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CARBOAMINATION REACTIONS USING TITANIUM PRE-CATALYSTS: A CATALYTIC PROSPECT TO PREPARING CONJUGATED C–N/C–C FRAMEWORKS

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We report in this account the synthesis of a series of titanium catalysts for the carboamination of internal aryl alkynes with aldimines to produce highly arylrated α,β-unsaturated imines. Early work on the $Cp_2Zr(NAr)$ compounds have laid the premise to develop more sophisticated, but reactive, titanium reagents supported by the popular β-diketiminates. This work has ultimately led to the preparation of simple titanium catalysts stemming from the protonation of commercially available compounds such $Ti(NMe_2)_4$. The latter reaction offers superior carboamination catalytic activity to the earlier Zr and Ti systems and provides an interesting approach to study how C–N and C–C bonds are formed.

1. INTRODUCTION

From a theoretical standpoint, catalysts accelerate reactions by reducing the activation barrier, and hypothetically speaking, should remain unchanged upon completion of the catalytic cycle. Depending on the efficacy of the catalyst, thermodynamically difficult steps can be overcome by lowering the energy of the activated complex. Likewise, waste (often generated by the single step synthetic alternatives) can be ultimately suppressed, with the product being conveniently produced for

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subsequent research such as the synthesis of fine chemicals or for use as commodity products. In some cases, however, the nature of the reaction or catalyst allows for "atom-efficient systems," where unwarranted byproducts are minimized with much cleaner, catalytic alternatives. The latter parameter is important for obvious environmental concerns, but this factor becomes a critical feature when the product is needed on a larger demand. For these reasons, our group has been exploring catalytic C–N and C–C forming reactions, since the products derived from these types of transformations offer the opportunity to study these systems from both an applied and fundamental point of view. Specifically, we are interested in α,β-unsaturated imine frameworks due to the formation of a new, highly arylated, organic archetype. This type of skeleton is interesting given the highly conjugated nature surrounding the ene-imine functionality as well as the mechanism to their formation, specifically, how C = C and C = N bonds are catalytically formed while C = N bonds are catalytically broken.

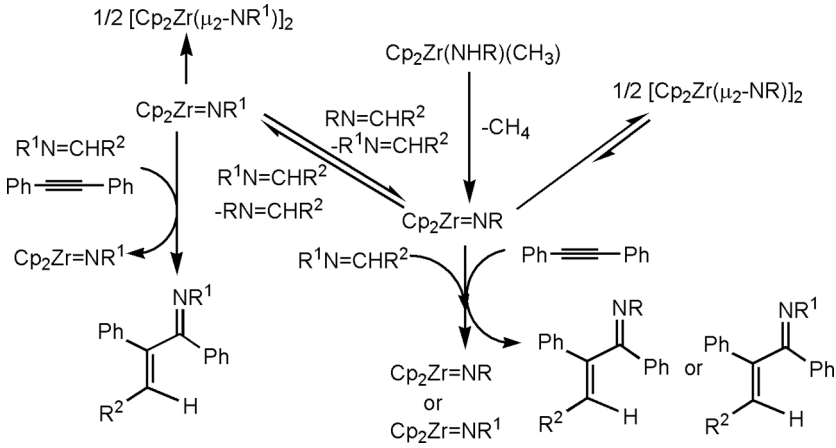
Our group has been exploring synthetic routes to preparing early-transition complexes containing metal-ligand multiple bonds such as alkylidenes,[1,2] alkylidynes,[1–4] phosphinidenes,[1,5–7] imides,[8,9] and nitrides.[8,10] Specifically, we are interested in incorporating these functional groups on the 3d metals given their ability to populate low-valent states and lower coordination environments.[11] In particular, titanium imides are undergoing a renaissance of reaction chemistries given their capacity to conduct catalytic processes such as intermolecular and intramolecular hydroamination of alkynes, allenes and alkenes,[12–23] hydrohydrazination of alkynes,[24] multi-coupling reactions to generate α,β-unsaturated β-aminoimines,[25] guanylations,[26] imine metathesis,[27] carbodiimide metathesis,[8,28] carboamination of alkynes with aldimines,[29–32] transamidations,[26] and cyclization reactions to produce multisubstituted quinolines,[31] among other important processes.[28] Recently, the use of titanium hydrazido complexes (e.g., $Ti=NNR_2$) has received attention given their ability to perform catalytic diamination (e.g., with NH_2 and NPh_2 groups) of alkynes to produce 1,2-diamino-substituted olefins.[33,34] In this account, we describe our approach to discovering highly efficient carboamination catalysts, stemming from our earlier observations with titanium–based β-diketiminate complexes to more applicable usage of commercially available reagents such as $Ti(NMe_2)_4$ and $[HNMe_2Ph][B(C_6F_5)_4]$. The following manuscript will discuss our work in this field, with particular emphasis on the role of the metal in the catalytic C–N

and C−C bond forming reaction. Likewise, we wish to present a cyclization process, discovered serendipitously, by which a α,β-unsaturated imine can be catalytically transformed into a multi-substituted quinolene.

2. PREVIOUS WORK ON CARBOAMINATION OF ALDIMINES WITH INTERNAL ALKYNES

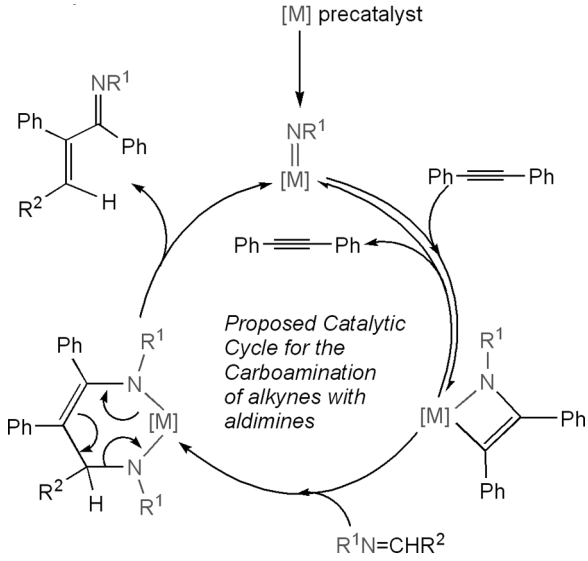
Carboamination can be defined as the insertion of an alkyne into an aldimine C=N bond to form an α,β-unsaturated imine. Bergman and co-workers were the first group to report catalytic carboamination of alkynes and aldimines promoted by zirconocene imido precursors (Scheme 1).[29,30] Cleverly, their system utilized a zirconium pre-catalyst, $Cp_2Zr(NHAr)(CH_3)$, which underwent α-hydrogen abstraction upon thermolysis to generate the transient imide $Cp_2Zr(NAr)$. In the presence of alkyne and aldimine, the imide catalyst performed carboamination, but the system was prone to dimerization in the absence of substrate (Scheme 1).[30] The latter step resulted ultimately in the death of the catalyst since bridging of the imide ligands was irreversible under their catalytic conditions. Despite this attractive entry to these new organic frameworks, typical reaction conditions required extended times, high temperatures, moderate to high catalyst loads (~10 mol%), and were often restricted to a limited range of functional group tolerance for both the aldimine and alkyne substrates. In addition, the zirconocene system was constrained to aldimine substrates having a degenerate aryl group with respect to the imide functionality.[30] The latter strategy avoided side reactions such as imine metathesis[8] from taking place, since this would ultimately lead to a mixture of α,β-unsaturated imines (Scheme 1). Consequently, this side reaction would also result in lower yield of the desired unsaturated product since a fraction of the mol% of catalyst would promote a secondary catalytic cycle (Scheme 1).

It has been proposed that carboamination involves an unsaturated transition metal imide (from an imide pre-catalyst), which undergoes reversible [2+2] cycloaddition of an alkyne to form an azametallacyclobutene intermediate, followed by insertion of the aldimine to yield a thermally unstable six-membered ring metallacycle.[29,30] Subsequent [4+2] retrocycloaddition of the latter species ensues regeneration of the imide linkage concomitant with extrusion of the α,β-unsaturated imine product (Scheme 2).[29,30] To our knowledge there are no other reported methods to catalytically generate α,β-unsaturated imines, so access to this type of



Scheme 1. Carboamination of alkynes with aldimines by transient $Cp_2Zr(NAr)$.

framework offers the possibility to probe their reactivity and study their photophysical properties while using an economical approach to their synthesis. In addition, the access to a wide range of aldimines and alkynes offers a unique opportunity to expand on the degree of

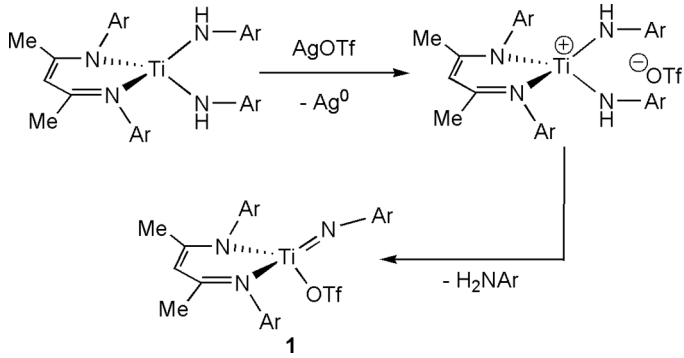


Scheme 2. Proposed catalytic cycle for the carboamination of alkynes with aldimines.

functional group tolerance. α,β-unsaturated imines are arguably similar to coumarins, an important class of natural product found in many plants, and are commonly used as an additive in foods and cosmetics,[35] as optical brightening agents, dispersed fluorescence and laser dyes.[36] For this reason, studying an immature field such as the carboamination of alkynes with aldimines not only offers an excellent opportunity to examine an important and unusual transformation involving C=C and C−N bond formation, but also provides access to an interesting organic material given its conjugated framework.

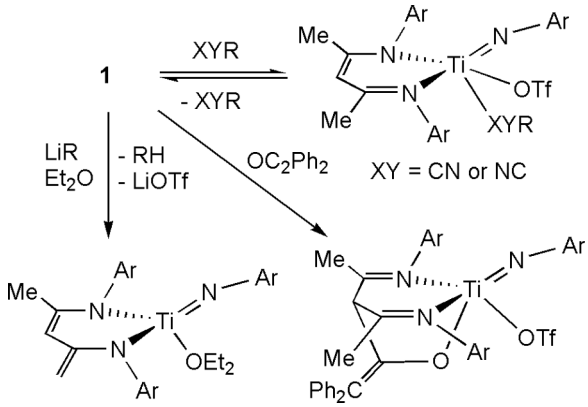
3. EARLY WORK ON TERMINAL TITANIUM IMIDES SUPPORTED BY THE β-DIKETIMINATE LIGAND $[ArNC(Me)]_2CH^-$

One of the key features to an effective carboamination catalyst (or pre-catalyst) involves the assembly of an unsaturated transition metal imide complex.[28d,29,30] The hypothesis that a metal imide is involved in the catalytic process originates from literature precedence.[28] Based on the work by Bergman and co-workers, one must first avoid divergent pathways such as dimerization via imide bridging, imine metathesis, as well as preserve an unsaturated metal unit in the catalytic cycle.[28d] In 2003 we reported a facile assembly of terminal titanium imides by a one-electron process that stimulated α-hydrogen abstraction.[37] This approach allowed us to prepare four-coordinate titanium complexes having terminal imides group as well as a substitutionally labile ligand such as $^-$OTf. As a result, a precursor such as (^{Me}nacnac)Ti(NHAr)$_2$ (^{Me}nacnac$^-$ = $[ArNC(Me)]_2CH$, Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$), prepared from the compound (^{Me}nacnac)TiCl$_2$(THF)[38,39] and 2 equiv of LiNHAr, could be readily oxidized with AgOTf to form the low-coordinate imide (^{Me}nacnac)Ti=NAr(OTf) (**1**) (Scheme 3). During formation of **1**, we were able to isolate the intermediate salt that preceded α-hydrogen abstraction, namely the complex [(^{Me}nacnac)Ti(NHAr)$_2$][OTf]. Intuitively, the one-electron oxidation step is not overall rate-determining given the reversibility of the anodic wave on the CV time scale for (^{Me}nacnac)Ti(NHAr)$_2$ (−0.89 V versus $Cp_2Fe^{0/+}$ at 0.0 V), therefore implying that $^-$OTf binding or α-hydrogen abstraction must be the slowest step in the reaction.[37] Unfortunately, complex **1** expressed more reactivity at the β-diketiminate ligand than the terminal imide group! While nitriles and isonitriles reversibly coordinated to the titanium center, powerful electrophiles such as $OCCPh_2$ were attacked by the



Scheme 3. Oxidatively induced α-hydrogen abstraction to prepare titanium complexes having a terminal imimide group.

γ-carbon composing the NCCCN backbone to produce a tripodal dimine-alkoxo ligand complexed to titanium (Scheme 4). The ability of the β-diketiminate to tautomerize also allowed for facile deprotonation since treatment of **1** with alkyl bases such as LiR (R=CH_3, $CH_2{}^tBu$, and CH_2SiMe_3) resulted in transformation of the β-methyl group to a chelating bis-anilide framework (Scheme 4).[40] Likewise, alkynes or imines failed to react with the imide group in **1**, thus implying that this ligand was far to robust to perform any type of catalytic N–C bond formation.

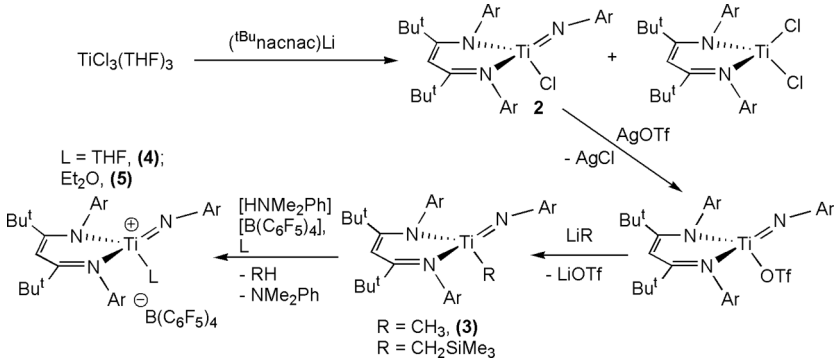


Scheme 4. Reactivity of complex 1 with reagents such as alkyls, nitriles, isonitriles, and ketenes.

4. SYNTHESIS OF REACTIVE, LATENT, AND LOW-COORDINATE TITANIUM IMIDES

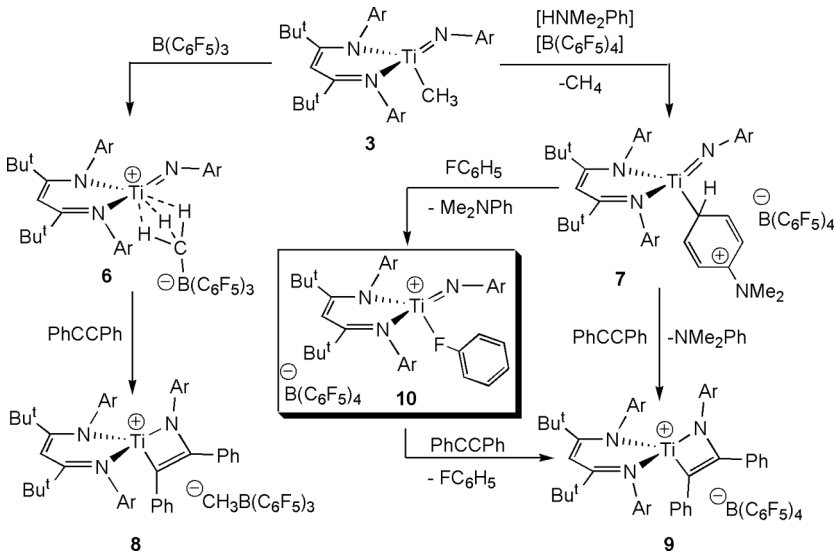
In order to prevent side reactions involving the original β-diketiminate ligand, $[ArNC(Me)]_2CH$, we resorted to a more sterically encumbered ligand originally reported by Budzelaar and co-workers, namely the β-diketiminate ^{tBu}nacnac$^-$, (^{tBu}nacnac$^-$ = $[ArNC(^tBu)]_2CH$, Ar = 2,6-$^i Pr_2C_6H_3$).[39,41] This ligand scaffold can inhibit electrophiles from reaching the hindered γ-carbon and lacks the vulnerable methyl groups in the β-carbon position that are susceptible to tautomerization. Accordingly, preparation of the corresponding titanium complex entailed treating (^{tBu}nacnac)Li with $TiCl_3(THF)_3$ in toluene to produce a mixture of (^{tBu}nacnac)$TiCl_2$ and (^{tBu}nacnac)Ti = NAr(Cl) (**2**) (Scheme 5). Compound **2** can be readily separated from the mixture by fractional recrystallization, albeit in moderate yield. Although **2** fails to react with alkylating reagents such as $LiCH_3$, or KCH_2Ph, replacement of the chloride for triflate allows for smoother substitution. Hence, treatment of **2** with AgOTf (to produce (^{tBu}nacnac)Ti = NAr(OTf)), and subsequent transmetallation with LiMe or $LiCH_2SiMe_3$ provides a facile entry to rare examples of terminal titanium imides having alkyl ligands, (^{tBu}nacnac)Ti = NAr(R) (R=CH_3, (**3**); CH_2SiMe_3) (Scheme 5).[41,42]

To generate highly reactive titanium systems by exposing the imide functionality, we removed the methyl ligand of complex **3** with $[HNMe_2Ph][B(C_6F_5)_4]$ in THF or Et_2O to produce the salts [(^{tBu}nacnac)Ti = NAr(L)][$B(C_6F_5)_4$] (L = THF, (**4**); Et_2O, (**5**), Scheme 5). These



Scheme 5. Synthesis of neutral and cationic titanium imides having a sterically encumbering β-diketiminate ligand.

systems readily abstract halide from CH_2Cl_2 or $CHCl_3$ to reform **2**. However, complexes **4** and **5** fail to react with alkynes and/or perform catalytic carboamination, thus implying that the Lewis base is strongly coordinated to the metal center. When **3** is treated with $B(C_6F_5)_3$ or $[HNMe_2Ph][B(C_6F_5)_4]$ in FC_6H_5 the latent low-coordinate imides (^{tBu}nacnac)Ti=NAr(μ_2-Me)$B(C_6F_5)_3$ **(6)** or [(^{tBu}nacnac)Ti=NAr(η^1-$C_6H_5NMe_2$)][$B(C_6F_5)_4$] **(7)** are formed, respectively (Scheme 6).[41] Unlike complexes 2, (^{tBu}nacnac)Ti=NAr(OTf), and 3–5 compounds **6** and **7** readily [2 + 2] cycloadd PhCCPh to afford rare examples of azametallacyclobutenes [(^{tBu}nacnac)TiNArCPhCPh][$CH_3B(C_6F_5)_3$] **(8)**[41,43] and [(^{tBu}nacnac)TiNArCPhCPh][$B(C_6F_5)_4$] **(9)** (Scheme 6).[31] These results suggested that these complexes should in principle serve as "NAr" delivery reagents. Complex **7**, however, was exceedingly reactive and FC_6H_5 solutions gradually transformed to a new compound, namely the first titanium(IV) fluorobenzene adduct [(^{tBu}nacnac)Ti=NAr(FC_6H_5)][$B(C_6F_5)_4$] **(10)** (Scheme 6).[31,44] It is noteworthy to highlight structural features for compound **10**. In the molecular structure of **10**, the Ti–F interaction is strong, thus elongating the F–C bond (1.417(3) Å) from that observed for free fluorobenzene (~1.36 Å). Most notably, the electrophilic nature of the titanium center renders the coordination



Scheme 6. Synthesis of latent low-coordinate titanium imides and subsequent [2 + 2]-cycloaddition reaction with PhCCPh.

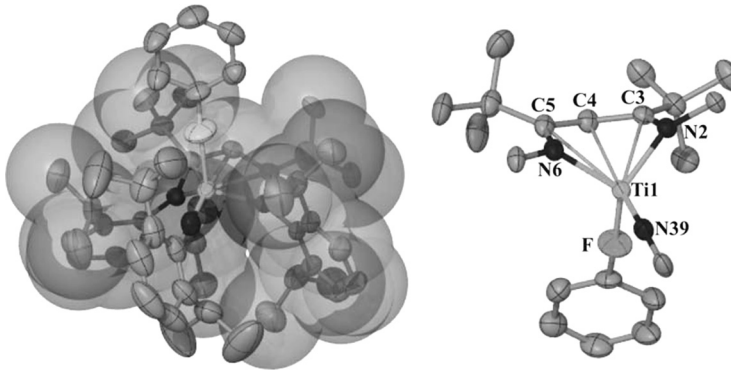


Figure 1. Molecular structure of $[(^{tBu}\text{nacnac})\text{Ti}=\text{NAr}(\text{FC}_6\text{H}_5)]^+$ (left). A simplified structure of the cationic skeleton of **10** is depicted on the right with omitted aryl groups for N6, N2, and N39 (with the exception of ipso carbons).

mode of the β-diketiminate ligand to adopt a rare conformation hapticity–η^5 hapticity as a result of significant deviation of the Ti atom above the NCCCN imaginary mean plane (∼1.297 Å, Figure 1). Not surprisingly, complex **10** reacts with PhCCPh to afford the azametallacyclobutene **9** concurrent with free fluorobenzene (Scheme 6).[31] We were able to obtain structural data for **9** (Figure 2) and the geometry clearly favors the hypoth-

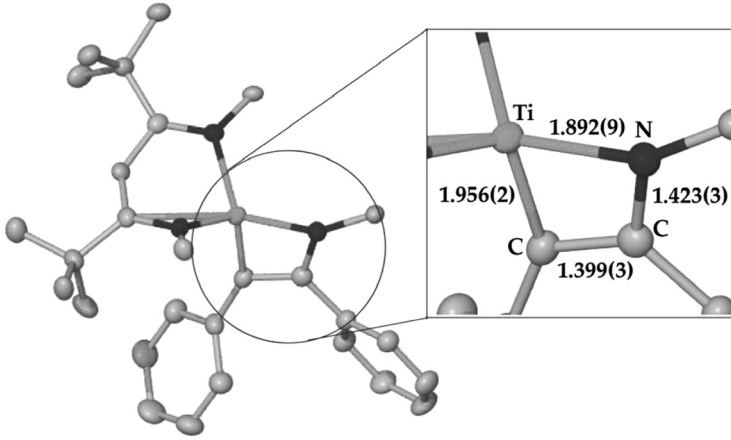
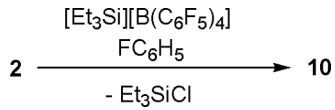


Figure 2. Molecular structure of cationic component of complex **9** displaying thermal ellipsoids at the 50% probability level, as well as an expanded view of the TiNCC metallacycle. Aryl groups on nitrogens (with the exception of the ipso carbon) have been omitted for the purpose of clarity. The anion has been also omitted.

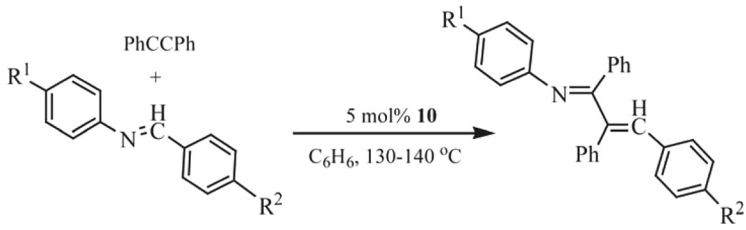
esis that cycloaddition is likely occurring along the catalytic carboamination cycle. While examples of azametallacyclobutenes are scarce,[13c,28f,46] the cationic component, [(^{tBu}nacnac)TiNArCPhCPh], unambiguously portrays a low-coordinate species having a strained TiNCC ring framework, which results in interaction of the electron deficient metal system with both the β- and γ-carbon atoms composing the NCCCN of the β-diketiminate (Figure 2). This result provides credible evidence for azametallacyclobutene formation as opposed to a 1,2-insertion mechanism along a possible C−N bond forming step. Inconveniently, compounds **7** and **10** react irreversibly with Lewis bases such as THF and Et_2O to produce **4** and **5**, respectively. Traces of these volatile Lewis bases result in gradual poisoning of these catalysts. As it will be demonstrated later, this poisoning by Lewis bases plays an important parameter in the role of the living catalyst. To bypass the multi-step synthesis to the fluorobenzene adduct **10**, it was determined that such a complex could be prepared independently in one single step (74% isolated yield) by utilizing $[Et_3Si][B(C_6F_5)_4]$[47] and **2** in FC_6H_5 (Scheme 7).[31]

Gratifyingly, it was found that complex **10** catalyzes carboamination reactions of PhCCPh and aldimines to produce highly arylated α,β-unsaturated imines with exclusive (*E, E*)-configuration at the olefin and imine residues according to Table 1.[31] Whereas electron-poor aldimines fail to afford products, electron-rich *p*-aryl substituted substrates react smoothly to afford eneimines in >70% isolated yield using low catalyst loads (5 mol%), and short time periods (24–36 hrs, Table 1). Catalyst loadings as low as 2.5 mol% also work but reaction times extend to 84 hrs. Complexes **6** and **7** also catalyze carboamination reactions of alkynes with aldimines (analogous to those substrates reported in Table 1). The usage of more electron rich aldimines with **10** does not afford the expected α,β-unsaturated imines. Instead, triaryl substituted quinolines are obtained in moderate yield upon workup of the reaction mixture (Table 2).[31] Formation of the quinoline from the latter substrates likely occurs from vinylic and ortho-aryl C−H bond ruptures and ring closure of a α,β-unsaturated imine substrate. Monitoring the



Scheme 7. Direct entry to a cationic titanium imide.

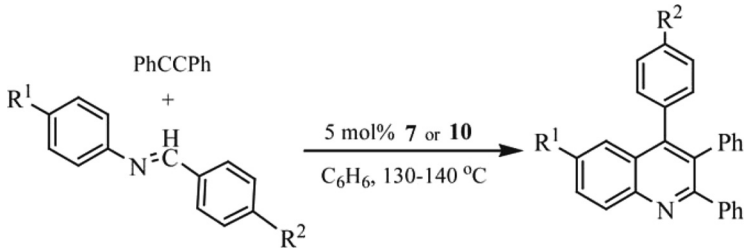
Table 1. Catalytic carboamination of alkynes with aldimines



Entry	Imine	Product	Yield (%)
1	$R^1 = H$, $R^2 = H$	$R^1 = H$, $R^2 = H$	74
2	$R^1 = CH_3$, $R^2 = CH_3$	$R^1 = CH_3$, $R^2 = CH_3$	72
3	$R^1 = H$, $R^2 = OCH_3$	$R^1 = H$, $R^2 = OCH_3$	71
4	$R^1 = CH_3$, $R^2 = OCH_3$	$R^1 = CH_3$, $R^2 = OCH_3$	70

reaction mixture by ^1H NMR spectroscopy (in C_6D_6) indicates that the α,β-unsaturated imine forms and decays during the catalytic process, thus suggesting that the quinoline most likely originates from the corresponding α,β-unsaturated imine.[31] Independently we have found that treatment of **10** with 1 equiv of an aldimine in the presence of the electron-rich α,β-unsaturated imines where R^1=CH_3 and R^2=NMe_2 (prepared using any of our catalysts or Bergman's), generates the corresponding quinoline in

Table 2. Catalytic formation of substituted quinolines



Entry	Imine	Product	Yield (%)
5	$R^1 = CH_3$, $R^2 = NMe_2$	$R^1 = CH_3$, $R^2 = NMe_2$	68
6	$R^1 = OCH_3$, $R^2 = NMe_2$	$R^1 = OCH_3$, $R^2 = NMe_2$	66

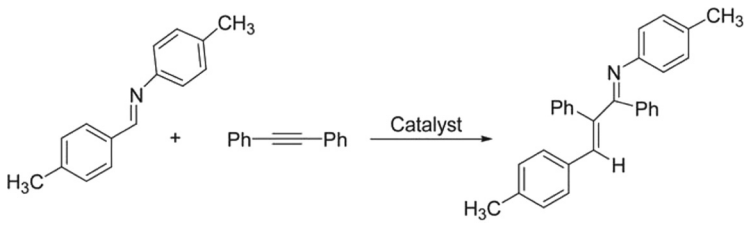
Table 2 (Entry 5). As a result, we speculate that a putative [(nacnac)-Ti = Nar'(FC_6H_5)][$B(C_6F_5)_4$] might be responsible for the eneimine to quinoline conversion under these reaction conditions.

5. OPTIMIZATION OF THE CATALYST AND EASE TO CATALYST FORMATION

Although the Ti(IV) fluorobenzene pre-catalyst **10** was effective in performing catalytic carboamination reactions, the exceedingly reactive nature of this complex limited with the handling of this system under traces of donors (or impurities) as well as explore functional group tolerance. As noted earlier, complexes **6**, **7**, and **10** are readily poisoned with traces of THF or Et_2O to form the stable cations [(^{tBu}nacnac)Ti=NAr(THF)]$^+$ and [(^{tBu}nacnac)Ti=NAr(Et_2O)]$^+$, respectively.[31,41] Consequently, these limitations have prompted us to seek other catalysts or pre-catalysts that would not only reduce the reaction time frames and expand the degree of functional group tolerance, but be both facile to prepare and manipulate. Previous studies by Odom,[16b] Schafer,[22] and Lorber[17] have demonstrated that common reagents such as $Ti(NMe_2)_4$ can serve as competent pre-catalysts for the hydroamination of alkynes and alkenes,[48] respectively. Unfortunately for us, $Ti(NMe_2)_4$ alone was not efficient in catalyzing carboamination reactions using di-*p*-tolylaldimine and PhCCPh in the presence or absence of *p*-toluidine (Table 3, entries 1–2). Realizing that the carboamination pre-catalyst **10** is a salt-like, latent low-coordinate titanium imide reagent having a labile ligand (e.g., FC_6H_5),[31] we hypothesized whether protonation with [$HNMe_2Ph$][$B(C_6F_5)_4$][49] could render $Ti(NMe_2)_4$ a more reactive species due to a potentially good leaving group such as $HNMe_2$.

This combination of ingredients proved fruitful since a 1:1:1 C_6D_6 solutions of 10 mol% $Ti(NMe_2)_4$, [$HNMe_2Ph$][$B(C_6F_5)_4$], and *p*-toluidine catalyzed carboamination reactions in considerably shorter reaction times (16 hrs), and lower temperatures (125°C) when compared to the Cp_2Zr-[29,30] and (^{tBu}nacnac)Ti-based[31] catalysts (Table 3, entry 3).[32] To our surprise, though, the same carboamination reaction also proceeded smoothly but in the absence of the aniline (Table 3, entry 4).[32] Since early-transition metal-imides have been proposed to be active intermediates along the carboamination cycle, the absence of aniline in the latter reaction suggests that aldimine could be playing a role as an imide-transfer reagent.[50] The titanium reagent, $Ti(NMe_2)_4$, is critical in these reactions

Table 3. Catalytic carboamination of alkynes with aldimines

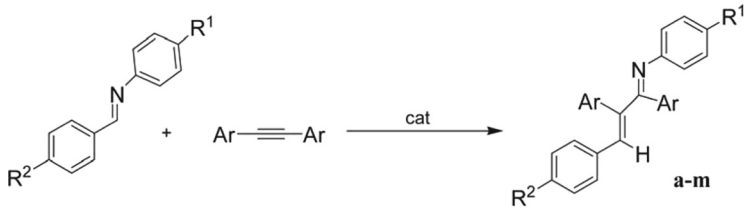


Entry	Catalyst	Time (h)	Yield (%)
1	$Ti(NMe_2)_4$ (20 mol%)	120	traces
2	$Ti(NMe_2)4/4\text{-}CH_3C_6H_4NH_2$(20 mol% each)	120	traces
3	$Ti(NMe_2)_4/4\text{-}CH_3C_6H_4NH_2/[HNMe_2Ph][B(C_6F_5)_4]$ (10 mol% each)	16	80–90
4	$Ti(NMe_2)_4/[HNMe_2Ph][B(B(C_6F_5)_4]$ (10 mol% each)	16	80–90

since 10–20 mol% of $[HNMe_2Ph][B(C_6F_5)_4]$ alone failed to show any conversion to the α,β-unsaturated imine product.[32]

Based on these preliminary experiments, reactions for a series of aldimines and alkynes were carried out according to the conditions described in entry 4 of Table 3. Aldimines bearing electron-donating groups such as *p*-methyl, *p*-methoxy, and *p*-dimethylamino groups gave the corresponding α,β-unsaturated imine derivatives in good yields (Table 4, entries 1–8), whereas aldimines bearing an electron-withdrawing trifluoromethyl group did not afford the desired product. Alkynes such as bis(*p*-methylphenyl)acetylene and bis(*p*-methoxyphenyl)acetylene containing electron-donating groups also gave the respective α,β-unsaturated imine derivatives in good yields (Table 4, entries 9–12). No cyclization was observed in these catalytic reactions when judged by ^1H NMR spectroscopy. The carboamination of bis(*p*-bromophenyl)acetylene afforded the corresponding dibromo substituted α,β-unsaturated imine (**m**) in 32% yield (Table 4, entry 13).[32] Formation of product **m** represents an exciting result since this organic framework can be further expanded via aryl C−C coupling reactions. It was also found that asymmetrical alkynes such as $PhCC(4\text{-}CH_3C_6H_4)$ did not exhibit regioselective carboamination. As previously observed for the products from other catalytic

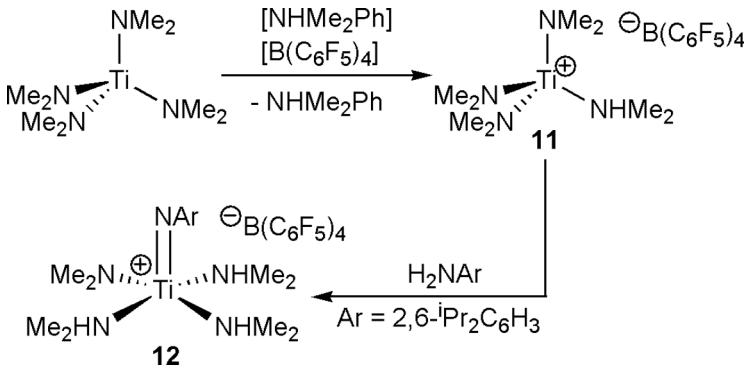
Table 4. Catalytic carboamination of alkynes with aldimines



Entry	Aldimine	Alkyne	Product	Yield (%)
1	$R^1 = R^2 = H$	Ar = Ph	a	71
2	$R^1 = R^2 = CH_3$	Ar = Ph	b	69
3	$R^1 = CH_3$, $R^2 = OCH_3$	Ar = Ph	c	70
4	$R^1 = OCH_3$, $R^2 = CH_3$	Ar = Ph	d	68
5	$R^1 = NMe_2$, $R^2 = OCH_3$	Ar = Ph	e	70
6	$R^1 = R^2 = OCH_3$	Ar = Ph	f	68
7	$R^1 = OCH_3$, $R^2 = NMe_2$	Ar = Ph	g	75
8	$R^1 = CH_3$, $R^2 = NMe_2$	Ar = Ph	h	72
9	$R^1 = OCH_3$, $R^2 = NMe_2$	Ar = 4-$CH_3C_6H_4$	i	72
10	$R^1 = CH_3$, $R^2 = NMe_2$	Ar = 4-$OCH_3C_6H_4$	j	76
11	$R^1 = R^2 = OCH_3$	Ar = 4-$CH_3C_6H_4$	k	62
12	$R^1 = OCH_3$, $R^2 = CH_3$	Ar = 4-$OCH_3C_6H_4$	l	64
13	$R^1 = CH_3$, $R^2 = NMe_2$	Ar = 4-BrC_6H_4	m	32

carboamination reactions,[29–31] the α,β-unsaturated imines generated from these processes have exclusive (*E,E*)-configuration at the olefin and the imine residues (Table 4, entries 1–13).[32] Most notably, in all cases the reaction times are dramatically reduced from 24–96 hrs to 16–24 hrs and allow for a more extended degree of functional group tolerance using this combination of ingredients.[32]

We have probed for the active intermediates or pre-catalyst resting state(s) in order to understand both the role of the acid, the metal complexes and aldimine. As a result we have examined the products generated by various combinations of $Ti(NMe_2)_4$, $[HNMe_2Ph][B(C_6F_5)_4]$, diphenylacetylene, and *p*-tolylaldimine. For instance, treatment of $Ti(NMe_2)_4$ with one equivalent of $[HNMe_2Ph][B(C_6F_5)_4]$ generated the tris-dimethylamide monoamine salt $[Ti(NHMe_2)(NMe_2)_3][B(C_6F_5)_4]$**(11)** in 85% yield (Scheme 8).[32] Complex **11** has been fully characterized and the solid state structure of the cationic



Scheme 8. Protonation of $Ti(NMe_2)_4$ with $(HNMe_2Ph]B(C_6F_5)_4]$ and H_2NAr to afford compounds **11** and **12**, respectively.

component is depicted in Figure 3.[32] In fact, our hypothesis that aldimine might play a role as an imide transfer reagent in the catalytic cycle proved reasonable inasmuch as isolated samples of complex **11** catalyze carboamination reactions of alkynes with aldimines with similar catalytic activity to the $Ti(NMe_2)_4/[HNMe_2Ph][B(C_6F_5)_4]$ mixture reported in entries 2, 4, 6, and 7 of Table 4, and in the absence of aniline (vide supra).[32] Unfortunately, we have been unable to isolate a complex from

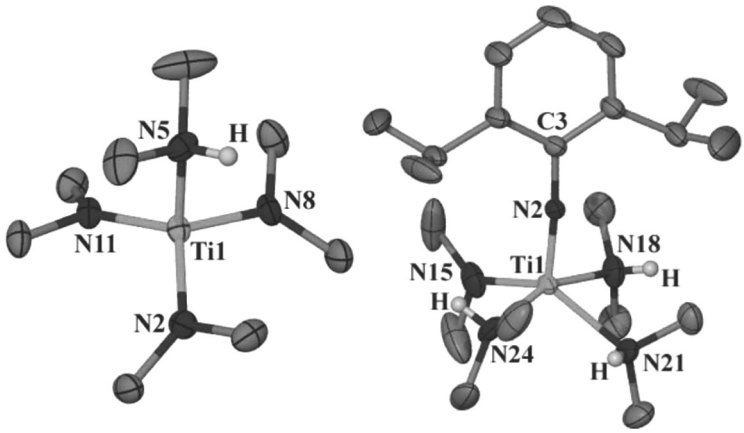


Figure 3. Molecular structure of cationic components of complexes **11** and **12** displaying thermal ellipsoids at the 50% probability. Only α-hydrogens are depicted.

the stoichiometric reaction mixtures containing $Ti(NMe_2)_4$, $[HNMe_2Ph][B(C_6F_5)_4]$ and *p*-tolylaldimine in the presence or absence of diphenylacetylene, but we are currently pursuing putative intermediates via other synthetic routes.

Despite this limitation, we reasoned that a titanium-imide might be playing a role in these carboamination reactions since previous work on this type of reactions has proposed terminal imido ligands to be participants in the catalytic cycle. In accord with this hypothesis, we prepared a titanium-imide analogue using a more hindered aniline H_2NAr ($Ar = 2,6\text{-}^{i}Pr_2C_6H_3$) to afford the five-coordinate titanium imide $[Ti=NAr(NHMe_2)_3(NMe_2)][B(C_6F_5)_4]$ **(12)** in excellent yield from precursor **11** and the corresponding aniline (Scheme 8).[32] In addition to solution NMR spectroscopic characterization, the connectivity of this complex was established by single crystal X-ray diffraction studies (Figure 3). As anticipated, complex **12** also catalyzes carboamination reactions comparable to that of the *in situ* generated catalyst system,[32] thereby hinting that an imide functionality should be involved in the catalytic process. Therefore, these results show that $[HNMe_2Ph][B(C_6F_5)_4]$ can transform a commercially available starting material such as $Ti(NMe_2)_4$ into an efficient catalyst for the carboamination of alkynes and aldimines, thus providing a facile protocol for the synthesis of highly arylated α,β-unsaturated imines. The fact that complex **11** catalyzes carboamination reactions of alkynes with aldimines in the absence of aniline suggests tantalizingly that aldimine might be playing a role as an imide group-transfer reagent to titanium.[43,50]

6. EPILOGUE AND FUTURE OUTLOOK

Systematically, we have discovered how to synthesize relatively simple catalysts that perform the carboamination of aldimines with internal diarylalkynes to form highly conjugated α,β-unsaturated imines. This work involved the seminal use of cyclopentadienyl and β-diketiminate ligands to an optimized version, which surprisingly invoked a more ubiquitous dimethylamide surrogate. Despite our facile entry into highly arylated α,β-unsaturated imines, the titanium catalysts presented here fail to show compatibility with alkynes or aldimines having electron withdrawing groups. However, we have been able to generate (albeit in low yield) dibromo substituted α,β-unsaturated imine via the carboamination of bis(*p*-bromophenyl)acetylene (Table 4, vide supra).[32] Given the

versatility of our strategy to generate reactive cations or zwitterions, optimization of the catalyst is imminent and aimed at expanding the degree of functional group tolerance.[43] For example, the idea of switching from $Ti(NMe_2)_4$ to d^1 $V(NMe_2)_4$,[51] to d^0 $M(NMe_2)_5$ (M=Nb or Ta)[52] or d^2 $Mo(NMe_2)_4$[53] might provide enhanced catalytic proficiency and resistance to a more expanded array of functional groups. In addition, $V(NMe_2)_4$ could be oxidized to the d^0 cation in hopes of generating an isoelectronic, $Ti(NMe_2)_4$ analogue.[43] The role of the activator (e.g., $[HNMe_2Ph][B(C_6F_5)_4]$) should also be explored given the importance of the weakly coordinating anion in the catalytic cycle. Understanding the mechanism to formation of the α,β-unsaturated imines will unavoidably aid in the development of more reactive and resistant catalysts. It has been proposed by Bergman that the slowest step in the catalytic carboamination cycle is insertion of the aldimine into the M−C linkage of the azametallacyclobutene intermediate.[29,30] This proposal is substantiated by the fact that the more hindered imines fail to work for this type of reaction. Likewise, the electronic nature of the aldimine feedstock has dramatic consequences to the catalytic cycle as demonstrated from our work. We discovered that the nature of the aldimine altered the carboamination reaction leading instead to formation of triaryl substituted quinolines.[31] The latter was shown to be the product resulting from a cyclization of the electron-rich α,β-unsaturated imine generated during the catalytic cycle. However, we can avoid this pathway by optimizing the pre-catalyst, as in the case of complexes **11** and **12**. We are currently exploring the above set of hypotheses as well as addressing the mechanism behind formation of these quinolines since this type of reaction might involve, under a catalytic process, selective C−H activation pathways to afford multi substituted *N*-heterocycles.

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REFERENCES

1. Mindiola, D. J. 2006. *Acc. Chem. Res.*, **39**, 813.
2. Mindiola, D. J., B. C. Bailey, and F. Basuli, 2006. *Eur. J. Inorg. Chem.*, 3135.
3. Bailey, B. C., H. Fan, E. W. Baum, J. C. Huffman, M.-H. Baik, and D. J. Mindiola, 2005. *J. Am. Chem. Soc.*, **127**, 16016.
4. Bailey, B. C., H. Fan, J. C. Huffman, M.-H. Baik, and D. J. Mindiola, 2007. *J. Am. Chem. Soc.*, **129**, 8781.
5. Basuli, F., J. Tomaszewski, J. C. Huffman, and D. J. Mindiola, 2003. *J. Am. Chem. Soc.*, **125**, 10170.
6. Basuli, F., B. C. Bailey, J. C. Huffman, M.-H. Baik, and D. J. Mindiola, 2004. *J. Am. Chem. Soc.*, **126**, 1924.
7. Zhao, G., F. Basuli, U. J. Kilgore, H. Fan, H. Aneetha, J. C. Huffman, G. Wu, and D. J. Mindiola, 2006. *J. Am. Chem. Soc.*, **128**, 13575.
8. Fout, A. R., U. J. Kilgore, and D. J. Mindiola, 2007. *Chem. Eur. J.*, **13**, 9428.
9. Bailey, B. C., F. Basuli, J. C. Huffman, and D. J. Mindiola, 2006. *Organometallics*, **25**, 2725.
10. Bailey, B. C., A. R. Fout, H. Fan, J. C. Huffman, J. B. Gary, M. J. A. Johnson, and D. J. Mindiola, 2007. *J. Am. Chem. Soc.*, **129**, 2234.
11. Hirsekorn, K. F., E. B. Hulley, P. T. Wolczanski, and T. R. Cundari, 2008. *J. Am. Chem. Soc.*, **130**, 1183.
12. For some recent reviews on hydroamination reactions involving alkynes. (a) Pohlki, F. and S. Doye, 2003. *Chem. Soc. Rev.*, **32**, 104. (b) Bytschkov, I. and S. Doye, 2003. *Eur. J. Org. Chem.*, 935.
13. (a) Lee, S. Y. and R. G. Bergman, 1995. *Tetrahedron*, **51**, 4255. (b) Baranger, A. M., P. J. Walsh, and R. G. Bergman, 1993. *J. Am. Chem. Soc.*, **115**, 2753. (c) Walsh, P. J., A. M. Baranger, and R. G. Bergman, 1992. *J. Am. Chem. Soc.*, **114**, 1708. (d) Straub, B. F. and R. G. Bergman, 2001. *Angew. Chem. Int. Ed.*, **40**, 4632.
14. Hill, J. E., R. D. Profilet, P. E. Fanwick, and I. P. Rothwell, 1990. *Angew. Chem. Int. Ed.*, **29**, 664.
15. Ackermann, L. 2003. *Organometallics*, **22**, 4367.
16. (a) Odom, A. 2005. *Dalton Trans.*, 225. (b) Shi, Y., J. T. Ciszewski, 2001. A. L. Odom, *Organometallics*, **20**, 3967. (c) Cao, C., J. T. Ciszewski, and A. L. Odom, 2001. *Organometallics*, **20**, 5011. (d) Ramanathan, B., A. J. Keith, D. Armstrong, and A. L. Odom, 2004. *Org. Lett.*, **6**, 2957.
17. Lorber, C., R. Choukroun, and L. Vendier, 2004. *Organometallics*, **23**, 1845.
18. Ward, B. D., A. Maisse-Francois, P. Mountford, and L. H. Gade, 2004. *Chem. Commun.*, 704.
19. Tillack, A., H. Jiao, I. G. Castro, C. G. Hartung, and M. Beller, 2004. *Chem. Eur. J.*, **10**, 2409.

20. (a) Pohlki, F. and S. Doye, 2001. *Angew Chem. Int. Ed.*, **40**, 2305. (b) Haak, E., I. Bytschkov, and S. Doye, 1999. *Angew. Chem. Int. Ed.*, **38**, 3389. (c) Pohlki, F., I. Bytschkov, H. Siebeneicher, A. Heutling, W. A. König, and S. Doye, 2004. *Eur. J. Org. Chem.*, 1967. (d) Marcseková, K., B. Wegener, and S. Doye, 2005. *Eur. J. Org. Chem.*, 4843. (e) Haak, E., I. Bytschkov, and S. Doye, 2002. *Eur. J. Org. Chem.*, 457. (f) Bytschkov, I. and S. Doye, 2001. *Eur. J. Org. Chem.*, 4411.
21. Ong, T.-G., G. P. A. Yap, and D. S. Richeson, 2002. *Organometallics*, **21**, 2839.
22. Zhang, Z. and L. L. Schafer, 2003. *Org. Lett.*, **5**, 4733.
23. Ackermann, L., L. T. Kaspar, and C. J. Gschrei, 2004. *Org. Lett.*, **6**, 2515.
24. (a) Li, Y., Y. Shi, and A. L. Odom, 2004. *J. Am. Chem. Soc.*, **126**, 1794. (b) Cao, C., Y. Shi, and A. L. Odom, 2002. *Org. Lett.*, **4**, 2853.
25. Cao, C., Y. Shi, and A. L. Odom, 2003. *J. Am. Chem. Soc.*, **125**, 2880.
26. Ong, T.-G., G. P. A. Yap, and D. S. Richeson, 2003. *J. Am. Chem. Soc.*, **125**, 8100.
27. (a) Meyer, K. E., P. J. Walsh, and R. G. Bergman, 1994. *J. Am. Chem. Soc.*, **116**, 2669. (b) Zuckerman, R. L., S. W. Krska, and R. G. Bergman, 2000. *J. Am. Chem. Soc.*, **122**, 751. (c) Krska, S. W., R. L. Zuckerman, and R. G. Bergman, 1998. *J. Am. Chem. Soc.*, **120**, 11828.
28. For some comprehensive reviews on imides and their reactivity. (a) Wigley, D. E. 1994. *Prog. Inorg. Chem.*, **42**, 239. (b) Nugent, W. A. and J. M. Mayer 1988. *Metal-Ligand Multiple Bonds*, John Wiley & Sons, New York. (c) Gade, L. H. and P. Mountford, 2001. *Coord. Chem. Rev.*, **216–217**, 65. (d) Duncan, A. P. and R. G. Bergman, 2002. *Chem. Rec.*, **2**, 431. (e) Nugent, W. A. and B. L. Haymore, 1980. *Coord. Chem. Rev.*, **31**, 123. (f) Hazari, N. and P. Mountford, 2005. *Acc. Chem. Res.*, **38**, 839.
29. Ruck, R. T. and R. G. Bergman, 2004. *Organometallics*, **23**, 2231.
30. Ruck, R. T., R. L. Zuckermann, S. W. Krska, and R. G. Bergman, 2004. *Angew. Chem. Int. Ed.*, **43**, 5372.
31. Basuli, F., H. Aneetha, J. C. Huffman, and D. J. Mindiola, 2005. *J. Am. Chem. Soc.*, **127**, 17992.
32. Aneetha, H., F. Basuli, J. Bollinger, J. C. Huffman, and D. J. Mindiola, 2006. *Organometallics*, **25**, 2402.
33. Selby, D., C. D. Manley, M. Feliz, A. D. Schwarz, E. Clot, and P. Mountford, 2007. *Chem. Commun.*, 4937.
34. Mindiola, D. J. 2007. *Angew. Chem. Int. Ed.*, **47**, 1557.
35. O'Kennedy, R. and R. D. Thornes, 1997. *Coumarins: Biology, Applications and Mode of Action*, Wiley & Sons, Chichester.
36. (a) Zahradnik, M. 1982. *The Production and Application of Fluorescent Brightening Agents*, Wiley & Sons, New York. (b) Maeda, M. 1994. *Laser Dyes*, Academic Press, New York.

37. Basuli, F., B. C. Bailey, J. C. Huffman, and D. J. Mindiola, 2003. *Chem. Commun.*, 1554.
38. Basuli, F., B. C. Bailey, J. Tomaszewski, J. C. Huffman, and D. J. Mindiola, 2003. *J. Am. Chem. Soc.*, **125**, 6052.
39. Budzelaar, P. H. M., A. B. Van Oort, and A. G. Orpen, 1998. *Eur. J. Inorg. Chem.*, 1485.
40. Basuli, F., J. C. Huffman, and D. J. Mindiola, 2003. *Inorg. Chem.*, **42**, 8003.
41. Basuli, F., R. L. Clark, B. C. Bailey, D. Brown, J. C. Huffman, and D. J. Mindiola, 2005. *Chem. Commun.*, 2250.
42. Bolton, P. D., E. Clot, A. R. Cowley, and P. Mountford, 2005. *Chem. Commun.*, 3313.
43. Basuli, F., H. Aneetha, J. C. Huffman, M. Pink, and D. J. Mindiola, *Manuscript in preparation.*
44. Bouwkamp, M. W., P. H. M. Budzelaar, J. Gercama, I. Del Hierro Morales, J. de Wolf, A. Meetsma, S. I. Troyanov, J. H. Teuben, and B. Hessen, 2005. *J. Am. Chem. Soc.*, **127**, 14310.
45. For a comprehensive review of β-diketiminate ligands: Bourget-Merle, L., M. F. Lappert, and J. R. Severn, 2002. *Chem. Rev.*, **102**, 3031.
46. (a) Ward, B. D., A. Maisse-Francois, P. Mountford, and L. H. Gade, 2004. *Chem. Commun.*, 704. (b) Polse, J. L., R. A. Andersen, and R. G. Bergman, 1998. *J. Am. Chem. Soc.*, **120**, 13405. (c) Wang, H., H.-S. Chan, and Z. Xie, 2005. *Oganometallics*, **24**, 3772. (d) Vaughan G. A., G. L. Hillhouse, A. L. Rheingold, 1990. *J. Am. Chem. Soc.*, **112**, 7994.
47. Lambert, J. B., S. Zhang, Sol M. Ciro, 1994. *Organometallics*, **13**, 2430. (b) Scott, V. J., R. Celenligil-Cetin, and O. V. Ozerov, 2005. *J. Am. Chem. Soc.*, **127**, 2852.
48. Bexrud, J. A., J. D. Beard, D. C. Leitch, and L. L. Schafer, 2005. *Org. Lett.*, 1959.
49. Tjaden, E. B., D. C. Swenson, R. F. Jordan, and J. L. Petersen, 1995. *Organometallics*, **14**, 371.
50. Gómez-Sal, P., A. Martín, M. Mena, M. C. Morales, and C. Santamaría, 1999. *Chem Commun.*, 1839.
51. (a) Alyea, E. C., D. C. Bradley, M. F. Lappert, and A. R. Sanger, 1969. *J. Chem. Soc., Chem. Commun.*, 1064. (b) Lorber, C., R. Choukroun, and B. Donnadieu, 2002. *Inorg. Chem.*, **41**, 4217. (c) Bradley, D. C. and M. H. Gitlitz, 1969. *J. Chem. Soc. A*, 980.
52. (a) Riley, P. N., J. R. Parker, P. E. Fanwick, and I. P. Rothwell, 1999. *Organometallics*, **18**, 3579. (b) Bradley, D. C. and I. M. Thomas, 1962. *Can. J. Chem.*, **40**, 1355. (c) Bradley, D. C. and I. M. Thomas, 1962. *Can. J. Chem.*, **40**, 449.
53. Bradley, D. C. and M. H. Chisholm, 1971. *J. Chem. Soc. A*, 2741.