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Report

nickel catalysis, cross-coupling, aryl pivalates, cyclobutanols

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Nickel-Catalyzed Cross-coupling of Aryl Pivalates with Cyclobutanols involving C–O and C–C Bond Cleavage

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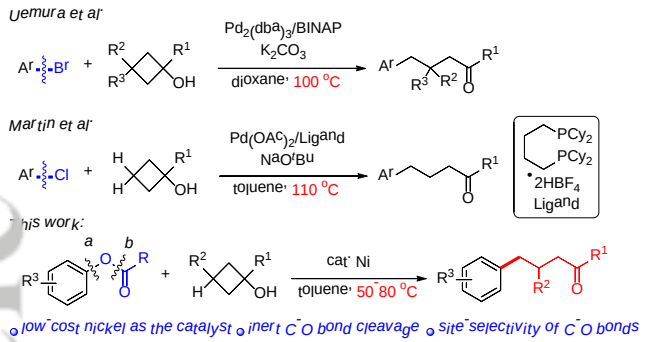
Summary of main observation and conclusion An efficient nickel-catalyzed cross-coupling of aryl pivalates with cyclobutanols is described. The use of $Ni(cod)_2/PCy_3$/base as the catalytic system enables the cleavage of inert C–O bond and C–C bond under mild conditions, thus providing a facile access to γ-arylated ketones in generally good to excellent yields. This transformation is also characterized by wide substrate scope and functional group compatibility, for example, methoxy, *N*,*N*-dimethylamino, keto, ester, fluoro and TMS groups are well-tolerated during the reaction process.

Background and Originality Content

Ketones are highly important structural motifs which are not only widespreadly present in organic compounds but also can be conveniently transformed to other functional groups. Generally, α-substituted ketones can be synthesized by electrophilic substitution of the ketone enolates or metal-catalyzed α-functionalization of carbonyl compounds.[1] β-Substituted ketones can be prepared by Michael addition to α,β-unsaturated ketones etc.[2] Recently, the catalytic ring-opening coupling of *tert*-cyclobutanols has proven to be promising protocols for the construction of γ-substituted ketones.[3] The C–C bond cleavage of cyclobutane derivatives is prone to occur due to the strain energy (26.3 kcal/mol for unsubstituted cyclobutane)[4]. There are two major pathways for the cleavage of C–C bonds in cyclobutanols: (a) transition metal such as palladium or rhodium-catalyzed ring-opening of cyclobutanols via β-carbon elimination;[5] (b) oxidative ring-opening of cyclobutanols via β-carbonyl radical intermediates.[6] In 1999, Uemura and co-workers reported a Pd-catalyzed arylative ring-opening of cyclobutanols using aryl bromides as the coupling reagents leading to γ-arylated ketones.[5a] However, this reaction was limited to 3-substituted or 3,3-disubstituted cyclobutanols in order to avoid the β-hydride elimination of the alkyl-Pd intermediates. In 2012, Martin et al. described a Pd-catalyzed coupling of cyclobutanols with aryl chlorides at 110 °C, in which a bulky and electron-donating ligand played a key role in facilitating the oxidative addition of the C–Cl bond and inhibiting the β-hydride elimination.[5d] However, hazardous halogen-containing waste was generated by using these electrophiles.

Noticeably, phenol-derived electrophiles are more attractive coupling partners compared with aryl halides due to their low toxicity and readily availability. However, the transformations of phenol derivatives are highly challenging owing to the high dissociation energy of the C–O bond.[7] In this context, nickel-based catalyst systems are more attractive compared with that of palladium not only due to their low cost but also because of their high reactivity towards C-O bond oxidative addition. Since the first report related to the activation of C–O bonds in aryl or vinyl methyl ethers via nickel catalysis in 1979,[8] nickel-catalyzed reactions have attracted much attention in the transformation of C–O electrophiles.[9] Although much progress has been achieved, most of the studies concentrate on the use of relatively reactive aryl sulfonates such as triflates, mesylates or tosylates as the coupling partners, the employment of the less reactive aryl carboxylates[10] is far less developed because it poses formidable challenges such as high activation barrier for the aryl C–O bond cleavage (106 kcal/mol for the aryl acetate)[7] and the site-selectivity issue between the aryl C–O bond and carbonyl C–O bond (Scheme 1, a vs b). Nevertheless, through the judicious choice of the catalysts, ligands and other reaction conditions, aryl carboxylates have recently been used successfully to react with organoboronic reagents,[11] organozinc reagents,[12] silylboranes,[13] amines,[14] P–H compounds[15] and ketones[16] etc. under nickel catalysis. However, nickel-catalyzed cross-coupling reactions of these "inert" O-based electrophiles with cyclobutanols have not been reported.[17] Herein, we report a nickel-catalyzed cross-coupling of aryl pivalates with cyclobutanols for the synthesis of γ-arylated ketones via inert C–O and C–C bond cleavage under milder reaction conditions (50-80 °C).

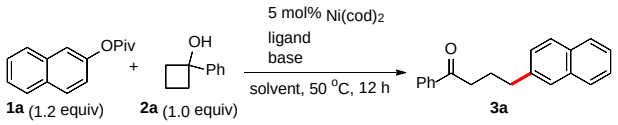
Scheme 1 Metal-catalyzed ring-opening/coupling of cyclobutanols with aryl electrophiles



Results and Discussion

We began our investigation by examination of the reactivity of naphthalen-2-yl pivalate (**1a**) with 1-phenylcyclobutan-1-ol (**2a**), and the results were shown in Table 1. To our delight, 17% of the desired cross-coupling product **3a** was detected when PBu_3 was used as ligand in the presence of 5 mol% $Ni(cod)_2$ as the catalyst and 1.2 equiv LiO^tBu as the base. This result encouraged us to further screen different ligands. Unfortunately, monodentate ligands such as PPh_3 or $PCyPh_2$ provided **3a** in only 3-15% yields (entries 2-3). Higher yield of **3a** (36%) could be observed using PCy_2Ph as the ligand (entry 4). Pleasantly, the electron-rich and bulky ligand PCy_3, which was widely used in the inert C–O bonds activation and functionalization, generated the desired product **3a** efficiently in 87% yield (entry 5). Further ligand screening revealed that bidentate ligands such as dppb and dppf were ineffective for this reaction (entries 6-7). The use of dcype, which has been shown to be an active ligand in Ni-catalyzed C–H/C–O coupling of azoles with aryl pivalates,[18] failed to promote this coupling (entry 8). Considering the high yield of the product obtained using PCy_3 as the ligand, other reaction parameters were evaluated in the presence of PCy_3. $Ni(acac)_2$ resulted in lower conversion to **3a** (entry 9). Attempt to generation of Ni(0) species from $Ni(PCy_3)_2Cl_2$ and a reductant (Zn) failed to catalyze this transformation (entry 10). It was found that inorganic bases such as NaO^tBu or KO^tBu had a deleterious effect on the reaction efficiency, affording **3a** in low yields (10-37%). The results suggested that the Li^+ counter ion may play an important role for this reaction (entries 11-12). A comparison of entry 5 vs entries 13 and 14 indicated that the use of a strong base with a steric bulk counter anion is necessary for this reaction. Other solvents were also examined. Changing the solvent to hexane, THF, or 1,4-dioxane gave the ketone **3a** in 37-61% yields (entries 15-17). However, changing the solvent to CH_3CN failed to give the desired product (entry 18). Reducing the amount of LiO^tBu to 1.0 equiv provided 87% yield of **3a** (entry 19). However, when the amount of LiO^tBu was decreased to 0.5 equiv, the yield of **3a** was reduced rapidly (entry 20). In the absence of base, only a trace of **3a** was observed (entry 21). We envisioned that the base plays a role in the facilitating the formation of nickel alcoholates. It should be mentioned that no desired product was observed in the absence of $Ni(cod)_2$ or PCy_3, demonstrating that nickel catalyst and the ligand are needed for the success of this transformation (entries 22 and 23).

Table 1 Optimization of the Reaction Conditions



1a (1.2 equiv) **2a** (1.0 equiv) **3a**

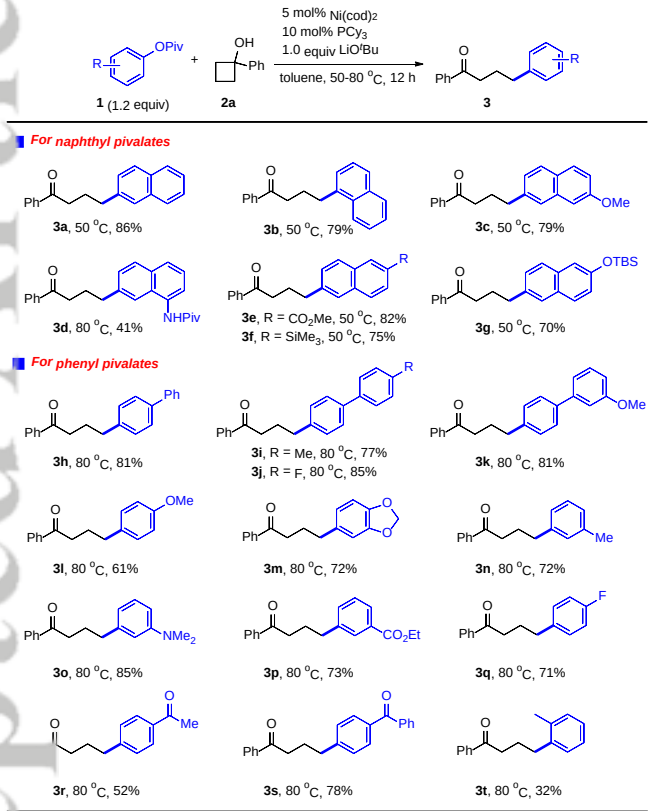
entry	ligand (mol%)	base (equiv)	solvent	yield (%)[a]
1	PBu_3 (10)	LiO^tBu (1.2)	toluene	17
2	PPh_3 (10)	LiO^tBu (1.2)	toluene	3
3	$PCyPh_2$ (10)	LiO^tBu (1.2)	toluene	15
4	PCy_2Ph (10)	LiO^tBu (1.2)	toluene	36
5	PCy_3 (10)	LiO^tBu (1.2)	toluene	87
6	dppb (5)	LiO^tBu (1.2)	toluene	2
7	dppf (5)	LiO^tBu (1.2)	toluene	5
8	dcype (5)	LiO^tBu (1.2)	toluene	0
9[b]	PCy_3 (10)	LiO^tBu (1.2)	toluene	25
10	-[c]	LiO^tBu (1.2)	toluene	5
11	PCy_3 (10)	NaO^tBu (1.2)	toluene	37
12	PCy_3 (10)	KO^tBu (1.2)	toluene	10
13	PCy_3 (10)	LiOMe (1.2)	toluene	15
14	PCy_3 (10)	LiHMDS (1.2)	toluene	37
15	PCy_3 (10)	LiO^tBu (1.2)	hexane	61
16	PCy_3 (10)	LiO^tBu (1.2)	THF	37
17	PCy_3 (10)	LiO^tBu (1.2)	1,4-dioxane	47
18	PCy_3 (10)	LiO^tBu (1.2)	CH_3CN	0
19	PCy_3 (10)	LiO^tBu (1.0)	toluene	87 (86)[d]
20	PCy_3 (10)	LiO^tBu (0.5)	toluene	47
21	PCy_3 (10)	-	toluene	2
22[e]	PCy_3 (10)	LiO^tBu (1.0)	toluene	0
23	-	LiO^tBu (1.0)	toluene	0

[a]NMR yields using 1,3,5-trimethoxybenzene as the internal standard. [b]Using 5 mo% $Ni(acac)_2$ as the catalyst. [c]5 mol% $Ni(PCy_3)_2Cl_2$ and 20 mol% Zn were used. [d]Isolated yield. [e]In the absence of $Ni(cod)_2$.

With the optimized reaction conditions in hand (Table 1, entry 19), the substrate scope of this coupling reaction with respect to various aryl pivalates was first evaluated using *tert*-cyclobutanol **2a** as the coupling partner. To our delight, a wide range of aryl pivalates bearing electron-donating and electron-withdrawing substituents could be accommodated in this reaction (Scheme 2). For example, a sterically demanding 1-naphthyl pivalate coupled cleanly with *tert*-cyclobutanol **2a** at 50 °C to afford **3b** in 79% yield. Naphthyl derivatives bearing methoxy, amide or ester groups were tolerated, providing the corresponding ketones **3c-3e** in 41-82% yields. Good yield was also obtained with the substrate

bearing a silyl group, which might be transformed to other functional groups through coupling reactions (**3f**). Although nickel-catalyzed reactions of aryl silyl ethers have previously been reported,[19] the aryl–OTBS bond could be tolerated under the present reaction conditions (**3g**). Phenyl pivalates, which were proved to be more challenging electrophiles than naphthyl pivalates in Ni-catalyzed cross-coupling via C–O bond activation, were also proved to be good substrates. In these cases, increasing the reaction temperature to 80 °C was required. Biphenyl pivalates showed a high reactivity for this reaction. For example, biphenyl **1h** provided **3h** in 81% yield. Biphenyl pivalates bearing a methyl or methoxy group were also compatible to provide **3i** and

Scheme 2 Scope of aryl pivalates[a]

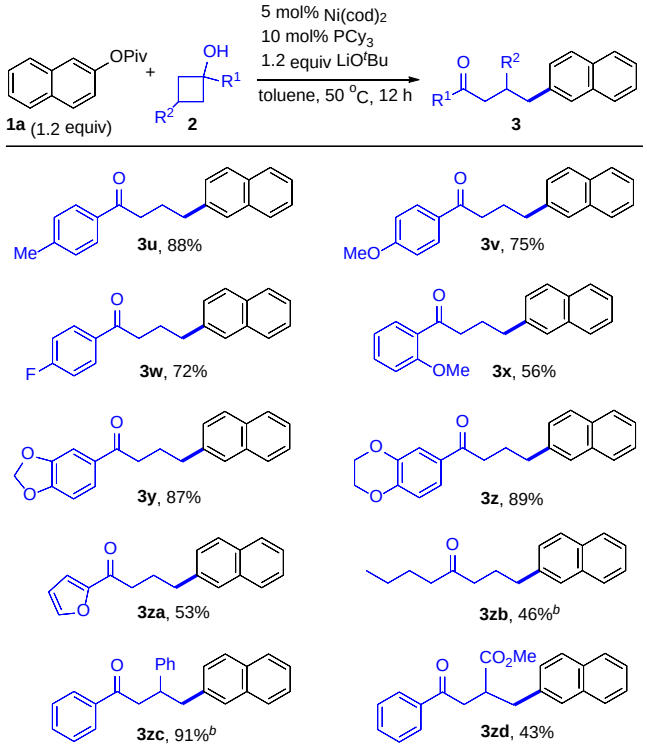


[a]Isolated yield.

3k in 77% and 81% yield, respectively. Especially, the presence of an aryl fluoride moiety did not interfere, providing the corresponding product **3j** in 85% yield. Strikingly, less reactive aryl pivalate possessing an electron-rich group at the *para* position converted to ketone **3l** in 61% yield. Substrate with a methylenedioxy group also showed a high reactivity (**3m**). Phenyl pivalates with methyl, *N*,*N*-dimethylamino or ester groups in the *meta*-position coupled well with **2a**, leading to **3n**-**3p** in 72-85% yields. Aryl pivalate with an electron-withdrawing fluoro substituent converted efficiently to **3q**. The presence of an acetyl group on the aryl ring resulted in moderate yield (52%) of **3r**, possibly due to that the side reactions such as ketone α-arylation might also occur. However, the reaction of aryl pivalate bearing a benzoyl group proceeded efficiently to give **3s** in 78% yield. When the substrate bearing an *ortho*-substituent on the aryl ring was employed, the desired **3t** was formed in a lower yield (32%).

Next, the scope of cyclobutanols **2** was examined (Scheme 3). The reaction of C1-aryl-substituted cyclobutanols bearing an electron-donating group such as 4-Me, 4-OMe on the phenyl ring worked well to give **3u** and **3v** in 75-88% yields. A 4-F substituent on the phenyl ring was compatible (**3w**). In addition, the presence of a sterically demanding *ortho*-methoxy group was also suitable, furnishing **3x** in 56% yield. Substrates bearing a 1,3-benzodioxole or a 1,4-benzodioxan ring showed a high reactivity for this reaction, affording **3y**-**3z** in 87-89% yields. Coupling of heteroaryl-substituted cyclobutanol with **1a** afforded **3za** in 53% yield. Besides, alkyl-substituted cyclobutanols also coupled well (**3zb**). Moreover, cyclobutanols with a C-3-substitutent such as Ph or CO_2Me group also worked well, leading to the corresponding products **3zc**-**3zd** in 43-91% yields.

Scheme 3 Scope of cyclobutanols[a]

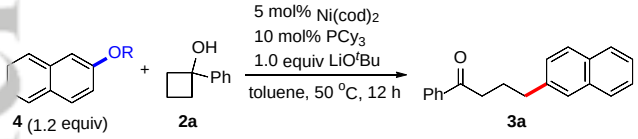


[a]Isolated yield. [b]80 °C.

Next, the reactivity of phenol derivatives with different protection groups was also investigated. Gratifyingly, good product yields were achieved using 2-naphthyl triflate, mesylate or tosylate as the substrates (Table 2, entries 1-3). Aryl sulfamate, which shows a low reactivity towards coupling with Grignard reagents under palladium catalyst,[20] afforded the product **3a** in 76% yield (entry 4). Further studies indicated that 2-naphthyl

carbamate (**4e**) showed low reactivity and the desired product **3a** was obtained in 18% yield (entry 5). When 2-naphthyl acetate **4f** was employed as the substrate, only 10% NMR yield of **3a** was obtained, accompanying with the byproduct derived from hydrolysis of **4f** (entry 6). The results indicated that the substrate of aryl acetate is less stable in the presence of strong base than that of aryl pivalates. Aryl methyl ether (**4g**) was failed to give the desired product possibly due to the inertness of the aryl–OMe bond toward oxidative addition to nickel complex under the standard conditions (entry 7).

Table 2 Scope of phenol derivatives



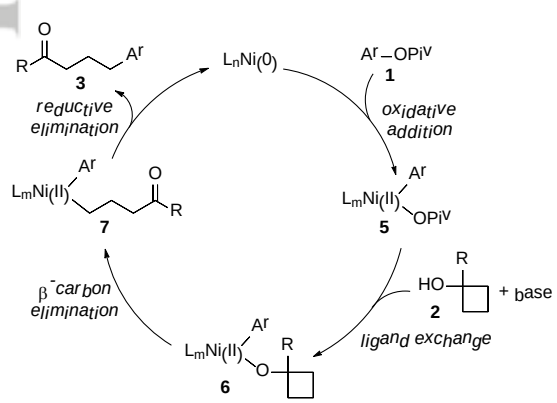
4 (1.2 equiv) **2a** **3a**

entry	R	yield(%)[a]
1	Tf (**4a**)	87
2	Ms (**4b**)	80
3	Ts (**4c**)	73
4	SO_2NMe_2 (**4d**)	76
5	$CONMe_2$ (**4e**)	18
6	Ac (**4f**)	10[b]
7	Me (**4g**)	0[b]

[a]Isolated yield. [b]NMR yields using 1,3,5-trimethoxybenzene as internal standard.

Based on the previous reports,[5a,21] a plausible reaction mechanism is proposed as depicted in Scheme 4. Initially, oxidative addition of aryl pivalate to Ni(0) species gives an arylnickel(II) intermediate **5**. Subsequently, a ligand exchange between **5** and cyclobutanol in the presence of a base occurs to give a nickel(II)-alcoholate **6**, which is followed by β-carbon elimination to produce an alkylnickel complex **7**. Finally, reductive elimination of **7** delivers the γ-arylated ketones **3** and regenerates the Ni(0) species.

Scheme 4 Possible Reaction Mechanism



Conclusions

In summary, we have developed a nickel-catalyzed cross-coupling of aryl pivalates with cyclobutanols via the cleavage of inert C–O bond and C–C bond under mild conditions. The method provides an efficient route to γ-arylated ketones with wide functional group compatibility. A broad variety of aryl pivalates or cyclobutanols are suitable for use in this catalytic system. In addition, aryl triflates, mesylates, tosylates and sulfamates all coupled well with cyclobutanols. Further investigations on the coupling of cyclobutanols with other electrophiles are in progress in our laboratory.

Experimental

Typical procedure for the synthesis of 4-(naphthalen-2-yl)-1-phenylbutan-1-one (3a).

The reaction was conducted in an oven-dried screw-cap vial (volume: 8 mL) equipped with a magnetic stir bar. In a nitrogen-filled glove box, 1-phenylcyclobutan-1-ol (44.5 mg, 0.3 mmol), naphthalen-2-yl pivalate (82.2 mg, 0.36 mmol), LiO^tBu (24.0 mg, 0.3 mmol), $Ni(cod)_2$ (4.1 mg, 0.015 mmol), PCy_3 (8.4 mg, 0.03 mmol) and toluene (3 mL) were added sequentially to a screw-cap vial. The vial was sealed with a screw cap featuring a PTFE/silicone septum and taken outside the glove box. The vial was immersed into an oil bath preheated at 50 °C. After stirring for 12 h, the mixture was cooled down to room temperature, filtered through a short pad of silica gel and washed with ethyl acetate. The organic solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 50/1) to afford the desired product **3a** in 86% yield (70.5 mg) as a white solid. M.p.: 83.2-84.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11-2.19 (m, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.37-7.44 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.61 (s, 1H), 7.74-7.79 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.37, 35.17, 37.50, 125.11, 125.85, 126.50, 127.20, 127.35, 127.53, 127.91, 128.44, 131.96, 132.86, 133.49, 136.84, 139.09, 199.99. IR (neat): 3055, 2953, 2888, 2846, 1681, 1597, 1576, 1449, 1370, 1330, 1258, 1199, 977, 846, 822, 748, 732, 689 cm^{-1}. HRMS (ESI) for $C_{20}H_{19}O$ $[M+H]^+$: calcd 275.1430, found 275.1439.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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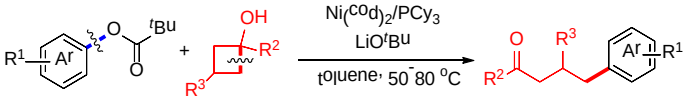
Nickel-Catalyzed Cross-coupling of Aryl Pivalates with Cyclobutanols involving C–O and C–C Bond Cleavage

Yi Gan, Shaoxu Huang and Yuanhong Liu



R^2 = aryl or alkyl; R^3 = H, Ph, CO_2Me

- low-cost nickel as the catalyst
- inert C-O and C-C bond cleavage
- wide functional group compatibility
- mild reaction conditions

An efficient nickel-catalyzed cross-coupling of aryl pivalates with cyclobutanols is described. The use of $Ni(cod)_2/PCy_3$/base as the catalytic system enables the cleavage of inert C–O bond and C–C bond under mild conditions, thus providing a facile access to γ-arylated ketones in generally good to excellent yields. This transformation is also characterized by wide substrate scope and functional group compatibility, for example, methoxy, *N*,*N*-dimethylamino, keto, ester, fluoro and TMS groups are well-tolerated during the reaction process.

