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Nickel-Catalyzed Cross-Dehydrogenative Coupling of α-C(sp^3)−H Bonds in *N*-Methylamides with C(sp^3)−H Bonds in Cyclic Alkanes

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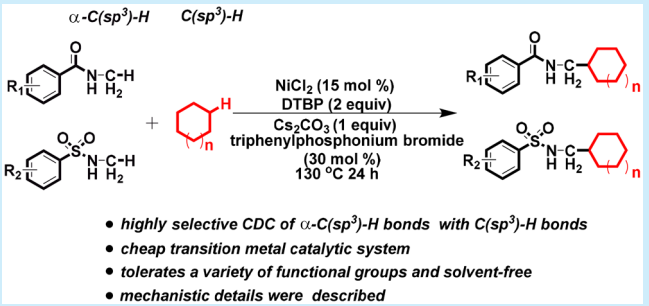
Supporting Information

ABSTRACT: A nickel-catalyzed cross-dehydrogenative coupling reaction of α-C(sp^3)−H bonds in *N*-methylamides with C(sp^3)−H bonds from cyclic alkanes has been developed, which offers a cheap transition-metal-catalyzed C−H activation method for amides without the requirement for any extraneous directing group. This new strategy is highly selective and tolerates a variety of functional groups. Mechanistic investigations into the reaction process are also described in detail.



Aryl amides and sulfonamides are privileged structural motifs that have found widespread application in agrochemicals, pharmaceuticals, natural products, dyes, polymers, and drugs.[1] For example (Figure 1), chlorantraniliprole (**1**) is an efficient insecticide and BMS-193884 (**2**) is a modulator of vascular tone, cell proliferation, and hormone production.

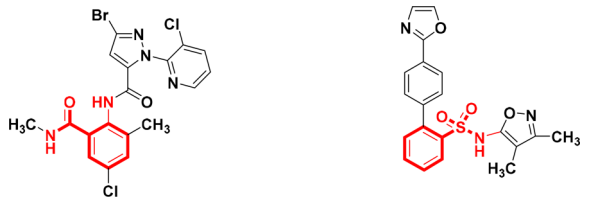
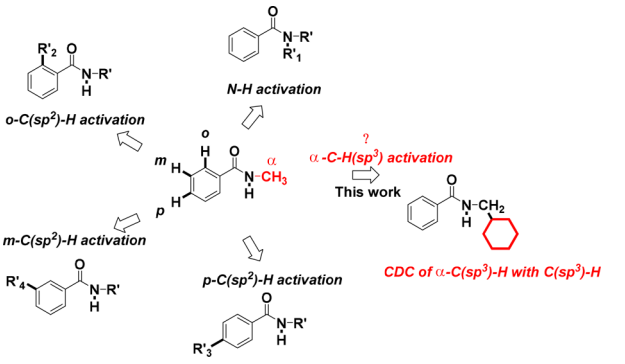


Figure 1. Drugs containing the aryl amide and sulfonamide functional groups.

Over the past decade, transition-metal-catalyzed C−H/N−H activation of aryl amides has emerged as a new and efficient procedure for the synthesis of selectively substituted amides. Traditional methods can be roughly divided into the following two categories: N−H/C−H activation coupling in −NHR[2] and selective C−H activation in aryl[3−5] (Scheme 1).

Examples include work in N−H/C−H activation coupling by Hartwig's group,[2c] who established a set of rare copper-catalyzed reactions of alkanes with simple amides, sulfonamides, and imides, which achieved the functionalization at secondary C−H bonds over tertiary C−H bonds and even occur at primary C−H bonds. Then an efficient oxidative C(sp^3)−H/N−H coupling of sulfoximines and amides with

Scheme 1. Representative Examples of Activation of N−H and C−H Bonds in Amides



simple alkanes was provided by Cheng and co-workers;[2g] this reaction employs simple alkanes without prefunctionalization and does not require strong base. Furthermore, Bolm's team[2d] developed an iron-catalyzed hetero-cross-dehydrogenative coupling reaction of sulfoximines with diarylmethanes, showing a new route to *N*-alkylated sulfoximines which are otherwise difficult to prepare. On the other hand, much effort has been put into the selective C−H activation of aryl rings to achieve regioselectivity. As a representative example, a ligand-promoted rhodium(III)-catalyzed ortho C−H activation of amides was reported in 2017 by Yu,[3a] which has overcome the limitations of palladium(II)-catalyzed C−H amination reactions. Almost at the same time, Bolm's team[3b] described a procedure for the direct mechanochemical rhodium(III)-

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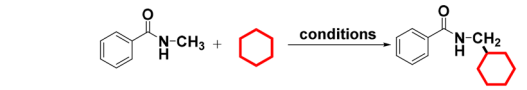
catalyzed ortho C−H bond activation of amides with 1,4,2-dioxazol-5-ones as the nitrogen source which avoided the use of solvents and additional heating. In 2015,[4e] Kanai's group established a meta-selective C−H borylation, directed by a secondary interaction between ligand and substrate, which showed good control of the regioselectivity. In addition, a free-radical-promoted para-selective C−H silylation of amides using hydrosilanes was described by Liu et al.;[5c] this cross-dehydrogenative silylation enables both electron-rich and electron-poor aromatics to afford the desired arylsilanes with unique selectivity. Although all of the previously developed methodologies for the functionalization of amides were efficient and regioselective, C(sp^3)−H activation in the *N*-methylamides still poses a significant challenge.

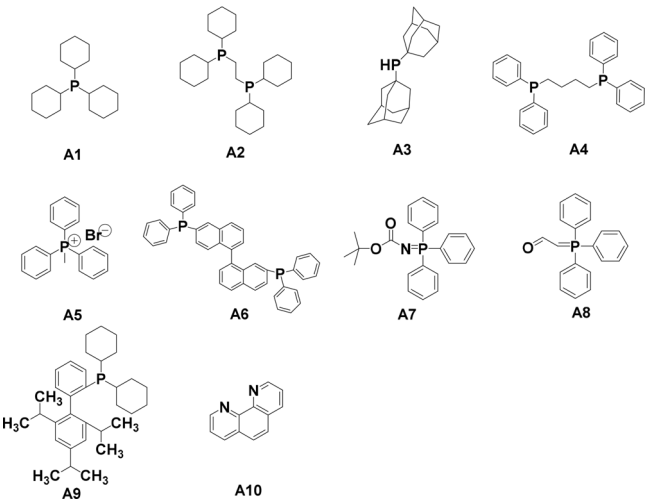
Most recently, a protecting-group-free approach for the α-functionalization of cyclic secondary amines was introduced by Seidel and co-workers,[6a] who made a breakthrough in α-C(sp^3)−H bond functionalization. Similarly previous work that used early-transition-metal (Ti, Zr, Ta, Ir)[6] catalysts has been largely limited to alkenes. The catalytic CDC (cross dehydrogenative coupling) reaction between unactivated C(sp^3)−H bonds and versatile C(sp^3)−H bonds, however, remains a challenging issue, especially the use of a cheap transition-metal catalytic system. Nickel[7] is one of the most abundant, inexpensive, environmentally friendly metals and plays a very important role in the field of C−H activation.

Inspired by this, we herein report the first example of a nickel-catalyzed highly selective cross-dehydrogenative coupling (CDC) of α-C(sp^3)−H bonds in *N*-methylamides with the C(sp^3)−H bonds of cyclic alkanes that proceeds without any extraneous directing group. Compared with previous research studies, this transformation (1) achieves a highly selective CDC of C(sp^3)−H bonds with C(sp^3)−H bonds, (2) tolerates a variety of functional groups and is solvent-free, (3) employs a cheap transition-metal catalytic system, (4) does not require an extraneous directing group to be used, thus avoiding the preparation of raw materials and waste of resources, and (5) has its mechanistic details described herein.

We initiated our studies by exploring reaction conditions for the cross-dehydrogenative coupling of C(sp^3)−H bonds in *N*-methylbenzamide **1a** with the C(sp^3)−H bonds of cyclohexane **2a**. Initially, a number of Ni catalysts were surveyed, including $NiCl_2$, $Ni(OAc)_2$, $Ni(OTf)_2$, and $Ni(acac)_2$ (Table 1, entries 1−4). The results showed that $NiCl_2$ displayed the highest catalytic activity for this reaction (entry 1). Thereafter, we explored various additives, with A5 and A8 furnishing particularly effective catalysts (entries 5−13). In addition, we explored the influence of peroxide on the yield (entries 14−16). Unfortunately, TBHP (*tert*-butyl hydroperoxide) and DCP (dicumyl peroxide) were inefficient for the coupling. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) operated similarly. As to the nature of the bases, the most effective C−H alkylation was accomplished with Cs_2CO_3 (entries 17−20). Notably, decreasing the reaction temperature (entries 21 and 22) reduced the yield. Next, we explored the influence of reaction time on yield, and the results showed that 24 h was the best (entries 23 and 24). Finally, optimizations in various solvents were conducted (entries 25−28), with cyclohexane proving the most suitable for this transformation. Polar solvents such as DMF and DMSO would compete with the reaction between **1a** and **2a** and thus inhibited the formation of desired products. On the other hand, cyclohexane (1 or 5 equiv) is transferred from liquid to gas under our procedure, thus resulting in a decrease of yield.

Table 1. Optimization of the Reaction Conditions[a]





entry	cat.	additive	peroxide	base	yield[b] (%) of **3a**
1	$NiCl_2$	A1	DTBP	Na_2CO_3	42
2	$Ni(OAc)_2$	A1	DTBP	Na_2CO_3	33
3	$Ni(OTf)_2$	A1	DTBP	Na_2CO_3	trace
4	$Ni(acac)_2$	A1	DTBP	Na_2CO_3	16
5	$NiCl_2$	A2	DTBP	Na_2CO_3	36
6	$NiCl_2$	A3	DTBP	Na_2CO_3	0
7	$NiCl_2$	A4	DTBP	Na_2CO_3	40
8	$NiCl_2$	A5	DTBP	Na_2CO_3	58
9	$NiCl_2$	A6	DTBP	Na_2CO_3	27
10	$NiCl_2$	A7	DTBP	Na_2CO_3	31
11	$NiCl_2$	A8	DTBP	Na_2CO_3	49
12	$NiCl_2$	A9	DTBP	Na_2CO_3	10
13	$NiCl_2$	A10	DTBP	Na_2CO_3	trace
14	$NiCl_2$	A5	TBHP	Na_2CO_3	11
15	$NiCl_2$	A5	DCP	Na_2CO_3	trace
16	$NiCl_2$	A5	DDQ	Na_2CO_3	trace
17	$NiCl_2$	A5	DTBP	$NaHCO_3$	trace
18	$NiCl_2$	A5	DTBP	tBuOK	22
19	**$NiCl_2$**	**A5**	**DTBP**	**Cs_2CO_3**	**71**
20	$NiCl_2$	A5	DTBP	$Zn(OTf)_2$	0
21[c]	$NiCl_2$	A5	DTBP	Cs_2CO_3	32
22[d]	$NiCl_2$	A5	DTBP	Cs_2CO_3	0
23[e]	$NiCl_2$	A5	DTBP	Cs_2CO_3	37
24[f]	$NiCl_2$	A5	DTBP	Cs_2CO_3	60
25[g]	$NiCl_2$	A5	DTBP	Cs_2CO_3	0
26[h]	$NiCl_2$	A5	DTBP	Cs_2CO_3	0
27[i]	$NiCl_2$	A5	DTBP	Cs_2CO_3	0
28[j]	$NiCl_2$	A5	DTBP	Cs_2CO_3	17[k]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mL), cat. (15 mol %), additive (30 mol %), peroxide (2 equiv), base (1 equiv), 130 °C, 24 h. [b]Isolated yield. [c]120 °C. [d]100 °C. [e]12 h. [f]36 h. [g]**2a** (1 equiv), DMF (1.5 mL). [h]**2a** (5 equiv), DMF (1.5 mL). [i]**2a** (5 equiv), DMSO (1.5 mL). [j]**2a** (5 equiv), benzene (1.5 mL). [k]Determined by GC−MS.

With the optimal reaction conditions in hand, we examined a series of substituted amides to establish the scope. Gratifyingly, this transformation showed excellent tolerance

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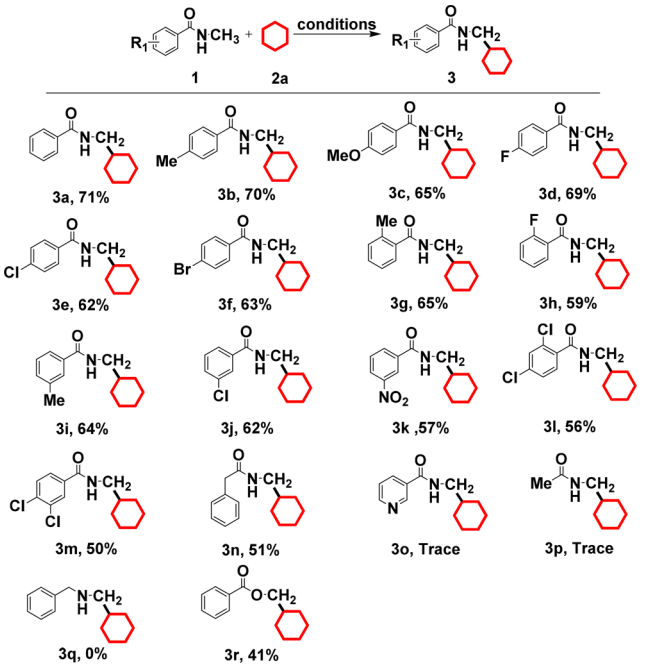
for various benzamides and provided the corresponding alkylation products in good to excellent yields. As can be seen from Scheme 2, substituted substrates with electron-donating groups, such as Me and OMe, produced the desired products in 70% and 65% yields, respectively (**3b**,**c**). Meanwhile, benzamides bearing electron-withdrawing groups, such as F, Cl, and Br produced the desired products in good yields (**3d**–**f**). Moreover, when ortho-substituted benzamides (**3g**–**h**) and meta-substituted benzamides (**3i**–**k**) were applied in the reaction under standard conditions, the alkylation proceeded smoothly to generate the desired products, which showed that the regiochemistry of the substituent on the benzamides did not have a significant effect on the reaction yields. To our delight, 2,4-dichloro-*N*-methylbenzamide (**3l**) and 3,4-dichloro-*N*-methylbenzamide (**3m**) also reacted with cyclohexane to afford the corresponding products in good yields. *N*-Ethyl-2-phenylacetamide was well tolerated too (**3n**). When heterocyclic amide (**3o**), methanamide (**3p**), and benzylamine (**3q**) were applied in the reaction under standard conditions, the alkylation reaction did not proceed smoothly. It is worth noting that methyl benzoate was tolerated well in this procedure (**3r**). Encouraged by the above results, we investigated the use of this catalytic system for other amides (Scheme 3). The benzenesulfonamides with electron-donating (**4a**,**b**) or electron-withdrawing (**4c**–**e**) substituents afforded the desired products in satisfactory yield (54–66%). Other benzenesulfonamides including ortho-substituted *N*-methyl-1-phenylmethanesulfonamide (**4f**–**h**) and *N*-methyl-1-phenylmethanesulfonamide (**4i**) also worked well.

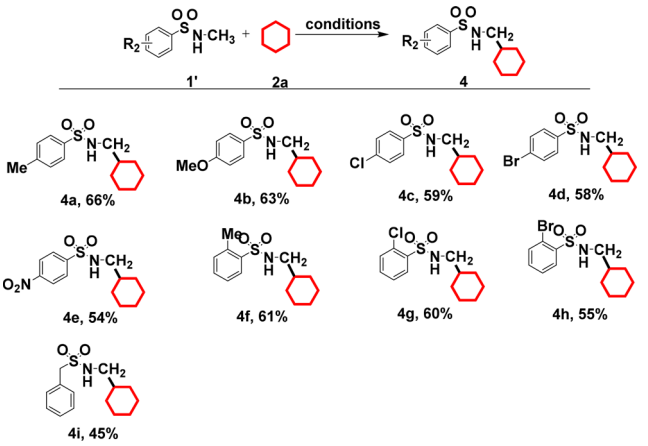
The success of the benzamides and other amides encouraged us to extend this procedure to other cyclic alkanes. As expected, most substituted amides underwent the reaction to give good yields of the corresponding alkylation products (Scheme 4). Unfortunately, octane (**5j**) and dioxane (**5o**) did not couple well under the standard conditions (checked by GC–MS).

Scheme 2. Nickel-Catalyzed Cross-Dehydrogenative Coupling of α-C(sp^3)–H Bonds in Amides and C(sp^3)–H Bonds from Cyclohexane[a]



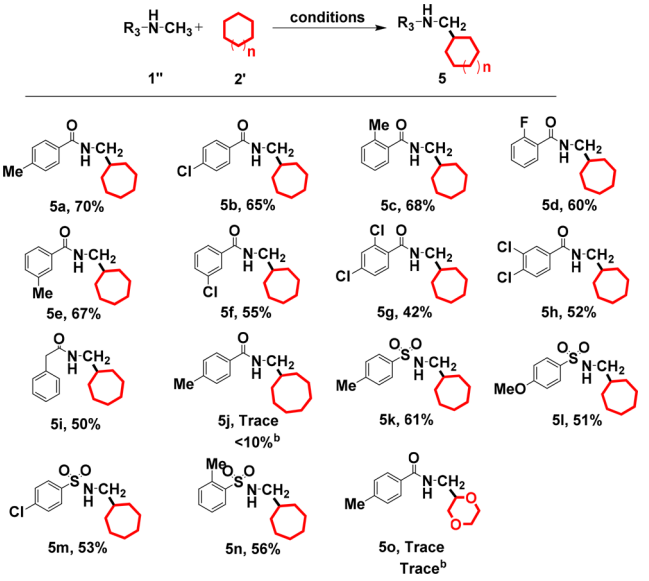
[a]Reaction condition: amides (0.5 mmol), **2a** (1.5 mL), $NiCl_2$ (15 mol %), additive A5 (30 mol %), DTBP (2 equiv), Cs_2CO_3 (1 equiv), 130 °C, 24 h.

Scheme 3. Nickel-Catalyzed Cross-Dehydrogenative Coupling of α-C(sp^3)–H Bonds in Sulfonamides and C(sp^3)–H Bonds from Cyclohexane[a]



[a]Reaction condition: amides (0.5 mmol), **2a** (1.5 mL), $NiCl_2$ (15 mol %), additive A5 (30 mol %), DTBP (2 equiv), Cs_2CO_3 (1 equiv), 130 °C, 24 h.

Scheme 4. Nickel-Catalyzed Cross-Dehydrogenative Coupling of α-C(sp^3)–H Bonds in Amides and C(sp^3)–H Bonds from Other Cyclic Alkanes[a]



[a]Reaction condition: amides (0.5 mmol), **2a** (1.5 mL), $NiCl_2$ (15 mol %), additive A5 (30 mol %), DTBP (2 equiv), Cs_2CO_3 (1 equiv), 130 °C, 24 h. [b]140 °C.

Some experiments were investigated to gain insight into the reaction mechanism. First, under the standard conditions, 4 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), BHT (butylated hydroxytoluene), or 1,1-diphenylethene were added to the alkylation reaction as radical scavengers. The cross-dehydrogenative coupling process (Scheme 5, S_21, S_22, and

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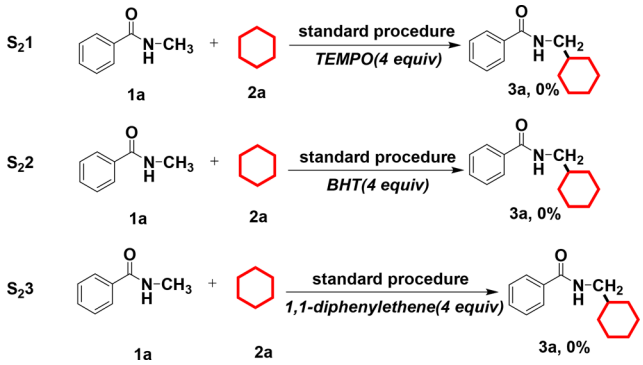
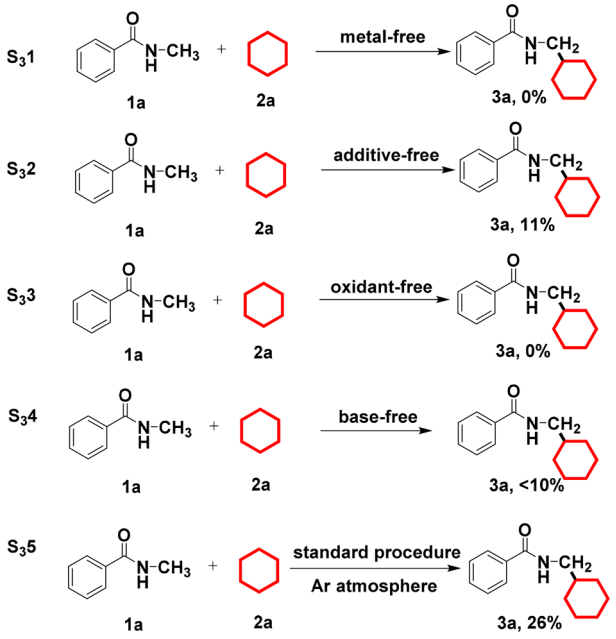
S_23) was completely inhibited as expected (determined by GC−MS), indicating that the alkylation might be proceeding through a radical pathway.

Scheme 5. Control Experiment



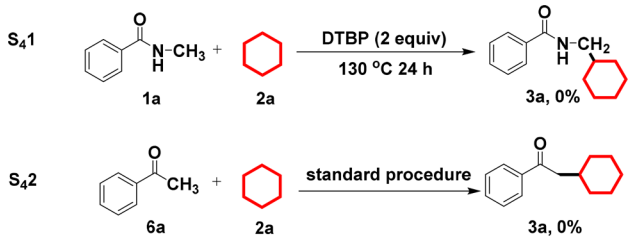
Subsequently, other experiments were also conducted. For example, when the reaction was run without catalyst, no product was obtained (Scheme 6, S_31), revealing that $NiCl_2$

Scheme 6. Control Experiment



was necessary for this procedure. Meanwhile, when the reaction was run without additive, only 11% yield product was obtained (Scheme 6, S_32). Additive A5, triphenylphosphonium bromide, might activate the catalyst to facilitate the reaction; on the other hand, it might serve as a phase-transfer catalyst to facilitate the reaction too. In addition, the procedure did not proceed well under DTBP-free conditions or N_2 atmosphere (determined by GC−MS), suggesting that the procedure is very dependent on DTBP and O_2 plays a role in oxidation to a certain extent (Scheme 6, S_33 and S_35). Notably, less than a 10% yield of the alkylation product was observed without base (Scheme 6, S_34), showing that Cs_2CO_3 has a significant effect on deprotonation. In order to further explore the reaction process, control experiments were carried out in Scheme 7. On the one hand, we have not detected the

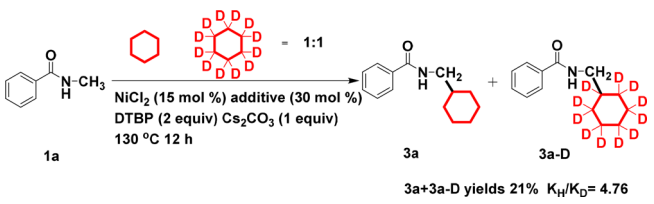
Scheme 7. Control Experiment



presence of alkylation product when 2 equiv of DTBP was used (determined by GC−MS), suggesting that this reaction is not an oxidant-catalyzed cross-dehydrogenative coupling process. On the other hand, when we changed the material from **1a** to **6a**, the alkylation reaction could not be carried out (determined by GC−MS).

Meanwhile, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out (Scheme 8). As is

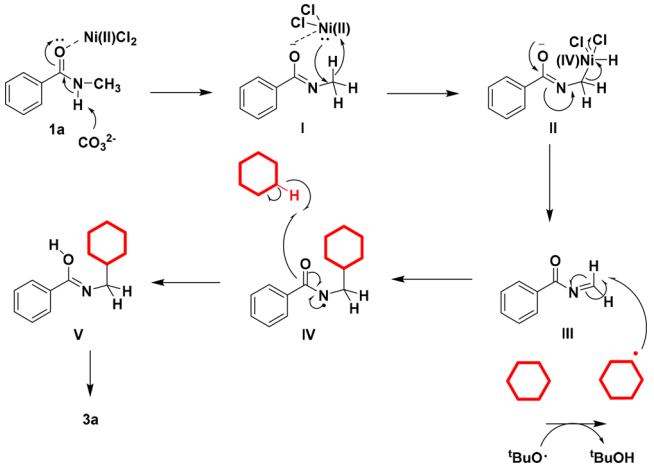
Scheme 8. KIE Experiment



depicted, a significant KIE was observed with K_H/K_D = 4.76. (The KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of 3a vs 3a-D.) This result indicates that C(sp^3)−H bond cleavage of cyclohexane may be the rate-determining step of this procedure.

On the basis of the above experiments and previous work,[8] a plausible reaction mechanism for this Ni-catalyzed cross dehydrogenative coupling is presented in Scheme 9. First,

Scheme 9. Proposed Reaction Mechanism



$NiCl_2$ complexation facilitates enolation to give **I**. The Ni(II) complex then oxidatively adds into the proximal NMe group to give **II**, which undergoes E1cb elimination to provide **III**. Subsequently, the latter reacts with cycloalkyl radical to give **IV**. Finally, H atom abstraction and protonation of **V** give the product **3a**. It is worth mentioning that one of the side

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products was 1,1′-bi(cyclohexane) from homocoupling of two cyclohexane radicals, and the yield of 1,1′-bi(cyclohexane) was 11% under the optimal reaction conditions (determined by GC−MS).

In summary, the first example of nickel-catalyzed cross-dehydrogenative coupling of α-C(sp^3)−H bonds in *N*-methylamides and C(sp^3)−H bonds from cyclic alkanes is described here. In this procedure, no extraneous directing groups are used, thus avoiding a waste of resources. This new protocol is highly selective and tolerates a variety of functional groups. Mechanistic investigations toward the CDC reaction process were also presented.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02736.

Experimental procedures and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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