _L = Ethyl	62:38	75
2	R _L = <i>i</i> -Pr	80:20	64
3	R _L = <i>t</i> -butyl	100:0	64
4	R _L = TMS	100:0	83

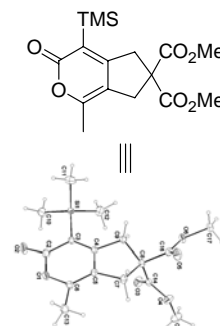


Figure 1.

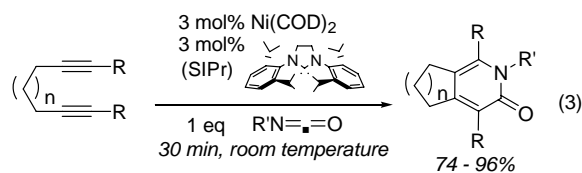
EXPANDING THE SUBSTRATE SCOPE

It seemed likely that the same mechanistic features that govern pyrone formation would be relevant in all Ni-catalyzed cycloadditions of unsaturated hydrocarbons (alkynes and alkenes) and heteroatom-containing substrates. As such, we surmised that the same catalyst system could be employed to mediate other useful cycloadditions and set out to evaluate other substrates.

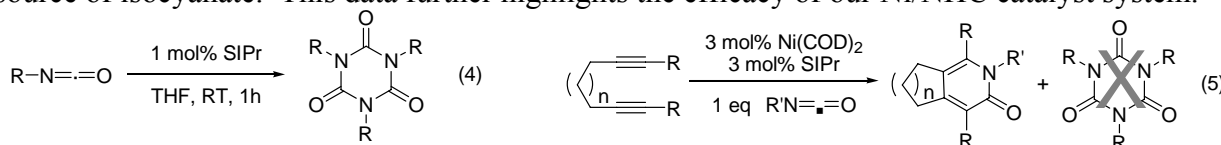
I. CYCLOADDITION OF DIYNES AND ISOCYANATES^{3,4}

Since isocyanates undergo facile oxidative coupling with alkynes, we pursued a strategy for catalyst discovery, similar to our approach for CO₂ cycloadditions, for the cycloaddition of diynes and isocyanates. Ultimately, we found that a combination of Ni(0) and SIPr catalyzed the cycloaddition of diynes with isocyanates under the mildest conditions to date (Equation 3). In particular, excellent yields of pyridones are obtained from diynes and isocyanates at room temperature using only 3 mol% catalyst. Both aryl and alkyl isocyanates were readily converted to their respective 2-pyridone. Sterically-hindered substrates appeared to have very little effect on the reaction as excellent yields of product were obtained with bulky isocyanates and bulky

diynes. In addition, the cycloaddition of an unsymmetrical diyne and butyl isocyanate afforded a pyridone as a single isomer demonstrating isocyanate and CO₂ cycloadditions follow analogous mechanisms, as expected.

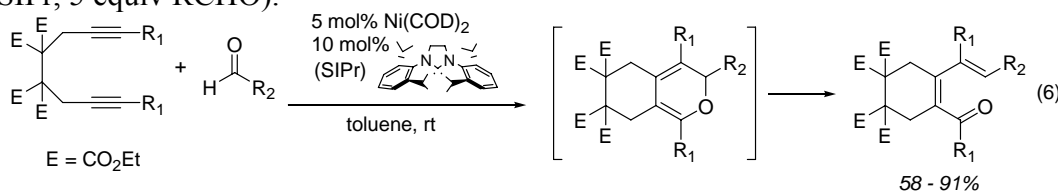


Interestingly, imidazolyidenes were found to react with isocyanates but afforded isocyanurates, rather than analogous imidazolylidene amidates (Equation 4). Although SIPr was found to be an effective catalyst for isocyanurate formation (for a wide variety of isocyanates), no isocyanurate is observed in most Ni-catalyzed cycloaddition reactions of diynes and isocyanates (Equation 5). Furthermore, isocyanurates are not formed reversibly during the course of the reaction as no pyridones were formed when isocyanurates were used as the sole source of isocyanate. This data further highlights the efficacy of our Ni/NHC catalyst system.



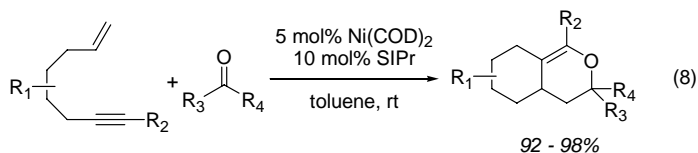
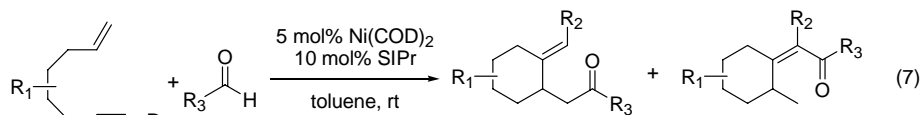
II. CYCLOADDITION OF DIYNES AND ALDEHYDES⁵

The recent advances in Ni-catalyzed reductive couplings of alkynes and simple aldehydes suggested that aldehydes could serve as an effective ‘electrophile’ in our cycloaddition protocol. Indeed, our standard protocol involving the Ni/SIPr catalyst cleanly afforded dienone products (derived from electrolytic ring opening of the initial pyran) from diynes and various aldehydes *at room temperature* (Equation 5). The cycloaddition of an aryl aldehyde bearing an electron-donating group (*p*-OMe) afforded the dienone product in a higher yield than the reaction of an aryl aldehyde possessing an electron-withdrawing group (*p*-CF₃). Aliphatic aldehydes also underwent facile cycloaddition using slightly modified conditions (10 mol% Ni(COD)₂, 10 mol% SIPr, 5 equiv RCHO).⁶



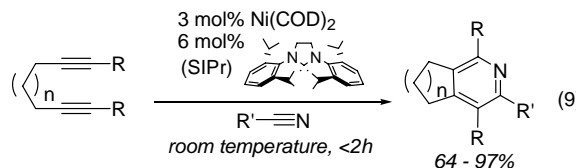
III. CYCLOADDITION OF ENYNES AND CARBONYLS⁷

Given the efficacy of the cyclizations of diynes and aldehydes, we tested the potential of our Ni catalysts for the cycloaddition reaction of enynes. We found that aldehydes undergo a smooth reaction with a variety of enynes. Interestingly, two different products, an enone and a ketone, are formed. It appears that the ratio of the product distribution greatly depends on the steric hinderance on the alkyne substituent (Equation 7). We have also found success in catalyzing the cycloaddition of more challenging substrates, specifically enynes and ketones. Interestingly, we found that in almost all cases, pyrans can be obtained regioselectively and in excellent yields (Equation 8).



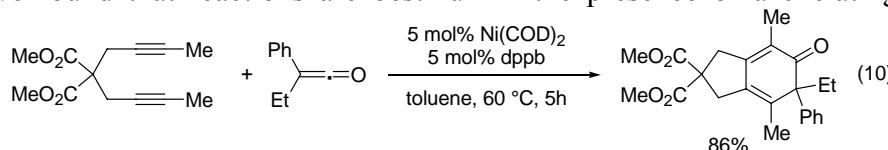
IV. CYCLOADDITION OF DIYNES AND NITRILES^{8,9}

We were pleased to discover that our Ni/SIPr system catalyzed the cyclotrimerization of alkynes and nitriles to afford pyridines (Equation 9). This reaction is intriguing for a number of reasons: 1) Ni complexes readily undergo oxidative addition of R-CN bonds; 2) Ni complexes are known to cause homodimerization of nitriles; 3) Ni complexes catalyze the carbocyanation of alkynes; and 4) the oxidative coupling of an alkyne and a nitrile is *sluggish* at best for Ni (although the resultant nickelacycle can be prepared through the stoichiometric transmetallation between an azazirconacyclopentenone and Ni(PPh₃)₂Cl₂). It is likely the high nucleophilic character of our Ni/NHC system allows for the facile oxidative coupling of the alkyne and the nitrile which thereby leads to efficient cycloaddition.



V. CYCLOADDITION OF DIYNES AND KETENES

Recently, we found that diynes and ketenes undergo Ni catalyzed cycloaddition reactions to form highly substituted arene products (Equation 10). Although nickel catalysts have been used to catalyze the cycloaddition of diynes with a variety of substrates, no reports to date involve the use of ketenes as substrates. Given the importance of quaternary carbon centers in synthetic chemistry, we have embarked on a study to further develop this chemistry. We have begun to investigate the scope of diynes as well as ketenes that can be employed as substrates in this reaction. Importantly, since ketenes are generally reactive and hard to handle substrates, we will evaluate methods to generate ketenes *in situ* to be used directly in cycloaddition reactions. Furthermore, since we have found that reactions are best run in the presence of a chelating phosphine, we hope to develop an asymmetric variant of this cycloaddition reaction.



UNDERSTANDING THE MECHANISM OF CO₂ ACTIVATION

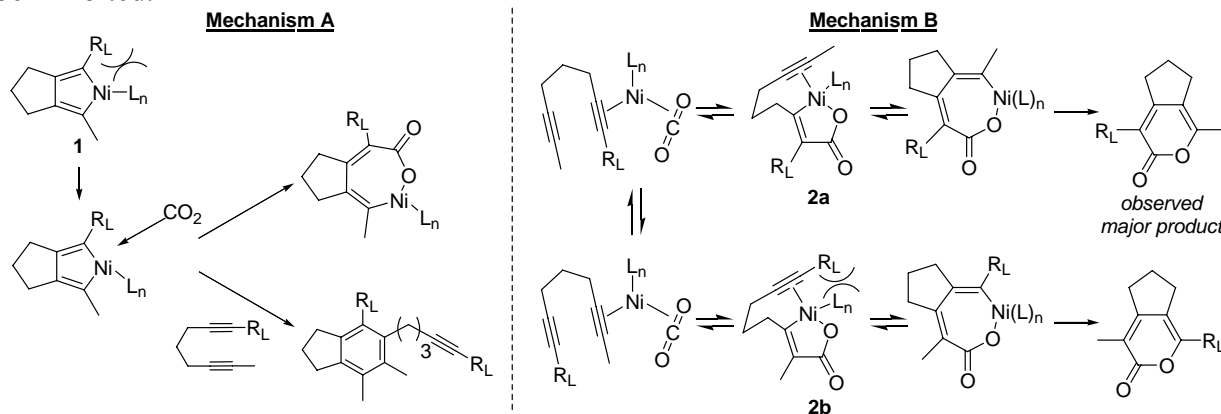
Our efforts to delineate the mechanism of the diyne/CO₂ cycloaddition reaction are ongoing. In addition to guiding the design of advanced catalysts, we hope to gain a deeper understanding of the fundamental principles of activating CO₂ *via* transition metals, particularly Ni. For example, Nature employs a metalloenzyme, carbon monoxide dehydrogenase/acetyl-CoA synthase (CODH/ACS) that utilizes Ni for binding and activating CO₂. Nature's motivation for choosing Ni remains unknown.

I. REGIOSELECTIVITY STUDIES²

At the onset of our research, previous reports suggested that oxidative coupling between the sterically-unhindered alkyne and CO₂ preceded all other cycloaddition steps and that the pyrone product would possess the larger substituent in the 6-position. However, single crystal X-ray analysis of the major isomer revealed that the larger substituent, i.e. TMS, was located at the 3-position of the pyrone ring (Figure 1, *vide supra*). These findings warranted a re-evaluation of our proposed mechanism.

A possible explanation for the observed regioselectivity could be that our Ni/IPr-catalyzed cycloaddition actually proceeds through a mechanism involving a metallocyclopentadiene

intermediate **1** (Scheme 1). Thus, when an asymmetrical diyne is employed, CO₂ could insert at two distinct positions (Mechanism A). In order to relieve steric crowding between the relatively bulky group and the ligand, CO₂ insertion into the side containing the bulkier R group would be expected to be favored and afford pyrones with the bulky substituent at the 3-position. Although Mechanism A explains the observed regioselectivity, other data must be considered. Specifically, when asymmetrically diynes were used as substrates, increased amounts of oligomerized products (i.e., cyclotrimerized aromatics) were formed. Thus, it is unlikely that increasing the steric crowding around the nickel center would inhibit CO₂ insertion while favoring subsequent alkyne insertion. It is more likely that both CO₂ and alkyne insertion would be inhibited.



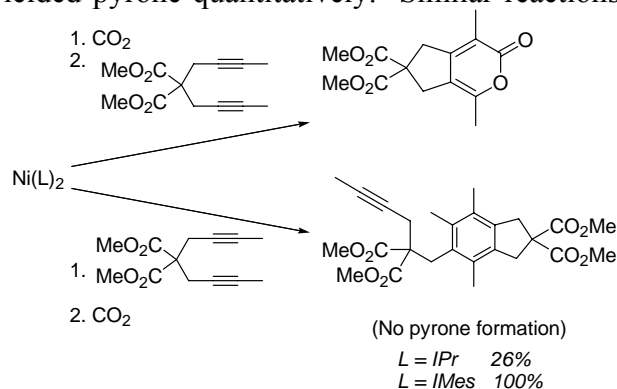
Scheme 1. Possible mechanisms for the cycloaddition of diynes and CO₂

An alternative explanation is depicted in Mechanism B of Scheme 1. Mechanism B involves initial binding of CO₂ followed by oxidative coupling with an alkynyl unit to afford a five-member nickelacycle intermediate (**2a** or **2b**). The pendant alkynyl unit then inserts to form a seven-member nickelacycle which subsequently reductively eliminates to afford the pyrone product. When asymmetrically-substituted diynes are employed, two regioisomeric products are possible and their formation is ultimately dependent on the five-member nickelacycle intermediate. Initial oxidative coupling between the larger alkynyl unit (R_L) and CO₂ leads to the formation of nickelacycle **2a**. Subsequent insertion of the pendant alkynyl unit affords pyrones with the bulky R_L group in the 3-position. Although binding and oxidative coupling of the least sterically hindered alkynyl unit (to form **2b** and ultimately 6-substituted pyrones) is favored, subsequent insertion should be inhibited since it requires the bulky alkynyl unit to be placed adjacent to the imidazolyliene ligand. The formation of **2b** represents a catalytic sink unless oxidative coupling is reversible and can rearrange to afford **2a**. Inhibited oxidative coupling and molecular rearrangement would slow the overall rate of pyrone formation and permit the formation of side products to become competitive. Thus, Mechanism B also explains why increased amounts of oligomeric side products are observed when asymmetrically diynes are used as substrates.

II. REACTIONS WITH WELL-DEFINED NICKEL COMPOUNDS: ORDER OF ADDITION

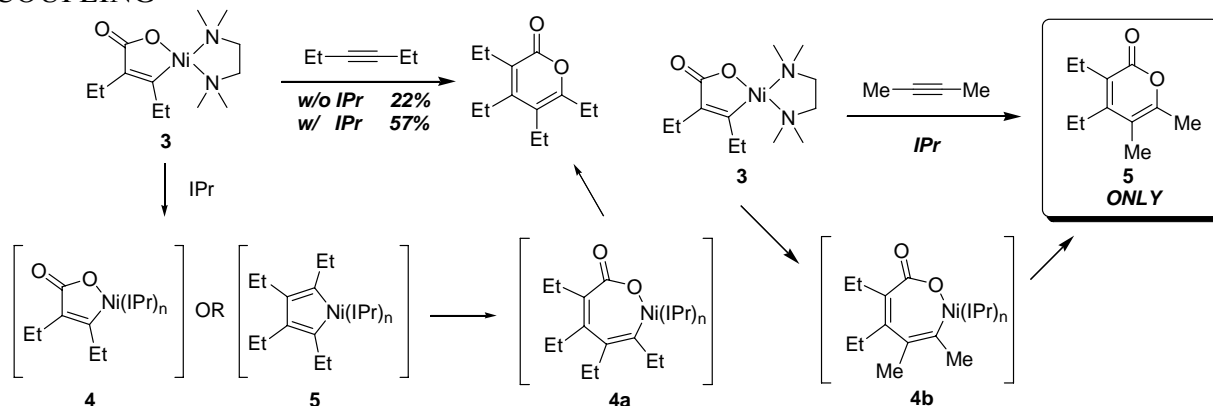
Our regioselectivity studies on asymmetrical diynes provided excellent qualitative evidence that mechanism B in Scheme 1 was the operative pathway. It also provided the first insight that insertion/reductive elimination may be rate determining. We intended to substantiate our findings by performing detailed kinetic analysis of the cycloaddition. Unfortunately, these experiments were complicated by a reaction between the IPr ligand and CO₂ (*vide infra*).

To circumvent the complications associated with the kinetic analysis, stoichiometric reactions were performed with well-defined nickel complexes. Reactions between $\text{Ni}(\text{IPr})_2$ and diyne or $\text{Ni}(\text{IPr})_2$ and CO_2 were individually monitored by ^1H NMR spectroscopy. Remarkably, $\text{Ni}(\text{IPr})_2$ did not readily react with diyne to form nickelole **1** at room temperature (Scheme 1). Even under more forcing conditions (60°C), the reaction between the Ni complex and the diyne was slow. Addition of CO_2 did not lead to pyrone formation and instead only a complex mixture which included a cyclotrimer/arene by-product was observed. In contrast, $\text{Ni}(\text{IPr})_2$ reacted quantitatively with CO_2 (in the absence of diyne) at room temperature to afford mixture of products which included $\text{Ni}(\text{IPr})_2(\text{CO}_2)$, a complex structurally related to its phosphine analogue $\text{Ni}(\text{PR}_3)_2(\text{CO}_2)$. Subsequent addition of diyne yielded pyrone quantitatively. Similar reactions were performed with $\text{Ni}(\text{IMes})_2$. $\text{Ni}(\text{IMes})_2$ reacted rapidly with diyne to afford arene. Pyrone was only observed when CO_2 was added to the catalyst before diyne. Scheme 2 summarizes these results. It is likely that when the IPr ligand is bound to Ni, the high steric crowding of the four ortho isopropyl units protects the Ni atom and inhibits nickelole formation. Regardless, these results verified that nickelacycle **1** formation led to a side reaction that forms cyclotrimeric by-products.



Scheme 2. Sequential addition of substrates to $\text{Ni}(\text{L})_2$

III. REACTIONS WITH WELL-DEFINED NICKEL COMPOUNDS: OXIDATIVE COUPLING¹⁰



Scheme 3. Stoichiometric reactions with isolated nickelacycles

Subsequent stoichiometric reactions which were designed to address oxidative coupling partners were also examined. Specifically, nickelacycle **3** prepared by reaction of $\text{Ni}(\text{COD})_2$, TMEDA (TMEDA = tetramethyl ethylene diamine), 3-hexyne, and CO_2 , was subjected to 3-hexyne in the presence and absence of the IPr ligand (Scheme 3). Tetraethylpyrone formed in both cases, however yields were enhanced when the imidazolylidene ligand was added (57% vs. 22%, respectively). (It is important to note that TMEDA does not act as an efficient ligand in the cycloaddition reactions with diynes.) Although it seemed likely that the higher pyrone yields obtained upon the addition of IPr was due to a more facile C-O bond forming reductive elimination (*via* **4a**), complete dissociation of **4** and re-oxidative coupling (to form **5**) could not be ruled out. However, **5** was the only pyrone observed in a crossover experiment performed with 2-butyne. If dissociation of nickelacycle **4** was relevant, then other pyrone isomers (such as

tetramethylpyrone) would have been detected. Thus, we believe that the first step in pyrone formation requires a Ni mediated oxidative coupling between an alkyne and CO₂.

III. REACTIONS WITH WELL-DEFINED NICKEL COMPOUNDS: C-O BOND-FORMING REDUCTIVE ELIMINATION¹¹

Little is known about both Ni-imidazolylidene mediated C-C and C-Y (Y = heteroatom) bond-forming reductive elimination. Nevertheless, the formation of heterocycles and carbocycles hinges on the ability to form C-C and C-Y bonds through reductive elimination. As such, we have begun a program revolved around the understanding of this fundamental process. Intimately tied to this research is the side β -H elimination reaction, which can impede product formation in some cases.

Our initial synthetic plan to access the well-defined Ni imidazolylidene species required to evaluate such reactions lead to some intriguing discoveries. Although oxidative addition of aryl halides to Ni(0) complexes has been demonstrated numerous times, the corresponding oxidative addition to Ni(0)-NHC complexes has only been shown in a single experiment. Nevertheless, we presumed oxidative addition should be straightforward and should afford (NHC)₂Ni(Ar)(X) complexes in a rapid fashion. With those complexes in hand, we would then substitute the halide (X) for either an alkyl or a heteroatom-containing ligand and subsequently monitor the rates of reductive elimination as a function of NHC ligand. Surprisingly however, (NHC)₂Ni(Ar)(X) complexes were not obtained. Instead, we found that regardless of ArX, a nickel(I) species, (NHC)₂Ni(X), were formed. Although the reaction of nickel phosphines and aryl halides had been shown to provide Ni(I) complexes, such reactions typically provided low amounts of Ni(I). In addition, no structural information could be obtained when phosphines were employed as ligands.

Given of the importance of aryl halide oxidative addition, not only in our research but in the vast field of coupling chemistry, we are examining the reaction of Ni⁰(NHC)_n and aryl halides. Our studies suggest that (NHC)₂Ni(Ar)(X) forms first and then readily converts to (NHC)₂NiX complexes. We can confirm the formation of the (NHC)₂NiX complexes by synthesizing them directly via the disproportionation between (NHC)₂NiX₂ and (NHC)₂Ni. Disproportionation affords the (NHC)₂NiX product in high yields and in a higher purity than in reactions involving the addition of aryl halide to Ni(0). We have crystallized a series of (IMes)₂Ni(X) (X = I, Br, or Cl, see Figure 2). Our EPR measurements on these complexes further substantiate the formation of Ni(I) species.

Currently, we are exploring other synthetic avenues to the desired (NHC)₂Ni(R)(Y) complexes so that C-Y bond-forming reductive elimination and β -H elimination can be studied in detail.

IV. EVALUATION OF NITRILE CYCLOADDITION

A kinetic analysis of a cycloaddition reaction was crucial to corroborate our stoichiometric studies involving well-defined nickel complexes and CO₂. Thus, we embarked on a detailed kinetic analysis of the cycloaddition of diynes and nitriles since this cycloaddition likely mirrored the chemistry between diynes and CO₂ yet didn't suffer from side reactions between the imidazolylidene and the nitrile.

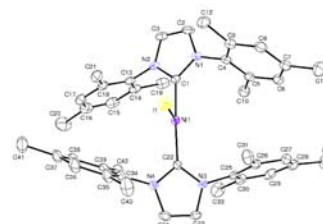


Figure 2. X-ray analysis of Ni(IMes)₂(I)

We suspected that a key step to the reaction was the initial displacement of the imidazolylidene ligand and binding of the nitrile substrate. Early evidence for this came with the isolation of an interesting eta-2 bound nitrile complex (Figure 3). However, although this dimeric species did catalyze cycloaddition of diynes and nitriles, it was not catalytically competent and appeared to be a catalyst ‘sink’.

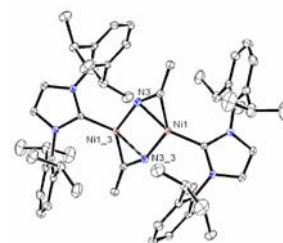
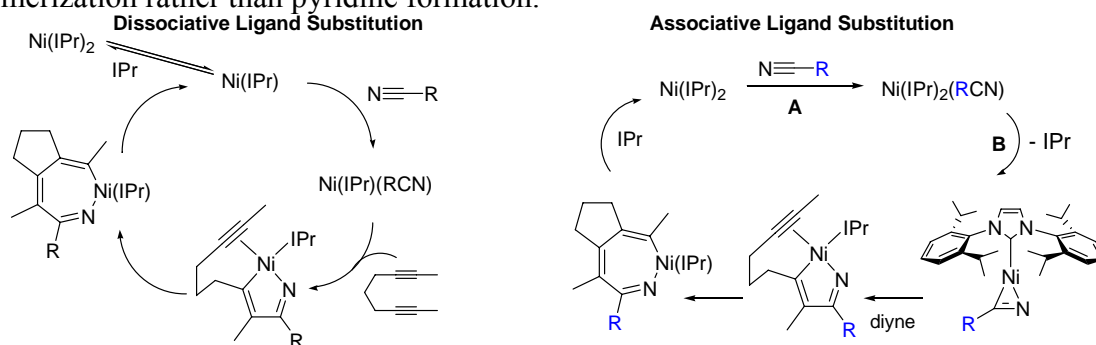


Figure 3. Eta-2 bound nitrile complex $[(\text{IPr})\text{Ni}(\text{MeCN})]_2$

Subsequent to this discovery, we evaluated the kinetics of the $\text{Ni}(\text{IPr})_2$ catalyzed cycloaddition of diynes and nitriles. These efforts have led to some intriguing discoveries. As expected, cycloadditions showed a first order dependence on $\text{Ni}(\text{IPr})_2$. However, reactions run with excess nitrile showed a zero order dependence for IPr, nitrile, as well as diyne. What is even more perplexing is that although reactions display a zero order dependence in nitrile concentration, the *identity* of the nitrile does influence the rate of the reaction. For example, reactions run with benzonitrile are significantly faster than those run with acetonitrile. Furthermore, reactions run with isopropyl nitrile display a first order dependence in nitrile concentration. It is possible that we are in the range of saturation kinetics with respect to nitrile concentration. Unfortunately, reactions run with excess diyne, rather than excess nitrile, undergo rapid and irreversible diyne oligomerization rather than pyridine formation.



Scheme 4. Kinetic analysis of $\text{Ni}(\text{IPr})_2$ catalyzed cycloaddition of diynes and MeCN

Reasonable mechanisms for this reaction are depicted in Scheme 4. Given our kinetic data, we were able to rule out a dissociative ligand substitution mechanism since this mechanism would require the observation of either an inverse first order in ligand or reaction rates that were identical regardless of the identity of the nitrile. Although at first glance, a mechanism involving an associative ligand substitution may not seem to account for all of the kinetic data, a deeper look would reveal that such a mechanism is possible if the rate determining step is dependent on the nitrile. Specifically, if a bulky nitrile such as *i*PrCN is used, the rate determining step is association of the nitrile. Under these circumstances, we would expect to see and do observe first order in $\text{Ni}(\text{IPr})_2$ and *i*PrCN as well as zero order in IPr and diyne. However, when a smaller nitrile such as MeCN is employed, binding of the nitrile may be fast and irreversible. As such, the new resting state of the catalyst would be $\text{Ni}(\text{IPr})_2(\text{RCN})$ and the rate determining step would be loss of IPr. Our kinetic data fit this scenario. Because formation of the Ni-RCN dimer likely arises from dimerization of $\text{Ni}(\text{IPr})(\text{RCN})$, we anticipate that investigation of the mechanism of Ni-RCN dimer formation will corroborate our mechanistic conclusion. Thus, we are currently investigating the mechanism of Ni-RCN dimer formation and hope to have those results straightaway.

METAL-FREE CO₂ ACTIVATION^{12,13}

In the course of our studies, we discovered that IPr reacted with CO₂ to afford an imidazolylidene carboxylate in excellent yield (90%). Further cursory investigations have shown that the ability of the imidazolylidene to bind CO₂ is directly related to the size of its N-substituents. We have since prepared a large variety of imidazolylidene carboxylates and evaluated how slight structural features affect the properties of these interesting compounds (Figure 4).

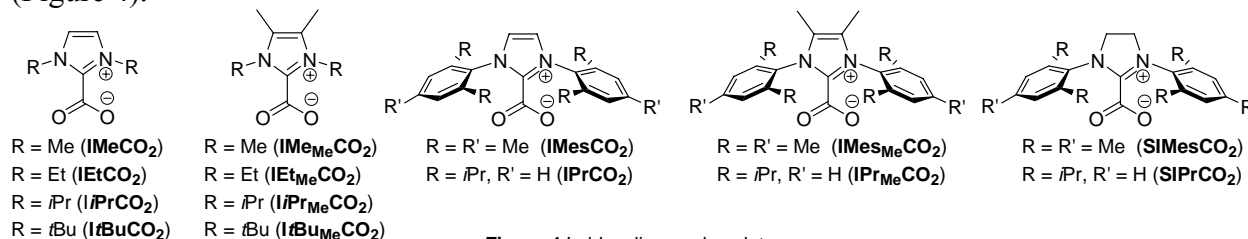
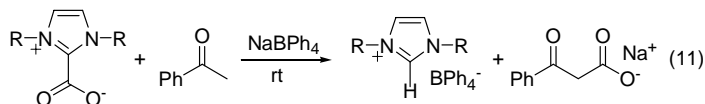


Figure 4. Imidazolium carboxylates

We have learned a great deal from these studies. In practical terms, we have discovered that N-aryl imidazolylidene carboxylates are much more soluble (and thereby easier to handle) than the corresponding N-alkyl imidazolylidene carboxylates. In addition, thermogravimetric analysis of the carboxylates confirmed our earlier findings that decarboxylation is indeed dependent on the size of the N-substituent. For example, a gradual decrease in decarboxylation temperature was observed in the TGA of the **I'R'_{Me}CO₂** series (i.e., *t*Bu > *i*Pr > Et > Me). Interestingly, we found, counterintuitively, increasing the basicity of the imidazolylidene lead to a decrease in decarboxylation temperature. Both **IPrMeCO₂** and **SIPrCO₂** underwent more facile decarboxylation than **IPrCO₂**. Despite these differences, all imidazolylidene carboxylates displayed almost identical IR C=O stretching frequencies.

Ultimately, we seek to develop carboxylation reactions that employ these compounds as reactive intermediates. **IMeCO₂** does react with NaBPh₄ and acetophenone to afford a β-keto acid. However, the transfer of CO₂ is limited to acetophenone as a substrate (Equation 11).



We believe further advancement of this process hinges on understanding the mode of reaction for the imidazolylidene carboxylates and have embarked on investigating the mechanism of this reaction. Thus far, we have learned that product formation does not involve the formation of a free carbene (which can presumably act as a Brønsted base) or an imidazolylidene carbonate (as has been observed in similar DBU-mediated carboxylations).

We have successfully isolated an imidazolylidene carboxylate complex of NaBPh₄ (**[(IPrCO₂Na)(BPh₄)]₂**); this complex carboxylates acetophenone directly. Although **[(IPrCO₂Na)(BPh₄)]₂** has similar properties to **IPrCO₂** (C-C bond length, C=O stretching frequency, decarboxylation temperature), one striking feature stands out – an increase in the carboxylate pitch (Figure 5). Our current working hypothesis is that Na acts as a Lewis base that binds the imidazolylidene carboxylate. Binding serves to effectively ‘neutralize’ the

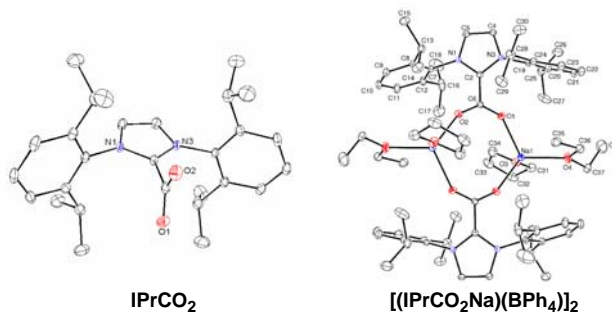


Figure 5. Carboxylate Pitch, (N(3)-C(2)-C(6)-O(2)):
IPrCO₂ = 88°, **[(IPrCO₂Na)(BPh₄)]₂ = 151°**

carboxylates negative charge (thereby making a better electrophile). In addition, an increase in the carboxylate pitch relieves steric crowding thereby making the electrophile more susceptible for nucleophilic attack. We are now posed to exploit the steric and electronic features of these imidazolylidene carboxylates and are currently working on expanding the scope of substrates amenable for carboxylation. In addition, we anticipate that an asymmetric variant can be developed and will be evaluating chiral imidazolylidenes as potential reagents.

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