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Nickel Complex Catalyzed Efficient Activation of sp^3 and sp^2 C–H Bonds for Alkylation and Arylation of Oxygen Containing Heterocyclic Molecules

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Abstract A nickel(II) complex (**1**) of *N*,*N*′-bis(2,6-diisopropylphenyl)-2,6-pyridinedicarboxamido (**L**) ligand was examined for catalytic coupling of Grignard reagents with the C–H bond of oxygen containing heterocyclic compounds such as tetrahydrofuran and furan. The nickel(II) complex showed excellent activity in catalyzing C–H activation and further coupling with various Grignard reagents. The effective activation of the C–H bond proceeded under ambient reaction conditions with a short reaction time (1–2 h). The catalyst (**1**) displays high turnover frequency of 4,130 h^{-1} with catalyst loading as low as 0.01 mol%. This catalytic route could prove to be an efficient mode of activation of sp^3 and sp^2 C–H bonds in various heterocycles for the preparation of synthetically and pharmaceutically relevant molecules.

Keywords Nickel(II) complex · Oxygen containing heterocyclics · Grignard reagents · sp^3 and sp^2 C–H bond activation

1 Introduction

Cross coupling reactions resulting in the formation of new C–C bonds have been an important part of synthetic chemistry. Since the first discovery of C–H bond activation by transition metal in the 1960s [1], a significant amount of research has been done on transition metal catalyzed C–H bond activation [2–8] and cross coupling reactions by various research groups [11, 12] for the synthesis of different molecules including natural products [9, 10]. A great deal of research on C–H bond activation since the 1980s involved thermodynamic and kinetic investigations, along with intermediate isolation has resulted in a greater understanding of the mechanism [3–26].

Based on the use of different coupling partners, multiple methods have been developed using various organic nucleophiles and electrophiles [27, 28]. As a mode of formation of new C–C bonds, cross coupling reactions generally employ compounds with functionalities such as C–X (X = Halogen) bonds or C–H bonds which require costly and wasteful pre-activation for further functionalization. However, the direct and selective activation of C–H bonds, which is the most abundant functionalizable bond in organic molecules, is still challenging and a major area of interest in the recent decades. Especially activation of sp^2 and sp^3 C–H bonds in heterocyclic molecules has generated much interest in recent years, owing to their wide range of applications in the pharmaceutical industry [9, 10]. Direct activation of C–H bonds using transition metals catalysts [2–8] can serve as a more efficient way to facilitate organic transformations, limiting the dependence on organic nucleophiles [29, 30] and at the same time expanding the scope of various organic compounds [31].

The selective and effective C–H bond activation using transition metals for direct catalysis of alkylation has been generally dependent on the use of directing groups contained in the compound [32]. The alkylation resulting from these activations is generally an ortho-alkylated product. Many of the previously reported C–H activations and direct alkylation methods employ a sp^2 C–H bond using various transition metals [33–35]. The activation of sp^3 C–H bond

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is very complex, hence reports are limited [36–39]. This complexity may be a result of sp^3 C–H bond's lack of π orbitals to interact with the metal center, resulting in a kinetic advantage for the sp^2 C–H bonds. This makes sp^3 C–H bond more difficult to activate over sp^2 and sp C–H bonds. However, sp^3 C–H bonds adjacent to the heteroatom are weaker than the simple sp^3 C–H bonds of an alkane. Taking advantage of this, Murai et al. activated the C–H bond in pyrrolidine and piperidine using a $Ru_3(CO)_{12}$ complex for coupling with unactivated alkenes [40]. Since then the presence of an α–heteroatom for sp^3 C–H activation has become an essential configuration for such reactions.

Various nucleophiles such as alkyl halides [41–45], olefins [46, 47] and organometallic reagents such as alkyl [48] or aryl [48–50] boronic acid, organotin, Grignard reagents [33] etc. have been employed for cross coupling reactions. Though Grignard reagents have been used for C–C coupling reactions, their use as nucleophiles for coupling with a C–H bond has not been applied to a large extent. The use of iron(III) acetylacetonate, along with zinc chloride ($ZnCl_2$) and tetramethylethylenediamine (TMEDA) for C–H bond transformation of benzoquinoline and phenylpyridine derivatives with Grignard reagents leading to the formation of a $C(sp^2)$–$C(sp^3)$ bond, is one such example [51]. Use of cobalt(III) acetylacetonate with TMEDA for similar transformation [33], using Grignard reagent as coupling partner, further widened the scope of 1st row transition metals for such reactions. Use of a nickel catalyst for the alkylation of a sp^2 C–H bond of N-aromatic heterocycles using Grignard reagents was also developed [52]. More recently, Lei and co-workers reported oxidative coupling of sp^3 C–H bonds of oxygen and nitrogen containing heterocycles with arylboronic acids for $C(sp^3)$–$C(sp^2)$ bond formation using Ni(II) acetylacetonate along with triphenylphosphine as catalyst [53]. This motivated the development of nickel complexes for such C–H activation and functionalization reactions with Grignard reagents.

Here, we report in detail, the catalytic activation of a sp^3 C–H bond of a heterocyclic molecule THF and its coupling with various aryl and alkyl Grignard reagents using nickel(II) complex (**1**) (Fig. 1). The present study uses a pincer ligand based on a diamidopyridine ligand (**L**, N2, N6-bis(2, 6-diisopropylphenyl)pyridine-2,6-dicarboxamide). The synthesis and characterizations of the nickel and ruthenium complexes using the deprotonated form of the ligand (**1**) was reported by Wasilke et al. [54], which were used for ring closing metathesis reaction. Recently, we employed the complex **1** for the efficient catalytic reaction of polychlorinated molecules with various Grignard reagents under ambient reaction conditions [55]. Apart from this, the nickel complexes of the ligand (**L**), and analogous ligands have been reported for the effective reaction with carbon dioxide and other small molecules or ligands [56, 57].

The uniqueness of the present research work is that to the best of our knowledge this is the first example of a nickel based catalyst, which is capable of catalyzing C–C cross-coupling reactions involving various aryl or alkyl Grignard reagents and a sp^3 C–H bond in oxygen containing heterocyclic molecules. In this work we present cross coupling reaction for the formation of different type of C–C bonds, namely $C(sp^3)$–$C(sp^3)$, $C(sp^2)$–$C(sp^3)$ and $C(sp^2)$–$C(sp^2)$. These reactions were carried out under ambient reaction conditions within short period of time. The C–H bond activation and subsequent coupling with Grignard reagents were selective towards the second position (C atom adjacent to the hetero atom) of the heterocyclic molecule. Similar activation of α sp^3 C–H bond of cyclic aliphatic ethers using iron catalyst for direct arylation/alkylation at α-position has been reported recently [58]. Catalyst **1** showed high efficiency with TOF, as high as 4,130 h^{-1} at a considerably low catalyst loading of 0.01 mol%. Such high catalytic activity is the highest for such cross-coupling reactions. Beside THF, dioxane and 2-methyltehrahydrofuran were also used to the alkylation process. Interestingly, **1** was also used to activate sp^2 C–H bond in heterocyclic ethers (e.g. furan) and was successfully coupled with Grignard reagents. The catalytic system described here could potentially be applied to the efficient activation of both sp^3 and sp^2 C–H bonds for the synthesis

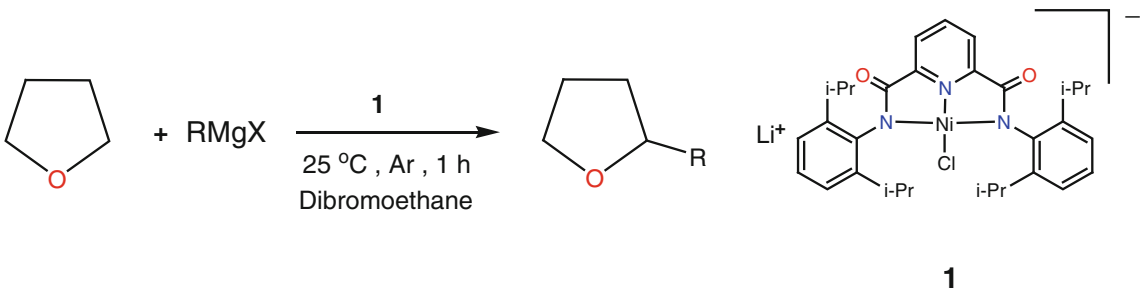


Fig. 1 Use of Grignard reagents for the synthesis of 2-substituted tetrahydrofurans using a nickel(II) pincer catalyst (**1**)

of various 2-substituted oxygen containing heterocyclic molecules which have synthetic and pharmaceutical importance.

2 Experimental

2.1 Materials and Methods

All the chemicals and solvents were obtained from Aldrich Chemical Co., USA and Fisher Scientific Company, USA. Chemicals were used as obtained without further purification unless otherwise stated. Tetrahydrofuran (THF), furan and dibromoethane were purified according to the literature procedure [59]. Electrospray ionization mass spectra (ESI–MS) were obtained using an Agilent 100 series MSD VL spectrometer. Gas chromatography mass spectra (GC–MS) were obtained using an Agilent technologies 6890N network GC system equipped with an Agilent Technologies 5975 inert XL mass selective detector. Ultraviolet visible spectra (UV–Vis) were recorded using a Varian Cary 5000 UV–Vis–NIR spectrophotometer.

2.2 Synthesis of Nickel(II) Complex (**1**)

The nickel(II) complex (**1**) was synthesized following the previously reported literature method [55]. Ligand *N*2,*N*6-bis(2,6-diisopropylphenyl)pyridine-2,6-dicarboxamide (**L**) was deprotonated using *n*-butyllithium in cool (0 °C), dry THF under a nitrogen atmosphere followed by the addition of solid anhydrous dimethoxyethane adduct of nickel(II) chloride, yielding the deep red nickel(II) complex (**1**) (Fig. 1). **1** was characterized by ^{1}H NMR, ESI–MS, FT–IR, UV–Vis, and elemental analysis. Detailed synthesis and characterization methods are described in our previous work employing **1** [55]. The complex (**1**) is an ionic compound with lithium (Li^{+}) as the counter cation.

2.3 Cross Coupling of Tetrahydrofuran with Grignard Reagents

Owing to the small amount of catalyst needed (0.1–1.0 mg), a stock solution of 1 mg mL^{-1} of **1** in THF was prepared and used accordingly. Phenylmagnesium chloride in THF (25 %) was used for all initial optimization reactions unless otherwise specified. Cross coupling reactions of Grignard reagents with tetrahydrofuran were performed according to the following general method.

Catalyst **1** (0.1 mg, 0.174 μmol) in 0.1 mL THF was added using a gas-tight syringe to a 5 mL round bottom flask purged with Ar. To this solution, phenylmagnesium chloride in THF (0.5 mL, 0.92 mmol) was added. Total volume of the solution was made up to 3.5 mL by adding additional THF. Dibromoethane (90 μL, 1.04 μmol) was added to the reaction mixture. Samples were collected for analysis after 1 h. At the end of the reaction, excess Grignard reagent was destroyed using methanol (1 mL) and the reaction products were analyzed by GC–MS using either by comparing with commercially available compounds or an internal standard (2-methyltetrahydrofuran) to quantify product formation. Product yields were reported in turnover number (TON; moles of product formed per mole of catalyst used) and turnover frequency (TOF; moles of product formed per mole of catalyst in unit time).

2.4 Cross Coupling of Other Oxygen Containing Heterocyclics with Grignard Reagents

Cross coupling reactions of Grignard reagents with other heterocyclics such as furan and methyl-tetrahydrofuran were performed according to the following general method.

Catalyst **1** (0.1 mg, 0.174 μmol) in 0.1 mL ether was added using a gas-tight syringe to a 5 mL round bottom flask purged with Ar. To this solution, phenylmagnesium chloride in diethyl ether (0.92 mmol) was added. Total volume of the solution was made up to 3.5 mL by adding additional THF. Dibromoethane (90 μL, 1.04 μmol) was added to the reaction mixture. Samples were collected for analysis after 1 h. At the end of the reaction excess Grignard reagent was destroyed using excess methanol (1 mL), and the reaction products were analyzed by GC–MS using an internal standard to quantify product formation. Similarly product yields were reported in TON and TOF.

3 Results and Discussions

Initial studies to optimize the reaction conditions were carried out using varying amounts of catalyst **1** required for catalyzing the reaction of phenylmagnesium chloride (0.5 mL, 0.92 mmol) with THF. As seen in entry 1, Table 1, in the absence of **1**, only trace/no amount of phenyl substituted tetrahydrofuran was observed. However with the addition of just 0.05 mg (0.087 μmol, 0.01 mol%) of **1**, 39 % of the phenylmagnesium chloride coupled up with THF giving a TOF of 4,130 h^{-1}. A maximum yield of 66 % with a TOF of 3,490 h^{-1} was obtained when 0.1 mg (0.174 μmol, 0.02 mol%) of nickel(II) complex was used. As seen in the entry 3–5 in Table 1, the yield of phenyl tetrahydrofuran decreased as the amount of catalyst was increased. This resulted in a dramatic decrease in the TOF of the reaction. Increasing the amount of **1** resulted in an increase of side reactions (such as homocoupling) rather than the desired coupling reaction. It was also observed that a small amount of additive dibromoethane was necessary for the reaction to proceed. As shown in entry 6,

only 14 % product was obtained in the absence of dibromoethane in the reaction. As 0.1 mg of catalyst (0.02 mol% of **1**) gave significant yield as well as TOF, further reactions were carried out using 0.02 mol% of **1** in order to check the effect of the other parameters on the catalysis.

As it was observed that the coupling reaction of the Grignard reagent with THF required dibromoethane in addition to **1**, similar reactions were performed using other additives that have been reported in literature for C–H activation reactions [60]. However additives such as dichloroethane did not yield a significant amount of product (see Supporting information, Table S1). Further optimization of the amount of dibromoethane was performed by using varying equivalents (0–48 eq.; 0–720 μL) of dibromoethane with respect to **1**. Figure 2 shows the increase in yield of phenyltetrahydrofuran, as the ratio of dibromoethane to nickel complex **1** was increased from 0 to 48. As seen in Fig. 2, reaction yield increased from about 54–66 % as the amount of dibromoethane to **1** increased from 3 to 6 equivalents. The addition of 12 equivalents of dibromoethane further increased the yield to 69 %. Further increasing the amount of dibromoethane did not significantly increase the yield of product. Hence 45–90 μL of dibromoethane (which is 3–6 times the amount of **1**) was found to be ideal for the reaction, hence further studies were carried out using these amounts.

The effect of varying amounts of Grignard reagent was also evaluated while maintaining the other parameters constant. The reactions were set up using **1** (0.1 mg, 0.174 μmol) and 90 μL (6 eq. with respect to **1**) of dibromoethane at room temperature for 1 h. Varying amounts of phenylmagnesium chloride in THF 0.1–2 mL (0.184–3.68 mmol) were added to the reaction. As seen in the Fig. 3, the percent (%) yield increased form 59 to 70 % when the amount of Grignard reagent was increased from 0.184 to 0.46 mmol (from about 1,000 to 2,500 eq. with respect to the catalyst **1**). Increase in the Grignard reagent to 0.5 mL (0.92 mmol, 5,000 eq. to **1**) decreased the yield slightly to 66 %. Further increasing the amount of Grignard reagent lead to subsequent decrease in the yield of desired product. This may be due to the increased Grignard reagents concentration resulting in side reactions such as homocoupling reactions.

Reactions were additionally carried out to check for the effect of temperature on the yield and the selectivity of the coupling reaction towards the product. Reactions were set up using **1** (0.1 mg, 0.174 μmol) and phenylmagnesium chloride in THF (0.5 mL, 0.92 mmol) and dibromoethane (45 μL, 0.52 μmol) and (90 μL, 1.04 μmol) at various reaction temperatures ranging from −15 to 70 °C. The increase in temperature, as expected, resulted in a faster reaction with higher yields of phenyltetrahydrofuran obtained within 5 min of the reaction time. The reaction yield and turnover number (TON) in 5 min increased from a mere 5 % and 265 at −15 °C to about 37 % yield and 1960 at 70 °C using 3 eq. of dibromoethane. Similar trends were also observed in reactions employing 6 eq. of dibromoethane, with a maximum yield of 43 % at 70 °C. Different reaction temperatures showed little or no selectivity of the substituted THF over the undesirable homocoupled product (Fig. 4).

To assess the generality of the reaction, this protocol of direct C–H alkylation was extended to a range of aryl Grignard reagents. As seen in entry 1 and 2 in Table 2, the

Table 1 TOF of the reactions with different substrate to catalyst ratio

Entry	Catalyst 1 (mol%)	Dibromoethane (μL)	Yield (%)	TOF (h^{-1})
1	0.0	90	Trace	–
2	0.01	90	39	4,130
3	0.02	90	66	3,490
4	0.1	90	49	520
5	0.2	90	44	230
6	0.01	0	14	740

25 % Phenylmagnesium chloride in THF (0.5 mL, 0.92 mmol), dibromoethane (90 μL, 1.04 μmol) at room temperature. Reaction time 1 h. Yield (%) is the percent of phenylmagnesium chloride coupled with THF

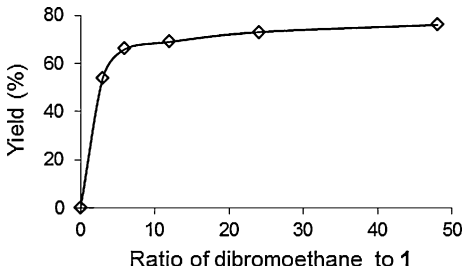


Fig. 2 Effect of ratio of dibromoethane to catalyst **1** on the coupling reaction. **1** (0.1 mg, 0.174 μmol), phenylmagnesium chloride in THF (0.5 mL, 0.92 mmol), 25 °C, 1 h

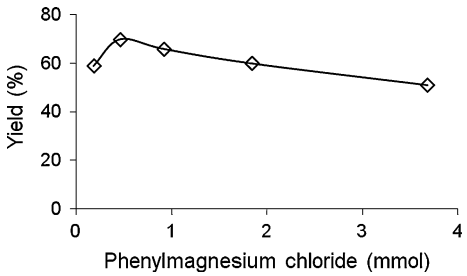


Fig. 3 Effect of amount of Grignard reagent (phenylmagnesium chloride) on the coupling reaction. **1** (0.1 mg, 0.174 μmol), dibromoethane (90 μL, 1.04 μmol), phenylmagnesium chloride in THF (0.1–2 mL), 25 °C, 1 h

use of phenylmagnesium bromide showed slight improvement over its chloride counterpart. However it is worthwhile to note that both of them accounted for very high yield, showing the high reactivity and selectivity of phenyl Grignard reagents for such coupling reactions. Use of phenylmagnesium iodide yielded a similarly high yield of 79 % with a TOF of about 4,180 h^{-1}. Further use of various aryl Grignard reagents with various substituents yielded significantly high yields of the corresponding products. As seen in entry 4, use of 4-bromoanisol yielded 72 % of the coupled product. Using 2-bromoanisol slightly increased the yield to about 78 %. 2-bromo biphenyl also underwent a cross-coupling reaction to the corresponding 2-biphenyltetrahydrofuran product, however the yield was comparatively less which may be due to its bulkier nature.

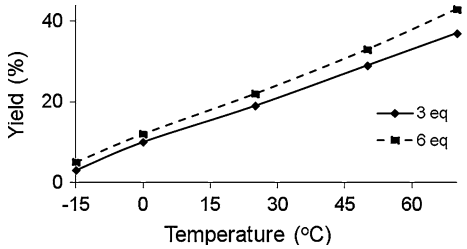
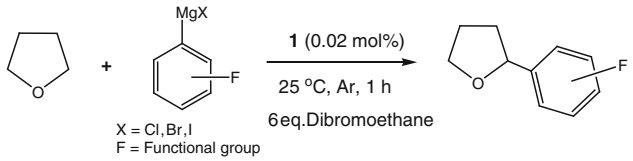
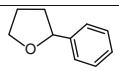
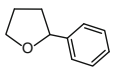
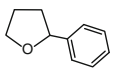
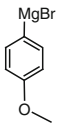
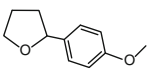
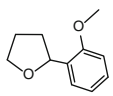
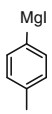
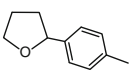
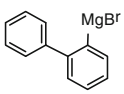
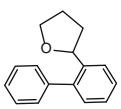


Fig. 4 Effect of temperature (−15 to 70 °C) on the coupling reaction. **1** (0.1 mg, 0.174 μmol), phenylmagnesium chloride in THF (0.5 mL, 0.92 mmol), dibromoethane (3 eq., 45 μL, 0.52 μmol) and (6 eq., 90 μL, 1.04 μmol), reaction time 5 min

The cross coupling of the C–H of THF with various alkyl Grignard reagents were also performed for the successful synthesis of new C–C sp^3–sp^3 bonds. As seen in Table 3, the reaction of THF with alkylmagnesium chloride was found to be less effective comparatively than the aryl Grignard reagents such as phenylmagnesium chloride (entry 2, Table 2). Use of ethylmagnesium chloride (entry 1, Table 3) gave a yield of 47 % in 2 h with a TON of

Table 2 Cross coupling reaction of tetrahydrofuran with various substituted phenyl Grignard reagents



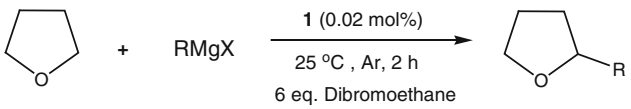
	Grignard reagent	Product	Time (h)	Yield (%)	TON
1			1	82	4340
2			1	66	3490
3			1	79	4180
4			1	72	3810
5			1	78	4130
6			1	80	4240
7			1	54	2862

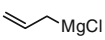
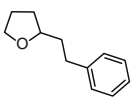
Grignard reagent in THF (0.92 mmol), dibromoethane (90 μL, 1.04 μmol) at 25 °C, 1 h. Yield (%) is percent of Grignard reagent coupled with THF

2,490. Further, the gradual increase in the carbon chain length of the Grignard reagent resulted in a steady decrease in the yield of desired product. As seen in entry 4, use of octylmagnesium chloride yielded a mere 27 % product with a TON of 1,430. Even lower C–H activated product was observed when allylmagnesium chloride was used, with only 12 % of 2-substituted product (entry 6, Table 3). Use of Grignard reagents with a phenyl aromatic ring resulted in better yields with benzylmagnesium chloride and phenyethylmagnesium chloride yielding 51 and 44 % (entries 9 and 10, Table 3) respectively.

Our preliminary observations on the mechanism of the cross-coupling reaction in relation to the formation of the 2-substituted product, suggest that an intermediate alkyl or aryl complex of **1** may be responsible for enabling and/or governing the substrate interactions and the catalytic cycle. Formation or presence of such intermediates in the catalytic cycles have been detected and postulated in various other coupling reactions involving Grignard reagents [61–63]. The presence of this non-transient intermediate was evident in a rapid solution color change upon the addition of various Grignard reagents to a solution of **1** in THF, and is explained in detail in our previous work employing **1** with Grignard reagents [55]. Further confirmation by UV–Vis spectrum indicates a disappearance of the characteristic 404 nm peak of the nickel(II) catalyst (**1**) and the appearance of a new peak at around 450–500 nm (depending upon the Grignard reagent used) (Supporting information, Fig. S12a). The formation of such a non-transient intermediate was also detected using ESI–MS. The butyl intermediate of the nickel(II) complex was detected by the ESI–MS with *m/z* 598.1 (Supporting information, Fig. S12b). The stability of these intermediates was also studied using UV–Vis spectroscopy. The phenyl intermediate for example, formed, through the interaction of **1** with phenylmagnesium chloride showed a persistent peak at 460 nm with minimal decrease in the absorbance over 20 min. However with the addition of dibromoethane to the phenyl intermediate, the catalytic cycle is promoted which is observed by the marked decrease in the peak absorbance (Supporting information, Fig. S13) with respect to time. The peak disappeared within 10 min. Immediate inspection of the reaction mixture using GC–MS reveals the formation of phenyltetrahydrofuran, refuting the assumption that the

Table 3 Synthesis of substituted tetrahydrofurans using various Grignard reagents



	Grignard reagent	Product	Time (h)	Yield (%)	TON
1			2	47	2490
2			2	41	2170
3			2	30	1590
4			2	27	1430
5			2	29	1530
6			2	12	630
7			2	34	1800
8			2	51	2700
9			2	44	2330

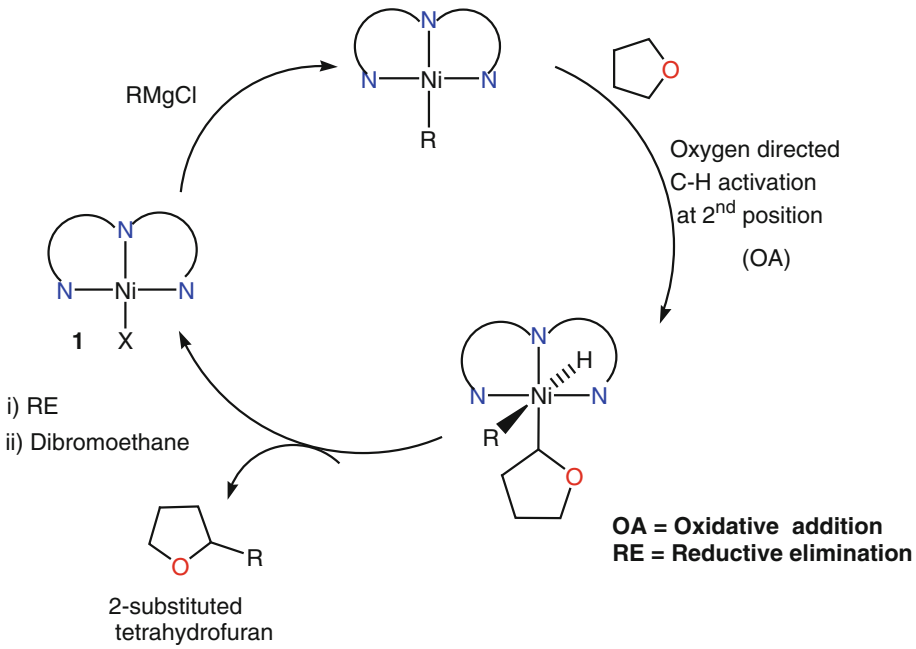
Grignard reagent in diethylether (0.92 mmol), dibromoethane (90 μL, 1.04 μmol) at 25 °C. Reaction time 1–2 h. Yield (%) is percent of Grignard reagent coupled to THF

intermediate degraded by itself or was used up in the formation of other side products.

Nevertheless, the interaction of the nickel(II) complex (**1**) with THF cannot be denied. The interactions of heterocycles with the metal complexes to form an alkylated intermediate resulting in the formation of coupling product are not new, and have been reported earlier. Similar interaction of thiophenes and furans to produce the iron-heteroaryl complexes is one such example [64]. These interactions lead to the activation of α C–H bonds to the heteroatom resulting in 2-substituted products. Thus we presume that the nickel metal center of **1** interacts with Grignard reagent and THF, which upon reductive elimination, results in the substituted THF. α C–H bond in THF is relatively weak (~80 kcal mol^{-1}) and therefore can easily be activated. It is also not unlikely that Grignard reagent may reduce the metal center to lower valency which may facilitates the C–H bond activation. The role of dibromoethane in this reaction is unclear, but it is believed to be required for regeneration of the Ni metal center to its active form (possibly by destroying hydride ligand) to maintain the catalytic cycle. Using such molecules for regeneration the metal center is not new and is in accordance with some previously reported C–H activation work [52]. Presence of bromine in intermediates/side products (e.g. bromobenzene) (Fig. S14, Supporting information) shows that the nickel center does interact with the dibromoethane (only source of bromine in the reaction mixture), which is the only route possible for the incorporation of bromine into the phenyl structure.

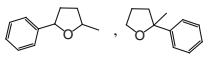
The presence of any free radical mechanism/route in the reaction was checked using a control reaction in the presence of an excess amount of free radical trap TEMPO. No significant reduction in the yield was observed, negating the possibility of radical pathway in the mechanism. Based of these information a possible mechanism of the reaction is proposed in Scheme 1. However, more work is necessary in this context.

The feasibility of using other oxygen containing heterocyclic molecules was also checked for their functionalization using Grignard reagents. Reactions were carried out using similar five and six member ring heterocyclic molecules. 2-methyltetrahydrofuran is one such example where one of the 2 positions is already occupied by a methyl group. Successful C–H activation of the C–H group (5th position) was observed in 2-methyltetrahydrofuran with about 41 % yield (entry 1, Table 4). However the activation was observed in both the α C–H bonds (2 and 5) resulting two products, as observed in the GC–MS (Supporting information, Fig. S16). Use of an unsaturated five member heterocyclic molecule, furan, resulted in 48 % yield of the 2 phenyl-substituted product. The catalyst **1** was successful in catalyzing the coupling of furan with various other alkyl Grignard reagents as seen in Table 4, with the formation of new sp^2(C)–sp^3(C) bonds. The use of butylmagnesium chloride with furan yielded 37 % of butylfuran as product (Supporting information, Fig. S17). Additionally, the catalyst **1** was also successful in the C–H activation in six member heterocyclic molecule 1,4 dioxane. About 61 % yield of the 2 phenyl-substituted product was observed in the GC (Supporting information, Fig. S20), showing the efficiency of the process in selective activation of α sp^3 and sp^2 C–H in oxygen containing



Scheme 1 Proposed reaction mechanism

Table 4 C–H bond activation of different oxygen containing heterocyclics for the cross coupling reaction with Grignard reagents

Entry	Heterocyclic substrate	Grignard reagent	Product	% Yield
1				41
2				61
3				48
4				37
5				40
6				32

Grignard reagent in diethylether (0.92 mmol), dibromoethane (90 μL, 1.04 μmol) at 25 °C. Reaction time 1 h. Yield (%) is percent of Grignard reagent coupled to the oxygen containing heterocyclic molecules

heterocyclic molecules using complex **1**. Interestingly, all the Grignard reagents in the above-mentioned reactions (Table 4) were prepared and used in diethyl ether. However, no cross coupled reaction product involving C–H bond activation of diethyl ether was obtained indicating the selectivity of the catalyst for C–H activation towards cyclic ethers.

4 Conclusion

A nickel(II) pincer complex (**1**) was used for efficient activation of sp^3 C–H bond in oxygen containing heterocyclic molecules particularly in THF. The application of **1** for activation of α sp^2 and sp^3 C–H bonds in other oxygen containing heterocyclic molecules were also examined with successful catalysis. The nickel(II) complex enabled the activation of the C–H bond for cross coupling with various Grignard reagents at room temperature in less than 1 h. The complex (**1**) is the first such nickel based pincer complex which was used in the activation of a sp^3 C–H bond in THF and C–C bond formation by cross coupling reactions with Grignard reagents. **1** has shown excellent reactivity and efficiency with turnover frequency (TOF) of 4,130 h^{-1} with catalyst loading of only 0.01 mol%. To the best of our knowledge such high catalytic activity using a nickel complex is unknown in the literature for cross-coupling reaction involving activation of an α sp^3 C–H bond in heterocyclic molecules. The method could prove as a valuable route for the production of value added products, under mild reaction conditions. Currently, we are also utilizing the nickel catalyst for activation of C–H bonds in many other heterocyclic molecules.

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