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An $Al(OTf)_3$-catalyzed environmentally benign process for the propargylation of indoles

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ABSTRACT

$Al(OTf)_3$ catalyzed the alkylation of indoles using secondary/tertiary propargylic alcohols to produce 3-propargylated indoles in excellent yields with high selectivity. The reactions were performed in air with commercial grade solvents, and water was the only side product of the process. The catalyst was recovered after completion of the reaction and re-used with minimum loss of activity over three cycles.

The indole moiety is a very common heterocyclic structure found in nature[1] and is present in many pharmacologically and biologically active compounds.[2] Among these, 3-substituted indoles show significant biological activity and as such are precursors for the synthesis of various natural and synthetic pharmaceuticals.[3,4] In this regard, propargylation of indoles is an important process to give access to various pharmaceutical intermediates and other important heterocycles via simple functionalization of the triple bond.[5] Several approaches for the preparation of 3-propargyl indoles have been described in recent years. The most useful are based on transition metal,[6] Lewis[7] and Brønsted acid[8] catalyzed methods for the direct nucleophilic substitution reactions of alcohols with indoles, which, furthermore, produces only water as the byproduct.

Silveira et al.[9] recently described the $CeCl_3$-catalyzed propargylation of indoles where ZnO was used as an additive in equivalent amounts. From an environmental point of view, this process is unattractive as it produces excessive amounts of metal waste. Sanz et al.[8c] disclosed a Bronsted acid catalyzed propargylation methodology, though the isolated yields of the products were not satisfactory. The aforementioned procedures and other reported methods[10] are hampered by the cost and availability of the catalysts, excessive catalyst loading, and reagents being toxic and/or moisture-sensitive, thus rendering them impractical for large-scale industrial synthesis.

From a recent literature search, we did not find any efficient general synthetic methods for the direct nucleophilic substitution of propargylic alcohols with indoles which were equally efficient for both 2° and 3° propargylic alcohols. In most reports of catalyzed propargylation reactions, benzylic propargylic alcohols (1-aryl-prop-2-yn-1-ol derivatives) are employed as alkylating agents. Only a few methods have been reported for 3° propargylic alcohols, which might be attributed to the tendency of 3° propargylic alcohols to form allenium intermediates,[11] or to eliminate water in acidic medium. [8a] Therefore, to find an efficient general methodology for C3 propargylation of indoles with 3° as well as 2° propargylic alcohols is a challenge.

Metal triflates have received wide attention for their role as Lewis acids in a number of reactions.[12] Water-tolerant metal triflates are especially attractive from an environmental point of view as they can be easily and repeatedly recycled. In this regard, $Al(OTf)_3$ was found to be a potent, water-tolerant, efficient, and reusable catalyst.[13] To date, it has not been explored as extensively as other metal triflates, the rare earth metal triflates in particular, despite it being comparatively more affordable. We now report that this versatile catalyst is also highly efficient for the direct nucleophilic substitution of propargylic alcohols with a variety of indoles in order to prepare the corresponding 3-propargylated indoles.

Initially, to optimize the conditions, we performed the reaction with indole (**1a**) (1 mmol) and alkynol **2a** (1.15 mmol) using 5 mol % of aluminum triflate in CH_3CN (1.5 ml) at temperatures ranging from room temperature to reflux. Though the reaction did proceed at room temperature, it progressed very slowly and required more than 10 h for completion. The rate of the reaction was accelerated by increasing the temperature; at reflux conditions (ca. 85 °C) the reaction proceeded to completion (monitored by GC–MS and TLC) within 90 min to give 3-substituted indole **3aa** in 88% yield (Scheme 1). Since the 3-position of indoles is highly electron-rich and serves as the primary nucleophilic site during reactions with electrophiles,[14] electrophilic attack by the Lewis acid activated

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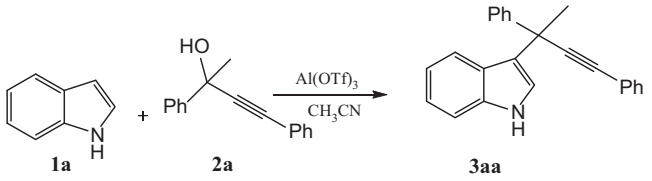


Scheme 1. Propargylation of indole **1a**

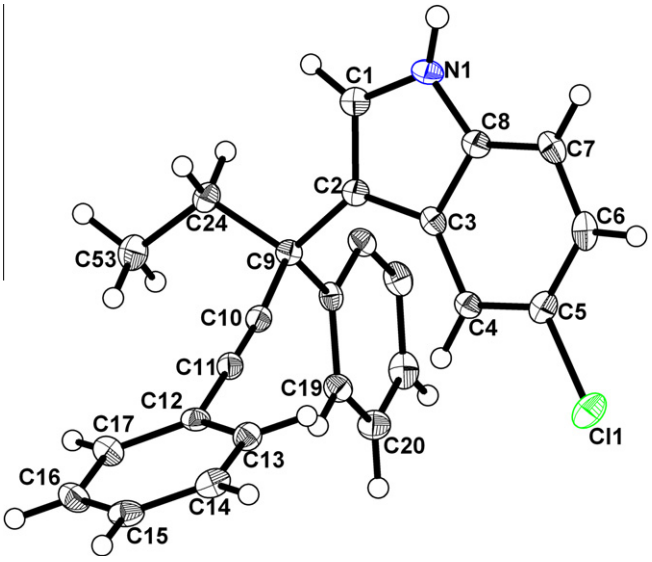


Figure 1. X-ray structure of product **3dd**.

propargylic entity would undoubtedly be directed to position C-3 of the indole moiety. This was confirmed by the chemical shift (δ >7.00 ppm) of the residual proton on the heterocyclic ring of all of the products along with a single-crystal X-ray structure of product **3dd** (Fig. 1).[15]

Table 1
Optimization of the reaction conditions[a]

Entry	Al(OTf)$_3$ (mol %)	Time (min)[b]	Yield (%)[c]
1	5	90	88
2	3	100	89
3	2	110	94
4	1	160	87
5	0.5	8 h	70

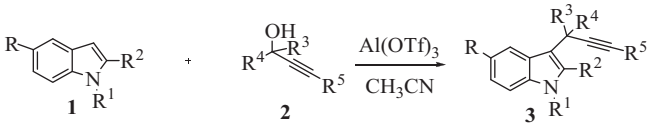
[a] All reactions were carried out with **1a** (1 mmol) and **2a** (1.15 mmol, 1 equiv) in refluxing CH_3CN.
[b] Time required for complete consumption of **2a** as determined by GC–MS.
[c] Isolated yield.

To determine the effectiveness of the catalyst, reactions were run with different concentrations of Al(OTf)$_3$ (0.5–3 mol %) in refluxing CH_3CN (Table 1) and 2 mol % was found to be the optimum amount (Table 1, entry 3). Decreasing the catalyst concentration reduced the yield and also gradually reduced the rate of the reaction (Table 1, entries 4 and 5). Increasing the concentration also decreased the yield rather than improving it, most probably due to decomposition of the final products at high concentrations of Al(OTf)$_3$, although the rate of the reaction did increase (Table 1, entries 1 and 2).

We thus investigated the scope and general applicability of the reaction with other indoles, including indoles possessing electron-withdrawing (Table 2, entry 4) and electron-releasing groups (Table 2, entry 5) on the benzenoid ring, and also carried out the reactions with *N*-methyl **1b** (Table 2, entry 2) and 2-methyl **1c** substituted indoles (Table 2, entry 3). In all cases C3-propargylated indoles were obtained in excellent yields ($\geqslant$88%).

In order to investigate the propensity toward nucleophilic substitution versus competitive water elimination, [8c] alkynols **2d** and

Table 2
Substitution of propargylic alcohols **2** with indoles **1**[a]



Entry	Indole	R	R^1	R^2	Alkynol	R^3	R^4	R^5	Time (min)	Product[b]	Yield[c] (%)
1	**1a**	H	H	H	**2a**	Me	Ph	Ph	110	**3aa**[8a]	94
2	**1b**	H	Me	H	**2a**	Me	Ph	Ph	120	**3ba**[8a]	90
3	**1c**	H	H	Me	**2a**	Me	Ph	Ph	110	**3ca**[8a]	89
4	**1d**	Cl	H	H	**2a**	Me	Ph	Ph	110	**3da**	93
5	**1f**	OMe	H	H	**2a**	Me	Ph	Ph	110	**3fa**	88
6	**1a**	H	H	H	**2b**	Me	C_6H_4(*p*-Cl)	Ph	180	**3ab**[9]	90
7	**1a**	H	H	H	**2c**	Me	C_6H_4(*p*-OMe)	Ph	70	**3ac**[9]	92
8	**1d**	Cl	H	H	**2d**	Et	Ph	Ph	120	**3dd**	92
9	**1a**	H	H	H	**2e**	*c*-C_3H_5	Ph	Ph	100	**3ae**[7a]	92
10	**1a**	H	H	H	**2f**	Me	Ph	Bu	150	**3af**[8a]	85
11	**1a**	H	H	H	**2g**	Me	*c*-C_3H_5	Ph	100	**3ag**[8a]	94
12	**1c**	H	H	Me	**2g**	Me	*c*-C_3H_5	Ph	100	**3cg**[8a]	92
13	**1a**	H	H	H	**2h**	H	Ph	Ph	100	**3ah**[7c]	88
14	**1b**	H	Me	H	**2h**	H	Ph	Ph	100	**3bh**[7g]	90
15	**1d**	Cl	H	H	**2h**	H	Ph	Ph	120	**3dh**	90
16	**1c**	H	H	Me	**2h**	H	Ph	Ph	120	**3ch**[7g]	85
17	**1a**	H	H	H	**2i**	H	C_6H_4(*p*-Cl)	Ph	160	**3ai**	83
18	**1a**	H	H	H	**2k**	H	C_6H_4(*p*-OMe)	Ph	70	**3ak**[10a]	90
19	**1a**	H	H	H	**2l**	H	Ph	Bu	160	**3al**[7e]	88
20	**1a**	H	H	H	**2m**	Me	Me	Ph	200	**3am**[8a]	54

[a] Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), Al(OTf)$_3$ (2 mol %), acetonitrile under reflux, at 85 °C.[16]
[b] References to full analytical data for known compounds.
[c] Isolated yield.

Table 3
Reusability of the $Al(OTf)_3$ catalyst

Entry	Product	1st cycle	2nd cycle	3rd cycle
1	**3aa**	94	94	93
2	**3ag**	88	87	87

2e were subjected to reactions with indoles **1d** and **1a**, respectively (Table 2, entries 8 and 9). No indication of elimination was present and the obtained products could be ascribed exclusively to the direct nucleophilic substitution reaction of the alkynol **2d** or **2e** OH functionality with the indole.

Encouraged by these results with 3° benzylic propargylic alcohols, we extended the strategy to the reaction of a 2° benzylic alkynol **2h** with indole **1a**, and were pleased to find that the reaction proceeded smoothly within an acceptable amount of time in excellent yield (100 min, 88%, Table 2, entry 13). Similarly, we performed reactions between the 2° benzylic alkynol **2h** and various substituted indoles, including an indole with electron-withdrawing Cl substituent **1d** (Table 2, entry 15), and other substituted indoles such as *N*-methylindole (**1b**) (Table 2, entry 14) and 2-methylindole **1c** (Table 2, entry 16), and found that all these reactions gave C3-propargylated indoles in a very good to excellent yield (85–90%).

Alkynols with different substitution patterns, both at the terminal (R^5) and propargylic (R^3 and R^4) positions were also evaluated. When the phenyl substituent at the propargylic position (R^4) was changed into an electron-donating or electron-withdrawing aromatic entity, for both tertiary (Table 2, entries 6 and 7) and secondary propargylic alcohols (Table 2, entries 17 and 18), the desired C3-propargylated indoles were still obtained in high yield (83–92%). Replacement of the aromatic group of the alkynol at the terminal (R^5) (Table 2, entries 10 and 19) or propargylic position (R^3) by an aliphatic group (Table 2, entry 20), however, only gave good to moderate yields of the desired products (85, 88 and 54%, respectively). Substituting the aromatic group at the propargylic position (R^4) with a cyclic aliphatic group (Table 2, entries 11 and 12) again led to excellent yields (94 and 92%, respectively). The higher yields obtained with the phenyl substituent at both the terminal and propargylic positions compared to the corresponding alkyl substituted analogues can be ascribed to the stabilization of the (incipient) benzylic carbocation, whereas the anomalous behavior of the linear alkyl and cyclopropyl substituted alkynols is believed to be due to the known ability of the cyclopropyl group to stabilize (partially) positively charged intermediates.[11]

Electron-donating substituents at the *para* position of the R^4 aromatic ring of the alkynols were found to enhance reactivity, thus increasing the rate of the reaction (Table 2, entries 7 and 18 vs entries 1 and 13, respectively), while electron-withdrawing substituents at the same position slowed the substitution (Table 2, entries 6 and 17 vs entries 1 and 13, respectively).

The catalyst was recovered according to a previously reported procedure [13b] and re-used three times under our optimized reaction conditions without any significant loss of activity (Table 3).

In conclusion, $Al(OTf)_3$ was found to be a highly effective and reusable Lewis acid catalyst for the direct nucleophilic substitution of the OH of propargylic alcohols by indoles, thus providing important 3-substituted propargylated products in excellent yields and high selectivities. Moreover, this is the first example of an efficient process which could be successfully applied to both 3° and 2° propargylic alcohols for the preparation of C3-propargylated indoles in very high yields.[16]

Acknowledgments

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15. The crystallographic data for product **3da** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication

number CCDC 879847. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

16. *General reaction procedure*: $Al(OTf)_3$ (2 mol %) was added to a solution of the indole **1** (1 mmol) and alkynol **2** (1.15 mmol, 1.15 equiv) in CH_3CN (2.00 ml) and the reaction mixture was refluxed with stirring for the time indicated in Table 2. After completion of the reaction (monitored by GC–MS), the solvent was removed in vacuo and the residue purified by column chromatography on silica gel (EtOAc:hexane 5:95, v/v). All obtained products were fully characterized by spectroscopic analysis (^1H NMR, ^{13}C NMR and MS). The physical data of known compounds were identical to those published (see references in Table 2).

*5-Chloro-3-(2,4-diphenylbut-3-yn-2-yl)-1H-indole (**3da**)*: Pale yellow solid; mp 77–78 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.60 (td, J = 2.9, 1.7 Hz, 2H), 7.55 (d, J = 1.9 Hz, 1H), 7.53–7.47 (m, 2H), 7.38–7.24 (m, 7H), 7.20 (d, J = 2.5 Hz, 1H), 7.13 (dd, J = 8.6, 2.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8 (C), 135.5 (C), 131.8 (2× CH), 128.4 (2× CH), 128.3 (2× CH), 128.0 (CH), 126.9 (C), 126.7 (CH), 126.6 (2× CH), 125.1 (C), 123.6 (C), 122.8 (CH), 122.5 (CH), 121.7 (C), 120.6 (CH), 112.2 (CH), 94.6 (C), 83.5 (C), 39.9 (C), 31.1 (CH_3); HRMS m/z calcd for $C_{24}H_{18}ClN$ 355.1128, found 355.1226.

*5-Methoxy-3-(2,4-diphenylbut-3-yn-2-yl)-1H-indole (**3fa**)*: Yellowish solid; mp 85–86 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.66–7.61 (m, 2H), 7.50–7.45 (m, 2H), 7.34–7.22 (m, 7H), 7.17 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 3.68 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6 (C), 146.1 (C), 132.3 (C), 131.8 (C), 128.3 (4× CH), 127.9 (CH), 126.7 (C), 126.5 (CH), 126.3 (C), 123.9 (C), 122.2 (CH), 121.6 (C), 112.4 (CH), 111.8 (CH), 103.0 (CH), 95.0 (C), 83.2 (C), 55.8 (OCH_3), 39.94 (C), 31.0 (C); HRMS m/z calcd for $C_{25}H_{21}NO$ 351.1623, found 351.1617.

*3-[2-(4-Chlorophenyl)-4-phenylbut-3-yn-4-yl]-1H-indole (**3ab**)*[9]: White solid; mp 89–90 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.56–7.52 (m, 2H), 7.49–7.43 (m, 3H), 7.38 (d, J = 8.2 Hz, 1H), 7.32–7.26 (m, 5H), 7.23 (d, J = 2.5 Hz, 1H), 7.20–7.00 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9 (C), 137.2 (C), 132.3 (C), 131.8 (2× CH), 128.4 (2× CH), 128.3 (2× CH), 128.2 (2× CH), 128.0 (CH), 125.7 (C), 123.7 (C), 122.3 (C), 121.6 (CH), 121.4 (CH), 121.2 (CH), 119.6 (CH), 111.3 (CH), 94.5 (C), 80.1 (C), 39.6 (C), 31.1 (CH_3); HRMS m/z calcd for $C_{24}H_{18}ClN$ 355.1128, found 355.1048.

*3-[2-(4-Methoxyphenyl)-4-phenylbut-3-yn-4-yl]-1H-indole (**3ac**)*[9]: Dense pale yellow liquid; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.61–7.54 (m, 3H), 7.52–7.46 (m, 2H), 7.41–7.27 (m, 4H), 7.23–7.13 (m, 2H), 7.08–6.85 (m, 3H), 3.82 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2 (C), 138.5 (C), 137.2 (C), 131.7 (2× CH), 128.3 (2× CH), 127.8 (2× CH), 125.8 (C), 123.9 (C), 122.1 (CH), 122.0 (C), 121.5 (CH), 121.3 (CH), 120.2 (CH), 119.4 (CH), 113.5 (2× CH), 111.2 (CH), 95.4 (C), 82.9 (C), 55.3 (OCH_3), 39.3 (C), 31.2 (CH_3); HRMS m/z calcd for $C_{25}H_{21}NO$ 355.1623, found 355.1543.

*5-Chloro-(1,3-diphenylpent-1-yn-3-yl)-1H-indole (**3dd**), mp 95–96 °C*: ^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.60-7.49 (m, 5H), 7.34–7.30 (m, 5H), 7.28–7.22 (m, 3H), 7.10 (dd, J = 8.6, 2.0 Hz, 1H), 2.55 (dq, J = 14.6, 7.3 Hz, 1H), 2.32 (dq, J = 14.5, 7.3 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): 144.1 (C), 135.5 (C), 131.8 (2× CH), 128.4 (2× CH), 128.3 (2× CH), 127.9 (CH), 127.3 (2×CH), 127.1 (C), 126.7 (CH), 125.1 (C), 123.8 (C), 123.0 (CH), 122.5 (CH), 121.2 (C), 120.7 (CH), 112.2 (CH), 93.0 (C), 85.3 (C), 45.3 (C), 34.8 (CH_2), 10.0 (CH_3); HRMS m/z calcd for $C_{25}H_{20}ClN$ 369.1284 found, 369.1268.

*5-Chloro-3-(1,3-diphenylprop-1-yn-3-yl)-1H-indole (**3dh**)*: White solid; mp 105–106 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.56–7.47 (m, 4H), 7.40–7.25 (m, 6H), 7.18–7.14 (m, 2H), 5.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.8 (C), 135.1 (C), 131.7 (2× CH), 128.6 (2× CH), 128.3 (2× CH), 127.9 (CH), 127.8 (2× CH), 127.1 (C), 127.0 (CH), 125.4 (C), 123.9 (CH), 123.5 (C), 122.6 (CH), 119.1 (CH), 116.8 (C), 112.3 (CH), 90.0 (C), 83.6 (C), 35.36 (CH); HRMS m/z calcd for $C_{23}H_{16}ClN$ 341.0971, found 341.0955.

*3-[1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl]-1H-indole (**3ai**)*: Brown dense liquid; ^1H NMR (600 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51–7.45 (m, 4H), 7.39 (d, J = 8.2 Hz, 1H), 7.33–7.31 (m, 5H), 7.24–7.09 (m, 3H), 5.46 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.9 (C), 136.8 (C), 132.7 (C), 131.8 (2× CH), 129.4 (2× CH), 128.7 (2× CH), 128.4 (2× CH), 128.1 (CH), 126.0 (C), 123.5 (C), 122.7 (CH), 122.5 (CH), 119.9 (CH), 119.6 (CH), 116.5 (C), 111.4 (CH), 90.0 (C), 83.8 (C), 35.1 (CH); HRMS m/z calcd for $C_{23}H_{16}ClN$ 341.0971, found 341.0955.