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Computationally-Guided Investigation of Dual Amine/pi Lewis Acid Catalysts for Direct Additions of Aldehydes and Ketones to Unactivated Alkenes and Alkynes

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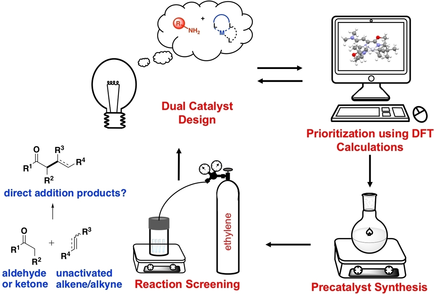
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# Graphical Abstract

Density functional theory calculations were performed to identify dual amine/pi Lewis acid catalyst systems that could promote challenging C−C bond formations. Calculations of a pyridine-bis(oxazoline)-Pt(II) catalyst combined with a bulky organocatalyst suggested that alkenes and alkynes could be activated for outer-sphere attack without metal/organocatalyst or metal/enamine poisoning. Reaction screening confirmed that this novel catalyst system facilitated an intramolecular addition (Conia-ene type reaction) with a formyl alkyne substrate.

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# Abstract

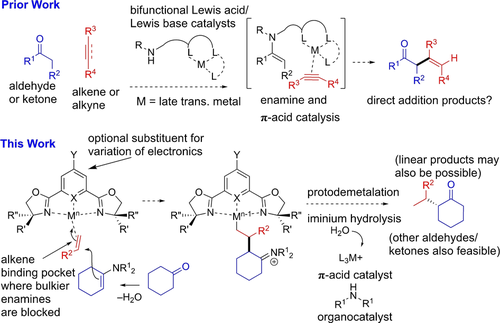
Dual amine/pi Lewis acid catalyst systems have been reported for intramolecular direct additions of aldehydes/ketones to unactivated alkynes and occasionally alkenes, but related intermolecular reactions are rare and not presently of significant synthetic utility, likely due to undesired coordination of enamine intermediates to the metal catalyst. We reasoned that bulky metal ligands and bulky amine catalysts could minimize catalyst poisoning and could facilitate certain examples of direct intermolecular additions of aldehydes/ketones to alkenes/alkynes. Density Functional Theory (DFT) calculations were performed that suggested that pyridine-2,6-bis(oxazoline) (PyBOX)-Pt(II) catalysts for alkene/alkyne activation could be combined with MacMillan's imidazolidinone organocatalyst for aldehyde/ketone activation to facilitate desirable C−C bond formations, and certain reactions were calculated to be more exergonic than catalyst poisoning pathways. Consistent with the calculations, preformed enamines generated from the MacMillan imidazolidinone did not displace ethylene from a biscationic (*t*-Bu)PyBOX-Pt2+ complex. The desired intermolecular C−C bond formation was not observed under several different conditions, but this novel catalytic system facilitated an intramolecular C−C bond formation (Conia-ene type reaction) with a formyl alkyne substrate.

# Introduction

New methodology for the forging of carbon-carbon bonds under mild conditions continues to be a major focus of organic chemistry research. Alkenes represent one of the most readily available functional groups for C−C bond forming reactions, as they can be directly obtained from petrochemical feedstocks. Despite their wide utilization in important metal-catalyzed C−C bond formations such as metathesis and Heck reactions, and various Michael-type reactions involving formal nucleophilic additions to activated alkenes possessing electron-withdrawing groups, nucleophilic additions to unactivated alkenes are still rather limited. Catalytic direct additions of carbon nucleophiles (or pronucleophiles) to unactivated alkenes are uncommon, but with suitable catalysts and pronucleophiles could represent a more general strategy for C−C bond formation. Such reactions are highly desirable for their perfect atom economy.

Amine-based organocatalysts can generate reactive enamine nucleophiles from aldehyde/ketone pronucleophiles, and these have been frequently used for catalytic direct additions to electrophiles such as aldehydes (aldol reaction) and imines (Mannich-type reactions), although substrate scopes can still be limited.**1**-**4** Alternatively, enamine intermediates for catalytic additions to alkenes and alkynes have some precedent but have not been widely used or reported. Most common are intramolecular examples such as Conia-ene-type reactions with alkyne substrates.**5** Several intermolecular additions of activated 1,3-dicarbonyl compounds to unactivated alkenes catalyzed by group 10 metals have been disclosed, including reports from Widenhoefer**6** and Vitagliano;**7** these examples do not require amine co-catalysts. Intermolecular direct additions of unactivated aldehydes/ketones to unactivated alkenes and alkynes are particularly rare, and to our knowledge the only general examples have been reported by Dong, who disclosed a Rh(I)/aminopyridine co-catalytic system that is thought to proceed via a ketone C−H activation mechanism.**8**,**9** Alternatively, isolated examples of direct additions of weakly acidic carbon nucleophiles such as lactams and amides to unactivated alkenes using a catalytic strong base have also been reported.**10**,**11**

Efforts in our laboratories have been focused on the preparation and study of bifunctional catalysts that have the potential to activate both aldehyde/ketone “donors” (pronucleophiles) and various “acceptors” (electrophiles),**12**,**13** most recently alkenes and alkynes (Figure **1**, top).**14**,**15** The strategy is centered on the use of an amine to activated the donor substrate, which is tethered to a *π*-Lewis acid suitable for electrophilic activation of alkenes/alkynes. This strategy was driven by our hypothesis, substantiated by certain NMR studies,**14** that additions of enamine intermediates to unactivated alkenes/alkynes are complicated by the fact that the enamines may be superior ligands for *π*-Lewis acids than the alkene/alkyne acceptors.

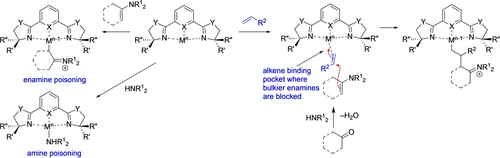
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**Figure 1** Prior and current work.

The use of a bifunctional catalyst is one potential solution to this problem, whereby the amine/enamine is held far enough away from the *π-*Lewis acid to avoid self-quenching, but remains close enough to facilitate the desired C−C bond formation between donor and acceptor. Several bifunctional amine/Lewis acid catalysts have been reported,**16** primarily for aldol-type reactions, and key examples include those from the labs of Ito and Hayashi,**17** Mlynarski,**18** Wang,**19** and Dixon.**20** We developed a density functional theory (DFT)-based approach to prioritizing our own bifunctional catalyst designs, which estimates the free energy change upon C−C bond formation within the putative catalytic cycle.**14**,**15** It should be emphasized that rational *de novo* catalyst design has yet to be established as a reliable strategy, though in recent years successful examples of the modification of established organometallic catalysts driven by computation have been reported.**21**-**23** Thus far, our approach has been complicated by apparent catalyst-catalyst interactions, which current work is aiming to minimize. We reasoned that an alternative strategy to preventing undesired amine/enamine-Lewis acid interactions would be to utilize a dual amine/Lewis acid system with separate and discrete catalysts, an approach which has been reviewed numerous times in recent years.**24**-**29** A bulky amine catalyst could be used with a *π*-Lewis acid with bulky ligands, with the catalyst shapes matched to permit only the desired attack of an enamine intermediate on a metal-coordinated alkene or alkyne (Figure **1**, bottom). This approach may necessarily have a limited substrate scope, particularly with respect to the alkene, but the lack of precedent for such reactions inspired us to explore certain dual catalyst combinations. The computational investigation of these dual catalysts and the experimental testing of the most promising combinations is described herein.

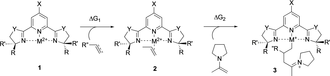
# Results and Discussion

A key challenge for the development of an effective dual catalyst system is that the Lewis acidic and Lewis basic catalysts must avoid poisoning each other. In this case under study, the desired alkene/alkyne activation via coordination to the π-acid metal could be in competition with direct coordination of the amine co-catalyst or enamine. Examination of the X-ray structures of several pincer-type complexes suggested that the pyridyl-bis(oxazoline) (PyBOX) ligand scaffold could be tailored to permit a binding pocket selective for smaller alkenes over bulkier enamines. In our design of a dual catalyst system, three key factors were studied: the steric environment around the alkene binding pocket, the electronics of the ligand, and the sterics of the secondary amine co-catalyst. These factors can be assumed to affect both the desired C−C bond formation step, as well as catalyst poisoning due to undesired coordination of the amine catalyst or an enamine intermediate to the Lewis acid. These competing processes are illustrated in Figure **2**, which are the basis for our DFT calculations in Tables **1** and **2**. Essentially, our strategy is dependent on the ability of a bulky enamine to attack a smaller, metal-coordinated alkene, with the sizes matched such that only the smaller alkene is able to coordinate effectively to the metal and become activated for outer sphere attack of the enamine intermediate.

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**Figure 2** Key intermediates in our proposed dual catalytic approach.

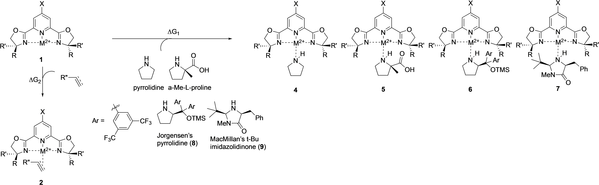
**Table 1.**DFT calculations of propylene complexation and iminium adduct formation[a]

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|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Entry** | **M** | **R** | **R’** | **X** | **Y** | **Propylene or (acetylene)[b] complexation, ΔG1 (kcal/mol)** | **Enamine addition,[b] ΔG2 (kcal/mol)** |
| 1 | Ni | Me | Me | NMe2 | O | 6.8 | –18.0 |
| 2 | Ni | Me | Me | H | O | 5.9 (–2.4) | –21.8 (–44.0) |
| 3 | Ni | Me | Me | H | NH | 7.7 | –17.1 |
| 4 | Ni | *i-*Pr | H | NMe2 | O | –3.6 | –14.7 |
| 5 | Ni | *i-*Pr | H | H | O | –3.2 (–8.0) | –20.2 (–42.3) |
| 6 | Ni | *i-*Pr | H | H | NH | –1.6 | –13.2 |
| 7 | Pt | Me | Me | NMe2 | O | –4.0 | –14.2 |
| 8 | Pt | Me | Me | H | O | –3.5 (–9.3) | –21.2 (–44.6) |
| 9 | Pt | Me | Me | H | NH | –2.4 | –16.5 |
| 10 | Pt | *i-*Pr | H | NMe2 | O | –9.6 | –15.0 |
| 11 | Pt | *i-*Pr | H | H | O | –8.6 (–11.0)[c] | –19.7 (–45.8) |
| 12 | Pt | *i-*Pr | H | H | NH | –7.1 | –15.8 |
| 13 | Pt | *t-*Bu | H | NMe2 | O | –4.2[c] | –16.5 |
| 14 | Pt | *t-*Bu | H | H | O | –2.3 | –16.1 |

[a] All calculations used the functional B3PW91 and basis set LANL2DZ for metals, and the basis set cc-pVDZ for all other atoms. DCM was the solvent. [b] Values in parentheses are for acetylene. [c] ΔG=–11.5 (entry 11) and –3.7 (entry 13) for 5-phenyl-1-pentyne complexation.

**Table 2.**DFT calculations for desired alkene and undesired amine coordination[a]

****

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Entry** | **M** | **R** | **R’** | **X** | **Solvent** | **Basis Set** | **Intermolecular Poisoning, ΔG1 (kcal/mol)** |  |  |  | **Coordination, ΔG2 (kcal/mol)** |  |  |
|  |  |  |  |  |  |  | **4** | **5** | **6** | **7** | **Ethylene** | **Propylene** | **5-phenyl-1-pentyne (6-phenyl-2-hexyne)** |
| 1 | Ni | Me | Me | NMe2 | DCM | cc-pVDZ | –15.8 | –5.1 | 4.3 | 3.4 | 1.5 | 6.8 |  |
| 2 | Ni | *i-*Pr | H | NMe2 | DCM | cc-pVDZ | –23.5 | –19.9 | –8.3 | –6.9 | –3.2 | –3.6 |  |
| 3 | Ni | *i-*Pr | H | NMe2 | DCM | Def2-QZVPP |  |  | –8.1 | –3.0 | 0.3 | 0.8 |  |
| 4 | Ni | *t-*Bu | H | NMe2 | DCM | cc-pVDZ | –16.5 | –7.2 | 3.0 | 5.0 | 4.1 | 5.6 |  |
| 5 | Ni | *t*-Bu | H | NMe2 | DCM | Def2-QZVPP |  |  |  | 9.8 | 5.4 | 7.6 |  |
| 6 | Ni | *i-*Bu | H | NMe2 | DCM | cc-pVDZ | –21.8 | –12.4 | –7.3 | –4.7 | –2.6 | –1.6 |  |
| 7 | Ni | Ph | H | NMe2 | DCM | cc-pVDZ | –24.1 | –16.6 | –7.0 | –6.9 | –5.4 | –3.9 |  |
| 8 | Pd | Me | Me | NMe2 | DCM | cc-pVDZ | –16.5 | –5.0 | 2.4 | 2.0 | –1.6 | 0.2 |  |
| 9 | Pd | *i-*Pr | H | NMe2 | DCM | cc-pVDZ | –19.6 | –17.9 | –7.2 | –7.0 | –6.8 | –5.0 |  |
| 10 | Pd | *t-*Bu | H | NMe2 | DCM | cc-pVDZ | –16.9 | –9.2 | NA | 2.6 | –0.4 | 1.4 |  |
| 11 | Pd | *i-*Bu | H | NMe2 | DCM | cc-pVDZ | –19.9 | –13.2 | –4.1 | –4.2 | –4.1 | –4.7 |  |
| 12 | Pd | Ph | H | NMe2 | DCM | cc-pVDZ | –24.2 | –16.2 | –9.8 | –9.2 | –8.3 | –7.9 |  |
| 13 | Pt | Me | Me | NMe2 | DCM | cc-pVDZ | –17.8 | –7.9 | 0.4 | 1.3 | –6.0 | –4.0 |  |
| 14 | Pt | *i-*Pr | H | NMe2 | DCM | cc-pVDZ | –23.0 | –20.5 | –9.2 | –6.0 | –12.3 | –9.6 | –11.8 (–13.0) |
| 15[b] | Pt | *i*-Pr | H | NMe2 | DCM | cc-pVDZ |  |  |  | –6.7 | –11.5 | –12.3 |  |
| 16 | Pt | *i*-Pr | H | NMe2 | DCM | Def2-QZVPP |  |  |  | –3.7 | –13.8 | –10.1 |  |
| 17 | Pt | *i*-Pr | H | NMe2 | NO2Me | cc-pVDZ |  |  | –5.7 | –4.1 |  | –4.8 | –7.1 (–6.5) |
| 18 | Pt | *t-*Bu | H | NMe2 | DCM | cc-pVDZ | –20.2 | –11.5 | –2.2 | 2.0 | –7.1 | –4.2 | –7.4 |
| 19[b] | Pt | *t*-Bu | H | NMe2 | DCM | cc-pVDZ |  |  | –2.4 | 2.1 | –7.4 | –6.4 |  |
| 20 | Pt | *t*-Bu | H | NMe2 | DCM | Def2-QZVPP |  |  | 5.4 | 5.3 | –8.3 | –4.2 |  |
| 21 | Pt | *t*-Bu | H | NMe2 | NO2Me | cc-pVDZ |  |  | 0.8 | 5.0 | –1.9 | 1.1 | –2.5 (–3.9) |
| 22 | Pt | *i-*Bu | H | NMe2 | DCM | cc-pVDZ | –21.8 | –14.4 | –7.7 | –4.7 | –9.5 | –9.2 |  |
| 23 | Pt | Ph | H | NMe2 | DCM | cc-pVDZ | –26.3 | –20.8 | –9.7 | –9.4 | –12.2 | –11.1 |  |
| 24[b] | Pt | Ph | H | NMe2 | DCM | cc-pVDZ |  |  | –10.0 | –8.4 |  | –13.8 |  |
| 25 | Pt | *t*-Bu | H | H | DCM | cc-pVDZ |  |  | –0.3 | 3.9 | –6.0 | –2.3 | –3.7 (–7.5) |
| 26 | Pt | *t*-Bu | H | H | NO2Me | cc-pVDZ |  |  | –0.2 | 6.0 | 0.0 | 3.2 | –0.8 (–0.2) |

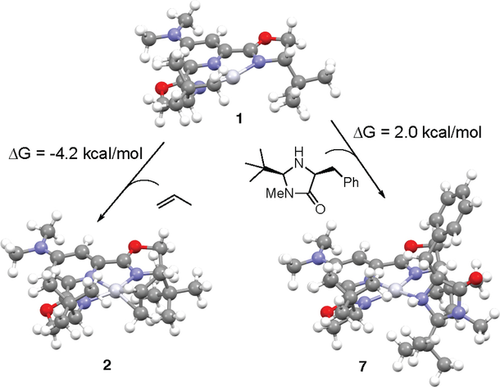
[a] Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent, unless otherwise noted. [b] An UltraFine integration grid was used instead of the default Gaussian 09 FineGrid. NA=Not available– the calculation did not converge.

The addition of the enamine derived from acetone and pyrrolidine was used for our initial studies, with Ni(II) and Pt(II) catalyst complexes. Calculations were performed to predict the effects the following variations would have on propylene/acetylene coordination and C−C bond formation: the presence of an electron-donating group (EDG) (X=NMe2) at the 4-position of the pyridine; flanking oxazoline versus imidazoline ligands; and bis-methyl or isopropyl substituents on the oxazolines or imidazolines (Table **1**). Propylene complexation was found to be unfavorable with the bulky tetramethyl-substituted nickel complexes (entries 1–3), whereas acetylene complexation was favorable (entry 2). The relatively less sterically congested isopropyl-substituted nickel complexes also led to favorable propylene and acetylene complexation (entries 4–6). With the platinum complexes, propylene complexation was found to be favorable for the tetramethyl-, isopropyl-, and tertbutyl-complexes (entries 7–14). C−C bond formations to give the iminium adduct intermediates **3** were calculated to be exergonic for both Ni2+ and Pt2+ in all cases. The electron-donating group (EDG) dimethylamine (entries 1, 4, 7, 10, and 13) was found to have a beneficial effect on alkene coordination with platinum (e. g. entries 10 vs. 11), which initially led us to prioritize its use in our calculations in Tables **1** and **2**. However, it attenuated the favorable free energy changes of the enamine addition (C−C bond formation), which is not surprising considering the alternate direction of electron flow between the two steps. For synthetic simplicity, we used the unsubstituted PyBOX complexes in our screening experiments (*vide infra*). The more electron rich pyridine-bis(imidazoline) systems gave relatively less favorable energetics for iminium adduct formation and propylene complexation (entries 3, 6, 9, and 12).

In the design of PyBOX ligands with selective binding pockets, the substituents (R, R′) on the oxazolines can be varied to selectively recognize smaller alkenes or alkynes, while making bulkier enamine organocatalysts less prone to direct coordination and metal poisoning (Figure **2**). Any interaction between the organocatalyst and Lewis acid should also be rapidly reversible. The metal could also be poisoned via aldehyde/ketone binding, which is more likely for the harder, more oxophilic Ni(II) salts. For our subsequent calculations, the 4-NMe2-PyBOX scaffold was selected due to its slightly improved energetics for propylene binding.

Next, we considered a variety of secondary amine co-catalysts, such as pyrrolidine, α-methyl-L-proline, Jørgensen's pyrrolidine **8**,**30** and MacMillan's *t*-Bu-imidazolidinone **9**.**31** DFT calculations were performed on combinations of PyBOX, organocatalyst, alkene (propylene and ethylene), and metal (Ni, Pd, Pt) to determine the energetics of alkene coordination versus poisoning of the metal via organocatalyst coordination (Table **2**).

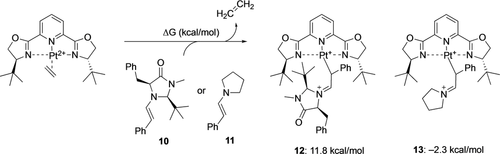
As expected, pyrrolidine was calculated to fit into the binding pocket of all complexes and had very favorable (though undesired) metal coordination (Table **2**, column 8). While the bulkier α-methyl-L-proline had diminished energetics for coordination, it was also predicted to have favorable coordination with every system (column 9), and coordination via the carboxylate is also possible (not calculated). The most promising organocatalysts were predicted to be Jørgensen's pyrrolidine **8** and MacMillan's imidazolidinone **9**. Lewis acid poisoning by these organocatalysts was calculated to be unfavorable with the bulkiest PyBOX systems (i. e. those with bis-*t*-Bu or tetramethyl substituents: entries 1, 4, 5, 8, 10, 13, and 18, columns 10 and 11). Coordination of propylene and ethylene in these systems was typically favored, with some exceptions, most notably the bulkier Ni complexes (entries 1, 3, and 4). Taking into account both organocatalyst poisoning and olefin coordination, the DFT calculations predicted MacMillan's organocatalyst with (4-NMe2-*t*-Bu-PyBOX)Pt2+ to be the most promising combination, due to the calculated endergonic coordination of the organocatalyst **9** (+2.0 kcal/mol) and the exergonic coordination of propylene (–4.2 kcal/mol) and ethylene (–7.1 kcal/mol) (Table **2**, entry 18; Figure **3**). Wheeler recently noted that the default Gaussian09 (75,302) grids can result in errors greater than 5 kcal/mol in relative free energies for several systems.**32** Thus, we repeated our calculations using a finer (99,590) grid size for several intermediates (Table **2**, entries 15, 19, and 24) and found the grid size to have relatively modest effects; importantly, it did not change the promising energetics of (*t*-Bu-PyBOX)Pt2+ and MacMillan's organocatalyst for use in the desired reaction (entry 18). The diastereomeric “poisoned” complex composed of the enantiomeric (*t*-Bu-PyBOX)Pt2+ and **9** was calculated to be slightly lower in energy (+2.1 kcal/mol versus +2.0 kcal/mol in entry 18).

[](https://chemistry-europe.onlinelibrary.wiley.com/cms/asset/2b111725-6f04-4ba9-baed-117a61bb17ec/slct202001840-fig-0003-m.jpg)

**Figure 3** Optimized structures for optimal combinations from Table **2** (entry 18). Propylene coordination to the Pt2+ complex (left) is calculated by DFT to be favorable, and organocatalyst coordination (right) unfavorable.

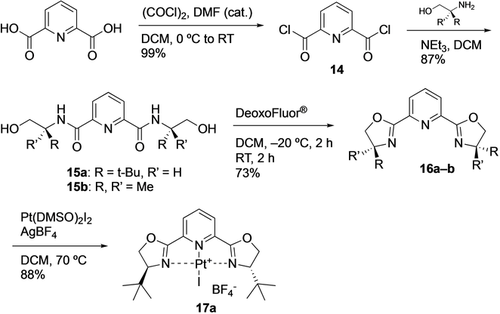
For select entries of interest, additional DFT calculations were made by performing a single-point correction using the larger basis set Def2-QZVPP in an attempt to increase the accuracy of these predicted energies (Table **2**, entries 3, 5, 16, and 20). In the case of the (*i*-Pr-PyBOX)-Ni2+ complex, the complexation of ethylene and propylene was no longer exergonic (entry 3). However, the calculations on the *i*-Pr- and (*t*-Bu-PyBOX)-Pt2+ complexes found relatively minor differences between basis sets for ethylene and propylene complexation, but organocatalyst **8** poisoning of the (*t*-Bu-PyBOX)-Pt2+ complex was now computed to be unfavorable (+5.4 kcal/mol) and similar to poisoning by organocatalyst **9** (+5.3 kcal/mol) (entry 20). Additionally, DFT calculations were performed taking into consideration alternative solvents. This became important since the bis-cationic PyBOX-metal complexes were found to have poor solubility in less polar solvents. Using NO2Me instead of DCM as the solvent (entries 17 and 21), the energies of alkene complexation were computed to be significantly different. Propylene was no longer computed to be exergonic for complexation to the (*t*-Bu-PyBOX)-Pt2+ complex (entry 21, column 13). However, complexation of a terminal alkyne (5-phenyl-1-pentyne) or internal alkyne (6-phenyl-2-hexyne) to the (*t*-Bu-PyBOX)-Pt2+ complex were still found to be exergonic (Table **2**, column 14). Additionally, coordination of MeCN to the (*t*-Bu-PyBOX)-Pt2+ was computed to be –15.3 kcal/mol when using the PCM solvation model with DCM. This is consistent with the fact that coordinating solvents can be problematic with highly electrophilic catalysts.

In addition to the organocatalysts or solvent acting as competing ligands for the π-acid, the electron-rich enamine intermediates could also coordinate competitively. We previously reported this observation for a Cu(I)-phenylacetylene complex, where the alkyne was displaced upon the addition of an enamine.**14** We hypothesized that a bulkier enamine would coordinate less favorably to the sterically congested π-acidic metal than a smaller alkene. To test this hypothesis, we performed ground state DFT calculations for the addition of enamines **10** or **11** to the (*t*-Bu-PyBOX)-Pt2+ ethylene complex (Figure **4**). The bulkier enamine derived from **9** and phenylacetaldehyde (**10**) was calculated to be very endergonic (+11.8 kcal/mol) for the displacement of ethylene, while displacement with the smaller pyrrolidine derived enamine (**11**) was found to be exergonic (–2.3 kcal/mol). Neither the bulkier imidazolidinone organocatalyst, nor its enamine intermediate were predicted to have more favorable interactions with the Pt2+ complex than ethylene.

[](https://chemistry-europe.onlinelibrary.wiley.com/cms/asset/12a97098-dea0-4929-83db-dea82db5eeb3/slct202001840-fig-0004-m.jpg)

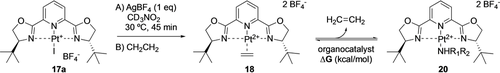
**Figure 4** DFT calculations for poisoning of (*t-*Bu-PyBOX)-Pt2+ complex by enamines.

Based on our DFT calculations, we decided to pursue the synthesis of Pt complexes from the tetramethyl- and *t*-Bu-PyBOX ligands **16 a–b** (Scheme **1**). While the NMe2 substitution at the 4-position of the PyBOX was calculated to be slightly more exergonic for ethylene complexation and C−C bond formation, we did not see any significant advantage of this ligand, which requires a lengthier synthesis. Therefore, we proceeded to prepare the parent PyBOX ligands. Treatment of 2,6-pyridinedicarboxylic acid with oxalyl chloride afforded **14** in excellent yield. Coupling of **14** with 2-amino-2-methyl-1-propanol or L-*tert*-leucinol yielded **15 a–b**. Oxazoline formation using Deoxo-Fluor®[33,34] proceeded smoothly to yield PyBOX ligands **16 a–b**. The Pt(II) precatalyst from ligand **17 a** was prepared according to a protocol adapted from that reported by Gagné.**35** Treatment of **16 a** with Pt(DMSO)2I2, prepared from a procedure reported by Vos,**36** and one equivalent of AgBF4 at 70 °C, yielded the cationic complex **17 a** in 88% yield. Elevated temperatures were found to be crucial for successful complexation. Attempts to isolate the cationic Pt(II) precatalyst from ligand **16 b** have been unsuccessful.

[](https://chemistry-europe.onlinelibrary.wiley.com/cms/asset/12367c64-f4c9-4dcd-809d-029205e4dd2e/slct202001840-fig-5001-m.jpg)

**Scheme 1** Synthesis of Pt-PyBOX complexes

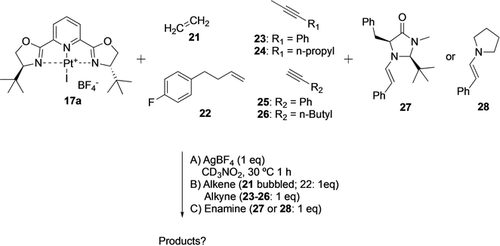
Prior to screening dual catalytic reactions, we wanted to confirm via NMR that the optimal organocatalyst **9** identified in our DFT calculations (Figure **4**) would not effectively compete with ethylene for complexation. For all of our NMR experiments and reaction screens, we generated the bis-cationic (*t*-Bu-PyBOX)Pt2+ ethylene complex *in situ* by heating a solution of **17 a** with one equivalent of AgBF4 in nitromethane at 40 °C for 1 h, and filtering off the silver salts using a syringe filter before bubbling ethylene into the solution. A downfield shift in the 1H NMR signal for ethylene was observed, from 5.39 ppm to 5.47 ppm in CD3NO2, which is consistent with the formation of Pt-ethylene complex **18** (Figure **5**). To the ethylene complex was added one equivalent of organocatalysts **8**, **9**, or MacMillan's imidazolidinone organocatalyst **19** (Table **4**). Upon the addition of **8** and **19**, ethylene shifted back upfield to its original position in the 1H NMR, thus suggesting coordination of these organocatalysts is highly favored over ethylene coordination. However, when **9** was added, the 1H NMR peak for ethylene did not shift completely back to its original position and only shifted from 5.47 ppm to 5.44 ppm. This is consistent with at least a measurable fraction of ethylene binding to the platinum complex in the presence of the bulkier *t*-Bu imidazolidinone **9**. These findings are in agreement with our DFT calculations, as coordination of **8** to the (*t*-Bu-PyBOX)-Pt2+ complex was calculated to be –0.2 kcal/mol, versus ethylene complexation (calculated to be 0.0 kcal/mol), while coordination of **9** to the (*t*-Bu-PyBOX)-Pt2+ complex was calculated to be +6.0 kcal/mol (Table **2**, entry 26).

[](https://chemistry-europe.onlinelibrary.wiley.com/cms/asset/77064952-2e11-4b6c-bfef-42bd2211943d/slct202001840-fig-0005-m.jpg)

**Figure 5** NMR and DFT study of the displacement of ethylene with pyrrolidine and imidazolidinone organocatalysts.

Therefore, **9** could be promising for use as an organocatalyst that does not poison the metal center. Additionally, *in situ* formation of the parent PyBOX-Pt2+ complex was confirmed via mass spectroscopy. After heating the solution of **17 a** with one equivalent of AgBF4 in nitromethane at 40 °C for 1 h, excess MeCN was added prior to using a direct inject LC–MS method with electrospray ionization. The m/z of 282.60 corresponds to the PyBOX−Pt(II)-MeCN complex (M2+/2).

While a variety of PyBOX−Pt(II) complexes have been previously reported by Gagné for the cyclization of polyenes,**35** to our knowledge there have been no reports of PyBOX−Pt(II) complexes with alkenes or alkynes. Our DFT calculations predicted that propylene (Table **2**, entry 18, –4.2 kcal/mol) and acetylene (Table **1**, entries 8, 11) coordination are both favorable in these systems. Upon the addition of alkenes/alkynes **22–26** to the *in situ* generated (*t*-Bu-PyBOX)-Pt(II) omplex **17 a** in CD3NO2, there were no observed 1H NMR shifts of the PyBOX ligand protons or of any of the substrates (Figure **6**). While this doesn't necessarily preclude catalytic activity, it does indicate no detectable amount of alkene or alkyne binding by NMR. After the addition of alkenes **21** or **22**, preformed enamine **27** was added as a solution in CD3NO2. After the addition, there was no observed displacement of ethylene and no peak shifts in the 1H NMR for either the PyBOX complex or **27**. These preliminary results align with our DFT calculations (Figure **4**) that predicted the enamine **27** to have unfavorable energetics of catalyst poisoning (+11.8 kcal/mol). The reactions were then heated at 80 °C for 24 h (50 psi of ethylene with **21**) and analyzed directly via GC-MS, which indicated no detectable alkylation or alkenylation reactions of phenylacetaldehyde.

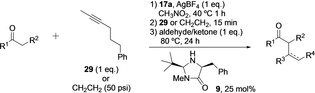
[](https://chemistry-europe.onlinelibrary.wiley.com/cms/asset/4249a3fe-a6c7-4a76-b26a-a260b8bee2e2/slct202001840-fig-0006-m.jpg)

**Figure 6** Addition of enamines to Pt-PyBOX alkene/alkyne complexes.

Alternatively, with the addition of less hindered enamine **28**, the solution immediately turned brown. We hypothesize that **28** underwent a redox reaction with the PyBOX−Pt(II) complex **17 a** to generate a stabilized radical cation intermediate. In any regard, enamine **28** was found experimentally to have undesirable interactions with **17 a**, which was predicted by our DFT calculations (–2.3 kcal/mol, Figure **4**). We hypothesize that the lack of reactivity of **18** with **27** may be due to **27** being stabilized by conjugation. Attempts to isolate the less stabilized enamines formed from butyraldehyde and **9** or **19** have been unsuccessful thus far.

Next, we proceeded to screen our prioritized dual catalyst system for the direct addition of aldehydes to alkenes and alkynes, using a catalytic amount of organocatalyst **9** and stoichiometric amount of the PyBOX−Pt(II) complex **17 a** (Table **3**). Ethylene was selected due to its observed coordination to our PyBOX−Pt(II) complex. Additionally, we included 6-phenyl-2-hexyne (**29**) as a representative alkyne substrate (with the aromatic handle included to facilitate product identification), and acetone, isovaleraldehyde, butyraldehyde, and phenylacetaldehyde as aldehyde/ketone substrates. Due to its polar, poorly-coordinating nature, and the inability of less polar solvents to dissolve the Pt precatalysts, nitromethane was used for all reactions. As previously discussed, we generated the bis-cationic PyBOX−Pt(II) precatalyst *in situ* from **17 a** using AgBF4, then bubbled ethylene gas into the solution or added a stock solution of alkyne **29**, followed by the addition of the respective aldehyde and organocatalyst **9**. After heating at 80 °C for 24 h, only starting materials were detected by GC-MS. The lack of desired products for the reactions with ethylene in entries 5–8 was confirmed by comparison to GC traces of commercially available materials.

**Table 3.**Reaction screening with stoichiometric Pt complex **17 a**

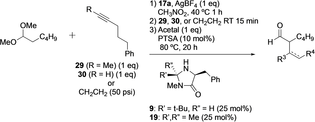
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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **R1** | **R2** | **Alkene/ Alkyne** | **Result[a]** |
| 1 | H | *i-*Pr | **29** | NR |
| 2 | H | Et | **29** | NR |
| 3 | H | Ph | **29** | NR |
| 4 | Me | H | **29** | NR |
| 5 | H | *i-*Pr | ethylene | NR |
| 6 | H | Et | ethylene | NR |
| 7 | H | Ph | ethylene | NR |
| 8 | Me | H | ethylene | NR |

[a] NR=no reaction detected by GC-MS.

We hypothesized that if the aldehyde substrates underwent oligomerization via aldol reactions, then using an acetal may minimize this by decreasing the concentration of reactive aldehyde. Therefore, we also performed a screen using 1,1-dimethoxyhexane as an aldehyde precursor (Table **4**). *p*-Toluenesulfonic acid monohydrate (PTSA) was added as a cocatalyst to generate *n*-hexanal, together with both the *tert*-butyl- (**9**) and dimethylimidazolidinone (**19**) organocatalysts. After heating at 80 °C for 20 h using undried nitromethane as solvent, the samples were analyzed by GC-MS. Results from entries 1 and 2 were compared to the GC trace for the desired product 2-ethylhexanal. Unfortunately, no reaction was observed, and no compounds other than starting materials and self-aldol condensation products were detected.

**Table 4.**Reaction screening using acetal substrate

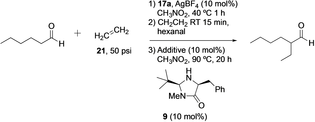
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|  |  |  |  |
| --- | --- | --- | --- |
| **Entry** | **Alkene/ Alkyne** | **Organocatalyst** | **Result[a]** |
| 1 | ethylene | **9** | NR |
| 2 | ethylene | **19** | NR |
| 3 | **29** | **9** | NR |
| 4 | **29** | **19** | NR |
| 5 | **30** | **9** | NR |
| 6 | **30** | **19** | NR |

[a] NR=no reaction detected by GC-MS.

While our reaction screening afforded no detectable desired alkylation products, there was the possibility that we were forming the intermediate PyBOX−Pt-alkyl+ complexes and unable to detect these intermediates via GC-MS. Such complexes may require an acid or proton shuttle to facilitate protonolysis.**35** We screened a range of additives, including proton donors and bulky bases, for the addition of *n*-hexanal to ethylene using stoichiometric Pt-complex **17 a** and organocatalyst **9** (Table **5**). After 20 h, the reactions were analyzed via GC-MS. For all of the additives except water, only a trace amount of aldol self-condensation byproduct from *n*-hexanal was detected, in addition to unreacted substrates.

**Table 5.**Additive screening

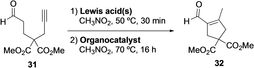
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|  |  |  |
| --- | --- | --- |
| **Entry** | **Additive** | **Result[a]** |
| 1 | H2O | NR |
| 2 | benzoic acid | A |
| 3 | *p*TsOH-H2O | A |
| 4 | acetic acid | A |
| 5 | 4-nitrophenol | A |
| 6 | Ph2NH | A |
| 7 | 2,6-di-*tert*-butylpyridine | A |
| 8 | none | A |

[a] NR=no reaction detected by GC-MS. A=trace amount of aldol condensation byproduct from *n*-hexanal was detected.

Next, we tested our dual catalytic system for the carbocyclization of a formyl alkyne to determine whether the C−C bond formation could alternatively proceed in an intramolecular fashion (Table **6**). This specific cyclization reaction was also reported by Kirsch using (PPh3)AuSbF6 and diisopropylamine catalysts,**37** and we prepared an authentic sample of the product **32** using a Cu(OTf)2, BINAP, and cyclohexylamine catalyst system reported by Michelet.**38** Due to difficulties in the isolation of **32** in the preparation of an authentic sample, we opted to use 1H NMR to measure yields for this reaction. Gratifyingly, alkyne **31** cyclized to afford enal **32** in 84% yield when initially using 50 mol% of the (*t*-Bu)PyBOX-Pt2+ complex and organocatalyst **9** (entry 1). Other less hindered organocatalysts were tested and found to have negligible activities (entries 2–4). This finding was in agreement with our DFT predictions and 1H NMR experiments that these would have favorable coordination with the π-Lewis acid and outcompete the binding of an alkene/alkyne substrate. Switching to a palladium(II) precatalyst generated *in situ* from **16 a** and Pd(CH3CN)4(BF4)2, was found to be ineffective with only a 13% yield (entry 5). Additionally, all control reactions had either negligible (<5%) or no detectible **32** when any combination of precatalyst **17 a** or organocatalyst **9** were omitted from the reaction mixture (entries 6–9). Interestingly, the reaction still produced some desired product when run without the addition of AgBF4 (entry 10) to pre-form the bis-cationic platinum complex. We presume that the alkyne is capable of displacing the iodide ligand, allowing the reaction to proceed to some extent.

**Table 6.**Intramolecular reaction screening

****

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry[a]** | **Lewis acid(s)** | **Lewis acid(s) (mol %)** | **Organocatalyst** | **Yield (%)[c]** |
| 1 | **17 a**, AgBF4 | 50 | **9** (50 mol%) | 84 |
| 2 | **17 a**, AgBF4 | 50 | **8** (50 mol%) | <5 |
| 3 | **17 a**, AgBF4 | 50 | cyclohexylamine (50 mol%) | <5 |
| 4 | **17 a**, AgBF4 | 50 | Pyrrolidine (50 mol%) | <5 |
| 5*b* | **16 a**, Pd(CH3CN)4(BF4)2 | 50 | **9** (50 mol%) | 13 |
| 6 | AgBF4 | 50 | **9** (50 mol%) | <5 |
| 7 | none | 0 | **9** (50 mol%) | NR |
| 8 | **17 a**, AgBF4 | 50 | none | NR |
| 9 | none | 0 | none | NR |
| 10 | **17 a** | 50 | **9** (50 mol%) | 11 |

[a] Reactions were performed with screening procedure A, unless otherwise noted. See Experimental Section for details. [b] Reaction screening procedure B was used. [c] Yields measured (n=1) by 1H NMR with pentachloroethane as an internal standard; NR=No desired product detected by GC-MS.

We next optimized the reaction in part by testing lower catalyst loadings (Table **7**). Reactions were run in CD3NO2 in order to measure NMR yields *in situ* without potentially degrading products (see intramolecular reaction screening procedure C). During these studies, 1H NMR peaks consistent with alkene **33** would appear as the reaction was checked at various time points, and peaks correlating to this structure would convert to those of the conjugated alkene **32** over time. The unconjugated alkene **33** was never observed when crude reaction mixtures were first run through a silica plug before analysis, which is not surprising due to its presumed instability to isomerization. Yields are reported as the sum of products of the desired C−C bond formation (**32** + **33)**. Lower catalyst loadings of 1 and 5 mol% (entries 1 and 2) produced similar results (34 and 39% yields respectively). Raising the catalyst loading to 10% (entry 3) produced a significant increase in yield to 51%. The optimal result came from a metal catalyst loading of 20 mol% (entry 4) which gave a 79% yield. The amount of organocatalyst **9** (20 mol%) compared to the amount used in Table **6** (50 mol%) indicates that it can be decreased without having a significant effect on the reaction yield.

**Table 7.**Catalyst loading studies

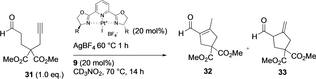
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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry[a]** | **Catalyst loading (mol %)** | **32 (%)[b]** | **33 (%)[b]** | **32 + 33 (%)[b]** |
| 1 | 1 | 29 | 5 | 34 |
| 2 | 5 | 32 | 7 | 39 |
| 3 | 10 | 46 | 5 | 51 |
| 4 | 20 | 79 | 0 | 79 |

[a] Reactions were performed using intramolecular reaction screening procedure C. [b] Yields measured (n=1) by 1H NMR using pentachloroethane as an internal standard.

We last chose to explore the effect of changing the steric bulk on the alkyl substituents of the PyBOX ligand (Table **8**). The *t*-Bu-PyBOX ligand (entry 1) gave a yield of 53%. This was slightly lower than previously observed (Table **7**, entry 4) presumably in part due to the decrease in reaction time. Less sterically hindered *i*-Pr- and Ph-PyBOX complexes also promoted productive reactions at 71% and 54% yields respectively (entries 2 and 3). Although our previously discussed calculations predicted that combination of organocatalyst **9** and (*t-*Bu-PyBOX)-Pt(II) complex **17 a** would be preferred for favorable ethylene binding, in this intramolecular addition to an alkyne, less sterically hindered PyBOX complexes were tolerated.

**Table 8.**PyBOX ligand studies

****

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry[a]** | **R** | **32 (%)[b]** | **33 (%)[b]** | **32 + 33 (%)[b]** |
| 1 | t-Bu | 40 | 13 | 53 |
| 2 | *i*-Pr | 50 | 21 | 71 |
| 3 | Ph | 42 | 12 | 54 |

[a] Reactions were performed using intramolecular reaction screening procedure D. [b] Yields measured by 1H NMR using pentachloroethane as an internal standard, as an average of two runs.

# Conclusions

In summary, we identified a dual amine/pi Lewis acid catalyst system using DFT calculations of putative catalyst intermediates. These calculations predicted the bulky *t*-Bu-imidazolidinone organocatalyst **9** and resulting enamines to have endergonic coordination to (*t*-Bu-PyBOX)-Pt2+ complexes, while alkene/alkyne coordination to these complexes was exergonic. While the dual amine/pi Lewis acid catalyst system **9** + **17 a** was not calculated by DFT to lead to self-quenching and did not appear to do so by 1H NMR, it did not promote the addition of several aldehydes/ketones to unactivated alkenes/alkynes in an intermolecular fashion. However, the same dual catalyst system was found to promote carbocyclization (Conia-ene type reaction) with a formyl alkyne substrate. Therefore, the work described here supports the use of DFT calculations to predict unproductive dual organocatalyst/Lewis acid combinations and to help identify dual catalysts with the potential to facilitate useful carbon-carbon bond formations.

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# Conflict of interest

The authors declare no conflict of interest.

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