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ABSTRACT: A nickel-catalyzed cross-coupling to construct $C(sp^2)-C(sp^3)$ bond was developed from two sustainable biomassbased feedstocks: phenol derivatives with umpolung aldehydes. This strategy features the *in situ* generation of moisture/air stable hydrazones from naturally abundant aldehydes, which act as alkyl nucleophiles under catalysis to couple with readily available phenol derivatives. The avoidance of using both halides as the electrophiles and organometallic or organoboron regents (also derived from halides) as the nucleophiles make this method more sustainable and renewable. *Water tolerance, great functional group* (*ketone, ester, free amine, amide etc) compatibility and late-stage elaboration of complex biological molecules* exemplified its practicability, unique chemo-selectivity over organometallic reagents.

Transition-metal-catalyzed cross-coupling reactions involving $C(sp^2)$ -O bond cleavage to construct C-C bond has attracted considerable attention in synthetic chemistry over the past decade,^[1] especially the nickel-catalyzed cross-coupling reactions of phenol derivatives with organometallic reagents.^[2] Compared to the traditional use of aryl halides, phenols and their derivatives are naturally abundant, readily available and often renewable from biomass. Representative excellent examples are the nickel-catalyzed Kumada-Tamao-Corriu (KTC) type reactions of phenolic electrophiles with Grignard reagents, pioneered by Wenkert,^[3] and developed by Dankwardt,^[4] Shi,^[5] Chatani,^[6] Martin,^[7] Rueping^[8] as well as (Scheme 1a). However, due to the high others^[9] nucleophilicity and basicity, robust organometallic reagents are typically moisture/air sensitive and display less functional group compatibility, making them inferior candidates for latestage manipulation of complex molecules or direct use under biocompatible conditions. In addition, the preparation of these organometallic reagents requires pre-synthesized halides and stoichiometric quantities of metals, thus producing copious metal wastes. To address these challenges, air/moisture stable organoboron reagents emerged as attractive coupling partners with O-based electrophiles (Scheme 1b). Chatani,^[10] Garg^[11], Shi^[12], Snieckus^[13] and others^[14] have made great contributions in the nickel-catalyzed Suzuki-Miyaura couplings to prepare biaryls between polycyclic aromatic phenol derivatives with aromatic boronic acids/esters. However, $C(sp^2)$ - $C(sp^3)$ cross-coupling remains challenging when phenol derivatives are employed as C–O electrophiles.^[5c,6a,8] Very recently, Rueping reported a practical alkylation of naphthol derivatives with B-alkyl-9-BBNs via nickel catalysis.^[15] Although organoboron reagents have widespread applications in various cross-couplings, most of them are obtained from organometallics or borylation of alkenes with expensive boron reagents.



Scheme 1. Representative Reagents in the Cross-Coupling Reactions Involving C-O Bond Cleavage.

As we know, tremendous efforts have been made by Barluenga,^[16] Wang^[17] and others^[18] employing electrophilic carbene from *N*-tosylhydrazones, however, the reversal electronic characteristic of simple hydrazones (from aldehydes) may offer new opportunities for chemical transformations. Recently, our group has disclosed novel and reliable ruthenium catalyzed nucleophilic additions to various π systems with hydrazones as carbanion equivalents.^[19] Earlier this year, we exemplified the feasibility of cross-couplings of aryl halides with hydrazones, albeit with very limited substrate scope, requiring strictly anhydrous conditions and suffering from hazardous halides.^[20] To overcome such limitations as well as towards the goal of green chemistry, herein, we wish to report

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a sustainable and practical nickel-catalyzed $C(sp^2)-C(sp^3)$ cross-coupling of phenol derivatives with umpolung aldehydes via C-O bond cleavage. Highlighted features of this strategy are: a) naturally abundant aldehydes as stable and environmentally benign alkyl nucleophiles; b) easily available O-based electrophiles from phenols; c) earth-abundant nickel as catalyst; d) broad substrate scope and water tolerance; e) unique chemo-selectivity; and f) great functional-group compatibility and late-stage elaboration of complex biological molecules.

Table 1. Optimization of the Reaction Conditions^a

ĵ.	N ₂ H ₄ · H ₂ O N ^{^N}	IH ₂ catalyst (10 mol%) ligand, base		TsO
Ph ⁻ `H 1a	THF, r.t., 30 min Ph H 2a	THF, 110 °C, 12 h	4aa	e 3a
entry	catalyst	ligand	base	4aa (%)
1	Ni(COD) ₂	-	DBU	N.D.
2	Ni(COD) ₂	PPh ₃	DBU	trace
3	Ni(COD) ₂	PCy ₃	DBU	trace
4	Ni(COD) ₂	PMe ₃	DBU	80 (75)
5	Ni(COD) ₂	PEt ₃	DBU	38
6	Ni(COD) ₂	dmpe	DBU	53
7	Ni(COD) ₂	dppf	DBU	71
8	Ni(COD) ₂	dppe	DBU	trace
9	Ni(COD) ₂	Xantphos	DBU	trace
10	Ni(COD) ₂	bpy	DBU	7
11	Ni(PPh ₃) ₄	PMe ₃	DBU	52
12	Ni(PPh ₃) ₄	-	DBU	N.D.
13	NiCl ₂	PMe ₃	DBU	52
14	$Ni(acac)_2$	PMe ₃	DBU	53
15	NiBr ₂ •glyme	PMe ₃	DBU	60
16	Ni(COD) ₂	PMe ₃	^t BuOK	37
17	Ni(COD) ₂	PMe ₃	K_3PO_4	trace
18	Ni(COD) ₂	PMe ₃	Cs ₂ CO ₃	trace
19	Ni(COD) ₂	PMe ₃	-	N.D.
20^{c}	Ni(COD) ₂	PMe ₃	DBU	N.D.
21^d	Ni(COD) ₂	PMe ₃	DBU	65
22 ^e	Ni(COD) ₂	PMe ₃	DBU	96
23 ^f	Ni(COD) ₂	PMe ₃	DBU	trace
Me P Me	Me P Me Ph P	Ph P P Ph Ph ₂ P	PPh ₂	Me Me
	dmpe o	dppe d	ppf	Xantphos

[a] Reaction conditions: **3a** (0.1 mmol), **1a** (0.3 mmol), N_2H_4 •H₂O (0.36 mmol), [Ni] (10 mol%), ligand (40 mol% for monodentate, 20 mol% for bidentate), base (0.3 mmol), THF (0.5 mL), 110 °C, 12 h under N₂ unless other noted. [b] NMR yields were determined by ¹H NMR using mesitylene as an internal standard (isolated yield in parenthesis). [c] The reaction was performed at 80 °C. [d] *p*-Tolyl mesylate was used instead of **3a**. [e] *p*-Triflate was used instead of **3a**. N. D.= not detected.

Initially, the cross-coupling reaction of p-tolyl tosylate (3a) and hydrazone generated *in situ* from benzaldehyde (1a) with hydrazine was chosen as the model to explore the reaction conditions (Table 1). Catalysts investigations revealed that nickel was the only metal candidate to favor this transfor-

mation (see Table S1 in Supporting Information), probably because nickel is more oxyphilic than palladium due to its smaller size and increased hardness.^[2] Ligand studies showed that less sterically hindered monodentate (PMe₃, PEt₃) or bidentate phosphine ligands (dmpe, dppf) facilitated this transformation (entries 1-10), and the best result was obtained when using PMe₃ as the ligand and DBU as the base (4aa, 80%) yield, entry 4). The combination of $Ni(PPh_3)_4$ with PMe₃ gave the desired product 4aa in 52% yield (entry 11), while it was totally inactive in the absence of ligand PMe₃ (entry 12). It is noteworthy that more convenient Ni(II) pre-catalysts could also facilitate this cross-coupling reaction, and moderate yields of 4aa were obtained (entries 13-15). The efficiency of this transformation was largely affected by the choice of base (entries 16-19). In addition, decreasing the reaction temperature to 80 °C resulted in no detection 4aa with all the starting material **3a** recovered (entry 20), which implies that the insertion of nickel catalyst to C-O bond has a high activation energy. Moreover, *p*-tolyl mesylate and *p*-tolyl triflate were also applicable (entries 21-22), while aryl pivalate gave only trace amount of cross-coupling product 4aa (entry 23).

Table 2. Scope of Aldehyde 1^{a,b}



[a] Reaction conditions: **3a** (0.2 mmol), **1** (0.6 mmol), N_2H_4 •H₂O (0.72 mmol), [Ni] (10 mol%), PMe₃ (40 mol%), DBU (0.6 mmol), THF (1.0 mL), 110 °C, 12 h under N₂. [b] Reported yields are the isolated ones.

With the optimized conditions identified, the substrate scope of aldehydes was investigated. As shown in Table 2, variations of electronic effects of the nucleophiles did not reduce the efficiency of this coupling reaction. Aldehydes bearing both electron-donating and electron-withdrawing substituents all reacted smoothly with phenyl tosylate **3a** to give the desired products **4ab-ap** in good to excellent yields. Various functional groups, such as methyl, methoxyl, chloro, fluoro, trifluoromethyl and even ester, were all tolerated under the optimized conditions. Hetero-aromatic aldehydes, such as furan-2-carbaldehyde, thiophene-3-carbaldehyde, pyridine-3-

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carbaldehyde and benzothiophene-3-carbaldehyde were well applicable for the present transformation (**4aq-at**). Furthermore, the aldehydes bearing naphthyl or phenanthryl substituents afforded the corresponding products (**4au-aw**) in excellent yields (> 90%). To our delight, the cross-coupling also occurred with cinnamaldehyde and phenylacetaldehyde as substrates, albeit with a slightly reduced reactivity (**4ax, 4ay**). Unfortunately, only trace amount of desired products were detected when simple aliphatic aldehydes were tested, probably due to the rapid competing formation of azines from the hydrazone intermediates under high temperature.

Table 3. Scope of Aryl/vinyl Tosylates 1^{a,b}



[a] Reaction conditions: **3** (0.2 mmol), **1a** (0.6 mmol), N_2H_4 •H₂O (0.72 mmol), [Ni] (10 mol%), PMe₃ (40 mol%), DBU (0.6 mmol), THF (1.0 mL), 110 °C, 12 h under N₂. [b] Reported yields are the isolated ones.

Subsequently, the scope of phenyl/vinyl tosylates was investigated, as summarized in Table 3. In general, substrate 3 with electron-donating (-OMe, -OPh, -Me, -iPr, -tBu, -Ph, etc.) on the para- and/or meta-position of phenyl ring all worked well to give the desired diarymethanes 4ac, 4ba-da, 4fa-ia, albeit with moderate yields observed when electronwithdrawing groups (-CN, -Cl, -F, -CF₃) attached (4ja, 4am, 4ai, 4al, 4ka). Product 4ea was obtained in 51% yield due to the ortho-steric hindrance of methyl group. When the tosylate of isoeugenol perfume was tested, the desired product 4la was obtained in 81% yield with olefin moiety untouched (E/Z derived from substrate). It is worth mentioning that other functional groups such as ester, amine and amide, which are fragile in the presence of Grignard reagents, were well tolerated under our conditions (4ma-oa). In addition, the N-heterocyclic (pyridine, indole and carbazole) tosylates, as important motifs in alkaloids, underwent efficient cross-couplings with benzaldehyde hydrazone (4as, 4pa, 4qa). As expected, the polycyclic (naphthyl or phenanthryl) tosylates were well applicable (4au**aw**, **4ra**). Moreover, the vinyl tosylates were also tested as suitable coupling partners, thus expanding the electrophile scopes to the cheap and natural abundant ketones (**4sa**, **4ta**).

Gratifyingly, the power and utility of this cross-coupling reaction was further demonstrated by its application to complex tosylate/triflate substrates. For example, the structural elaboration of tyrosine 5, which is a non-essential amino acid used by cells to synthesize proteins in biology, was readily accomplished using our nickel-catalyzed cross-coupling reaction with aldehydes as masked alkyl nucleophile (Scheme 2, Eq. 1). In addition, the alkylation of estrone proceeded smoothly and efficiently while using the corresponding tosylate 7 with the ketone moiety intact, impossible with organometallic reagents (Scheme 2, Eq. 2). Furthermore, the reaction of 1a with triflate of cholesterol was investigated under the standard reaction conditions. The expected alkylation product 10 was obtained in 82% yield (Scheme 2, Eq. 3). These results indicated that this protocol would enrich the tool box of chemists for the late-stage modification of complex molecules.



Scheme 2. Alkylative Elaboration of Complex Tosylates/triflates Derived from Natural Products.

Then the chemo-selectivity of this nickel-catalyzed crosscoupling reaction was explored. The chemo-specific alkylation of $C(sp^2)$ -OTs with hydrazone **1a** occurred with estradiol *di*tosylates **11** (Scheme 3, Eq. 1). To our delight, the chemoselective, sequential alkylation of substrate **13** was achieved by the unique tunable reactivity between aryl iodide and tosylate, thus delivering the asymmetrical dibenzyl product **15** in excellent yield (Scheme 3, Eq. 2).



Scheme 3. Chemo-Selectivity Tests.

Moreover, the efficiency of this transformation was not affected in the presence of H_2O , thus showing its distinct moisture tolerant character than organometallic reagents (Scheme 4).



Scheme 4. Water Tolerance Tests.

Although exact mechanism was still not clear at this stage, according to our previous works^[19] and literature reports,^[2] a plausible reaction pathway was depicted in Scheme 5. Similar to the Ni-catalyzed KTC type and Suzuki coupling reaction intensive studied by Chatani,^[21] Itami^[22] and Martin,^[23] the coordination of Ni (0) with π system and oxygen allowing the oxidative addition to give intermediate **B**, which underwent transmetallation with carbon-nucleophile **D** derived from deprotonation of hydrazone **2** to form intermediate **E**. Reductive elimination gave the diimide **F**^[24] and regenerated Ni (0) catalyst. Finally, the desired product **4** was formed by denitrogenation assisted with base.



Scheme 5. Proposed Mechanism.

In summary, we have developed a sustainable nickelcatalyzed cross-coupling of phenol-based electrophiles with aldehydes umpolung to construct $C(sp^2)-C(sp^3)$ bonds. This strategy features the *in situ* generation of moisture/air stable hydrazones from naturally abundant aldehydes, which act as alkyl nucleophiles under catalysis to couple with easily available phenol derivatives. The avoidance of using organometallic or organoboron regents derived from halides make this method more sustainable and renewable. Water tolerance, great functional group (ketone, ester, free amine, amide *etc*) compatibility and late-stage elaboration of complex biological molecules exemplified its practicability, unique chemo- selectivity over organometallic reagents. Further applications of aldehydes as alkyl nucleophiles in chemical transformations are ongoing in our lab.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

Screening data, experimental details, characterization of new compounds and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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