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Selective *cine*-arylation of *tert*-cyclobutanols with indoles enabled by nickel catalysis†

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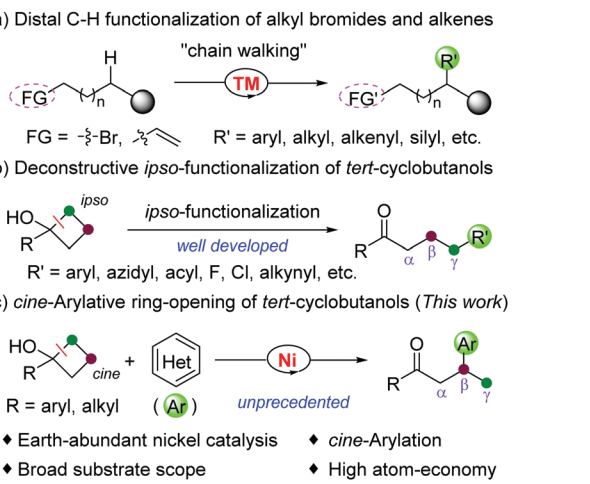
In previous literature, *tert*-cyclobutanols are widely studied for C–C bond activation exclusively leading to the formation of ordinary γ-substituted ketones. Herein, we first report a nickel-catalyzed *cine*-arylation of *tert*-cyclobutanols with indoles to access β-aryl ketones with an unusual site-selectivity at the C3-position of *tert*-cyclobutanols. The reaction features earth-abundant nickel catalysis, excellent regioselectivity, high atom-economy, and broad substrate scope.

Transition-metal catalyzed site-selective functionalization of inert C–H bonds is synthetically attractive yet challenging in organic chemistry. In this regard, great efforts have been devoted to the development of efficient strategies for selective incorporation of functional groups from the proximal to more challenging distal C–H bonds with or without the assistance of directing groups.[1,2] Notably, an expedient way to access selective distal C–H functionalization relies on metal migration *via* an iterative β-elimination/migratory reinsertion, also termed as a "chain walking" process, which can be hardly achieved by other conventional methods (Scheme 1a).[3] For instance, Martin and coworkers described an elegant nickel-catalyzed switchable site-selective carboxylation of alkyl bromides.[4] The *in situ* generated alkyl nickel species from bromoalkanes undergoes a divergent migration depending on the reaction temperature, leading to the formation of linear or branched carboxylic acid selectively. Although an unusual site-selectivity towards C–H bonds has been addressed, the transformations are often limited in substrates, such as linear alkyl olefins and bromides.[4,5] Further extending the scope of available substrates and novel coupling reactions merging selective C–H functionalization is still highly desirable.

On the other hand, C–C bond cleavage is blossoming as an alternative tool for the diversification of readily accessible cyclic skeletons.[6] This approach renders 1,*n*-bifunctionalized acyclic alkanes with a variable chain length dependent on the ring size. Among them, cyclobutanols are versatile building blocks that are capable of producing γ-substituted ketones *via* either a radical β-fragmentaion[7] or an organometallic β-carbon elimination[8] enabling a ring-opening process (Scheme 1b). As a result, a range of γ-(or *ipso*-) functionalization reactions such as halogenation, azidation, cyanation, arylation, alkynylation, *etc*. have been successfully developed over the past several decades.[7,8] In these events, however, the functional groups are exclusively introduced into the C2 (or C4) position, and the deconstructive functionalization of alicyclic hydrocarbons incorporating substituents adjacent to the cleaved C–C bond (*cine*-functionalization)[9] remains unexplored.

In light of the fantastic chemistry of *cine*-functionalization and diverse catalytic reactivity of nickel salts,[10] we envisioned an unprecedented nickel-catalyzed formal dehydrogenative coupling reaction[11] merging a C–C bond cleavage and migrated C–H functionalization.[12] Such a cascade process was visualized operating: (i) ring-opening of cyclobutanols *via* C–C bond cleavage; (ii) nickel-induced olefin isomerization; (iii) *cine*-arylation *via* a Michael



Scheme 1 Strategies for distal functionalization.

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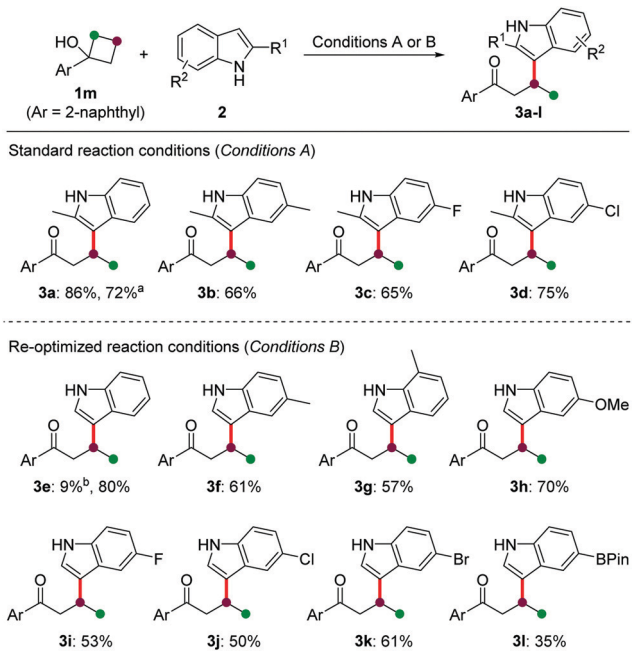
addition. Furthering our continued research work on nickel catalysis,[13] we herein present the first nickel-catalyzed *cine*-arylative ring-opening reaction of *tert*-cyclobutanols with indoles (Scheme 1c). Note that the C3-position of *tert*-cyclobutanols instead of the ordinary C2 or C4-position can be selectively functionalized thus featuring excellent regioselectivity and high atom-economy in this protocol.

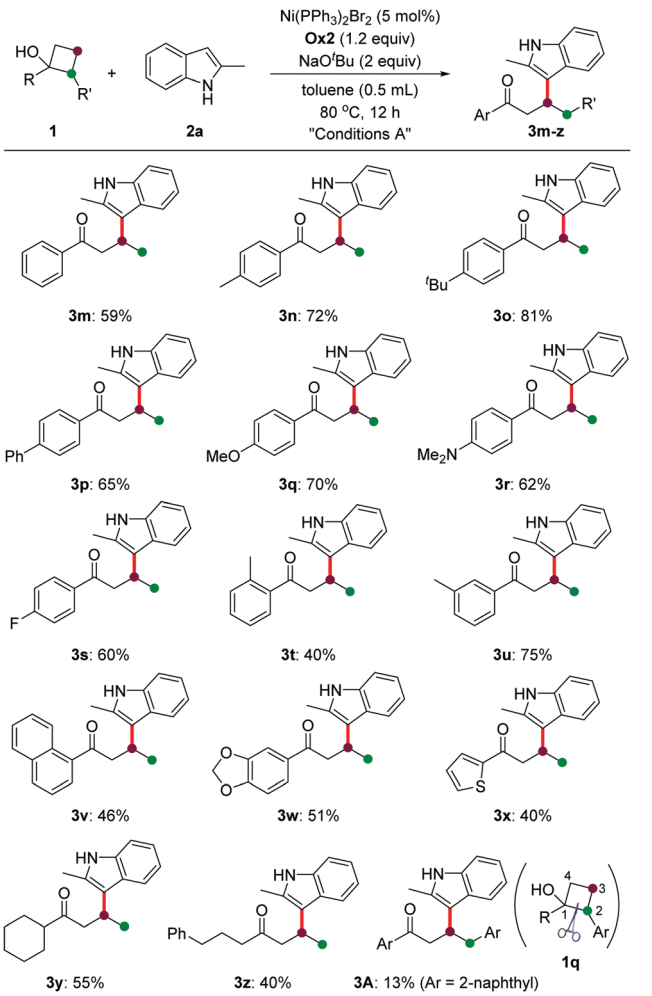
The standard reaction conditions in Scheme 2 were obtained by screening various reaction parameters (see the ESI† for details). We then commenced evaluating the substrate scope of indoles. As with the model substrate **2a**, other 2-methylindoles with different substituents at the 5-position were subjected to the optimized reaction (conditions A) providing the corresponding products in moderate to good yields (**3a–d**, Scheme 2). To further extend the generality of indole, we employed parent indole **2e** as a coupling partner instead of **2a**. Unfortunately, the desired product **3e** was isolated in a low yield (9%) under the standard reaction conditions. We again screened the reaction parameters and the yield of **3e** could be improved significantly by employing conditions B. In general, indoles bearing electron donating groups showed superior reactivity over those with electron withdrawing ones (**3f–l**, Scheme 2). Of note, the halogens such as Cl or Br and the BPin group were compatible in the reaction (**3j–l**, Scheme 2). Eventually, a gram-scale reaction of **1m** and **2a** was conducted. To our delight, the reaction proceeded smoothly under the standard reaction conditions affording the product **3a** in 72% yield.

Next, we continued to investigate the substrate scope of *tert*-cyclobutanols. First, 1-aryl substituted cyclobutanols were examined under the standard reaction conditions. A range of phenyl groups with electron donating groups were fairly tolerated giving the products in good yields (**3m–s**, Scheme 3). The reaction of *tert*-cyclolbutanols bearing *o*-tolyl or 1-naphthyl groups proceeded sluggishly, presumably due to the steric hindrance of alcohols (**3t** and **3v**, Scheme 3). 1-(Benzo[*d*][1,3]dioxol-5-yl)cyclobutan-1-ol **1k** and 1-(thiophen-2-yl)cyclobutan-1-ol **1l** were also viable substrates delivering the corresponding product **3w** and **3x** in 51% and 40% yield, respectively. In addition, less steric 1-alkyl substituted cyclobutanols underwent the transformation smoothly to provide the desired products in moderate yields (**3y–z**, Scheme 3). Finally, the reaction of 1, 2-disubstituted cyclobutanol **1q** with **2a** was examined and the product **3A** was isolated albeit in a low yield (**3A**, Scheme 3).

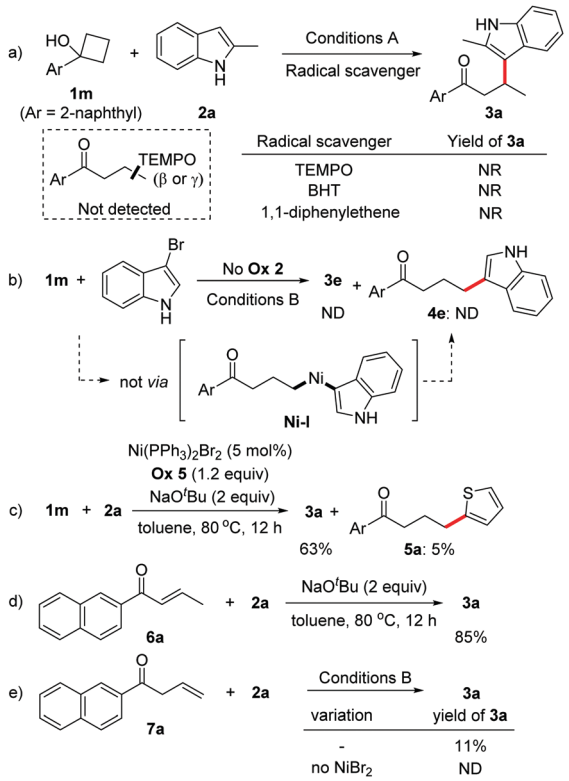
Further experiments were carried out to shed light on the plausible reaction mechanism. We first conducted a radical trapping experiment by using TEMPO, BHT, and 1, 1-diphenylethene as radical scavengers. As a result, all the reactions were thoroughly inhibited which suggested that a radical pathway might be involved in this transformation (Scheme 4a). However, the TEMPO-adduct could not be isolated



Scheme 2 Substrate scope of indoles. Conditions (A): **1m** (0.2 mmol), **2** (0.4 mmol), $Ni(PPh_3)_2Br_2$ (5 mol%), **Ox2** (1.2 equiv.), NaO^tBu (2 equiv.), Toluene (0.5 mL), at 80 °C for 12 h. Conditions (B): **1m** (0.2 mmol), **2** (0.4 mmol), $NiBr_2$ (20 mol%), **L3** (20 mol%), **Ox5** (1.2 equiv.), NaO^tBu (2 equiv.), Toluene (0.5 mL), at 80 °C for 12 h. [a] Conducted on a 5 mmol scale. [b] Under the standard reaction conditions (conditions (A))



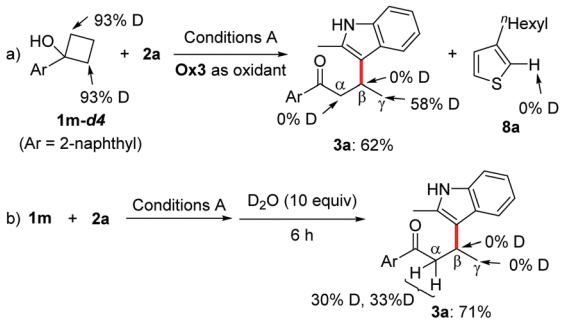
Scheme 3 Substrate scope of *tert*-cyclobutanols. Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(PPh_3)_2Br_2$ (5 mol%), **Ox2** (1.2 equiv.), NaO^tBu (2 equiv.), toluene (0.5 mL), at 80 °C for 12 h.



Scheme 4 Preliminary mechanistic experiments.

from the reaction. Next, we conducted the reaction of **1m** with 3-bromoindole in the absence of an oxidant (Scheme 4b). As a result, both **3e** and **4e** could not be detected which indicated that the intermediate **Ni-I** might not be involved in the catalytic cycle, while the **Ni-V** in Scheme 6 was a plausible intermediate since the reaction of **1m** with **2a** produced the side product **5a** albeit in a low yield (Scheme 4c). Furthermore, we examined the reaction of unsaturated ketones **6a** and **7a** with indole, respectively (Schemes 4d and e). Consistent with our initial assumption, product **3a** was isolated exclusively in both reactions. It could be inferred that **6a** and **7a** are probably the key intermediates in the migration reaction. However, no **3a** could be obtained if the reaction of **7a** with **2a** was conducted in the absence of nickel salt (Scheme 4e).

Deuterium experiments were then performed to clarify the detailed process for *cine*-arylation (Scheme 5). First, we prepared the deuterated *tert*-cyclobutanol **1m-*d*$_4$** and subjected it to the standard reaction by using **Ox3** as an oxidant (Scheme 5a). The product **3a** was isolated in 62% yield and the H/D exchange was examined by ^{1}H NMR analysis. It turned out that the deuterium atoms at one C2-position of **1m-*d*$_4$** almost remained intact at the γ-position of the product **3a-*d*$_2$**. However, the deuterium atom at the other C2-position was fully replaced by a hydrogen atom at the α-position of **3a-*d*$_2$** due to the rapid keto–enol tautomerism in the presence of a strong base.[14] This rapid H/D exchange was further supported by conducting a model reaction treated with D_2O (Scheme 5b). In addition, no deuterium was incorporated into the β-position of **3a-*d*$_2$** and the 3-hexylthiophene **8a** (Scheme 5a). These

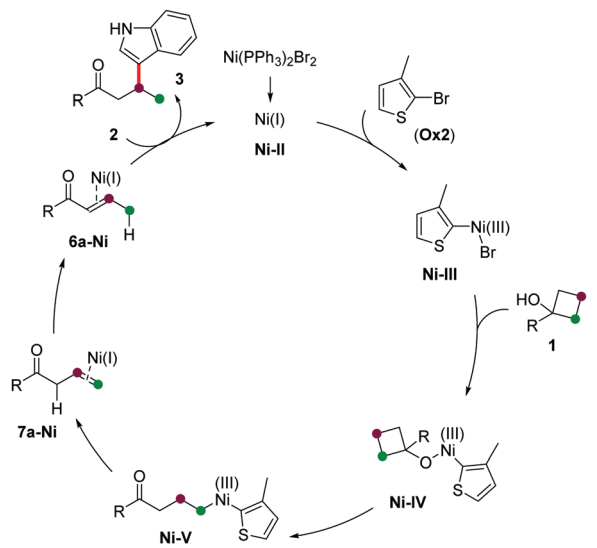


Scheme 5 Deuterium experiments.

deuterium experiments indicated that the alkene isomerization might take place *via* a Ni(I)-involved 1,3-*H* shift[15] and the resultant conjugated ketone was readily captured by the indole with the assistance of NaO^{t}Bu.

A possible reaction mechanism is depicted in Scheme 6 based on the preliminary mechanistic experiments and previous literature.[15–18] We conjecture that a low-valent nickel species **Ni-II** *in situ* generated from the nickel salt may trigger the catalytic reaction.[16] The oxidative addition of **Ox2** to **Ni-II** yields the intermediate **Ni-III** followed by ligand exchange with *tert*-cyclobutanol. The formed Ni alcoholate **Ni-IV** undergoes a ring opening process *via* C–C bond cleavage to produce an alkyl nickel species **Ni-V**. A reductive β-H elimination reaction[17] takes place to generate an intermediate **7a-Ni** which further transforms to **6a-Ni** *via* a radical alkene isomerization.[15] Finally, the Michael addition of **6a** with indole **2** provides the product **3** and releases the **Ni-II**.[18]

In conclusion, the first site-selective formal dehydrogenative coupling reaction of *tert*-cyclobutanols with indoles has been successfully developed. Surprisingly, an array of β-indolyl ketones were obtained in moderate to good yields featuring readily available nickel catalysis, excellent regioselectivity and a high atom economy. Further investigations on the site-selective



Scheme 6 Plausible reaction mechanism.

functionalization of less strained cycloalcohols enabled by nickel catalysis are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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