Regioselective Catalytic Alkylation of *N*-Heterocycles in Continuous Flow

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A novel method for C–H functionalization of heteroaromatic rings by using continuous-flow reactors is reported. Direct alkylation reactions were investigated under heterogeneous catalytic conditions using simple transition metal catalysts at elevated temperature and pressure. As a model reaction, the alkylation of indole was attempted using cheap Raney® Nickel catalyst. Alcohols served both as alkylating agent and as reaction media. The targeted 3-alkyl-indoles were obtained in moderate to good yield with reasonable selectivity. Transient protection on the N-atom increased the selectivity up to 80%. The scope and limitations were also investigated. In summary, direct alkylation with alcohols represents a rapid (residence time of <1 min) and traceless process with high atom economy (88–92%, in those cases where transient protection was not applied).

Keywords: flow chemistry, C–H activation, catalytic alkylation, nickel catalysis

1. Introduction

Direct C–C bond formation is rather uncommon in organic chemistry and typically requires multistep transformations [1]. In the 20th century, new catalyst systems opened the way for routine functionalization of relatively inert molecules. The widely used transition-metal catalyzed cross-coupling reactions involve an organometallic species and another organic molecule bearing a good leaving group (e.g., halides or tosylates). Unfortunately, such reactions generate waste, and the reactants or the side-products are often dangerous or toxic materials.

Replacing the standard cross-coupling methods by a direct, selective, and mild process that produces smaller amount of side products and waste would be highly attractive transformations for the pharmaceutical-, agro-, dye-, and polymer chemical industry [2, 3]. Currently, the most common catalysts for these type of transformations are Pd, Pt, Rh, Ru, Ir, and Os complexes [4–7]. These catalysts are expensive, and the reaction normally takes place in the homogeneous phase; accordingly, long and tedious workup is often necessary.

In the present work, cheap heterogeneous catalyst systems were investigated to perform C–C bond formation on substrates without leaving groups. As an additional advantage, neither acidic nor basic additives were applied.

2. Results and Discussion

Several research groups have been working on the alkylation of indoles as well as focusing on developing alternative (or green) procedures [8–11]. In order to achieve regioselectivity on indole derivates and related heterocycles alkylation, methods have been widely investigated [12–17]. The nucleophilic nature of the carbon atom in the 3-position [18] makes the indole susceptible towards direct alkylation reactions. Indole and its derivatives play an important role in many different areas of the chemical industry [19]. Therefore, we turned our attention to investigate the catalytic direct 3-alkylation of indole in continuous-flow systems.

Volk et al. reported the alkylation of oxindoles in the 3-position with primary alcohols using Raney® Nickel [20–22]. According to Shilov et al., this type of reaction can be referred as an indirect C–H activation [6], while others characterized this catalytic reaction as "borrowing hydrogen" methodology [23].

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Our objective was to investigate the direct alkylation of indoles with alcohols in the presence of Raney® Nickel type catalysts in a continuous-flow environment. The regioselective alkylation of indole was carried out in a modular flow instrument (Phoenix Flow Reactor™, ThalesNano Inc.). The reactions were carried out in a 1/4 inch outer diameter stainless steel high-performance liquid chromatography (HPLC) column with 1 mL inner volume. This column (catalyst cartridge) was packed with Raney® Nickel catalyst. The void volume of the catalyst bed is approximately 0.2 mL. The catalyst cartridge can be heated up to 450 °C. The reactor uses HPLC pumps to transport the solution. The Phoenix Flow Reactor™ can be connected with an H-Cube Pro™ reactor, which can control the system pressure up to 100 bar. The pressure allows keeping the organic solvents in liquid phase. This high temperature and pressure range has opened a novel "process window" for such reactions [24].

The use of heterogeneous catalyst simplifies product isolation and purification. As an initial test reaction, ethylation of indole (**1**) was chosen (Scheme 1).

Former attempts with a similar flow system showed that reaction temperature below 200 °C produces predominantly *N*-alkylated products [25]. These observations led to the conclusion that cleavage of the carbon–hydrogen bond might require higher temperature. The following reactor setup was assembled for the study (Figure 1).

In order to reach high conversion and good selectivity during the synthesis of **1a**, the parameters were optimized using a 0.1 M solution of the substrate (Table 1). Firstly, the effect of the temperature and the residence time (which depends on the flow rate) was investigated. The applied pressure was the highest achievable value on H-Cube Pro™ (100 bar). At lower pressures, sample collection became difficult due to the H_2 gas evolution. No desired product (**1a**) was formed at 200 °C at 0.5 mL/min flow rate. However, when the temperature was raised to 300 °C, the alcohol oxidation became so intense that the adjusted 100 bar pressure dropped and failed to keep the solvent in liquid phase. Evaporation of the solvent has dried the catalyst bed and caused clogging of the system.

Full conversion was achieved at 0.5 mL/min flow rate in the temperature range of 225–275 °C. Unfortunately, in spite of the good conversion, the selectivity to **1a** remained moderate. At 275 °C, the 1,3-dialkylated **1c** was found to be the main product. The optimal parameter set leading to the synthesis of **1a** was found to be 250 °C at 0.5 mL/min flow rate.

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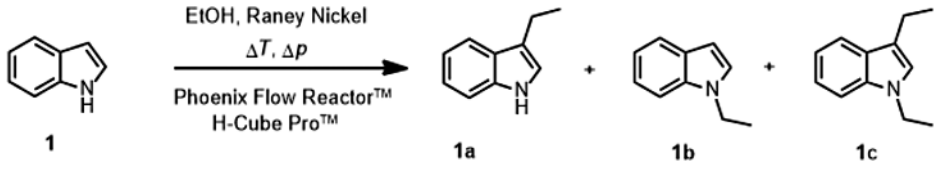
Scheme 1. Ethylation of indole at high temperature and pressure under flow conditions



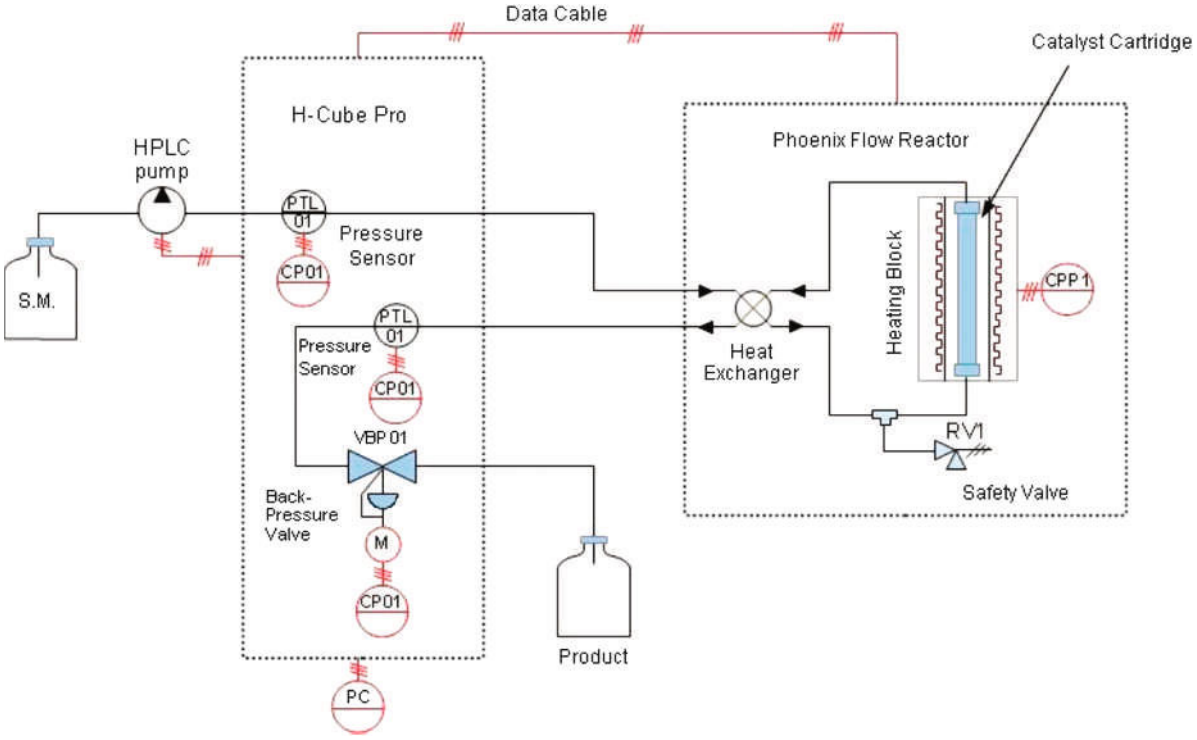


Figure 1. Modularly connected reactor system (a schematic view)

As a next step, the concentration dependence of the reaction was investigated. The applied indole derivatives are highly soluble in ethanol; hence, the concentration could be increased up to 0.5 M (Table 2).

The best selectivity towards **1a** was found at 0.2 M indole concentration. Unfortunately, concentration above 0.1 M resulted in a dark brown solution, which eventually caused blockage within the cartridge. Furthermore, 0.5 M indole concentration led to decreased conversion. Accordingly, 0.1 M concentration was chosen for further studies.

Longevity of heterogeneous catalysts is an important factor for practical applications. In case of a flow-through system, the starting materials reach the catalyst surface, and then, the product and the other formed species leave the reaction zone together with the solvent flow. This ability allows to protect the catalyst from poisoning and, therefore, to preserve its activity [26].

For longevity measurements, the optimized reaction conditions were used. After 24 hours of continuous running, the conversion of **1** decreased to 93%; however, the selectivity towards **1a** stayed constant within experimental error (Figure 2).

We envisioned that, upon transient protection [27] of the nitrogen atom, the amount of **1c** could be reduced. For this purpose, trimethylsilyl protecting group (TMS) seemed to be a reasonable choice. Chlorotrimethylsilane (TMS-Cl) was added to the solution of **1** in ethanol, and after a short stirring time, the mixture was passed through the flow reactor applying the same parameter set as before. High conversion rate was observed, and the selectivity

Table 1. Parameter optimization results of indole ethylation. General conditions: Raney® Nickel catalyst, 0.1 M **1** in abs. ethanol. Conversions and selectivities were determined based on GC–MS

Flow rate (mL/min)	Conversion (%)	**1a** (%)	**1b** (%)	**1c** (%)	Other (%)
200 °C					
0.5	41	<1	10	<1	32
225 °C					
0.5	86	32	30	22	16
0.75	80	30	32	21	17
250 °C					
0.5	>99	58	5	22	15
0.75	96	44	8	31	17
1.0	84	43	20	20	17
1.2	80	38	3	45	14
1.5	75	35	7	45	13
275 °C					
0.5	>99	27	<1	46	26
0.75	97	38	2	41	19
1.0	>99	44	6	34	16
1.2	98	20	3	56	21
1.5	>99	32	3	51	14
300 °C					
1.0	79	12	37	5	25
1.2	59	10	20	2	27
1.5	43	7	11	<1	25

Table 2. Concentration screening for indole ethylation. General conditions: Raney® Nickel catalyst, 250 °C, 0.5 mL/min. Conversions and selectivities were determined based on GC–MS

1 (mg)	$V_{(EtOH)}$ (mL)	Concentration (mol/dm^3)	Conversion (%)	**1a** (%)	**1b** (%)	**1c** (%)
58	10.0	0.05	>99	20	–	55
117	10.0	0.1	>99	58	5	22
234	9.7	0.2	97	58	–	16
351	9.5	0.3	>98	55	3	34
585	9.2	0.5	87	52	–	34

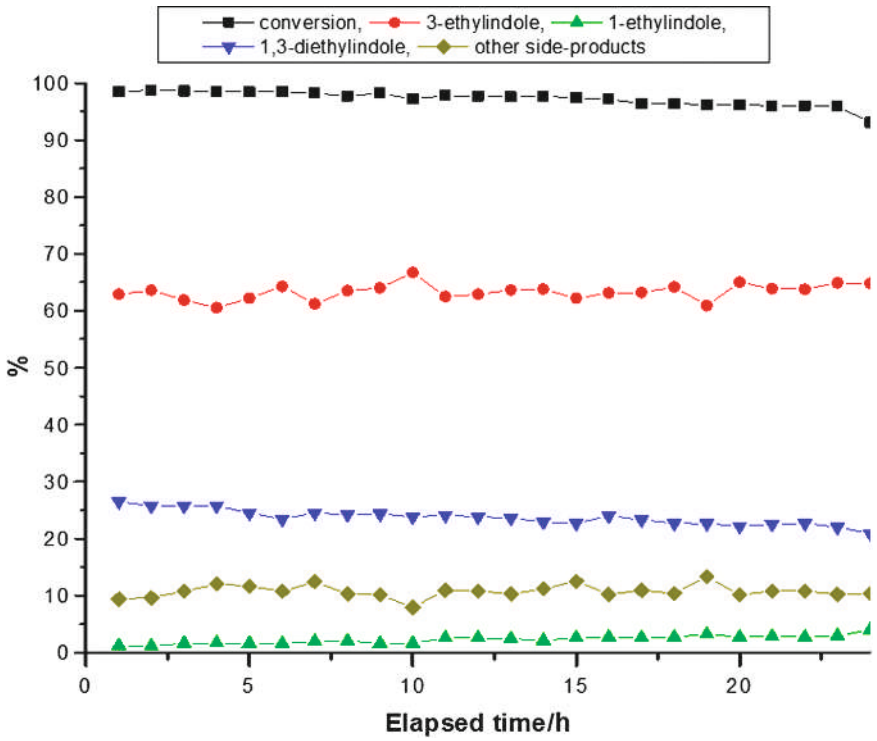


Figure 2. Longevity measurements for indole ethylation (based on GC–MS results), 250 °C, 0.5 mL/min, and 0.1 M solution at 100 bar pressure

reached 80%. As a drawback, the generated hydrochloric acid might be able to attack the nickel catalysts to form inorganic salts, which could also cause blockage in the cartridge. During the applied reaction time (<1 min), clogging was not observed.

Having these results in hand, we turned our attention towards alkylation using different alcohols and TMS protection (Table 3). At first, methanol was investigated. High temperatures led to decomposition of methanol to carbon monoxide and hydrogen on the activated nickel catalyst surface [28, 29]. As an additional limitation, to perform "borrowing hydrogen" type of reactions is not possible with tertiary alcohols.

The scope of the reaction was limited to primary and secondary alcohols. Alcohols with linear or branched alkyl chain with 3–5 carbon atoms were investigated. Indole is soluble in these alcohols, although the solubility slightly decreases with the increasing chain length. Fortunately, 0.1 M indole concentration was easily achieved with all the chosen alcohols.

The conversion was typically high (>90%) for these reactions, and the selectivity was >50% except for Entry 5 and 6. Primary alcohols gave the expected products with moderate to good yields. Interestingly, the reactions with isopropanol did not give the aromatic product. Gas chromatography–mass spectrometry (GC–MS) and nuclear magnetic resonance (NMR) measurements showed a fully reduced indole derivative (octahydro-*1H*-indole core) which was alkylated on its nitrogen atom (Table 3, Entry 7). The cyclic secondary alcohol, cyclohexanol (Table 3, Entry 5), gave the desired aromatic alkylated product with moderate conversion and selectivity.

As a comparison, we carried out the reactions shown in Table 3 without transient protection as well. The results (Table 4) clearly show the beneficial effect of TMS-Cl for C-3 selectivity. While the conversion rate was generally high, the selectivity was inversely proportional to the chain-length of the alcohol (Table 4).

The atom-economy (atom-efficiency, AE) [30] for these reactions are much higher than in the previously reported methods because of the lack of additives and reactants (Table 5). The only side-product is water; thus, the reaction can be referred as a traceless method. However, when the N-atom is transiently protected with TMS-Cl, the AE values were dropped significantly.

Additionally, nitrogen-containing heterocycles were tested in C–H functionalization. Substituted indole derivatives were targeted to examine the effect of the electron withdrawing or donating groups on the conversion and selectivity. 2-Methyl-indole was dissolved in ethanol, and the same parameter set was applied as in the former reactions (Scheme 2). To our delight, even without heteroatom protection, ~90% selectivity and 87.5% isolated yield were achieved.

This result suggests that an electron donating group strengthens the nucleophilic character of the C-3 carbon atom. Unfortunately, indole derivatives having an electron withdrawing group at the C-2 position were commercially not available, so the previous results could not be compared with such modifications.

Based on previous findings, it was assumed that alkylation of a partially saturated indole ring would go on a different pathway. To probe this assumption, the alkylation of an indoline derivative (**3**) was attempted using the same system. When 2-methyl-indoline was reacted with *n*-BuOH, an aromatized derivative, **3a** was isolated with 64% yield (Scheme 3).

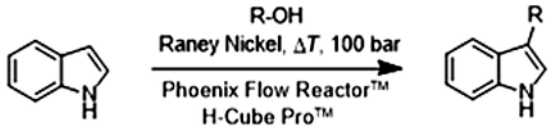
The oxidation of the indoline ring was rather surprising due to the fact that on the Raney® Nickel surface a massive volume of hydrogen gas is liberated via dehydrogenation of the alcohol. The only explanation for the aromatization is that first an alkylidene intermediate was formed [31], which then underwent rearrangement of the double bonds forming the most stable heteroaromatized ring.

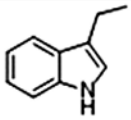
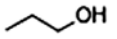
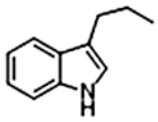
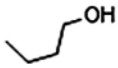
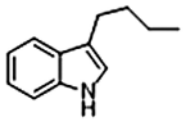
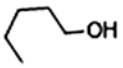
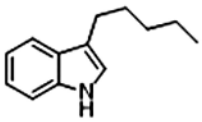
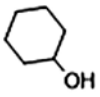
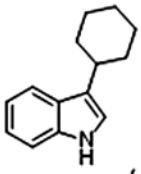
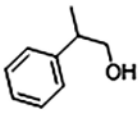
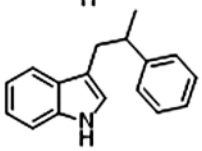
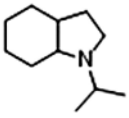
Alkylation of the quinoline (**4**) and isoquinoline (**5**) molecules significantly differs from the indole derivatives. The different electronic nature of the six-membered heteroaromatic ring does not allow double bond shift and delocalization to occur. In both cases, single product formed which corresponded to the *N*-alkylated species (**4a** and **5a**, respectively) (Scheme 4).

3. Experimental Section

Indole, pyrrole, quinoline, and isoquinoline were procured commercially and used without further purification. **2** was passed

Table 3. Alkylation of indole with primary and secondary alcohols. The reaction conditions were as follows: 250 °C, 0.5 mL/min flow rate, 100 bar, 0.1 M concentration for **1**, and transient protection with TMS-Cl



Entry	Alcohol	Product	Conversion	Product selectivity	Isolated yield
1		1a 	>98%	58%	41%
2		1d 	93%	74%	53%
3		1e 	93%	70%	50%
4		1f 	94%	63%	48%
5		1g 	74%	31.7%	15%
6		1h 	>99%	33%	25%
7		1i 	>99%	52%	50%

through on 60 Å silica gel (Sigma-Aldrich) column, using methylene chloride as eluent. The colorless fractions were collected. The reactions were performed in reagent grade solvents. The conversion of starting materials was monitored using an Agilent 6850 series II gas chromatograph (fitted with an HP-5MS-UI column [30 m × 0.25 mm × 0.25 μm]) coupled with an Agilent 5975C VL MSD system. The identity of all products was verified by recording their ^{1}H NMR spectra in DMSO-d_6. NMR spectra were recorded on a Bruker Avance NMR spectrometer at 300 MHz. Raney® Nickel catalyst (50% aqueous slurry) was provided by Sigma-Aldrich (Fluka) and ABCR.

The reactions were carried out in a ThalesNano's Phoenix Flow Reactor™ connected with an H-Cube Pro™ reactor as a backpressure moderating module [24].

3.1. Typical Experimental Procedure for Alkylating the Heterocycles. The catalyst bed was washed with distilled water. The pressure and the temperature were set with water before changing the inlet to the corresponding alcohol.

Table 4. Results of alkylation with and without transient protection. Reaction conditions as follows: 250 °C, 0.5 mL/min, 100 bar, and 0.1 M concentration for **1**. Conversions and selectivities were determined based on GC–MS

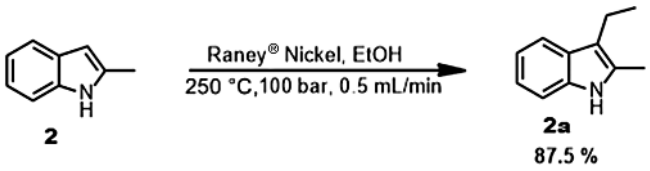
Alcohol	*N*-Protection	Conversion (%)	*C*-3-alkylated product (%)	*N*-alkylated side-product (%)	1,3-Substituted side-product (%)
MeOH	None	<1	–	–	–
EtOH	None	99	58	5	22
	TMS-Cl	90	80	–	16
n-PrOH	None	92	39	41	20
	TMS-Cl	93	74	<1	14
n-BuOH	None	91	40	30	29
	TMS-Cl	94	70	<1	15
n-Pentanol	None	82	7	61	4
	TMS-Cl	94	63	<1	15
i-PrOH	None	>99	–	–	–
i-BuOH	None	>99	–	–	–
t-BuOH	None	<1	–	–	–

Table 5. Atom-economy for indole alkylation reaction

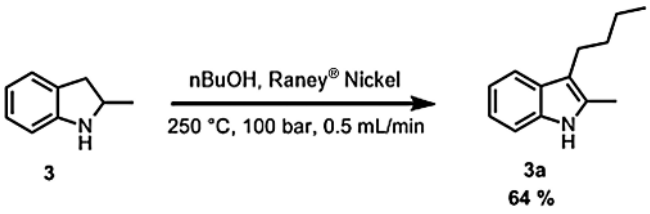
SM	$MW_{(SM)}$	Alkylating agent	$MW_{(alc)}$	AE%
1	117.2	EtOH	46.1	89
1	117.2	*n*-PrOH	60.1	90
1	117.2	*n*-BuOH	74.1	91
1	117.2	*n*-Pentanol	88.2	91
1	117.2	Cyclohexanol	100.2	92
1	117.2	2-Phenyl-1-propanol	136.2	93
Indole[a]	225.5	EtOH	46.1	53
Indole[a]	225.5	*n*-PrOH	60.1	56
Indole[a]	225.5	*n*-Butanol	74.1	58
Indole[a]	225.5	*n*-Pentanol	88.2	60

[a] Indole transiently N-protected with TMS-Cl (MW: 108.6).

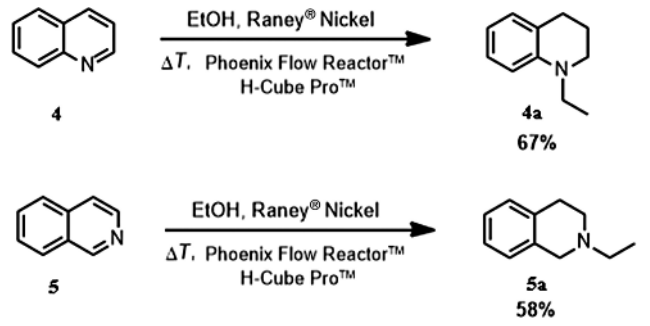
Scheme 2. Ethylation of 2-methyl-indole. General conditions: Raney® Nickel, 250 °C, 100 bar, 0.1 M concentration, and 0.5 mL/min flow rate



Scheme 3. Preparing indole derivative from the partly saturated starting material. Conditions: 250 °C, 100 bar at 0.5 mL/min with 0.1 M solution



Scheme 4. Ethylation of quinoline and isoquinoline at 250 °C, 100 bar, and 0.5 mL/min flow rate in 0.1 M concentration



The N-heterocyclic compound was dissolved in the corresponding alcohol. When N-protection was used, 1.1 equivalent of TMS-Cl was added to the solution. Without such transient protection, the starting solution was let through the reactor system without further action. After 5 min of stable run with the pure alcohols, the reaction started, by switching the solvent to the indole solution. Fraction collection was started after the calculated half-time of the dead volume. After all of the starting solution was let through the system, it was washed with pure alcohol until no reagent was observed (TLC plate with F^{254} silica at 254 nm UV).

NMR spectra of the products can be found in Supporting Information.

3.2. General Procedure for Purifying and Isolating the Compounds. After the sample collection was completed, the solution was concentrated at 45 °C in vacuo and a dark brown oil was obtained. In the case of *n*-BuOH and *n*-pentanol, due to their high boiling point, water was added to the solution and the evaporation was carried out at 65 °C. To remove the residual water from the remained oil, EtOH was used.

In the case of the reactions where transient protection was used, the workup process started with a hydrolysis of TMS group with water to get the unprotected product. The compounds were extracted with methylene-chloride three times, and the organic phase was collected. After drying the organic phase on dried magnesium sulfate, the solution was evaporated at low temperature.

The product was purified by column chromatography using 60 Å silica gel and *n*-hexane–chloroform mixture as eluent. The R_f differences were acceptable between the products, and isocratic eluent was sufficient in most cases. The fractions were monitored with TLC (F_{254}, NP silica on alumina), and although the compounds absorption at 254 nm was excellent, phosphomolybdic acid solution (1 g solved in 20 mL EtOH) was used for coloring the plates.

4. Conclusion

Regioselective 3-alkylation of indoles was achieved in a flow environment with good to excellent yields. Complex transition metal catalysts were successfully replaced with a cheap heterogeneous Raney® Nickel catalyst.

The method was optimized to the ethylation of indole, and the reaction scope was extended by alkylation with further primary alcohols. Transient protection of the N-atom led to improved selectivity, and the substitution of the nitrogen atom was avoided. The applied flow procedure has many favorable features (high atom economy, water is the only waste, short reaction time, high selectivity) which could make this reaction an attractive alternative of the standard (cross-coupling) reactions for the synthetic organic chemists.

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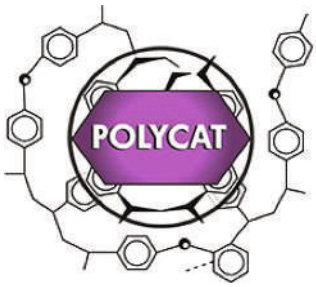

Conflict of Interest

The authors declare no competing financial interest.

Supporting Information

Electronic Supplementary Material (ESM) with ^{1}H-NMR spectra for compounds **1**, **1a-i**, **2**, **2a**, **3a**, **4a**, and **5a** and APT and HSQC spectra for compounds **4a** and **5a** can be found in the online version at doi: 10.1556/1846.2015.00030.

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