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Nickel-catalysed chemoselective C-3 alkylation of indoles with alcohols through borrowing hydrogen method

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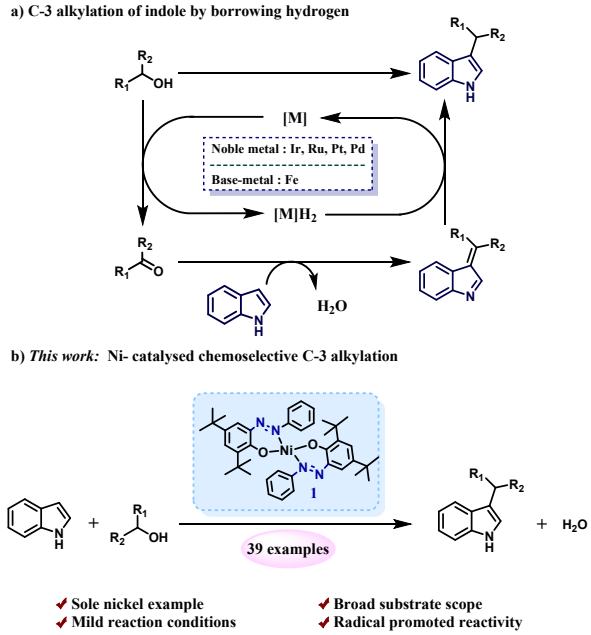
An inexpensive, air-stable, isolable nickel catalyst is reported that can perform chemoselective C3-alkylation of indoles with a variety of alcohols following "borrowing hydrogen". A one-pot, cascade C3-alkylation starting from 2-aminophenyl ethyl alcohols, and thus obviating the need for pre-synthesized indoles, further adds to the broad scope of this method. The reaction is radical-mediated, and is significantly different from other examples, often dictated by metal-ligand bifunctionality.

An indole is a privileged heterocycle that is found in a vast array of natural products, fine chemicals, and pharmaceutically important molecules.[1, 2] Substituted indoles often exhibit excellent binding activity to a large number of receptors with high affinity.[3] In this context, new methods toward their efficient synthesis and selective functionalization have been drawing great attention over many years. The earlier known pathway for the alkylation of indoles is the Friedel-Crafts reaction with haloalkanes and related alkyl agents mediated by Lewis acid.[4, 5] Furthermore, several Pd catalysts have also been scrutinized to steer C3-alkylation, where the alkyl halides, triflates and nonaflates have been used as the alkyl source.[6, 7] However, these methods often become problematic owing to over alkylation, toxic and mutagenic nature of many alkyl halides as well as the production of large quantity of inorganic waste. As a solution to this problem, methods relying on borrowing hydrogen (BH) which is atom economic, hydrogen neutral, and generates water as byproduct, has emerged as an extremely versatile technique.[8-11]

Utilizing BH-based technique, Grigg pioneered the C3-alkylation of indoles with benzyl alcohols as the alkyl source in the presence of an Ir-catalyst, $[Cp^*IrCl_2]_2$.[12] Several other homogeneous and heterogeneous catalysts have been developed further that primarily employ other precious metals such as Pt, Pd and Ru for this alkylation reaction (Scheme 1a).[13-17] In recent times, there is a significant shift of the focus to employ sustainable and less toxic base metals as the replacement of noble metals in catalysis. Notably, the base metal representatives for effective C3-alkylation of 1*H*-indole is very scarce and limit to only few examples of iron complexes. The groups of Piersanti,[18] Morrill[19] and Renaud[20] have used an iron phthalocyanine, and Knölker-type iron complexes for the alkylation process.



Scheme 1: Alkylation of indole via BH method catalysed by **1**

To this end, a significant opportunity remains for other base-metal catalysts that can provide a sustainable and easy synthesis method of this value-added product. Toward this goal, we chose to explore the potential of a nickel catalyst since nickel is cheap, it is the second most abundant transition metal present in the earth's crust, and fairly benign from toxicology side.[21] Herein, we wish to report a very inexpensive and air-stable, homogeneous nickel catalyst that can synthesize a plethora of C3-alkylated indoles under relatively mild reaction conditions. To the best of our knowledge, this is the single example, where a nickel catalyst monoalkylates indole in a chemoselective manner, and can further do the same by a cascade reaction, starting from amino alcohols. Furthermore, the reaction operates via a radical

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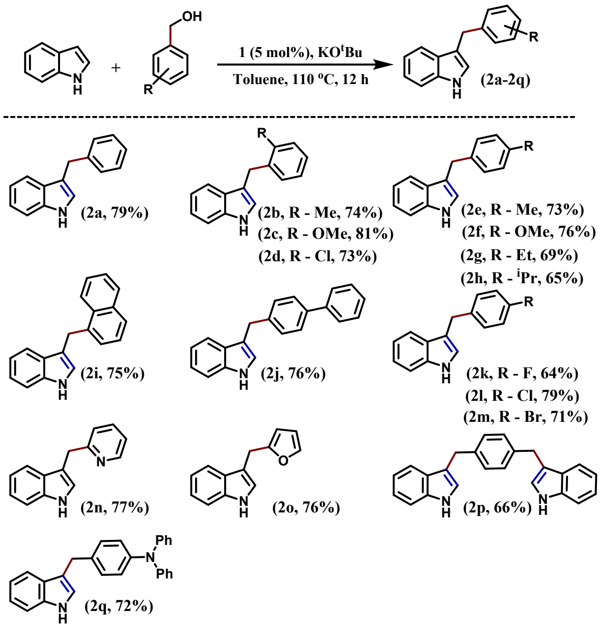
mechanism, which is truly different from other catalysts developed for this purpose, relying on metal-ligand cooperative bond activation.

In our continuing interest on base-metal catalysed BH or dehydrogenative coupling reactions, we recently discovered a nickel azophenolate complex, **1** which is highly active in reducing the polarized C=N bond to result alkylation of amines.[22] Based on both experimental results and supporting DFT calculations, we delineated the key features of the catalyst where a facile $2e^-/2H^+$ redox conversion between azo-hydrazo functionality plays a preponderant role in the dehydrogenation reactions. The dehydrogenating ability of the catalyst promises the generation of a more active and electrophilic carbonyls in a controlled manner, such that alkylation of indoles can be envisaged (Scheme 1b). To examine the catalytic ability of **1** toward C-3 alkylation of indole, various reaction parameters were screened with indole and benzyl alcohol as model substrates. When a mixture of indole (1 mmol), benzyl alcohol (2 mmol), **1** (2.5 mol%) and KO^tBu (0.25 eq) in 2 mL toluene was heated at 110 °C, 3-benzyl-1*H*-indole **(2a)** was obtained in only 16% yield. In an attempt to improve the yield of **2a**, catalyst loading was increased to 5 mol% and the amount of base loading was also screened (entries 2-4, Table S1). The reaction gave best yield when the catalyst loading was 5 mol% and the reaction was performed at 110 °C (entry 4). Surveying the scope of other bases like KOH, NaOH and K_2CO_3 resulted poor conversion to product under similar reaction conditions (entry 6-8, Table S1). While the use of NaO^tBu offered moderate yield (entry 9), further screening of the reaction conditions revealed KO^tBu was an effective base, and the reaction was complete in 12 h with its sub-stoichiometric (0.7 equiv) loading. Notably, the necessity of KO^tBu to promote the reaction was originated from its ability as a mild reductant that is required to initiate the azo-radical generation and further hydrogenation following a radical pathway.[22] Control reactions in the absence of any base and catalyst **1** completely failed to deliver the product, supporting the necessity of both components for the reaction (entries 10-11, Table S1). Only metal precursor, $NiCl_2$ was also unable to promote the reaction proving the unique catalytic activity of the complex **1** (entry 12, Table S1).
After having the optimized reaction conditions in hand, we attempted to test the generality of the developed protocol. As described in Table 1, a wide array of primary benzyl alcohols bearing both electron-donating and electron withdrawing groups was used as the source of alkyl group, resulting in 3-substituted indoles in good to excellent yield. Several ortho-substituted benzyl alcohols ranging from -Me, -OMe, -Cl offered the respective alkylated product (**2b**, **2c**, **2d**) in 73-81% yields. Similarly, the para-substituted benzyl alcohols ranging from alkyls (**2e**, **2g**, **2h**), alkoxy (**2f**), and halides (**2k**-**2m**) were also equally applicable as alkylating partner and the corresponding indoles were isolated in good yield. Similarly, 3-naphthylindole (**2i**) was constructed in 75% yield, using 1-naphthol as the alkylating agent under this reaction protocol.

Furthermore, a biphenyl group was installed at the 3-position of the indole (**2j**) starting from 4-phenyl benzyl alcohol. Intriguingly, alcohols with heterocyclic rings such as pyridine and furan survived well through the reaction conditions and furnished **2n** and **2o** in 76-77% yields. Similarly, a diol substrate, such as 1,4-phenylenedimethanol furnished the bisindole product **2p** in 66% yield. Also, a gram scale reaction resulted **2a** in 68% yield, proving that the scaling up of the reaction protocol is feasible. Encouragingly, our reaction conditions employed lower temperature and lesser reaction time compared to many catalysts that alkylate indoles from alcohols. Of note, our catalyst is advantageous to the iron catalysts based on Knölker's system, where pre-activation by sacrificial reagent Me_3NO or UV exposure is necessary.

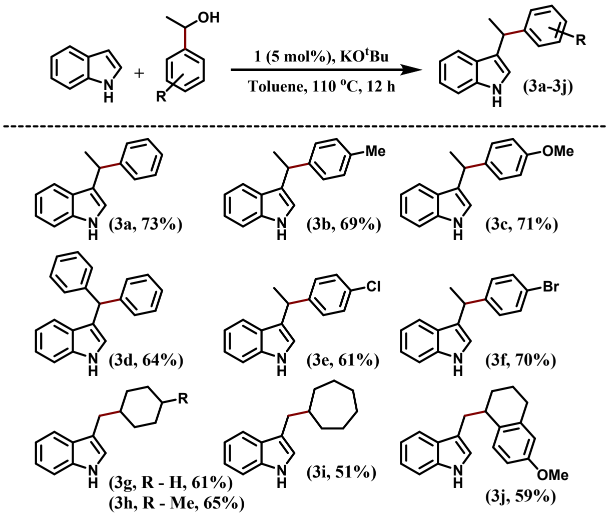
Table 1: Substrate scope for C-3 alkylation of indole with primary alcohols



Reaction conditions: **1** (5 mol%, with respect to indole), indole (1 mmol), primary alcohol (2 mmol), KO^tBu (0.7 mmol), toluene (2 mL), 110 °C (oil bath), 12 h.

After the successful alkylation with primary alcohols, we examined the scope of secondary alcohols (Table 2). As can be anticipated,

Table 2: Substrate scope of C-3 alkylation of indole with secondary alcohols



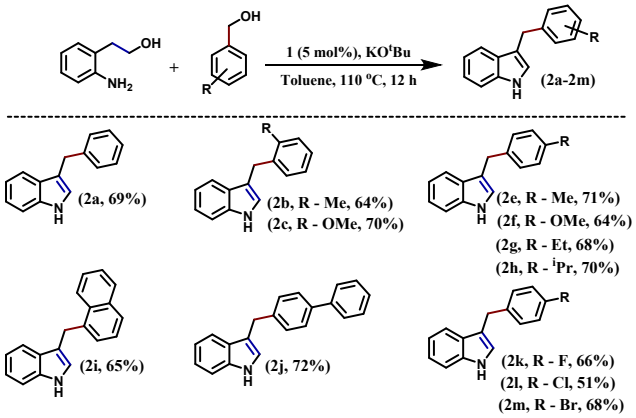
Reaction conditions: **1** (5 mol%, with respect to indole), indole (1 mmol), secondary alcohol (2.2 mmol), KO^tBu (0.7 mmol), toluene (2 mL), 110 °C (oil bath), 12 h.

secondary alcohols are less amenable to both condensation and hydrogenation steps compared to primary alcohols and regarded as challenging substrates for alkylation reactions. Accordingly, when a test substrate 1-phenyl ethanol was chosen, the C-3 alkylated 1*H*-3-(1-phenylethyl)-indole, **3a** was isolated in 73% yield under the same reaction conditions. Moreover, other secondary alcohols with *p*-Me and -OMe groups also assembled the 3-alkylated indole products (**3b**-**3c**) in 69-71% yields. Encouragingly, bulky secondary alcohols such as diphenylmethanol gave **3d** in 64% yield. In comparison, the halide substituted 1-phenyl ethanols furnished the respective substituted indoles (**3e**-**3f**) in 61-70% yields. Notably, alicyclic alcohols such as cyclohexanols were alkylating indoles successfully to offer products **3g**-**3h** in 61-65% yields. Additionally, cycloheptanol alkylated indole to give **3i** in moderate yield.

We further reason, since **1** competently dehydrogenates alcohols, the final product will likely be assembled even starting from amino alcohols that would prepare indole *in situ*. Starting with an amino alcohol will further increase the applicability of the alkylation protocol. The groups of Grigg and Yamaguchi have assembled indoles starting from amino alcohols employing the iridium catalyst.[12, 23] Henceforth, we started the reaction with 2-(2-aminophenyl) ethanol and benzyl alcohol as the model substrates. Notably, the N-heterocyclization of 2-(2-aminophenyl) ethanol and its derivatives is an attractive method, since such alcohols are easily obtained from 2-nitro toluene derivatives and formaldehyde.[24] To our delight, the final product **2a** was obtained in 69% yield via this one-pot synthesis protocol, with a 5% loading of the catalyst. A quick optimization for this reaction suggested that the reaction can perform well at 110 °C, under essentially same reaction conditions. A thorough literature survey reveals that, this is the only example of homogeneous nickel catalyst that performs oxidative N-heterocyclization of amino alcohols, followed by a chemoselective C3-alkylation of the *in situ* generated indole.

Applying this protocol, we have synthesized an array of 3-susbtituted indoles (Table 4), which are identical to the products from alkylation of prefabricated indoles. To our delight, in this one-pot cascade reaction, a large number of substituted benzyl

Table 3: Table 1: Substrate scope for the synthesis of C-3 alkylated indole from 2-(2-aminophenyl) ethanol

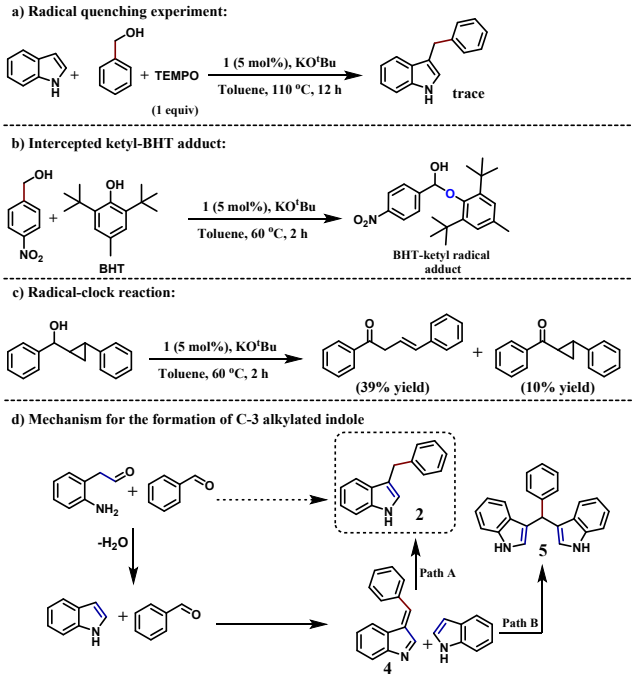


Reaction conditions: **1** (5 mol%, with respect to indole), 2-(2-aminophenyl) ethanol (1 mmol), primary alcohol (2.2 mmol), KO^{t}Bu (0.7 mmol), toluene (2 mL), 110 °C (oil bath), 12 h.

alcohols were converted to alkylated indoles in good yields. The overall catalytic cascade consists of two consecutive steps by **1**. The first part is the oxidative cyclization of the amino alcohol, while the second one is the C-3 alkylation of the *in situ* generated indole (Scheme 2d).

As shown in Table 3, the model substrates under optimized reaction conditions assembled 3-benzyl-1*H*-indole in 69% yield. The ortho-substituted alcohols bearing electron-donating groups such as -Me, -OMe offered the respective alkylated product (**2b**, **2c**) in good yields. Subsequently, the alcohols with an electron donating group at para-position were equally efficient in alkylating the *in situ* generated indole (**2e-2h**) in 64-71% yields. Notably, 1-naphthol and 4-phenyl benzyl alcohol were also used as alkylating partners to give the corresponding indole (**2i-2j**) in 65-72% yields. Encouragingly, alcohols with halide substitution survived well under this reaction protocol to give **2k-2m**, in 51-68% yields.

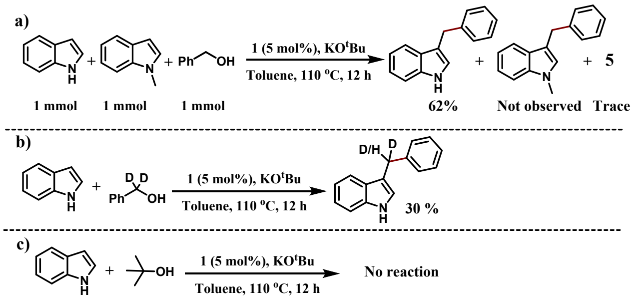
Mechanistically, the dehydrogenation of an alcohol to generate electrophilic carbonyls, follows a radical pathway. To prove that the reaction is radical mediated, we added a radical quencher, TEMPO (1 equiv) to the reaction mixture and found the reaction was fully prohibited (Scheme 2a). As a compelling proof for the radical-driven hydrogen atom transfer step from alcohol, we were able to intercept a resulting ketyl radical as its BHT adduct (Scheme 2b). The ketyl-BHT product was identified by high-resolution mass spectrometry (Figure S2). Additionally, a radical clock substrate, phenyl-(2-phenylcyclopropyl) methanol offered major amount of ring-opened product (39%) during the dehydrogenation reaction, further substantiating the radical mechanism. Significantly, the adoption of radical mechanism is distinctly different from other metal catalysed C3-alkylation of indoles.



Scheme 2: a)-c) Experiments supporting radical mechanism. d) Proposed mechanism for the formation of C-3 alkylated indole from 2-(2-aminophenyl) acetaldehyde, and formation of **5**.

After alcohol oxidation, the nucleophilic attack of the indole to the carbonyl of an aldehyde or ketone generates an alkylideneindolenine, **4** (this is a vinylogous imine, Scheme

2d) upon dehydration. Often alkylation of indole is marred with a byproduct, bis(3-indolyl) methane (**5**) which originates from the Michael addition of an indole to **4** (Path B).[25] Interestingly, our optimized reaction conditions supressed the formation of **5**, offering the alkylated indoles as the sole product. Since, the azo group in the catalyst backbone can be reversibly converted to the hydrazo moiety, the borrowed hydrogens from the alcohol substrates remain stored in the ligand backbone. This hydrazo will hydrogenate further the *in situ* generated vinylogous imine **4** to produce C-3 alkylated indole (Path A). To prove unambiguously that the alcohol was the source of hydrogen during the hydrogenation of **4**, we took 1 equiv of benzaldehyde and benzyl alcohol each, and the product **2a** was isolated in 66% yield (section 5c, ESI). This suggests that **4** forms the direct reaction of the aldehyde with indole and the borrowed hydrogens from benzyl alcohol dehydrogenation, hydrogenates it to form the alkylated indole. To further examine whether the activated indole ring has an influence on the reactivity, we started with an N-methylated indole, so that no deprotonation by a base is probable. A competition reaction was performed considering 1-*H* indole and its *N*-methyl analogue with 1 equiv of benzyl alcohol that yielded only 3-benzyl-1*H*-indole, **2a** in 62% yield. This result implicates that the base deprotonates the indole and makes it activated further for the electrophilic substitution reaction (Scheme 3a).



Scheme 3: Control experiments for the synthesis of C-3 alkylated indole.

To establish that the reaction is truly a borrowing hydrogenation catalysis, we studied the reaction further with d_2-benzyl alcohol. Significant amount of deuterium incorporation (30%) in the final product **2a** affirms the process to be BH in nature (Scheme 3b). To ensure further, that no alkylation happens through the formation of carbocation, we chose *t*-butanol as the alkylating substrate and observed only starting indole remained intact (Scheme 3c). Notably, under our reaction conditions, the C3-alkylation is exclusive and no formation of N-alkylated product is detected.

In conclusion, we described herein an efficient nickel catalyst that can effectively conduct the selective C3-alkylation of 1*H*-indoles with a variety of alcohols. The ease of the process prompted us further to perform C3-alkylation starting from 2-(2-aminophenyl) ethanol, rather than prefabricated indoles. The radical mechanism for the reaction is distinctly different from multiple other catalysts explored in this direction.

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1. T. Kagata, S. Saito, H. Shigemori, A. Ohsaki, H. Ishiyama, T. Kubota and J. i. Kobayashi, *J. Nat. Prod.*, 2006, **69**, 1517-1521.
2. T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y.-H. Wu and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2105-2108.
3. G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449-4465.
4. Y. Hui, Q. Zhang, J. Jiang, L. Lin, X. Liu and X. Feng, *J. Org. Chem.*, 2009, **74**, 6878-6880.
5. Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun.*, 2010, **46**, 3004-3006.
6. M. Yamaguchi, R. Hagiwara, K. Gayama, K. Suzuki, Y. Sato, H. Konishi and K. Manabe, *J. Org. Chem.*, 2020, **85**, 10902-10912.
7. S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873-2920.
8. R. H. Crabtree, *Chem. Rev.*, 2017, **117**, 9228-9246.
9. T. Irrgang and R. Kempe, *Chem. Rev.*, 2019, **119**, 2524-2549.
10. B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595-1607.
11. C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249-260.
12. S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299-3302.
13. C. Chaudhari, S. M. A. H. Siddiki, K. Kon, A. Tomita, Y. Tai and K.-i. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1064-1069.
14. N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926-2927.
15. N. Biswas, R. Sharma and D. Srimani, *Adv. Synth. Catal.*, 2020, **362**, 2902-2910.
16. S. Imm, S. Bähn, A. Tillack, K. Mevius, L. Neubert and M. Beller, *Chem. – Eur. J.*, 2010, **16**, 2705-2709.
17. S. M. A. H. Siddiki, K. Kon and K.-i. Shimizu, *Chem. – Eur. J.*, 2013, **19**, 14416-14419.
18. G. Di Gregorio, M. Mari, F. Bartoccini and G. Piersanti, *J. Org. Chem.*, 2017, **82**, 8769-8775.
19. M. B. Dambatta, K. Polidano, A. D. Northey, J. M. J. Williams and L. C. Morrill, *ChemSusChem*, 2019, **12**, 2345-2349.
20. C. Seck, M. D. Mbaye, S. Gaillard and J.-L. Renaud, *Adv. Synth. Catal.*, 2018, **360**, 4640-4645.
21. V. P. Ananikov, *ACS Catal.*, 2015, **5**, 1964-1971.
22. A. K. Bains, A. Kundu, S. Yadav and D. Adhikari, *ACS Catal.*, 2019, **9**, 9051-9059.
23. K.-i. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2002, **4**, 2691-2694.
24. S. Shimura, H. Miura, K. Wada, S. Hosokawa, S. Yamazoe and M. Inoue, *Catal. Sci. Technol.*, 2011, **1**, 1340-1346.
25. M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250-2293.

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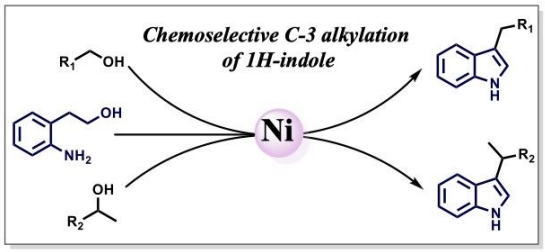

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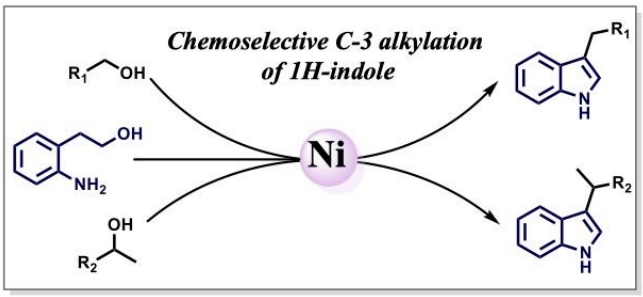

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