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Peter Szwedo
University of Arkansas at Little Rock
Raja Shekhar Kondrapolu
University of Arkansas at Little Rock
Pradip Munshi
CISCHEM, Kalpvruksh Complex
Anindya Ghosh
axghosh@ualr.edu

University of Arkansas at Little Rock

Research Article

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Pincer Nickel(II) Catalyzed Oxidative Carbonylation of Amines: A Phosgene-Free Synthesis for Isocyanates and Ureas

Peter Szwedo[1], Raja Shekhar Kondrapolu[1], Pradip Munshi[2]*, and Anindya Ghosh[1]*

[1]*Department of Chemistry, University of Arkansas at Little Rock, 2801 South University Avenue, Little Rock, AR 72204, USA*
[2]*CISCHEM, Centre for Innovation and Sustainable Chemistry, Kalpvruksh Complex, Vadodara, Gujarat 390021, India.*

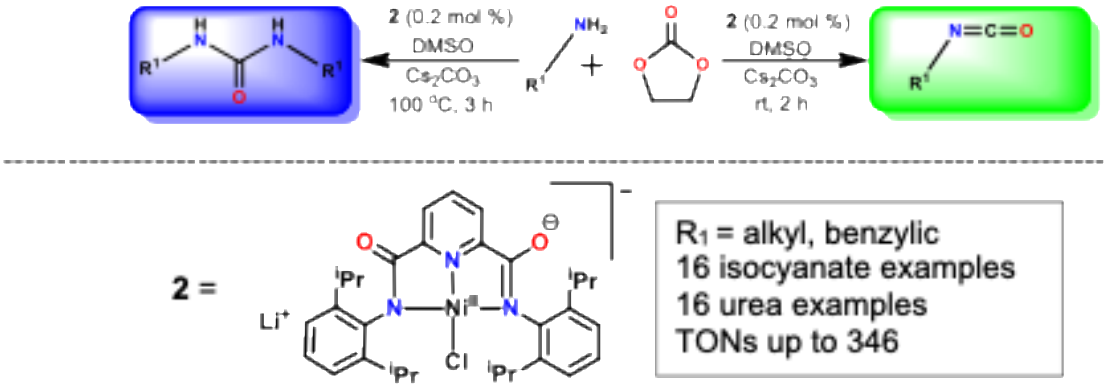
*corresponding author,
E-mail addresses of corresponding authors: axghosh@ualr.edu; pradip.munshi@cischem.org

Abstract

A novel phosgene-free process for isocyanate and urea formations from amines and cyclic carbonates catalyzed via a nickel(II) pincer complex (**2**) is demonstrated. Under relatively mild reaction conditions (2 hours and 25°C for isocyanates; 3 hours and 100°C), various aliphatic and substituted aromatic amines are converted into 32 different isocyanate and urea products. Upon optimization, moderate to good turnovers (TONs) for isocyanate formations were calculated with the highest TON for (3-isocyanatopropyl)benzene (**4d**, **277**). For ureas, moderate to good TONs were also observed with the highest TON for 1,3-bis(3-phenylpropyl)urea (**6g**, **346**). Kinetic studies were performed by varying the amount of amine, base, catalyst, and propylene carbonate substrates to determine the order of each individual component and establish the overall order to be 2. With the help of kinetic data and UV-vis spectra, a possible reaction pathway is proposed through a Ni(I)-Ni(III) pathway.

Keywords: non-phosgene route, isocyanate, urea, propylene carbonate, amine, nickel(II) pincer complex, oxidative carbonylation.

Graphical Abstract



1. Introduction

Isocyanates are versatile synthetic intermediates for highly sought-after C-N containing organic compounds and polymeric materials[1,2]. Due to their unique electrophilic nature[3], functionally modified isocyanates have the ability to react with a broad range of alcohols and amines to produce varieties of significant chemicals such as carbamates and ureas[4–6]. Diisocyanates are another important set of isocyanates primarily known as the precursors used for polyurethanes[7–9]. Further, isocyanates are used for industrial productions of materials such as elastomers, insulations, paints, and protective coatings[10]. Due to the demand of productions from isocyanates, the global market for them grows 5% each year with primary demand in polyurethane production[11]. Ureas are another class of C-N containing compounds that serves as a key basic raw chemicals[12]. Ureas are naturally occurring[13] but urea moieties are present in industrially significant chemicals such as agrochemicals, dyes, pharmaceuticals and resins[14–16]. Some key compounds featuring isocyanate or urea groups are illustrated in **Figure 1.**

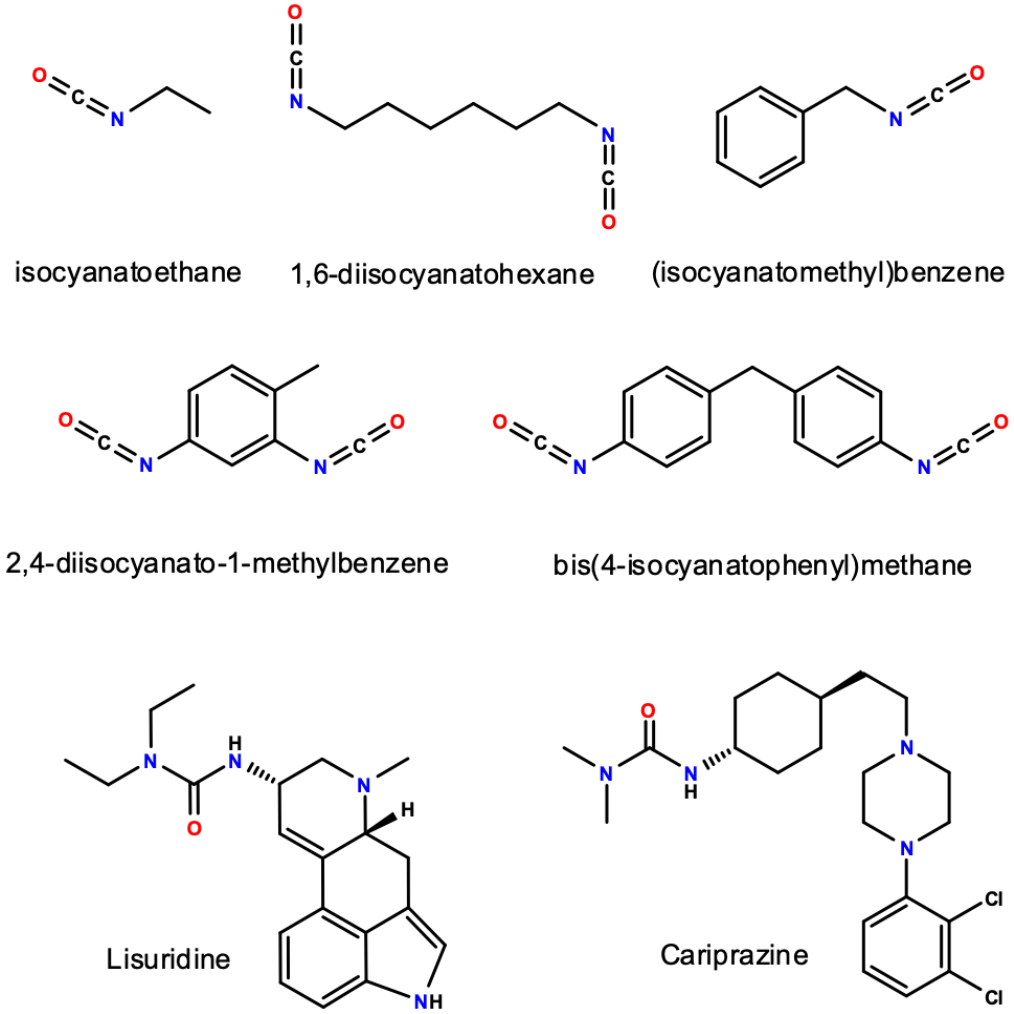


Figure 1. Important selected compounds containing the isocyanate and urea.

Despite the high demand and utilization for isocyanate and urea compounds, challenges remain in the synthetic processes[17,18]. Presently, industrial isocyanate production almost entirely relies on reacting primary amines with phosgene[19–22]. However, phosgene is a poisonous gas and

has been classified as a chemical weapon after being the most lethal chemical agent in World War One[23,24]. Further, the highly exothermic synthesis of phosgene involves the use of hazardous carbon monoxide and chlorine gases and hydrochloric acid which is produced as a byproduct[25]. Replacement of phosgene for synthesis of isocyanates has successfully been achieved utilizing carbonyldiimadizole (CDI); ironically however, phosgene is also a critical component in producing CDI[26]. Curtis, Hoffman, and Lossen rearrangements popularly produce isocyanates in lab settings, but the Curtis and Hoffman rearrangements are toxic and use halogenated species throughout the process[27–30]. Boc-anhydrides and primary amines along with leaving group displacement with metal cyanates have been reported to generate the isocyanate from primary amines[31,32]. Phosgene-free isocyanate productions through reductive carbonylation of CO from nitro-arene compounds[33] have been known since 1967 but not much progress on developing them has been made. Additionally, carbamates and ureas can be thermally induced to reform the original isocyanate product[10].

The primary method for simple urea synthesis involves variations of the Bosch-Meiser process but the process requires high pressure and temperature conditions[34,35]. However, designing complicated, substituted ureas is more challenging. CO_2 fixation and production of ureas from CO_2 and amines has been one such promising solution and a large area of focused research[36–40]. On the surface, the process involves reacting an amine and CO_2 to form carbamic acid and further reacted with an amine to produce a carbamate sale before undergoing dehydration and forming a newly substituted urea product[13]. However, the dehydration step is challenging and the transformation steps among CO_2 and amines are reversible[13,41]. The main industrial processes for polyurea synthesis involve additions of amines to isocyanates[42] and serves as another attractive route for complex synthetic urea productions[43,44].

To devise a more environmentally friendly and cost-effective process, there's interest in catalysts involving 3d metals[45]. Metals like cobalt, iron, and nickel are not only more affordable but also essential for life, making them attractive alternatives to heavier 4d and 5d metals[46]. Recent efforts have seen transition-metal catalyzed approaches using Cu, Ni, and Pd complexes for isocyanate and subsequent carbamate and urethane synthesis[47–49]. Oxidative carbonylations of amines catalyzed by Ni and Pd[45,50], but these reactions still require elevated pressures or temperatures and remain vastly underexplored[14]. Hence, innovating non-phosgene synthetic routes for isocyanate and urea synthesis holds substantial appeal for both academia and industry alike[46,51].

In this study, we employed an amide-based NNN nickel(II) pincer complex (**2**) for isocyanate and urea synthesis through oxidative carbonylation of amines using propylene carbonate as the carbonyl source. Oxidative carbonylations of alkanes[52–56] and alcohols to carbonates using carbon monoxide as the carbonyl source have been reported[57]. Additionally, conversions of amines to ureas via oxidative carbonylation using carbon monoxide as carbonyl source have also been reported[58–62]. More recently, oxidative carbonylation has been reported for the synthesis of drug molecules bearing unsymmetrical urea moieties using copper and cobalt catalysis[63]. However, oxidative carbonylations of amines to isocyanates synthesis have been limited to theoretical study[64] or to carbon monoxide or phosgene sources in several reports[65–67]. Therefore, we believe that our process for oxidative carbonylations of primary amine using cyclic carbonate as the carbonyl source is the non-phosphene route to synthesis of isocyanate and urea is the first of its kind ever being reported.

Though the nickel(II) pincer catalyst (**2**) used in this study has already introduced new methods for C-C and various C-N bond formations[68–72], this catalyst (**2**) has not yet been explored for synthesis of isocyanates and ureas as shown in **Figure 2** below. The methodology has huge

potential towards non-phosphene routes of synthesis for isocyanate and urea[73]. The present report highlights a one-pot process, converting cyclic carbonates and amines to isocyanates and urea derivatives with satisfactory yields—achieving turnover numbers (TONs) up to 276 for isocyanates and 346 for ureas (**Schemes 2 & 4**). The isocyanate reactions occur at room temperature with a base for 2 hours, while urea reactions require higher temperatures (100 °C) with a base in 3 hours. below

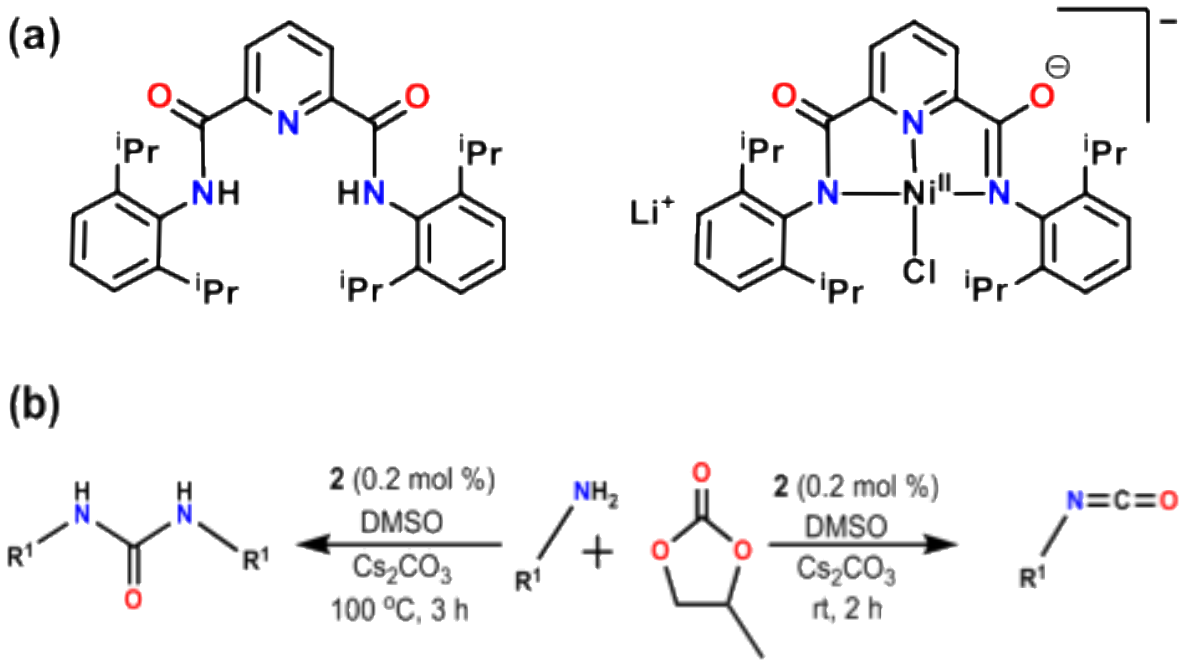


Figure 2. (a) Design of pincer ligand (**1**) and nickel(II) pincer complex (**2**). **(b)** The general reaction for isocyanates and ureas.

2. Results and Discussion

2.1. Optimization of base and solvent

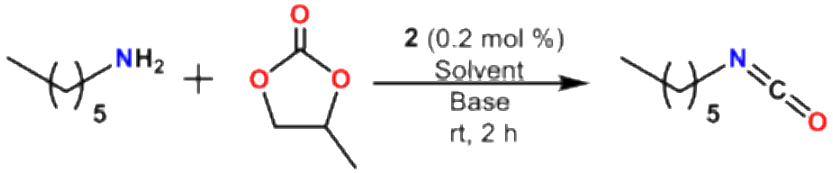
Initial observations of isocyanate production prompted a deeper exploration of this distinctive process for isocyanate formation. Efforts were made to optimize the substrate scope to achieve the desired isocyanate product. A significant part of this study was dedicated to optimizing the choice of base and solvent. Unless stated otherwise, all experiments employed the nickel(II) complex (**2**), propylene carbonate (500 eq, 146 µL, 1.71 mmol), and hexylamine (500 eq, 225 µL, 1.71 mmol). Each set of experiments was conducted in duplicate at 25 °C and stirred for a duration of 2 hours. The results of these experiments are summarized as mentioned previously in **Table 1**.

Firstly, we carried out base studies using 1.0 mL of dimethylsulfoxide (DMSO). Each base was tested at 100 molar equivalents relative to the nickel (II) complex (**2**). Our data indicated that non-nucleophilic bases enhanced the conversion rates of isocyanate products. Among the bases tested, cesium carbonate (Cs_2CO_3) was found to be the most effective in promoting isocyanate formation. Notably, the catalyst on its own showed significant conversion capability. Hence, we hypothesize that Cs_2CO_3 may act synergistically with the catalyst to boost the product yield. Numerous prior studies have highlighted a "cesium effect" in polar aprotic solvent systems, such

as those provided by DMSO and propylene carbonate. It's believed that cation solvation is particularly favored in these solvents. The findings are detailed as mentioned earlier[74,75].

Next, we evaluated various solvents against DMSO to determine their efficacy in isocyanatohexane synthesis. In each trial, cesium carbonate (Cs_2CO_3) (100 eq, 112 mg, 0.342 mmol) was incorporated. When no solvent was specified, the reaction utilized 1.0 mL of propylene carbonate. All other experiments adhered to the conditions mentioned earlier. Our results indicated that DMSO was the optimal solvent for facilitating isocyanatohexane production. This phenomenon can be attributed to the increased nucleophilicity that amine substrates exhibit when introduced into polar aprotic solvents like DMSO[76]. Remarkably, significant quantities of the isocyanate were produced when propylene carbonate functioned both as the solvent and reagent (in the no solvent setup).

Table 1. Optimization of base and solvent in terms of isocyanatohexane turnover number (TON) formation as a function of time.*



Entry	Base	Solvent	TON
1	No base	DMSO	23 ± 2
2	KOH	DMSO	54 ± 3
3	Cs_2CO_3	DMSO	162 ± 4
4	LiHMDS	DMSO	134 ± 3
5	K^{t}BuO	DMSO	71 ± 4
6	Cs_2CO_3	No Solvent	53 ± 3
7	Cs_2CO_3	DCM	97 ± 4
8	Cs_2CO_3	THF	151 ± 4
9	Cs_2CO_3	Toluene	88 ± 4
10	Cs_2CO_3	Cyclohexane	103 ± 2

*Yields represent an average of duplicate trials. TONs were calculated from GC-MS peak integrations using n-decane (25.0 µL, 1.28 x 10^{-4} mol) as the internal standard. Various bases: KOH = Potassium hydroxide. LiHDMS = Lithium bis(trimethylsilyl)amide. Various solvents: DMSO = Dimethylsulfoxide. DCM = Dichloromethane.

2.2. Optimization of time and temperature for isocyanate product

After identifying the most effective base and solvent in the scope of isocyanate product, we proceeded to examine the best time and temperature conditions. Each test utilized the nickel(II) complex (**2**), propylene carbonate (500 eq, 146 µL, 1.71 mmol), hexylamine (500 eq, 225 µL, 1.71 mmol) and Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol). These evaluations were conducted in duplicate and spanned various time intervals up to three hours, considering three different temperatures: room temperature (rt, 25 °C), 50 °C, and 100 °C. The most effective temperature for isocyanate formation was determined to occur at 25 °C. We found that 25 °C was the optimal temperature for isocyanate formation, and the ideal duration was 120 minutes. These results are summarized in **Figure 3a**. Remarkably, at elevated temperatures, we observed reduced isocyanate product TONs. The GC-MS analysis further highlighted the significant formation of urea products. Consequently, subsequent studies were oriented to assess both isocyanate and urea product yields over time.

After establishing the most optimal base, solvent, and temperature for the synthesis of the isocyanate product, we turned our attention to identifying the ideal reaction duration, particularly concerning urea product formation. Each trial, conducted in duplicate, employed the nickel (II) complex (**2**), propylene carbonate (500 eq, 146 µL, 1.71 mmol), hexylamine (500 eq, 225 µL, 1.71 mmol), and Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol) and was carried out at 100 °C. Drawing insights from the previous time study, we assessed urea TONs at different intervals over a three-hour period. The optimal duration for urea formation was identified as 180 minutes. The relationship between the diminishing isocyanate product and the increasing urea formation is detailed in the graphical representation provided in **Figure 3b**. The collected data indicates a potential equilibrium for the isocyanate product; the conversion of amines to isocyanates seems to occur at a rate similar to that of urea production between 15 – 90 minutes.

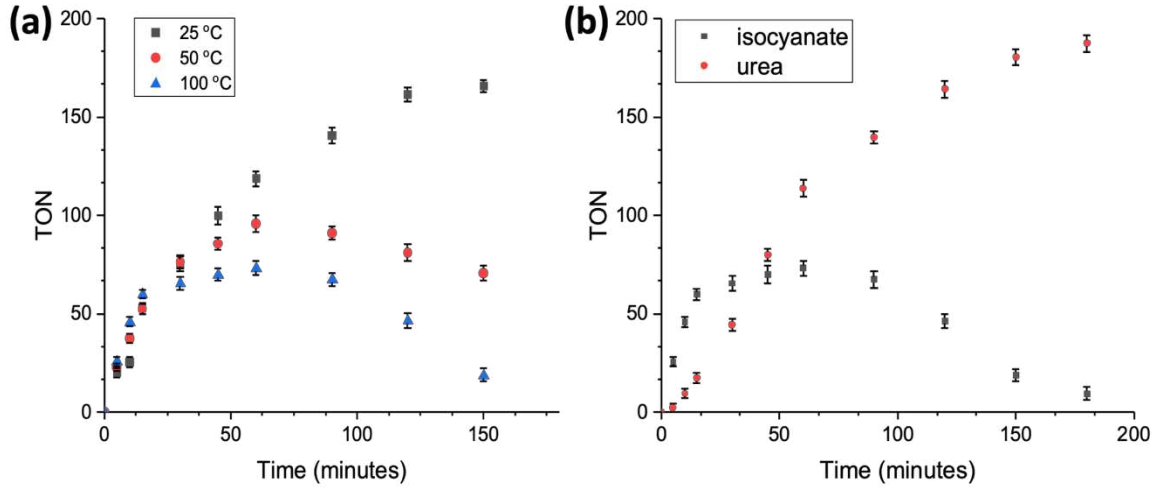


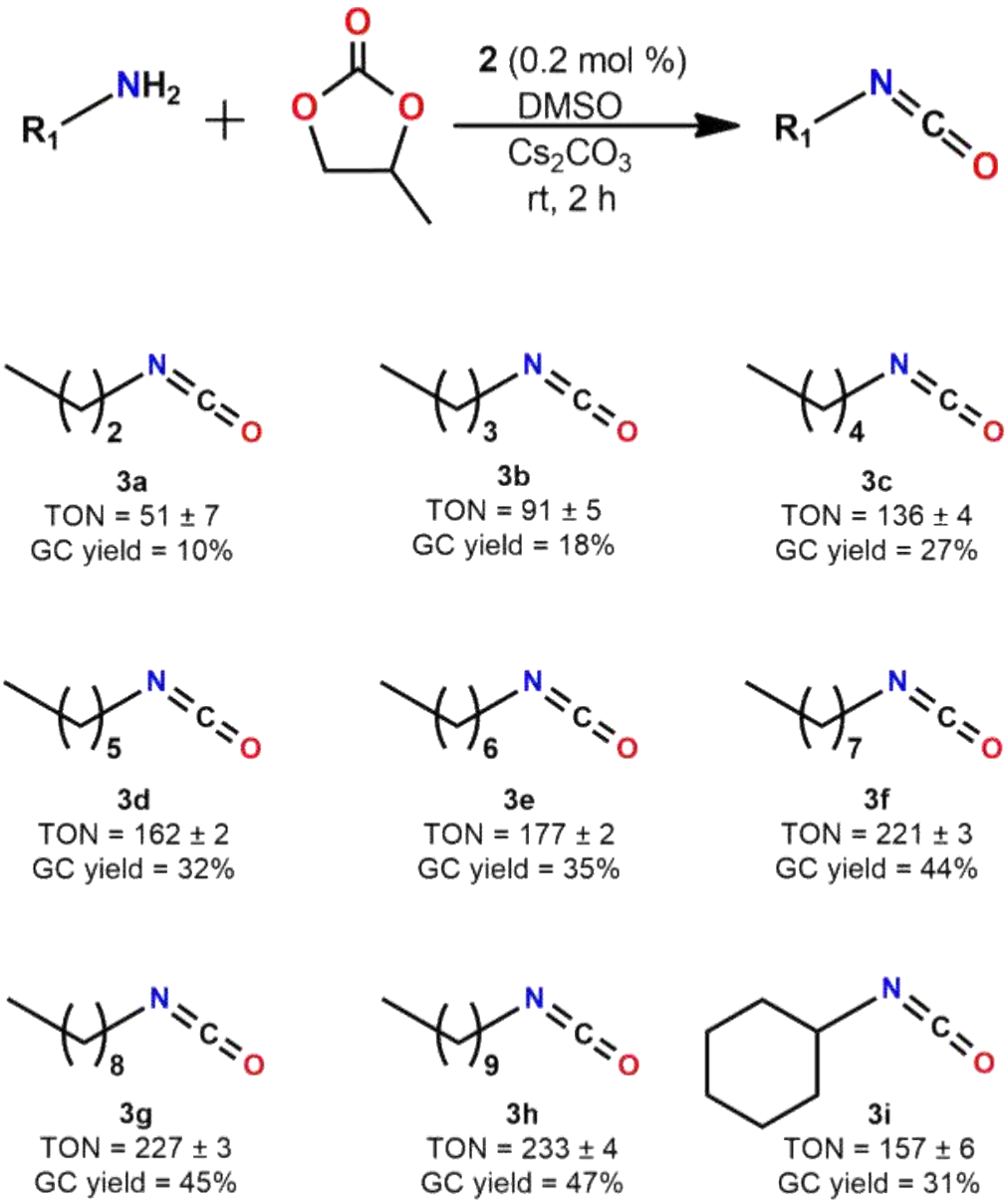
Figure 3. (**a**) Effects of temperature in terms of isocyanatohexane turnover number (TON) formation as a function of time over 150 minutes. (**b**) Effects of isocyanatohexane versus 1,3-dihexylurea turnover number (TON) formations at 100 °C as a function of time over 180 minutes. Conditions: Reactions for temperature studies were carried out with **2** (2 mg, 3.42 × 10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol),

hexylamine (500 eq, 225 µL, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for TON analysis was n-decane (25.0 µL, 1.28 x 10^{-4} mol).

2.3. Isocyanate formations in the scope of oxidative carbonyl additions to alkyl substituted amines.

After optimizing the reaction conditions, we carried out one-pot nickel-catalyzed oxidative carbonylations of amines using the previously established parameters. We used propylene carbonate as the carbonyl source and reacted it with various aliphatic amine nucleophiles. The resulting alkyl substituted isocyanate products are detailed in **Scheme 1**. In total, nine distinct products were synthesized, with yields ranging from fair to good for the target isocyanate products (**3a**, **51** – **5d**, **233**).

From our observations, the length of the carbon chain in the aliphatic, non-branched amine nucleophile seemed to correlate directly with the yield of the isocyanate product. This correlation is likely due to the increased nucleophilic strength of primary amines as the carbon chain extends[77]. As aliphatic chains grow longer, the nucleophilic strength of the amine-coupling partner enhances[78]. These factors may influence the reaction yield. Consequently, stronger, longer-chain amine nucleophiles showed higher TON conversions for isocyanate products compared to their less nucleophilic counterparts. This could also account for the observed decrease in isocyanate conversions for sterically hindered, branched aliphatic amines. Secondary amines are less nucleophilic because of the strengthened N-H bond in substituted amines[79]. However, a decent conversion was obtained for the isocyanatocyclohexane (**3i**, **157**). The highest TON that was recorded was for the isocyanatodecane product (**3h**, **233**) while the lowest yield that was recorded was for the isocyanatopropane product (**3a**, **51**).



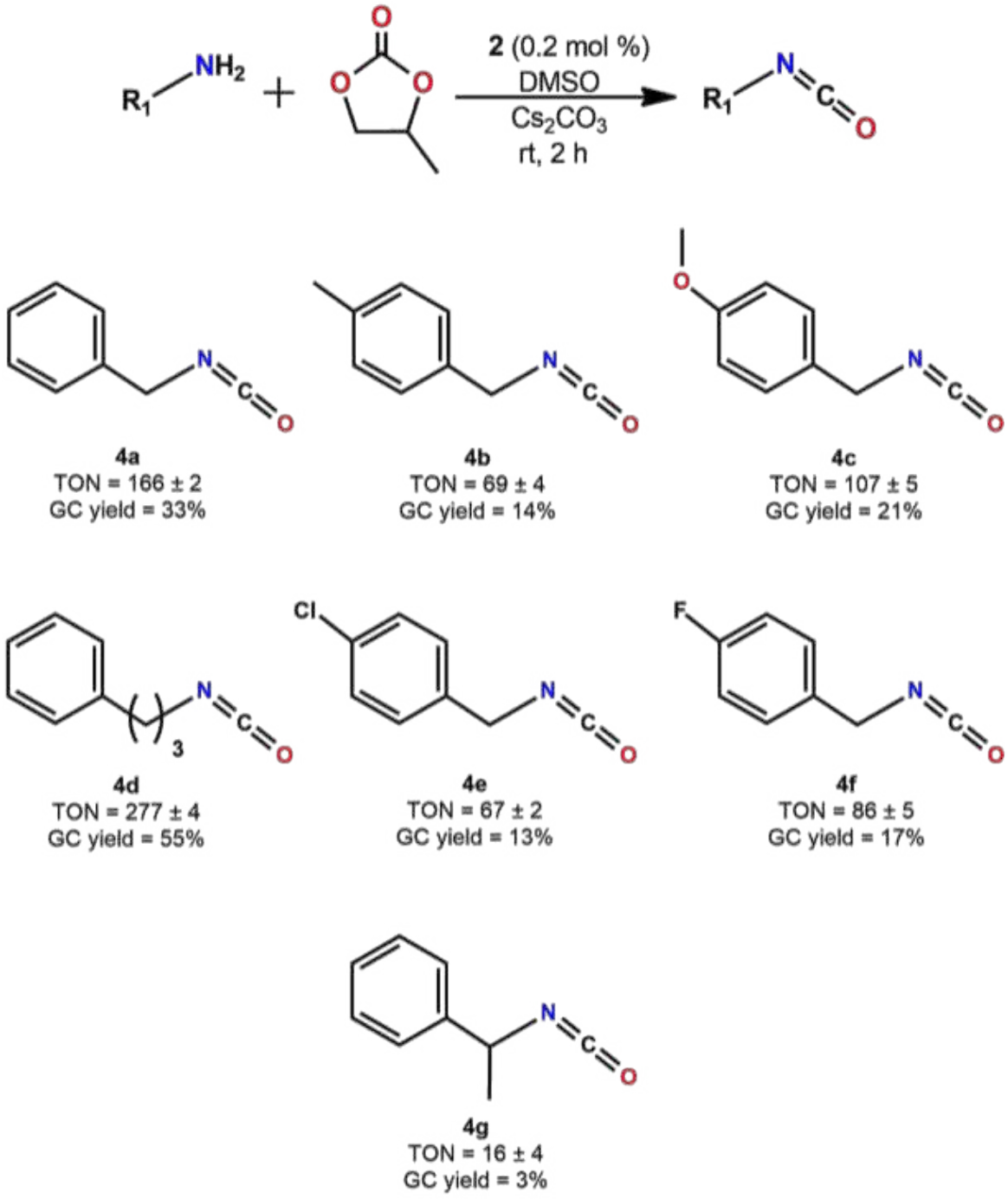
Scheme 1. Summary of isocyanate products formed via oxidative carbonylations of aliphatic amines. Conditions: Reactions were carried out with **2** (2 mg, 3.42×10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), amine (500 eq, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for TON analysis was n-decane (25.0 µL, 1.28×10^{-4} mol).

2.4. Isocyanate formations in the scope of oxidative carbonyl additions to aromatically substituted amines

After exploring the formation of aliphatic isocyanates, we turned our attention to the synthesis of aromatically substituted isocyanates. Using the established one-pot nickel-catalyzed

oxidative carbonylation of amines, propylene carbonate served as the carbonyl source. We reacted this with a range of aromatically substituted amine nucleophiles. The resulting aromatically substituted isocyanate products are detailed in **Scheme 2**. Overall, yields for the coupled products were ranging from 16 (**4g**) to 277 (**4d**).

In general, aromatic substituted isocyanate products exhibited lower TONs compared to their alkyl-substituted counterparts. The reduced reactivity of 1-methyl-4-(isocyantomethyl)benzene (**4b**, **69**) and 1-methoxy-4-(isocyantomethyl)benzene (**4c**, **107**) when compared to their non-substituted counterpart, (isocyanatomethyl)benzene (**4a**, **166**), can be attributed to steric effects. Moreover, electron-withdrawing substituents on the benzene ring seemed to depress the amine's reactivity. For halogenated substituents, the sigma electron-withdrawing properties of chlorine and fluorine reduced the reactivities of the benzylamine substrates. Particularly with fluorine, its short bond length and strong polarization of the fluorine-carbon bond likely reduced the electron density around the ipso carbon, which in turn lessened the amine's reactivity[80]. The 1-fluoro-4-(isocyanatomethyl)benzene product (**4f**, **86**) exhibited a higher TON than the 1-chloro-4-(isocyanatomethyl)benzene (**4e**, **67**), which can be attributed to chlorine's superior pi-electron donating properties to the benzene ring as compared to fluorine. The lowest TON was noted for (1-isocyanatoethyl)benzene (**4g**, **16**), possibly due to the reduced nucleophilicity of the sterically hindered, branched amine. Conversely, the 3-phenylpropylamine's increased nucleophilicity, thanks to its aliphatic chain group, resulted in the highest TON for (3-isocyanatopropyl)benzene (**4d**, **277**).

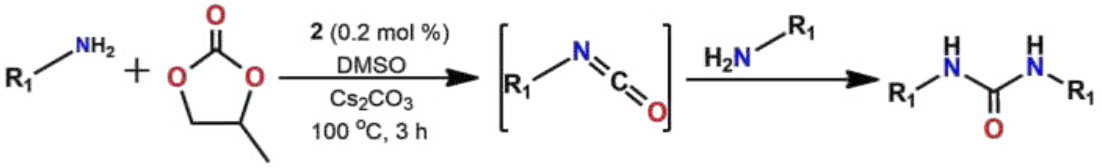


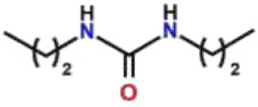
Scheme 2. Summary of isocyanate products formed via oxidative carbonylations of aromatically substituted amines. Conditions: Reactions were carried out with **2** (2 mg, 3.42×10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), amine (500 eq, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for TON analysis was n-decane (25.0 µL, 1.28×10^{-4} mol).

2.5. Symmetric urea formations in the scope of propylene carbonate sourced carbonyls oxidatively added to alkyl substituted amines

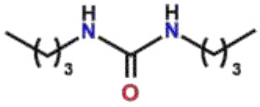
After completing the investigations on various isocyanate formations, we turned our attention to the synthesis of symmetric alkyl substituted ureas. Using the one-pot nickel-catalyzed oxidative carbonylation of amines, as described earlier, propylene carbonate served as the carbonyl source. This substrate was then reacted with a range of aliphatic amine nucleophiles. Initially, the associated isocyanate intermediate was formed, which was then further converted to yield symmetric urea products. These alkyl substituted urea products are detailed in **Scheme 3**.

In general, the yields for the urea products were fair to good, ranging from (**5a**, **64**) to (**5h**, **262**). The TONs for these alkyl-substituted urea products were slightly higher than those for the associated isocyanate products, as seen in **Scheme 1**. A clear trend emerged: the length of the carbon chain of the aliphatic amine nucleophile was directly proportional to the quantity of urea product formed. Longer aliphatic chains bolstered the amine nucleophilicity due to pronounced inductive effects. As a result, urea products synthesized from stronger amine nucleophiles had higher TON conversions compared to those from their less nucleophilic counterparts. No conversions were noted for sterically hindered, branched aliphatic amines. However, a commendable TON conversion was achieved for 1,3-dicyclohexylurea (**5i**, **206**). As expected, the highest TON recorded was for 1,3-didecylurea (**5h**, **262**), while the lowest was for 1,3-dipropylurea (**5a**, **64**).

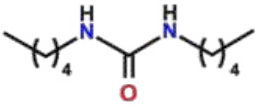




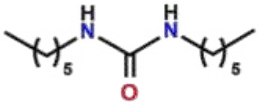
5a
TON = 64 ± 6
GC yield = 13%



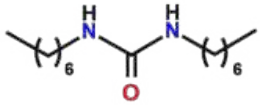
5b
TON = 99 ± 4
GC yield = 20%



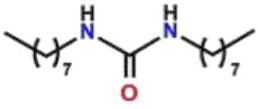
5c
TON = 147 ± 3
GC yield = 29%



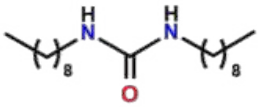
5d
TON = 186 ± 2
GC yield = 37%



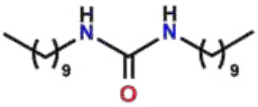
5e
TON = 192 ± 4
GC yield = 38%



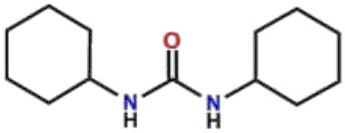
5f
TON = 234 ± 3
GC yield = 47%



5g
TON = 245 ± 5
GC yield = 49%



5h
TON = 262 ± 4
GC yield = 52%



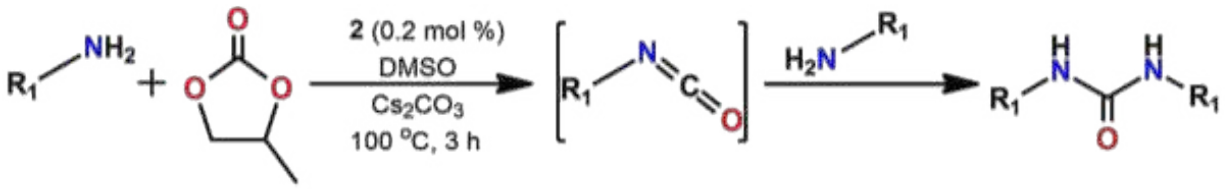
5i
TON = 206 ± 3
GC yield = 41%

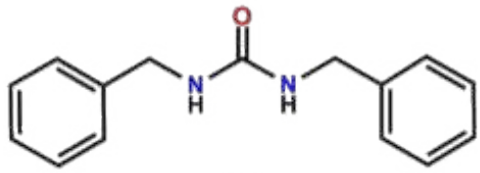
Scheme 3. Summary of urea products formed via propylene carbonate sourced carbonyls oxidatively added to various alkyl substituted amines. Conditions: Reactions were carried out with **2** (2 mg, 3.42×10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), amine (500 eq, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for TON analysis was n-decane (25.0 µL, 1.28×10^{-4} mol).

2.6. Symmetric urea formations in the scope of propylene carbonate sourced carbonyls oxidatively added to aromatically substituted amines

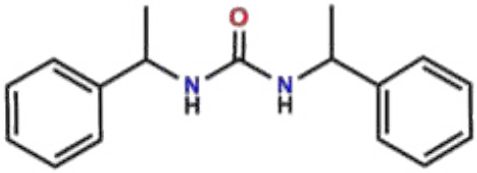
After exploring aliphatic urea formations, we shifted our focus to the synthesis of aromatically substituted ureas. The one-pot nickel-catalyzed oxidative carbonylations of amines were performed under the conditions previously described. In this series of experiments, propylene carbonate was employed as the carbonyl source, and the substrate was reacted with various aromatic amine nucleophiles. This sequence produced the associated isocyanate intermediate, which was then further processed to yield symmetric urea products. The results for the aromatically substituted urea products are detailed in **Scheme 4**.

In general, the yields for these urea products were fair to good, ranging from (**6b**, **47**) to (**6g**, **346**). The TONs for the aromatically substituted urea products were typically lower than those observed for alkyl substituted ureas. However, when compared to the TONs of their corresponding isocyanate products (as shown in **Scheme 2**), the aromatically substituted urea products had slightly higher values. It's noteworthy that a modest yet significant conversion was observed for the branched product, 1,3-bis(1-phenylethyl)urea (**6b**, **47**). A significant TON conversion was also noted for 1,3-dibenzylurea (**6a**, **202**). The highest TON was for 1,3-bis(3-phenylpropyl)urea (**6g**, **346**), while the lowest was for 1,3-bis(1-phenylethyl)urea (**6b**, **47**).

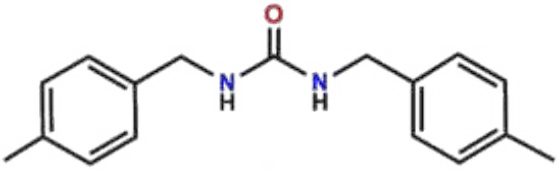




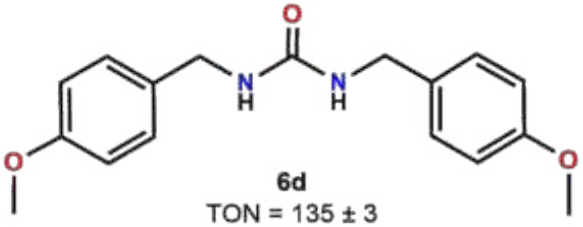
6a
TON = 202 ± 3
GC yield = 41%



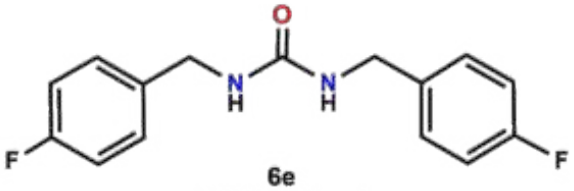
6b
TON = 47 ± 5
GC yield = 9%



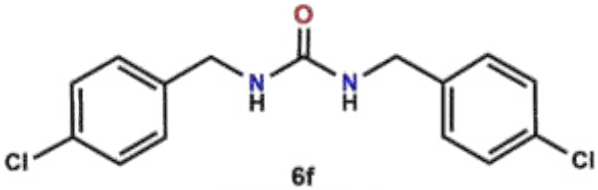
6c
TON = 102 ± 4
GC yield = 20%



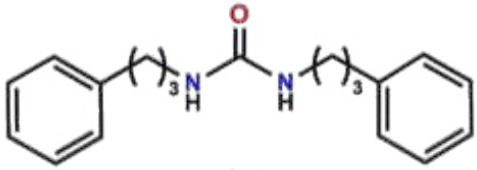
6d
TON = 135 ± 3
GC yield = 27%



6e
TON = 104 ± 4
GC yield = 21%



6f
TON = 74 ± 5
GC yield = 15%



6g
TON = 346 ± 4
GC yield = 69%

Scheme 4. Summary of urea products formed via propylene carbonate sourced carbonyls oxidatively added to various aromatically substituted amines. Conditions: Reactions were carried out with **2** (2 mg, 3.42×10^{-3} mmol), Cs_2CO_3

(100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), amine (500 eq, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for TON analysis was n-decane (25.0 µL, 1.28 x 10^{-4} mol).

2.7. Kinetics

The formation rates of isocyanatohexane in relation to the measured quantities of propylene carbonate, hexylamine, catalyst (**2**), and Cs_2CO_3 were individually examined. Each investigation involved adjusting the quantity of one starting material while keeping the amounts of the other three reagents consistent with the optimized reaction conditions. The reaction duration was consistently set at 2 hours. The reaction temperature was maintained at 25 °C. The presented data reflect the TON values across the entire 120-minute reaction period.

Initially, TON values were determined by adjusting the concentration of propylene carbonate between 1.66 and 3.39 M. Subsequently, the concentration of hexylamine was varied within the same range to obtain its TON values. In the third set of experiments, the concentration of the nickel(II) complex (**2**) was adjusted between 1.22 and 3.67 mmol to determine its TON values. Finally, by altering the concentration of the base cesium carbonate (Cs_2CO_3) between 0.244 and 0.489 mol, respective TON values were gathered. Graphical representations of these findings, plotting the logarithm of the rate against the logarithm of the concentration, are displayed in **Figure 4**.

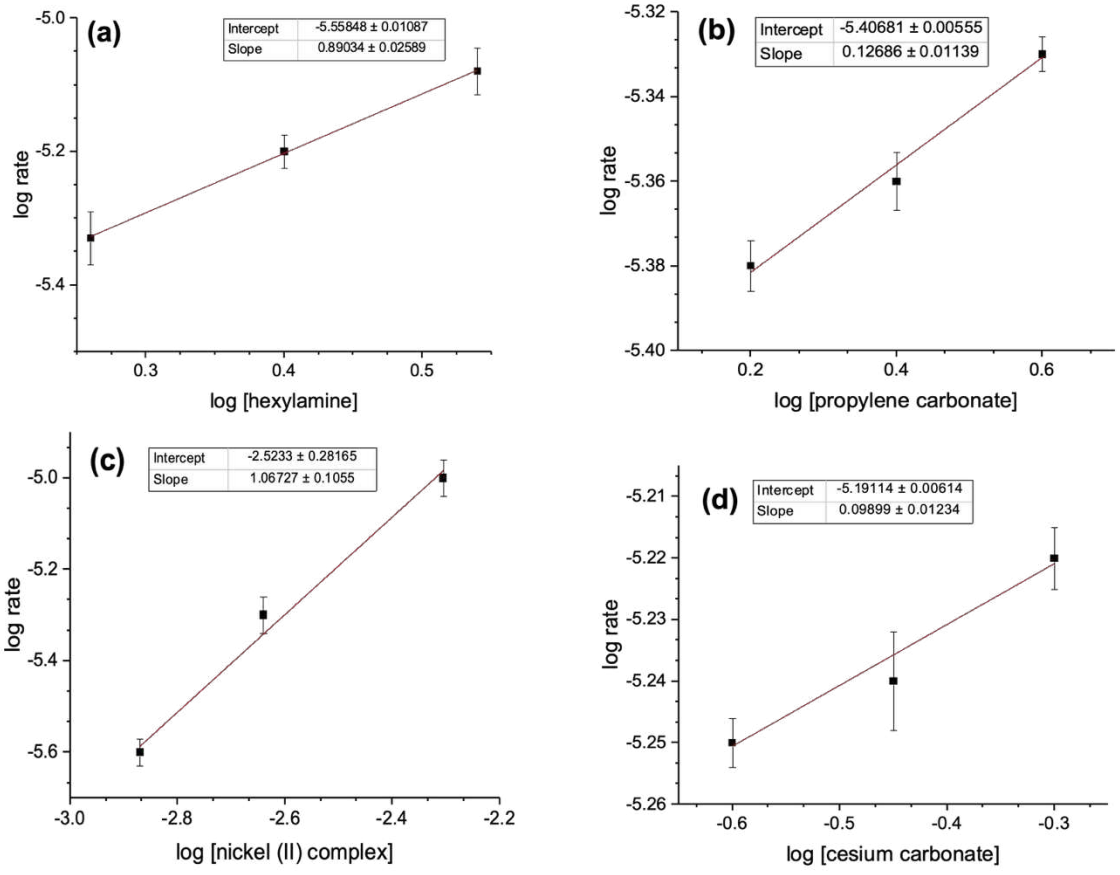


Figure 4. Plots of log rate of isocyanatohexane formation as a function of maintaining concentrations of other starting materials. (**a**) Log rate versus varying log [hexylamine], maintaining all other concentrations constant. (**b**) Log rate versus varying log [propylene carbonate], maintaining all other concentrations constant. (**c**) Log rate versus varying log [nickel(II) complex], maintaining all other concentrations constant. (**d**) Log rate versus varying log [cesium carbonate], maintaining all other concentrations constant. Conditions when maintaining concentrations: **2** (2 mg, 3.42 × 10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), hexylamine (500 eq, 225 µL, 1.71 mmol) in DMSO (1.0 mL). Duplicate trials were run. The internal standard used for yield analysis was n-decane (25.0 µL, 1.28 x 10^{-4} mol).

By applying differential rate laws, the order of each starting material can be deduced from the slope of the respective plots. For the base (Cs_2CO_3) and the carbonyl source (propylene carbonate), the reaction order appears to be zero, as indicated by a slope nearly equal to zero. In contrast, for the amine (hexylamine) and the catalyst **(2)**, the reaction demonstrates first-order behavior, as reflected by a slope close to one. This indicates that the system is of second order overall. These findings align with literature values previously reported for other nickel-catalyzed reactions[81].

2.8. Proposed Mechanism

Based on the above observations we have tried to elucidate the mechanistic pathway of isocyanate and urea formation catalyzed by the nickel(II) pincer complex **(2)**. The nature of Ni having wide span of oxidation states from Ni^0 to Ni^{IV} plays an important role in the catalytic cycle[82]. The formation of a divalent nickel (II) complex **(2)** potentially occurs in the presence of two deprotonated σ-donating amides of the ligand **(1)**[83–88]. Yet, given that catalyst **(2)** was synthesized using n-butyllithium, the catalyst **(2)** is expected to better mediate reactions in the presence of Li^+. Due to its small size, Li^+ can coordinate to donor oxygen atoms. It is plausible that catalyst **(2)** contains imine-type bonding within its structure, suggesting that the amide bonds in **(2)** could be in imine form. Such structures have been previously described in literature[89]. Past studies have offered NMR evidence for such structures, possibly arising from ligand asymmetry[90].

UV-vis spectroscopy was utilized to examine the interactions between complex **(2)** and various substrates and starting materials in DMSO. **Figure 5** depicts the changes in absorbance when the nickel(II) complex **(2)** is combined with different starting materials. Alone, the catalyst **(2)** exhibits an absorption onset at 550 nm, a shoulder at 500 nm, and peak absorption at 450 nm. Upon mixing with propylene carbonate, the absorbance curve closely mirrors the UV-Vis spectrum of the catalyst **(2)** on its own, suggesting no immediate interaction between **(2)** and propylene carbonate. Nonetheless, the combined absorbance curve with propylene carbonate and **(2)** shifts to a shorter wavelength, peaking at 440 nm. This shift is likely due to the solution's dilution by propylene carbonate. When the amine is introduced to the nickel complex **(2)**, the absorbance peak drastically moves to a shorter wavelength, and the shoulder vanishes, signaling a robust interaction between the amine and catalyst **(2)**. Incorporating the base Cs_2CO_3 into catalyst **(2)** results in a modest alteration of the UV-Vis spectrum, leaning towards the IR region. Absorption begins at 550 nm, peaking at 500 nm. A noteworthy observation is the UV-Vis spectrum's modification upon the addition of the base, a pivotal step in the catalytic process. It is postulated that the sterically hindered base converts the Ni (II) in catalyst **(2)** to a low-valent nickel(I)[91]. Additionally, no absorption in the visible spectrum is detected for either hexylamine or propylene carbonate.

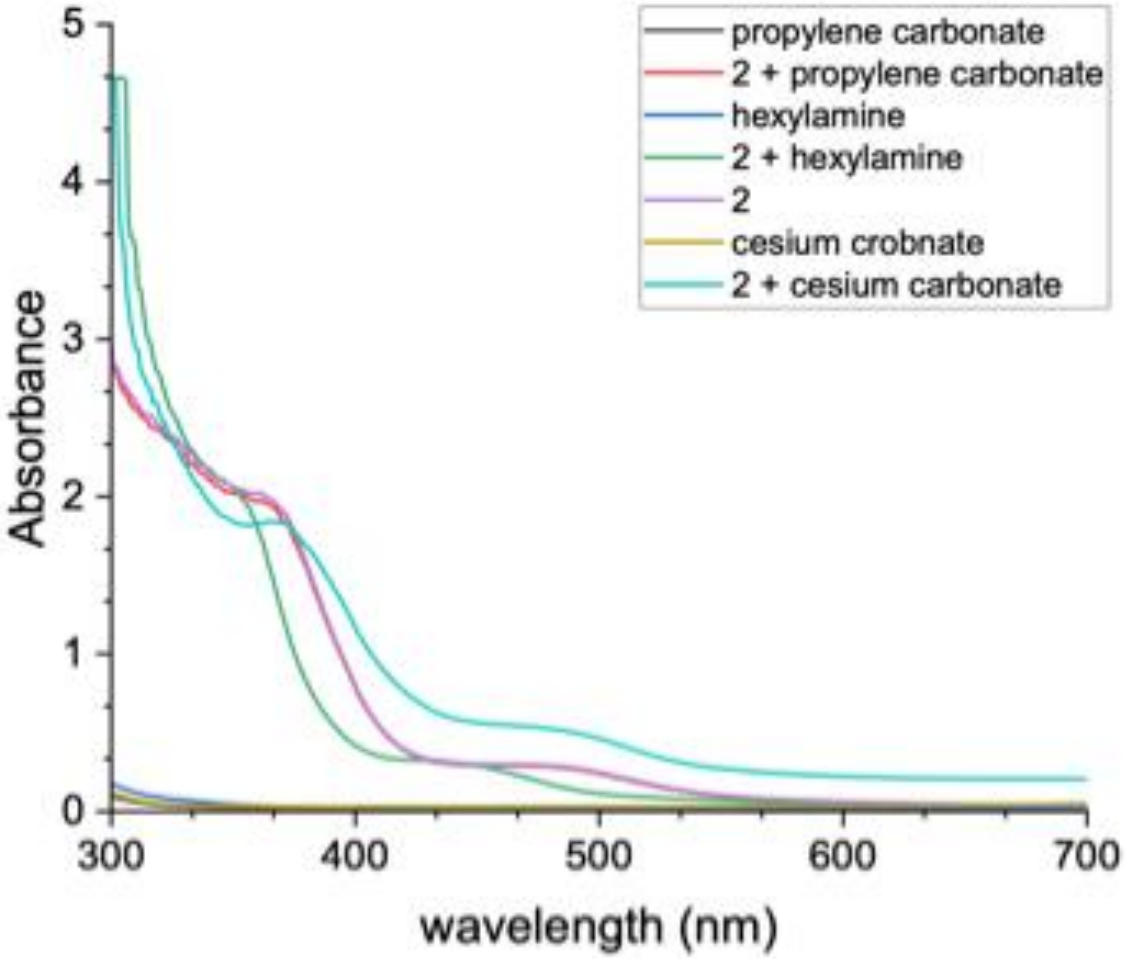


Figure 5. UV-vis studies for **(2)** and various starting materials for isocyanate formation. Conditions for reagents: **2** (2 mg, 3.42×10^{-3} mmol), Cs_2CO_3 (100 eq, 112 mg, 0.342 mmol), propylene carbonate (500 eq, 146 µL, 1.71 mmol), hexylamine (500 eq, 225 µL, 1.71 mmol) in DMSO (1.0 mL).

The proposed mechanism for our process begins with the amine playing a dual role: it primes the nickel catalyst **(2)** for reactivity and serves as an initial reductant. This facilitates the displacement of the chloride ligand, allowing an amine to coordinate and form an ammine-nickel complex. Upon oxidative addition, the propylene carbonate undergoes ring-opening. Concurrently, the initially coordinated amine is expelled, leading to the formation of an acyl alkoxy nickel (III)complex.

Subsequently, a proton transfer takes place from the amine nucleophile to the oxygen that was liberated during the ring-opening of propylene carbonate. Following this proton transfer, an intramolecular rearrangement occurs, wherein the amine nitrogen attacks the carbonyl carbon derived from the propylene carbonate. This results in the generation of another acyl nickel(III) intermediate, but with an alkoxy ligand now attached. The process culminates in reductive elimination, during which a new propylene carbonate molecule integrates into the catalytic cycle, and 2-methylethane-1,2-diol and the desired isocyanate are simultaneously formed. At elevated temperatures, the generated isocyanate further reacts with available amines to yield urea derivatives. The entirety of this catalytic sequence is represented in **Figure 6**.

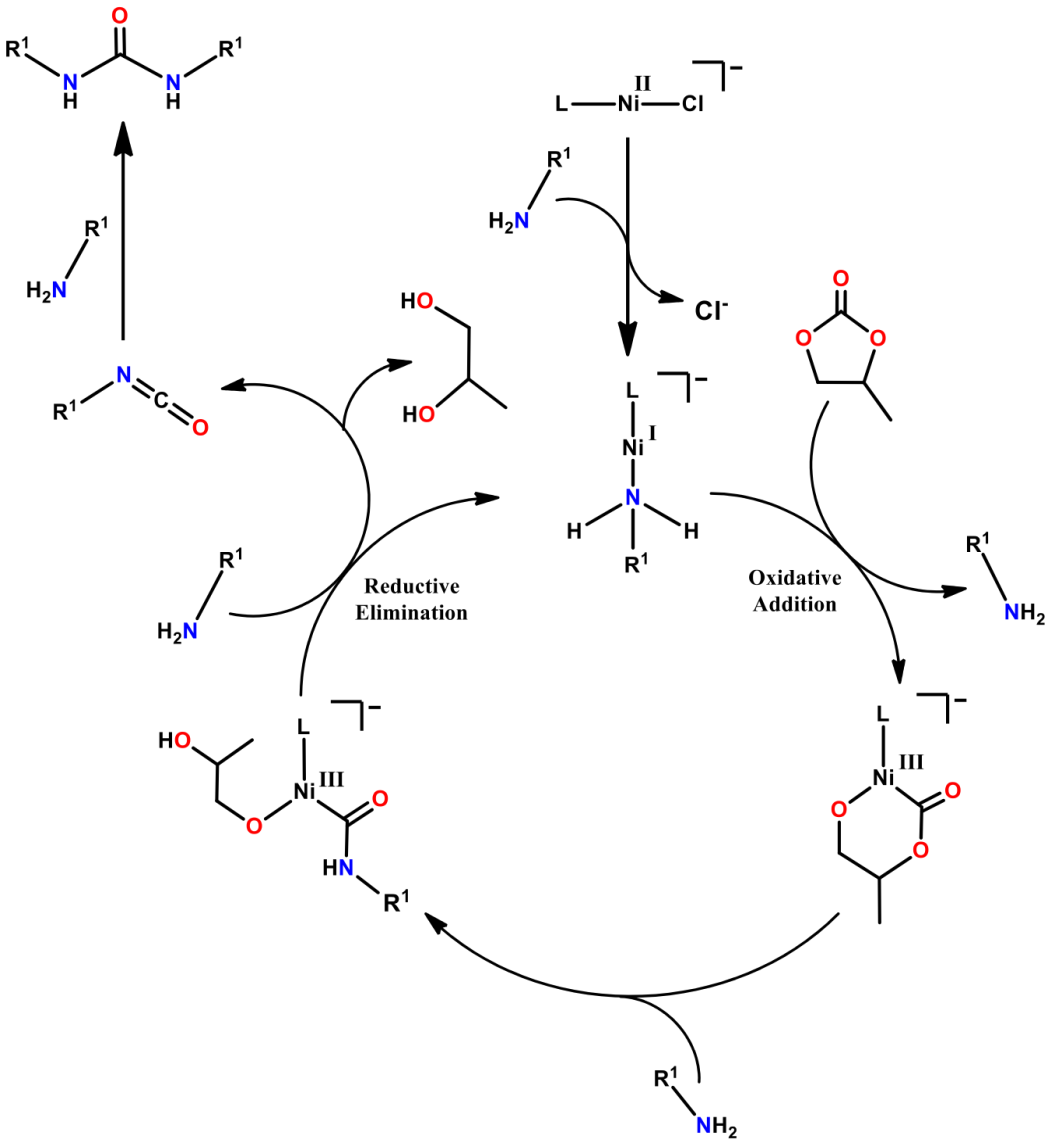


Figure 6. Proposed mechanism in the scope of isocyanates leading to urea formation.

3. Conclusion

This study demonstrates, and reports for the first time ever, a new synthesis route for isocyanates and ureas via oxidative carbonylations of amines from carbonyls sourced from cyclic carbonate catalyzed via a nickel(II) pincer catalyst (**2**). This distinctive pincer ligand-based nickel(II) complex (**2**) significantly improves catalytic efficiency, enabling the formation of numerous complex products. Without this catalyst, these products do not form, and even with the catalyst alone, product formation is minimal, highlighting the necessity of optimized conditions (base, solvent, temperature, and time). Kinetic studies show a second-order reaction behavior, with zero order for base and propylene carbonate, and first order for the nickel(II) complex and amine. The research also proposes a mechanistic cycle, giving insight into the catalytic pathway. Comprehensive GC-MS analysis confirms significant yields of isocyanate and urea products. The study indicates that the best results are achieved within the first 60 to 180 minutes of the reaction, with 32 different products identified. Alkyl-substituted amines generally show better reactivity

than aromatic ones. The calculated TONs for the isocyanate products ranged from moderate (**4g**, **16**) to good (**4d**, **277**), and for the urea products, from moderate (**6b**, **47**) to good (**6g**, **346**).

4. Experimental

4.1. Instrumentation, Materials and Methods

The chemicals used were purchased from, Alfa Aesar (Haverhill, MA, USA), Fischer Scientific Company (Waltham, MA, USA), Sigma-Aldrich (St. Louis, MO, USA), and VWR International (Radnor, PA, USA). Reagents were purified when and as needed. Argon (Ar) and nitrogen (N_2) were purchased from Air Gas. Solvents (SureSeal) were used as obtained and purged with Ar or N_2 after each use. Amine reagents (liquid) were passed through activated alumina columns and were subjected to Ar purge treatment prior to and after each use. Propylene carbonate was contained inside a SureSeal container and purged with Ar prior to and after use. ^{1}H NMR and ^{13}C NMR were recorded using a multi-nuclei JEOL 400 NMR. Electrospray ionization mass spectra (ESI-MS) was obtained using Agilent 100 series MSD VL. Gas chromatography/mass spectrometry (GC-MS) was used to analyze the isocyanate product conversions. The GC-MS used was a Shimadzu QP2010 Plus and Shimadzu QP2010 *ultra* electron ionization (EI) detection system. The stationary phase consists of a 30-meter DB-5 non-polar column and He gas is used as the carrier gas. Other GC-MS parameters to note include injection temperature (250°C), injection volume (1.0 μL), and run-time (37.5 minutes). Ultraviolet-visible spectra were obtained using a Perkin Elmer Lambda 365 UV-Vis. FT-IR spectra were obtained using a Thermo Fisher Scientific Nicolet 6700.

The internal standard method was used to calculate turnover numbers (TON) for the converted isocyanate products according to previously reported procedure[72]. The internal standard used was n-decane. Areas under the curve integrations of the internal standard peaks and target product peaks were ratioed and a dilution factor was applied to calculate the number of moles of product formed in the reaction mixture. TON was then calculated from the quotient of total moles of formed products and total moles of catalyst used. TON indicates the number of chemical conversions from the substrate added to the chemical reaction. GC yields are provided for a comparison of product formation.

4.2. Synthesis pincer ligand (1)

According to literature[89,92], ligand synthesis was performed under nitrogen (N_2) atmosphere, 2,6-pyridinedicarbonyl dichloride was dissolved in dichloromethane (DCM) and added dropwise to a solution of 2,6-diisopropylaniline and triethylamine (Et_3N). The reaction mixture was stirred and refluxed at 50 °C for six hours. The organic product remained in DCM and washed with aqueous solutions of 5% sodium bicarbonate ($NaHCO_3$) followed by 3% hydrochloric acid (HCl). Sodium sulfate (Na_2SO_4) was used to remove any remaining water in the DCM mixture prior to vacuum filtration. The solvent was then removed by roto-evaporation and the precipitated white solid was recovered. The product was recrystallized using hexanes. The resulting product was further dried overnight under negative pressure. After collecting the product, a white flaky solid residue was collected. The mass was recorded at 687 mg calculating an 87% yield. Characterizations for the ligand product **(1)** were performed via FT-IR, ^{1}H NMR and ^{13}C NMR.

4.3. Synthesis of nickel(II) complex (2)

According to literature[89,92,93], metalation of ligand was performed under N_2 atmosphere. **(1)** was dissolved in tetrahydrofuran (THF) and solution temperature was reduced to 0 °C. N-butyllithium (2.1 mol eq) was then slowly added to solution mixture. Maintaining the temperature, nickel(II) dichloride glyme ($C_4H_{10}Cl_2NiO_2$) (1.1 mol eq) was added to reaction mixture 15 minutes after addition of base. Low temperature was further maintained as the reaction mixture stirred overnight. A liquid nitrogen cold trap was used for solvent removal and resulting solid was dried under negative vacuum pressure. After collecting the fine wine-red powder product, the mass was recorded at 771 mg calculating a 93% yield. Characterizations for the nickel(II) pincer complex **(2)** were performed via ESI-MS negative mode and FT-IR. It is believed that the chlorometallated form (**2)** may get converted to hydroxymetallated catalyst in the presence of moisture, which could also exhibit catalytic activity[93,94].

4.4. General synthesis of isocyanates and ureas

C-N cross coupling reactions were performed in duplicate trials. Mixing of amines and propylene carbonate depended on target product and accomplished in a one pot process. The Ni(II) complex **(2)** (2 mg, 3.42 x 10^{-3} mmol) was weighed and added to a dry pyrex test tube then dissolved in anhydrous DMSO (1.0 mL) transferred to the test tube with a gas-tight syringe. All ensuing molar equivalents (eq's) for remaining starting materials were calculated from the initial molar amount of **(2)**. In sequence, cesium carbonate (Cs_2CO_3) (100 eq, 112 mg, 0.342 mmol) followed by the propylene carbonate (500 eq, 146 µL, 1.71 mmol) and corresponding amine (500 eq, 1.71 mmol) starting reagents were added to complete the final reaction mixture. The reaction mixture stirred at room temperature (r.t.) for 2 hours to produce isocyanate products. The reaction mixture stirred at 100 °C for 3 hours.

After the reaction was complete, the mixture was filtered through Celite® to remove any solid residues before preparing the sample for post-reaction analysis using GC-MS. A portion of the filtered reaction mixture (100.0 µL) was transferred to a GC-MS sample vial. An internal standard of n-decane (25.0 µL, 1.28 x 10^{-4} mol) was added, and the sample was then diluted with DCM to achieve a total volume of 1.50 mL. Subsequent to the GC-MS analyses, quantitative evaluations were conducted based on the peak area integrations of the standard n-decane and the desired isocyanate products.

5. Declarations

5.1. Acknowledgements

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2P20GM103429-19. P.S. and R.S.K. would also like to thank the UA-Little Rock Signature Experience for partially funding the research.

5.3. Author Contributions

A.G. conceived the research idea, designed the experiments, and contributed to interpreting the data and establishing the reaction mechanism. P.S. wrote the manuscript, performed and/or supervised each experiment, and contributed to interpreting the data and establishing the reaction mechanism. R.S.K, contributed to performing the experiments and interpreting the data. A.G., and P.M. contributed to writing the manuscript and P.M helped with interpreting some of the data and establishing the mechanism. All authors have read and agreed to this version of the manuscript.

5.4. Competing Interests

The authors declare no conflict of interest.

5.5. Clinical Trial Consent

This section is not applicable to this work.

5.6. Ethics Approval

This section is not applicable to this work.

5.7. Consent to Participate

This section is not applicable to this work.

5.8. Consent to Publish

This section is not applicable to this work.

5.9. Data Availability

The data described in this work can be freely and openly accessed on ***Figshare*** under 10.6084/m9.figshare.29579318.v1 and https://doi.org/10.6084/m9.figshare.29554619.v1. Additional data is contained in the Supplementary Information.

5.10. Code Availability

This section is not applicable to this work.

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