FULL PAPER

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Brønsted Acid-Catalyzed Alkylation of Indoles with Tertiary Propargylic Alcohols: Scope and Limitations

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The direct alkylation of indoles with a wide variety of tertiary propargylic alcohols under Brønsted acid catalysis has been studied. A general and environmentally friendly method for the synthesis of C3-propargylated indoles with a quaternary carbon at the propargylic position has been developed. The reactions are highly regioselective regarding both the indole and the alkynol counterparts. Only with *N*-unsubstituted-2-arylindoles a competitive S_N' reaction takes place affording 3-dienyl or 3-allenylindoles depending on the alkynol moiety. Reactions have been carried out in air with undried solvent, and water was the only side product.

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/. Full experimental procedures and characterization data for all the compounds reported in this work are included.

Introduction

The indole nucleus is one of the most ubiquitous heterocyclic structure found in nature and it is a fundamental constituent of a number of natural and synthetic products with biological activity.[1] Therefore, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.[2] In this context, functionalization of the indole ring at the C3-position is a fundamental synthetic task in the preparation of relevant molecules bearing the indole nucleus.[3] Indoles are electron-rich heteroaromatic systems which react much faster with electrophiles than most benzene derivatives. The most reactive position of indole towards electrophilic substitution is the C3 site and this susceptibility of indoles to electrophilic attack makes direct 3-alkylation by carbocations or ion pairs a feasible reaction.[4] However, this nucleophilic nature of indolyl compounds makes them quite reactive to protic and Lewis acids and, consequently, only procedures which generate carbocations under relatively mild conditions are likely to be successful. The Friedel-Crafts reaction, i.e. the electrophilic attack of carbocations or related electrophiles at aromatic systems,[5] is one of the most useful C–C bond-forming reactions in organic synthesis and many efforts have been devoted to the development of improved procedures for the catalytic Friedel-Crafts alkylations of indoles.[6] The large amounts of conventional Lewis acids usually required to promote typical Friedel-Crafts alkylation processes represent serious drawbacks (poor regioselectivities, undesired side-reactions of the electrophile, environmental concerns,…). In addition, the alkylation of indolyl compounds is usually performed with typical electrophiles such as carbonyl compounds,[7] imines,[8] electron-deficient C=C bonds,[9] epoxides and aziridines.[10] Also, the well-known Pd-catalyzed allylic substitution (Tsuji-Trost reaction) represents a useful approach.[11] Moreover, enantioselective Friedel-Crafts reactions of indoles with readily available prochiral electrophilic starting materials constitutes a simple strategy to access optically active indole derivatives.[12]

As mentioned above, the alkylation of indoles is usually carried out with typical electrophiles. However, the direct catalytic functionalization of indoles with alcohols is an attractive reaction due not only to the availability of the starting materials and the environmentally benign character of alcohols, but also to the fact that water is the only by-product of the process. Recently, the use of π-activated alcohols,[13] such as benzylic, propargylic and allylic ones, have led to the development of new catalytic methodologies for Friedel-Crafts reactions. In this field, several reports using different Lewis acids,[14] and late transition metal salts/complexes[15] as catalysts for the direct alkylation of indoles with alcohols have appeared in the last years, including few examples of intramolecular cyclialkylations.[16] However, the use of expensive, toxic and/or moisture-sensitive catalysts in some of these methods limits their practical usefulness in large-scale synthesis. Much more appealing is the use of Brønsted acids as catalysts in these processes, being a simple alternative to some toxic and precious metals.[17]

Among π-activated alcohols, propargylic alcohols are appropriate substrates for the catalyzed propargylic susbstitution reactions that have emerged as a useful synthetic tool.[18] However, the risk of competing allene formation due to the nature of propargylic cations, which are better represented with the corresponding allenyum species, as well as the tendency to suffer a competitive elimination reaction, are issues that need to be considered mainly in the case of tertiary propargylic alcohols (Figure 1). So, in most of the reports about catalyzed propargylation reactions, secondary benzylic propargylic alcohols (1-aryl-2-propyn-1-ol derivatives) are usually employed as alkylating agents.

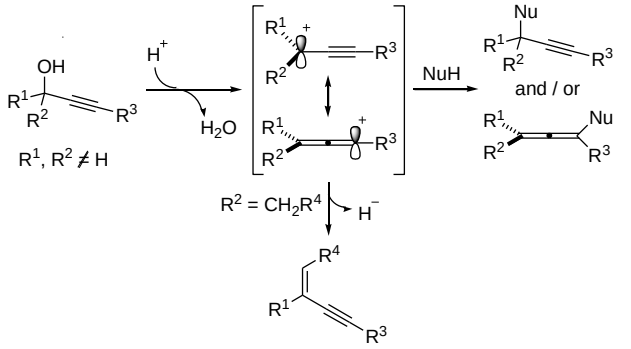


Figure 1. Propargylic cations from tertiary propargylic alcohols.

Although some methods have been reported for the preparation of 3-propargylindoles,[14c,e,g,h] a preparatively useful synthesis of these compounds bearing a quaternary center at the propargylic position had not been described until our preliminary reports.[19,20] Moreover, it should be noted that few methods for the direct introduction of quaternary carbons at the C3-position of indoles are known.[21] In addition, the usefulness of 3-propargylindoles for subsequent gold-catalyzed transformations involving a 1,2-indole migration has also been pointed out by our research group.[22] Following our interest in the development of strategies for the catalytic direct nucleophilic substitution of alcohols,[23] we wish to report our studies in this field by using indoles as nucleophiles and tertiary propargylic alcohols as electrophiles.

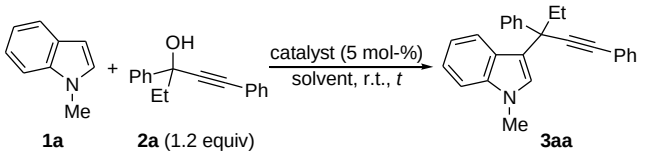
Results and Discussion

Optimization Studies

We initially selected the reaction of *N*-methylindole **1a** with tertiary alkynol **2a** as model system to assess the catalytic activity of several Brønsted and Lewis acids and to determine the optimum reaction conditions. Alkynol **2a** was chosen because it is an ideal substrate to test the nucleophilic substitution reaction *vs.* the competitive elimination reaction, as well as to check the regioselective outcome of the process. As shown in Table 1, reactions in MeCN at room temperature in the presence of simple Brønsted acid catalysts such as triflic acid (TfOH), 2,4-dinitrobenzenesulfonic acid (DNBSA), or *p*-toluenesulfonic acid (PTSA) occurred to afford the desired alkylated indole derivative **3aa** in good yields and short reaction times (entries 1–3). Several Lewis acids also catalyzed the process (entries 4–6); however, the substitution reactions were significantly slower and/or less efficient. As expected, the substitution reaction did not take place in the absence of catalyst (entry 7), while treatment of **2a** with PTSA (5 mol-%) in the absence of the indole counterpart gave rise to the stereoselective formation of the enyne derivative, (*Z*)-1,3-diphenylpent-3-en-1-yne, coming from an elimination process in **2a**. It is also interesting to note the complete regioselectivity observed for this process regarding both the nucleophile, only C3-attack takes place, and the alkynol, as exclusive substitution at the α-position of the propargylic moiety is observed. The no formation of allenic products is significant because the use of tertiary propargylic alcohols or their derivatives in nucleophilic substitution reactions usually afford mixture of regioisomers or, mainly, the allenyl derivative.[24]

We selected PTSA as the catalyst to screen different solvents due to its availability and easiness of handling. Although the alkylation process was also efficient in CH_2Cl_2 and $MeNO_2$ no significant improvement in yield or reactivity was observed with respect to our initial experiment with MeCN (entries 8–9). Therefore, we established PTSA as catalyst and MeCN as solvent at room temperature as the best reaction conditions to explore the scope and limitations of this Friedel-Crafts alkylation of indoles with alkynols.

Table 1. Evaluation of Brønsted and Lewis acid catalysts for the alkylation of *N*-methylindole **1a** with tertiary alkynol **2a**.



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

Entry	catalyst	solvent	*t* [h][a]	yield [%][b]
1	TfOH	MeCN	2	75
2	DBNSA	MeCN	3	68
3	PTSA	MeCN	2	78
4	$FeCl_3$	$MeNO_2$	24	64
5[c]	$InBr_3$	DCE	15	70[d]
6	I_2	MeCN	14	68
7	–	MeCN	24	–
8	PTSA	DCM	3	75
9	PTSA	$MeNO_2$	2.5	80

[a] Time needed for complete consumption of **1a** determined by GC-MS analysis. [b] Isolated yield of **3aa** after column chromatography. [c] Reaction performed at reflux under N_2 atmosphere. [d] ~15% of the elimination product was also formed.

Alkylation of 2-Unsubstituted-indoles

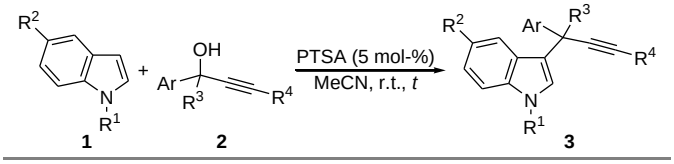
*Reactions with benzylic alkynols **2***

The results obtained in the reaction of a series of 2-unsubstituted indoles **1** with benzylic tertiary alkynols **2** catalyzed by PTSA (5 mol-%) under the optimized reaction conditions are summarized in Table 2. *N*-Methylindole **1a** was successfully coupled with different benzylic alkynols bearing either aromatic- (entries 1–7), heteroaromatic- (entry 8) or alkyl-substitution (entries 9–12) at the terminal position (R^4). Moreover, a wide variety of alkyl groups, linear (entries 1–3, 6–9, 11) or branched (entries 4–5, 10, 12), are tolerated at the propargylic position (R^3). In all cases the corresponding C3-propargylated indoles are regioselectively obtained, generally in high yields. Whereas functional groups, such as chlorine atoms, could be present at the aromatic group at the propargylic position (entries 6, 11 and 18), when we tested hindered alkynols **2m,n**, bearing substituents at the *ortho*-position of this aromatic group, no conversion was observed under the standard conditions. So, in these cases it was necessary to reflux the mixture in MeCN for 24 h in order to get the corresponding functionalized indoles **3**. Significantly, we could dramatically reduce the reaction times by performing the processes under microwave irradiation (entries 13–14). Anyway, indoles **3am** and **3an** were isolated in moderate yields.

Not only *N*-methylindole **1a**, but also *N*-unsubstituted ones (entries 15–25), including those with electron-withdrawing substituents at C-5 and consequently less nucleophilic (entries 20–25), were successfully coupled. Again, benzylic alkynols **2** with different substitution patterns, both at the terminal (R^4) and propargylic (R^3) positions, were appropriate counterparts for the reaction. All the reactions were followed and analyzed by GC-MS and we did not observe the presence of any byproduct in a significant amount. The moderate yields obtained in some cases are probably due to decomposition of the final indole derivative **3**

under the reaction or purification conditions, as no significant byproducts were observed in the crude reaction mixture.

Table 2. Alkylation of indoles **1** with benzylic alkynols **2**. Synthesis of 3-(1-aryl)propargylindoles **3**.[a]



1 **2** **3**

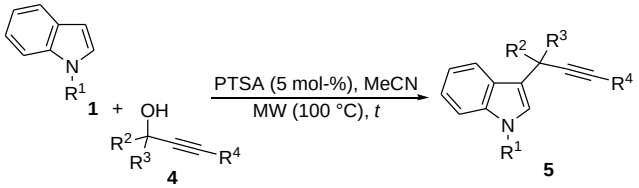
Entry	**1**	R^1	R^2	**2**	Ar	R^3	R^4	*t* [h]	**3**	Yield [%][b]
1	**1a**	Me	H	**2a**	Ph	Et	Ph	2	**3aa**	78
2	**1a**	Me	H	**2b**	Ph	Me	Ph	2	**3ab**	81
3	**1a**	Me	H	**2c**	Ph	*n*Pr	Ph	2	**3ac**	60
4	**1a**	Me	H	**2d**	Ph	*i*Pr	Ph	0.5	**3ad**	80
5[c]	**1a**	Me	H	**2e**	Ph	*c*C_3H_5	Ph	0.5	**3ae**	89
6	**1a**	Me	H	**2f**	4-ClC_6H_4	Me	Ph	8	**3af**	72
7	**1a**	Me	H	**2g**	2-Th	Me	Ph	1	**3ag**	85
8	**1a**	Me	H	**2h**	Ph	Me	3-Th	2	**3ah**	75
9	**1a**	Me	H	**2i**	Ph	*n*Pr	*n*Bu	1	**3ai**	80
10	**1a**	Me	H	**2j**	Ph	*i*Pr	*n*Bu	3	**3aj**	81
11	**1a**	Me	H	**2k**	4-ClC_6H_4	Me	*n*Bu	2	**3ak**	60
12	**1a**	Me	H	**2l**	Ph	*c*C_3H_5	*n*Bu	2	**3al**	82
13	**1a**	Me	H	**2m**	2-BrC_6H_4	Me	Ph	0.5	**3am**	54
14	**1a**	Me	H	**2n**	2,6-$F_2C_6H_3$	Me	*n*Bu	0.5	**3an**	35[d]
15	**1b**	H	H	**2b**	Ph	Me	Ph	2	**3bb**	70
16	**1b**	H	H	**2c**	Ph	*n*Pr	Ph	6	**3bc**	64
17	**1b**	H	H	**2g**	2-Th	Me	Ph	2.5	**3bg**	83
18	**1b**	H	H	**2k**	4-ClC_6H_4	Me	*n*Bu	5	**3bk**	51
19	**1b**	H	H	**2o**	Ph	Me	*n*Bu	0.5	**3bo**	62
20	**1c**	H	NO_2	**2b**	Ph	Me	Ph	1	**3cb**	74
21	**1c**	H	NO_2	**2i**	Ph	*n*Pr	*n*Bu	1	**3ci**	63
22	**1d**	H	CO_2Me	**2b**	Ph	Me	Ph	1	**3db**	81
23	**1d**	H	CO_2Me	**2o**	Ph	Me	*n*Bu	1	**3do**	65
24	**1d**	H	CO_2Me	**2p**	Ph	Et	*n*Bu	3	**3dp**	61
25	**1e**	H	Br	**2o**	Ph	Me	*n*Bu	2	**3eo**	59

[a] Reaction conditions: **1** (2 mmol), **2** (2.4 mmol), PTSA (0.1 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **3** after column chromatography. [c] Carried out at 100 ºC under microwave irradiation (see Supporting Information for details). [d] Isolated along with **1a**. 2-Th= 2-thienyl, 3-Th= 3-thienyl

*Reactions with dialkyl-substituted alkynols **4***

Next, we examined the alkylation of 2-unsubstituted indoles **1** with alkynols **4**, bearing two aliphatic substituents at the propargylic positions (Table 3). The reaction under the conditions described in Table 2 was slow and reflux of MeCN was required to get reasonable conversions. The difference in reactivity between alkynols **2** and **4a-e** is not surprising, as the stability of the propargylic carbocation proposed as an intermediate for the substitution reaction is significantly decreased when an aryl group at the propargylic position is changed by an alkyl group (see Figure 1). Once again, as in the reaction of hindered alkynols **2m,n**, microwave irradiation proved to be an advantageous methodology, particularly in terms of reaction times. Although both *N*-methylindole **1a** (entries 1–5) and indole **1b** (entries 6–7) could be coupled under these conditions, better results were obtained for the former, probably due to its higher nucleophilicity. Regarding the alkynol counterpart, linear aliphatic substituents (entries 1–2, 4–7), as well as cyclic ones (entry 3), are tolerated at the propargylic positions. In addition, the triple bond can bear either an aromatic (entries 1–3, 6–7), an alkenyl (entry 5) or an alkyl group (entry 4) at the terminal position. Although an excess of alkynol is always used,[25] the corresponding C3-propargylated indoles **5** were obtained in all cases in moderate yields.

Table 3. Alkylation of indoles **1** with dialkyl-substituted alkynols **4a–e**. Synthesis of 3-(1,1-dialkyl)propargylindoles **5**.[a]



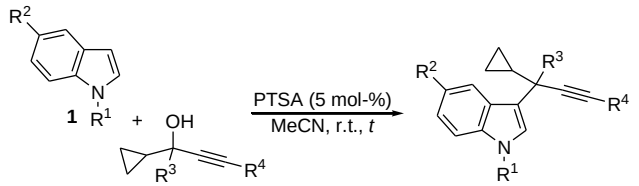
1 **4** **5**

Entry	**1**	R^1	**4**	R^2	R^3	R^4	*t* (min)	**5**	Yield [%][b]
1	**1a**	Me	**4a**	Me	Me	Ph	20	**5aa**	42
2	**1a**	Me	**4b**	Et	Et	Ph	20	**5ab**	47
3	**1a**	Me	**4c**	-$(CH_2)_5$-		Ph	70	**5ac**	38
4	**1a**	Me	**4d**	Me	Me	*n*C_5H_{11}	50	**5ad**	36[c]
5	**1a**	Me	**4e**	Me	Me	*c*C_6H_9	30	**5ae**	41[c]
6	**1b**	H	**4a**	Me	Me	Ph	60	**5ba**	30
7	**1b**	H	**4b**	Et	Et	Ph	60	**5bb**	40[c]

[a] Reaction conditions: **1** (2 mmol), **2** (2.4 mmol), PTSA (0.1 mmol) in MeCN (2 mL) at 100 ºC under microwave irradiation (see Supporting Information for details). [b] Isolated yield of **5** after column chromatography. [c] Yield estimated from the mixture of the corresponding propargylated indole **5** and the starting indole **1**. *c*C_6H_9 = 1-Cyclohexenyl.

Considering that the lower reactivity of dialkyl-substituted alkynols **4** compared to benzylic alkynols **2** is probably due to the inferior stability of the positively charged intermediate, and taking into account the known ability of the cyclopropyl group to stabilize carbocations,[26] we envisaged that cyclopropyl-substituted alkynols **6** could be appropriate substrates for the nucleophilic substitution with indoles **1** under mild conditions. Gratifyingly, we found out that the reaction of different 2-unsubstituted indoles **1** with a series of cyclopropyl alkynols **6** occurred in short times at room temperature, yielding the corresponding alkylated indoles **7** in high yields (Table 4).

Table 4. Alkylation of indoles **1** with cyclopropyl-substituted alkynols **6**. Synthesis of 3-(1-cyclopropyl)propargylindoles **7**.[a]



1 **6** **7**

Entry	**1**	R^1	R^2	**6**	R^3	R^4	*t* [h]	**7**	Yield [%][b]
1	**1a**	Me	H	**6a**	Me	Ph	1	**7aa**	85
2	**1a**	Me	H	**6b**	Me	3-Th	0.5	**7ab**	93
3	**1a**	Me	H	**6c**	Me	*c*C_3H_5	2	**7ac**	73
4	**1a**	Me	H	**6d**	Me	*n*Bu	13	**7ad**	77
5	**1a**	Me	H	**6e**	Me	*c*C_6H_9	0.5	**7ae**	92
6	**1a**	Me	H	**6f**	Me	C(Me)=CH_2	2	**7af**	85
7	**1a**	Me	H	**6g**	Me	$(CH_2)_2$Ph	2	**7ag**	79
8	**1a**	Me	H	**6h**	Me	$SiMe_3$	0.5	**7ah**	60
9	**1a**	Me	H	**6i**	Me	2-PhC_6H_4	1	**7ai**	82
10	**1a**	Me	H	**6j**	*c*C_3H_5	Ph	1.5	**7aj**	81
11	**1a**	Me	H	**6k**	2-Th	Ph	1	**7ak**	95
12	**1b**	H	H	**6a**	Me	Ph	1	**7ba**	71
13	**1b**	H	H	**6g**	Me	$(CH_2)_2$Ph	3	**7bg**	62
14	**1b**	H	H	**6l**	Me	*t*Bu	14	**7bl**	50
15	**1d**	H	CO_2Me	**6i**	Me	2-PhC_6H_4	24	**7di**	87

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **7** after column chromatography. 2-Th= 2-thienyl, 3-Th= 3-thienyl, *c*-C_6H_9= 1-Cyclohexenyl.

Furthermore, the process is broadly general and so, *N*-methylindole **1a** (entries 1–11), as well as *N*-unsubstituted ones such as **1b** (entries 12–14), and those with electron-withdrawing

substituents at the benzenoid moiety (entry 15), are suitable nucleophiles for the coupling. As for the cyclopropyl-substituted alkynol counterpart, aryl (entries 1, 9–12, 15), heteroaryl (entry 2), alkenyl (entries 5–6), linear-alkyl (entries 4, 7, 13), branched-alkyl (entry 14) and cyclic-alkyl (entry 3), as well as silyl (entry 8) groups are well tolerated at the terminal position of the triple bond, whereas the presence of a methyl or an additional cyclopropyl or heteroaromatic group at the other propargylic position leads to similar results (entry 1 *vs.* 10–11). It is interesting to note that the alkylation reactions take place with complete regioselectivity in all the cases regarding the cyclopropyl-substituted alkynol. No products arising from a competitive ring-opening pathway were observed, as it occurs in other related catalyzed nucleophilic substitution processes.[27]

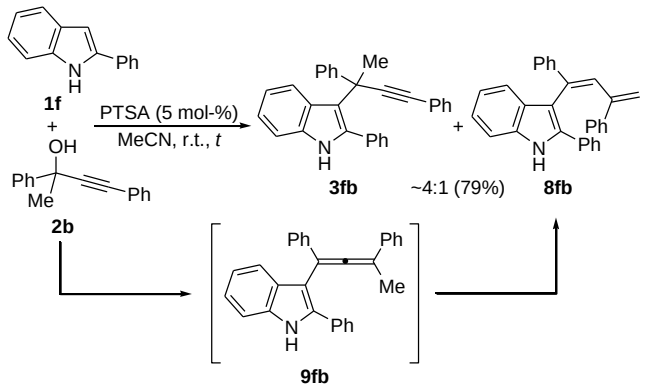
Alkylation of 2-substituted-*N*(H)-indoles

Once we had established the scope of the propargylation of 2-unsubstituted-indoles, we turned our attention to the alkylation of 2-substituted ones. We were interested in evaluating the effect that this additional group could have in the substitution reaction, and in the possibility of synthesizing 2,3-disubstituted-indoles following the developed methodology. First, we decided to use 2-arylindoles as the aromatic substituent at C-2 significantly increases the nucleophilic character of the indole nucleus.

Alkylation of 2-aryl-N-unsubstituted-indoles

*a) Reactions with benzylic alkynols **2***

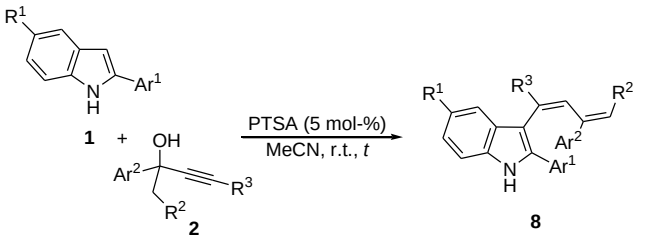
We started our studies by reacting commercially available 2-phenylindole **1f** with tertiary alkynol **2b**, under the conditions previously established as optimal for 2-unsubstituted indoles (Scheme 1). Thus, we found out that, although the expected C3-propargylated indole **3fb** was obtained as major product, the reaction was not completely selective in this case and a significant amount of C3-dienyl derivative **8fb** was also isolated. The generation of **8fb** could be explained through a competitive S_N' substitution reaction leading to an allene derivative, such as **9fb**, which undergoes further isomerization to the corresponding 1,3-diene. The driving force for this acid-promoted isomerization could be the extension of the conjugated system that stands from the phenyl group at position 2 of the indole to the terminal alkene.



Scheme 1. Reaction of 2-phenylindole **1f** with alkynol **2b** under PTSA-catalysis.

We reasoned that the allenylation pathway would be favored if the steric hindrance at the propargylic position of the starting alkynol increased. So, we performed the reaction of **1f** with alkynol **2a**, bearing a bulkier substituent than **2b** (Et instead Me), and in this case the C3-dienylindole **8fa** was exclusively obtained in good yield, thus confirming our hypothesis (Table 5, entry 1). As no methods are known for the direct synthesis of C3-dienyl indole derivatives from non-functionalized starting indole compounds,[28] we decided to evaluate the scope of this procedure for the synthesis of C3-dienylindoles. It should be noted that these compounds have been used as precursors for the synthesis of alkaloids via Diels-Alder cyclizations.[29] First, we studied the reaction of different 2-arylindole derivatives **1f-l** with tertiary benzylic alkynols **2** possessing linear substituents more sterically-demanding than methyl ($R^2 \neq H$) at the propargylic position (Table 5). When alkynol **2a** was tested against 2-phenylindoles containing electron-donating (entry 2) or electron-withdrawing (entry 3) groups at the benzenoid moiety the corresponding dienylindole derivatives **8** were exclusively obtained in good yields.[30] In addition, aryl groups with different electronic nature and substitution patterns (entries 6–8, 12) as well as an heteroaryl group (entry 9) are well tolerated at the C-2 of the indole, yielding also exclusively C3-dienyl derivatives. Regarding the substituent at the terminal position of the triple bond, it was found that alkynol **2i**, bearing an alkyl group at this position, mainly afforded C3-propargylated derivative **3fi** (entry 5). This seems to point out that an aryl group is required at the terminal position of the acetylene moiety in order to favor the formation C3-dienylindoles *vs.* C3-propargylindoles. In addition, functionalized aryl (entries 10–12) and heteroaromatic groups (entry 13) can be present at one of the propargylic positions, whereas different linear alkyl groups can be located at the other propargylic position.

Table 5. Alkylation of 2-arylindoles **1f-l** with benzylic α-monosubstituted-alkyl alkynols **2**. Synthesis of 3-dienylindoles **8**.[a]



Entry	**1**	R^1	Ar^1	**2**	Ar^2	R^2	R^3	*t* [h]	**8**	Yield [%][b]
1	**1f**	H	Ph	**2a**	Ph	Me	Ph	0.5	**8fa**	70
2	**1g**	OMe	Ph	**2a**	Ph	Me	Ph	1	**8ga**	69
3	**1h**	Cl	Ph	**2a**	Ph	Me	Ph	1	**8ha**	67
4	**1f**	H	Ph	**2c**	Ph	Et	Ph	0.5	**8fc**	66
5	**1f**	H	Ph	**2i**	Ph	Et	*n*Bu	1.5	–[c]	–
6	**1i**	H	4-FC_6H_4	**2a**	Ph	Me	Ph	4	**8ia**	70
7	**1j**	H	4-$MeOC_6H_4$	**2a**	Ph	Me	Ph	1	**8ja**	60
8	**1k**	H	2-$MeOC_6H_4$	**2a**	Ph	Me	Ph	1	**8ka**	65
9	**1l**	H	2-Th	**2a**	Ph	Me	Ph	3	**8la**	61
10	**1f**	H	Ph	**2q**	4-ClC_6H_4	Me	Ph	2	**8fq**	73
11	**1f**	H	Ph	**2r**	4-ClC_6H_4	Et	Ph	2	**8fr**	67
12	**1i**	H	4-FC_6H_4	**2q**	4-ClC_6H_4	Me	Ph	2	**8iq**	72
13	**1f**	H	Ph	**2s**	2-Th	Et	Ph	2	**8fs**	58

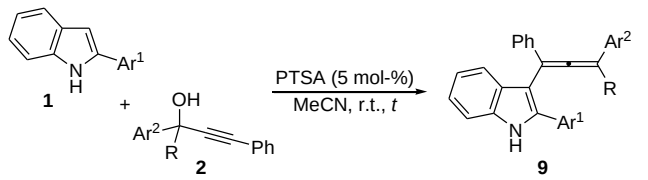
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), PTSA (0.025 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **8** after column chromatography. [c] 3-Propargylindole **3fi** was the major isomer in the crude reaction mixture and it was isolated in 65% yield. 2-Th= 2-thienyl

On the other hand, when we tested the reaction of 2-phenylindole **1f** with alkynol **2d**, bearing an isopropyl group at the propargylic position instead of a linear alkyl group as for the examples shown in Table 5, allene derivative **9fd** was isolated after purification on alumina (Table 6, entry 1). This result is in agreement with the idea that the allenylation pathway is favored over the propargylation pathway when bulky substituents are introduced at the propargylic position of the tertiary alkynol.

Moreover, the isomerization of the allene to the diene seems to be slowed down when the substituent is branched instead of linear, thus allowing in these particular cases the isolation of the corresponding 3-allenylindole derivatives **9**.

Considering the potential interest of C3-allenylindoles and the fact that a direct route to these compounds had not been previously described, we decided to synthesize a collection of allene derivatives **9** via PTSA-catalyzed reaction of 2-arylindoles **1**[31] with a series of benzylic branched-alkyl alkynols (Table 6). Indoles with different aryl substituents at the C-2 position, including electron-withdrawing (entry 2), electron-donating (entry 3) and heteroaromatic (entry 4) groups were efficiently coupled with alkynol **2d** to yield the corresponding allene derivatives **9**. Furthermore, not only the isopropyl group is tolerated at the propargylic position, but also cyclopropyl- (entries 5–7), cyclobutyl- (entry 8), cyclopentyl- (entries 9, 12, 14) and cyclohexyl-substituted alkynols (entries 10, 11, 13) behave in the same way, leading to C3-allenylindoles **9** in good yields and short reaction times. In most cases, indole derivatives **9** were easily isolated by simple filtration as they precipitated from the reaction medium, whereas variable amounts of the corresponding dienes **8** remain in solution. In some cases the starting compounds are not soluble in MeCN and then, a larger amount of PTSA (20 mol-%) had to be added to complete the reaction.

Table 6. Alkylation of 2-arylindoles **1** with benzylic branched-alkyl alkynols **2**. Synthesis of 3-allenylindoles **9**.[a]

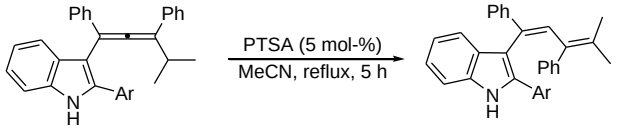


Entry	**1**	Ar^1	**2**	Ar^2	R	*t* [h]	**9**	Yield [%][b]
1	**1f**	Ph	**2d**	Ph	*i*Pr	1	**9fd**	65
2	**1i**	4-FC_6H_4	**2d**	Ph	*i*Pr	1	**9id**	67
3	**1j**	4-$MeOC_6H_4$	**2d**	Ph	*i*Pr	1	**9jd**	82[c]
4	**1l**	2-Th	**2d**	Ph	*i*Pr	2	**9ld**	70[d]
5	**1f**	Ph	**2t**	4-$MeOC_6H_4$	*c*C_3H_5	4	**9ft**	75[c]
6	**1j**	4-$MeOC_6H_4$	**2e**	Ph	*c*C_3H_5	3	**9je**	80[c]
7	**1j**	4-$MeOC_6H_4$	**2t**	4-$MeOC_6H_4$	*c*C_3H_5	4	**9jt**	75[c]
8	**1f**	Ph	**2u**	Ph	*c*C_4H_7	1	**9fu**	69
9	**1f**	Ph	**2v**	Ph	*c*C_5H_9	2	**9fw**	70
10	**1f**	Ph	**2w**	Ph	*c*C_6H_{11}	2	**9fw**	81
11	**1i**	4-FC_6H_4	**2w**	Ph	*c*C_6H_{11}	2	**9iy**	82
12	**1j**	4-$MeOC_6H_4$	**2v**	Ph	*c*C_5H_9	3	**9jv**	65[c]
13	**1j**	4-$MeOC_6H_4$	**2w**	Ph	*c*C_6H_{11}	2	**9jw**	82[c]
14	**1l**	2-Th	**2v**	Ph	*c*C_5H_9	2	**9lv**	68

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), PTSA (0.025 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **9**. [c] PTSA (20 mol-%, 0.1 mmol). [d] ~10% of the corresponding C3-propargylindole **3ld** was also detected. 2-Th= 2-thienyl

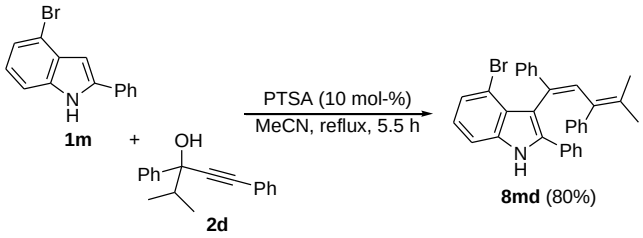
Besides, the acid-catalyzed isomerization of allenes **9** to dienes **8** has also been examined. C3-allenylindoles **9fd**, **9id** and **9jd** have been transformed into the corresponding C3-dienylindoles **8** in almost quantitative yield by refluxing an acetonitrile solution of the allenyl derivative in the presence of PTSA (5 mol-%) (Scheme 2). These results provide further evidence for the mechanism outlined in Scheme 1, supporting the intermediacy of allenes **9** in the formation of dienes **8**.

In addition, if the alkylation of a 2-arylindole, such as functionalized indole **1m**, with a benzylic branched-alkyl alkynol, such as **2d**, is carried out at reflux instead of room temperature, the corresponding 3-dienylindole **8md** is directly obtained and isolated in high yield (Scheme 3).[32]



9fd (Ar^1 = Ph) **8fd** (95%)
9id (Ar^1 = 4-FC_6H_4) **8id** (90%)
9jd (Ar^1 = 4-$MeOC_6H_4$) **8jd** (93%)

Scheme 2. Synthesis of 3-dienylindoles **8** from 3-allenylindoles **9**.

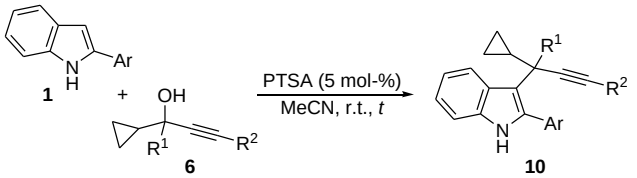


Scheme 3. Synthesis of 4-bromo-3-dienylindole **8md**.

*b) Reactions with cyclopropyl-substituted alkynols **6***

Once we had established the reactivity of 2-arylindoles with tertiary benzylic alkynols **2**, we turned our attention to their behavior towards tertiary cyclopropyl-substituted alkynols **6** that do not bear any aromatic group at the propargylic positions (Table 7). Different cyclopropyl-substitued alkynols **6** were coupled under the standard conditions with indoles bearing either an aryl (entries 1, 3–5) or heteroaryl (entry 2) group at C-2, to yield 2-aryl-3-propargylindoles **10** in good yields. Even for alkynols **6j** and **6m**, bearing sterically more-demanding groups than methyl at the other propargylic position, the direct substitution pathway was preferred (entries 4–5). These direct propargylation reactions are in contrast with the allenylation pathway observed for benzylic alkynols **2**, showing how the regioselectivity of the substitution (S_N *vs.* S_N´) in 2-arylindoles is controlled by the structure of the starting propargylic alcohol.[33] The S_N´ substitution leading to allenes or dienes seems to be favored only for tertiary propargylic alcohols with aryl substituents at both the propargylic and the terminal positions, and with a bulky substituent at the other propargylic position.

Table 7. Reaction of 2-arylindoles **1** with cyclopropyl-substituted alkynols **6**. Synthesis of 2-aryl-3-(1-cyclopropyl)propargylindoles **10**.[a]



Entry	**1**	Ar	**6**	R^1	R^2	*t* [h]	**10**	Yield [%][b]
1	**1f**	Ph	**6a**	Me	Ph	1	**10a**	67
2	**1l**	2-Th	**6a**	Me	Ph	1	**10b**	77
3	**1f**	Ph	**6c**	Me	*c*C_3H_5	1	**10c**	80
4	**1f**	Ph	**6j**	*c*C_3H_5	Ph	1	**10d**	76
5	**1f**	Ph	**6m**	Et	Ph	2	**10e**	75

[a] Reaction conditions: **1** (1 mmol), **6** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **10** after column chromatography. 2-Th= 2-thienyl

*Alkylation of 2-methylindole **1n***

At this point, we wondered if 2-alkylindoles followed the same behavior observed for 2-arylindoles or if, on the contrary, the regioselectivity of the substitution was also controlled by the nature of the substituent at the C-2 of the indole counterpart. To this aim, we started by performing the reaction of commercially available 2-methylindole **1n**, under the standard conditions, with benzylic alkynol **2b** bearing a methyl group at the propargylic position. As in the alkylation of 2-phenylindole **1f**, the corresponding C3-propargylated derivative **11a** was obtained in good yield (Table 8, entry 1). However, a distinctive outcome was observed for alkynols **2a** and **2d**, which possess a bigger linear- (entry 2) and a branched-substituent (entry 3) at the propargylic position. Whereas C3-allenylindoles **9** were obtained for 2-phenylindole **1f**, C3-propargylindoles **11** are now formed as major products in the reaction of 2-methylindole **1n**. Not surprisingly, the direct substitution pathway is also preferred for alkynols having an alkyl group at the terminal position of the triple bond (entries 4 and 5) and those bearing two alkyl groups at the propargylic positions (entry 6).

Table 8. Reaction of 2-methylindole **1n** with benzylic alkynols **2** and cyclopropyl-substituted alkynol **6a**. Synthesis of 2-methyl-3-propargylindoles **11**.[a]

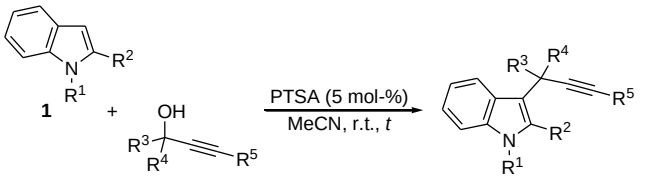
Entry	Alkynol	R^1	R^2	R^3	*t* [h]	**11**	Yield [%][b]
1	**2b**	Ph	Me	Ph	2.5	**11a**	72
2	**2a**	Ph	Et	Ph	2	**11b**	64[c]
3	**2d**	Ph	*i*Pr	Ph	1	**11c**	80
4	**2i**	Ph	*n*Pr	*n*Bu	3	**11d**	73
5	**2j**	Ph	*i*Pr	*n*Bu	2	**11e**	60
6	**6a**	*c*C_3H_5	Me	Ph	2	**11f**	71[d]

[a] Reaction conditions: 1n (1 mmol), 2 or 6 (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **11** after column chromatography. [c] The corresponding 3-dienylindole **8na** was also isolated (14%) and characterized. [d] Isolated along with trace amounts of **1n**.

Alkylation of 1,2-disubstituted-indoles

Considering that so far only the alkylation of 2-substituted-indoles with a free *N*-H had been discussed, we evaluated next the influence of the substitution at the nitrogen atom. Thus, the coupling of 1,2-dimethylindole **1o** and tertiary propargylic alcohols with different selected substitution patterns leads in all cases to C3-propargylindoles **12** in moderate to good yields (Table 9, entries 1–6). Next, we studied the reaction of 1-methyl-2-phenylindole **1p** and again the direct substitution pathway (S_N) was preferred for all the alcohols tested (Table 9, entries 7–15), including benzylic alkynols with alkyl groups bulkier than methyl at the propargylic position and an aryl group at the terminal position of the triple bond (entries 7 and 10). In contrast, these alkynol derivatives exclusively lead to the corresponding allene or diene derivatives, **8** or **9**, when coupled with 2-phenylindole **1f** (Tables 5 and 6). In these cases, the higher nucleophilicity of this indole **1p** probably accounts for the high yields obtained for the corresponding 1-methyl-2-phenyl-3-propargylindoles **13**. Therefore, it seems that the presence of a substituent at the nitrogen atom favors the S_N over the S_N' reaction. This hypothesis was further confirmed when the reaction with 1,2-diphenylindole **1q** was performed and C3-propargylindoles **14a** and **14b** were exclusively obtained in high yields (Table 9, entries 16 and 17), thus proving that substitution at the nitrogen atom, either with an aryl or alkyl group, suppresses the allenylation (S_N') pathway.

Table 9. Reactions of 1,2-disubstituted-indoles **1o-q** with alkynols **2**, **4** and **6**. Synthesis of 1,2-disubstituted-3-propargylindoles **12-14**.[a]



2 (R^3 = Ar)
4 (R^3, R^4 = Alk)
6 (R^3 = *c*C_3H_5, R^4 = Alk)

12 (R^1 = R^2 = Me)
13 (R^1 = Me, R^2 = Ph)
14 (R^1 = R^2 = Ph)

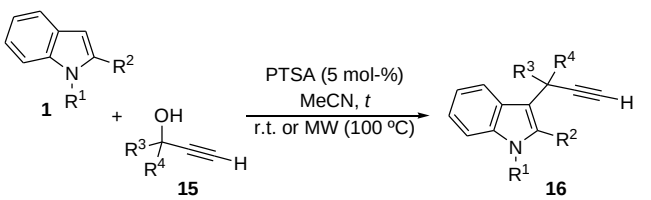
Entry	**1**	R^1	R^2	Alkynol	R^3	R^4	R^5	*t* [h]	**12-14**	Yield [%][b]
1	**1o**	Me	Me	**2a**	Ph	Et	Ph	2	**12a**	59[c]
2	**1o**	Me	Me	**2b**	Ph	Me	Ph	8.5	**12b**	69
3	**1o**	Me	Me	**2i**	Ph	*n*Pr	*n*Bu	4	**12c**	61
4	**1o**	Me	Me	**2m**	Ph	Me	*n*Bu	1	**12d**	81
5[d]	**1o**	Me	Me	**4a**	Me	Me	Ph	1	**12e**	40
6	**1o**	Me	Me	**6n**	*c*C_3H_5	*c*C_3H_5	*n*Bu	1	**12f**	60[e]
7	**1p**	Me	Ph	**2a**	Ph	Et	Ph	3	**13a**	84
8	**1p**	Me	Ph	**2b**	Ph	Me	Ph	4	**13b**	82
9	**1p**	Me	Ph	**2i**	Ph	*n*Pr	*n*Bu	8.5	**13c**	64
10	**1p**	Me	Ph	**2x**	2-Th	*c*C_3H_5	Ph	2	**13d**	81
11[d]	**1p**	Me	Ph	**4d**	Me	Me	*n*C_5H_{11}	0.3	**13e**	50[f]
12	**1p**	Me	Ph	**6c**	Me	*c*C_3H_5	*c*C_3H_5	2	**13f**	86
13	**1p**	Me	Ph	**6d**	Me	*c*C_3H_5	*n*Bu	2	**13g**	88
14	**1p**	Me	Ph	**6l**	Me	*c*C_3H_5	*t*Bu	2	**13h**	80
15	**1p**	Me	Ph	**6n**	*c*C_3H_5	*c*C_3H_5	*n*Bu	0.5	**13i**	92
16	**1q**	Ph	Ph	**2a**	Ph	Et	Ph	2	**14a**	89
17	**1q**	Ph	Ph	**2w**	Ph	*c*C_6H_{11}	Ph	1	**14b**	84

[a] Reaction conditions: **1** (1 mmol), alkynol (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **12-14** after column chromatography. [c] 3-Dienylindole **8oa** was also isolated (20%). [d] Carried out at 100 °C under microwave irradiation (see Supporting Information for details). [e] The corresponding 3-dienylindole was detected in trace amounts in the crude mixture. [f] Isolated along with small amounts of **1p**. 2-Th= 2-thienyl

Alkylation of indoles with tertiary terminal propargylic alcohols 15

Finally, the alkylation of a variety of *N*-substituted, 2-substituted, and 1,2-disubstituted indoles with the more challenging terminal benzylic alkynols **15a** and **15b** was considered (Table 10).

Table 10. Reaction of indoles **1** with terminal alkynols **15**.[a]



Entry	**1**	R^1	R^2	**15**	R^3	R^4	*t* [h]	**16**	Yield [%][b]
1	**1a**	Me	H	**15a**	Ph	*c*C_3H_5	1	**16aa**	74
2	**1f**	H	Ph	**15a**	Ph	*c*C_3H_5	1	**16fa**	77
3[c]	**1f**	H	Ph	**15b**	Ph	Et	0.5	**16fb**	51
4	**1n**	H	Me	**15a**	Ph	*c*C_3H_5	1	**16na**	70
5[c]	**1n**	H	Me	**15b**	Ph	Et	0.5	**16nb**	53
6	**1o**	Me	Me	**15a**	Ph	*c*C_3H_5	1	**16oa**	69

[a] Reaction conditions: **1** (1 mmol), **15** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at r.t. [b] Isolated yield of **16** after column chromatography. [c] Reaction performed at 100 °C under microwave irradiation (see Supporting Information for details).

Regardless of the structure of the indole, we isolated C3-propargylated indole derivatives **16** as main products in moderate to good yields after short reaction times. In the case of the less reactive alkynol **15b** it was necessary to heat the reaction mixture under microwave irradiation to obtain good conversions in short reaction times.

Conclusions

In summary, the scope and limitations of the Brønsted acid-catalyzed direct alkylation reaction of indoles with tertiary propargylic alcohols have been studied. The effect of the nature of the substituents at both the indole and the alcohol has been analyzed. Direct substitution leading to C3-propargylated indoles was found to be the preferred reaction pathway in most of the cases and only with *N*-unsubstituted-2-arylindoles a competitive S_N' reaction takes place affording 3-dienyl or 3-allenylindoles. Mild conditions were generally used and reaction times were kept short. Moreover, reactions were performed with undried solvent, out in air and water was the only side product. Therefore, we can conclude that a widely general, operationally simple and environmentally friendly procedure for the synthesis of C3-propargylated indoles with a quaternary carbon at the propargylic position has been established.

Experimental Section

General Procedure for the Synthesis of 3-Propargyl-1*H*-indoles 3, 7, 10-14, 16, and 3-Dienyl-1*H*-indoles 8. To a mixture of the corresponding alkynol (1.2 equiv) and indole derivative (1 equiv) in analytical grade MeCN (2 mL/mmol), PTSA (5 mol-%) was added. The reaction was stirred at room temperature until the indole was consumed, as determined by GC-MS and/or TLC. The crude mixture was neutralized by the addition of two drops of concd NaOH. H_2O (20 mL) and EtOAc (15 ml) were added. The separated aqueous phase was extracted with EtOAc (3 × 15 mL). The organic layer was dried over anhyd Na_2SO_4, and concentrated under reduced pressure. Alternatively, after the addition of concd NaOH, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: mixtures of hexane/Et_2O) to afford the corresponding 3-alkylated indoles.

Synthesis of 1-Methyl-3-(4-methyl-1,3-diphenylpent-1-yn-3-yl)-1*H*-indole (3ad; Table 2, entry 4). According to the general procedure from 4-methyl-1,3-diphenylpent-1-yn-3-ol **2d** (601 mg, 2.4 mmol) and *N*-methylindole **1a** (262 mg, 2 mmol) in MeCN (4 mL) under PTSA (19 mg, 0.1 mmol) catalysis. The reaction was stirred at r.t. for 30 min and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 10/1) to afford **3ad** (581 mg, 80%) as a white solid, which was recrystallized in hexane/Et_2O (2/1): m.p. 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.04 (d, ^3J(H,H) = 6.5 Hz, 3H, CH_3CHCH_3), 1.39 (d, ^3J(H,H) = 6.5 Hz, 3H, CH_3CHCH_3), 2.97 (sept, ^3J(H,H) = 6.5 Hz, 1H, $CH(CH_3)_2$), 3.79 (s, 3H, NCH_3), 7.07 (t, ^3J(H,H) = 7.5 Hz, 1H, Ar*H*), 7.15–7.23 (m, 2H, Ar*H*), 7.25 (s, 1H, NC*H*), 7.26–7.47 (m, 6H, Ar*H*), 7.55–7.68 (m, 2H, Ar*H*), 7.77 (d, ^3J(H,H) = 7.5 Hz, 2H, Ar*H*), 7.87 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 19.1 (CH_3), 20.3 (CH_3), 32.9 (CH_3), 36.3 (CH), 50.8 (C), 86.3 (C), 92.0 (C), 109.2 (CH), 118.7 (C), 118.8 (CH), 121.5 (CH), 121.6 (CH), 124.2 (C), 126.2 (CH), 126.68 (C), 126.74 (CH), 127.4 (2 × CH), 127.8 (CH), 127.9 (2 × CH), 128.3 (2 × CH), 131.8 (2 × CH), 137.5 (C), 144.8 (C); IR (KBr): ν = 2972, 2950, 1486, 1324, 763, 745, 721, 696 cm^{-1}; LRMS (70 eV, EI): *m/z* (%) 320 (M^+–C_3H_7, 100); HRMS (70 eV, EI): calcd for $C_{27}H_{25}N$, 363.1987; found, 363.1990; elemental analysis: calcd (%) for $C_{27}H_{25}N$ (363.2): C, 89.21; H, 6.93; N, 3.85; found: C, 89.04; H, 6.96; N, 3.82.

Synthesis of 3-(2-Cyclopropyl-4-(thiophen-3-yl)but-3-yn-2-yl)-1-methyl-1*H*-indole (7ab; Table 4, entry 2). According to the general procedure from 2-cyclopropyl-4-(thiophen-3-yl)but-3-yn-2-ol **6b** (230 mg, 1.2 mmol) and *N*-methylindole **1a** (131 mg, 1 mmol) in MeCN (2 mL) under PTSA (9.5 mg, 0.05 mmol) catalysis. The reaction was stirred at r.t. for 30 min and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 25/1) to afford **7ab** (284 mg, 93%) as a yellow oil: R_f = 0.29 (hexane/Et_2O, 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.62–0.70 (m, 2H, $CH(CHH)_2$), 0.77–0.88 (m, 2H, $CH(CHH)_2$), 1.46–1.60 (m, 1H, $CH(CH_2)_2$), 1.96 (s, 3H, CH_3), 3.81 (s, 3H, NCH_3), 7.15–7.17 (m, 1H, Ar*H*), 7.18 (s, 1H, Ar*H*), 7.21–7.30 (m, 2H, Ar*H*), 7.31–7.37 (m, 1H, Ar*H*), 7.40 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.44 (dd, ^3J(H,H) = 2.9, 1.1 Hz, 1H, Ar*H*), 8.13 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 2.2 (CH_2), 3.2 (CH_2), 21.2 (CH), 29.6 (CH_3), 32.7 (CH_3), 37.1 (C), 77.3 (C), 92.1 (C), 109.5 (CH), 118.8 (CH), 120.4 (C), 121.2 (CH), 121.5 (CH), 122.9 (C), 125.0 (CH), 125.6 (CH), 126.2 (C), 127.8 (CH), 130.2 (CH), 137.8 (C); LRMS (70 eV, EI): *m/z* (%) 305 (M^+, 59), 290 (77), 277 (56), 264 (92), 157 (45), 144 (100), 133 (51), 115 (54), 89 (48); HRMS (70 eV, EI): calcd for $C_{20}H_{19}NS$, 305.1238; found, 305.1234.

Synthesis of 5-Methoxy-2-phenyl-3-((1*Z*,3*E*)-1,3-diphenylpenta-1,3-dienyl)-1*H*-indole (8ga; Table 5, entry 2). According to the general procedure from 1,3-diphenylpent-1-yn-3-ol **2a** (123 mg, 0.52 mmol) and 5-methoxy-2-phenyl-1*H*-indole **1g** (112 mg, 0.5 mmol) in MeCN (2 mL) under PTSA (5 mg, 0.025 mmol) catalysis. The reaction was stirred at r.t. for 30 min and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 5/1) to afford **8ga** (152 mg, 69%) as a white solid: m.p. 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.58 (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3), 3.68 (s, 3H, OCH_3), 5.48 (dq, ^3J(H,H) = 6.9, 1.1 Hz, 1H, $CHCH_3$), 6.49 (d, ^3J(H,H) = 2.3 Hz, 1H, Ar*H*), 6.73–6.80 (m, 3H, Ar*H*), 6.85 (dd, ^3J(H,H) = 6.7, 3.0 Hz, 2H, Ar*H*), 7.01 (d, ^3J(H,H) = 8.7 Hz, 1H, Ar*H*), 7.13 (s, 1H, Ar*H*), 7.47–7.20 (m, 9H, Ar*H*), 7.62 (dd, ^3J(H,H) = 7.8, 1.6 Hz, 2H, Ar*H*), 7.76 (bs, 1H, N*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 15.2 (CH_3), 55.8 (CH_3), 102.7 (CH), 111.0 (CH), 113.0 (C), 121.1 (CH), 125.4 (CH), 126.2 (2 × CH), 126.7 (2 × CH), 126.9 (2 × CH), 127.3 (CH), 127.4 (2 × CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 129.6 (C), 131.0 (C), 132.8 (C), 136.9 (C), 137.3 (C), 139.9 (C), 141.9 (C), 142.4 (C), 153.9 (C); LRMS (70 eV, EI): *m/z* (%) 441 (M^+, 24), 412 (100), 380 (9); HRMS (70 eV, EI): calcd for $C_{32}H_{27}NO$, 441.2093; found, 441.2072.

Synthesis of 3-(2-Cyclopropyl-4-phenylbut-3-yn-2-yl)-2-(thiophen-2-yl)-1*H*-indole (10b; Table 7, entry 2). According to the general procedure from 2-cyclopropyl-4-phenylbut-3-yn-2-ol **6a** (224 mg, 1.2 mmol) and 2-(thiophen-2-yl)-1*H*-indole **1l** (199 mg, 1 mmol) in MeCN (2 mL) under PTSA (9.5 mg, 0.05 mmol) catalysis. The reaction was stirred at r.t. for 1 h and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 10/1) to afford **10b** (283 mg, 77%) as a white solid: m.p. 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.30–0.42 (m, 1H, $CHHCHCH_2$), 0.47–0.53 (m, 1H, CH_2CHCHH), 0.72–0.86 (m, 2H, $CH(CHH)_2$), 1.38–1.52 (m, 1H, $CH(CH_2)_2$), 1.86 (s, 3H, CH_3), 7.08 (dd, ^3J(H,H) = 5.1, 3.6 Hz, 1H, Ar*H*), 7.14–7.38 (m, 9H, Ar*H*), 7.42 (dd, ^3J(H,H) = 5.1, 1.0 Hz, 1H, Ar*H*), 7.95 (bs, 1H, N*H*), 8.33 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 2.9 (CH_2), 4.3 (CH_2), 22.0 (CH), 30.5 (CH_3), 38.3 (C), 83.3 (C), 93.1 (C), 110.8 (CH), 119.5 (CH), 120.0 (C), 122.3 (CH), 122.6 (CH), 124.0 (C), 125.9 (C), 126.7 (CH), 127.1 (CH), 127.3 (C), 127.6 (CH), 128.1 (2 × CH), 130.1 (CH), 131.7 (2 × CH), 135.5 (C), 135.6 (C); LRMS (70 eV, EI): *m/z* (%) 367 (M^+, 53), 352 (80), 338 (48), 326 (100), 291 (84), 223 (77), 199 (62), 152 (75), 127 (76); HRMS (70 eV, EI): calcd for $C_{25}H_{21}NS$, 367.1395; found, 367.1393.

Synthesis of 2-Methyl-3-(4-phenyldec-5-yn-4-yl)-1*H*-indole (11d; Table 8, entry 4). According to the general procedure from 4-phenyldec-5-yn-4-ol **2i** (276 mg, 1.2 mmol) and 2-methyl-1*H*-indole **1n** (131 mg, 1 mmol) in MeCN (2 mL) under PTSA (9.5 mg, 0.05 mmol) catalysis. The reaction was stirred at r.t. for 3 h and the residue was purified by column

chromatography on silica gel (eluent: hexane/Et_2O, 7/1) to afford **11d** (251 mg, 73%) as a yellow foam: R_f = 0.41 (hexane/Et_2O, 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.95–1.05 (m, 6H, $(CH_2)_2CH_3$ and $(CH_2)_3CH_3$), 1.44–1.68 (m, 6H, $CH_2CH_2CH_3$ and $CH_2(CH_2)_2CH_3$), 2.28–2.44 (m, 6H, $CHHCH_2CH_3$, $CH_2(CH_2)_2CH_3$ and $NCCH_3$), 2.63 (td, ^3J(H,H) = 12.3, 4.5 Hz, 1H, $CHHCH_2CH_3$), 6.98–7.05 (m, 1H, Ar*H*), 7.11 (td, ^3J(H,H) = 9,3 Hz, 1H, Ar*H*), 7.18–7.25 (m, 2H, Ar*H*), 7.27–7.34 (m, 2H, Ar*H*), 7.54–7.60 (m, 3H, Ar*H*), 7.73 (bs, 1H, N*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.8 (CH_3), 14.4 (CH_3), 14.5 (CH_3), 18.2 (CH_2), 19.2 (CH_2), 22.2 (CH_2), 31.2 (CH_2), 45.0 (CH_2), 45.5 (C), 84.7 (C), 84.9 (C), 110.2 (CH), 115.1 (C), 119.0 (CH), 120.5 (CH), 120.9 (CH), 126.0 (CH), 127.2 (2 × CH), 127.9 (2 × CH), 132.2 (C), 134.8 (C), 147.4 (C); IR (KBr): ν = 3396, 2955, 2926, 1699, 1682 cm^{-1}; LRMS (70 eV, EI): *m/z* (%) 343 (M^+, 11), 320 (100); HRMS (70 eV, EI): calcd for $C_{25}H_{29}N$, 343.2300; found, 343.2299.

Synthesis of 1,2-Dimethyl-3-(4-phenyldec-5-yn-4-yl)-1*H*-indole (12c; Table 9, entry 3). According to the general procedure from 4-phenyldec-5-yn-4-ol **2i** (276 mg, 1.2 mmol) and 1,2-dimethyl-1*H*-indole **1o** (145 mg, 1 mmol) in MeCN (2 mL) under PTSA (9.5 mg, 0.05 mmol) catalysis. The reaction was stirred at r.t. for 4 h and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 20/1) to afford **12c** (218 mg, 61%) as a yellow foam: R_f = 0.46 (hexane/Et_2O, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.10 (t, ^3J(H,H) = 7.2 Hz, 3H, $(CH_2)_nCH_3$), 1.13 (t, ^3J(H,H) = 7.4 Hz, 3H, $(CH_2)_nCH_3$), 1.51–1.80 (m, 6H, $CH_2CH_2CH_3$ and $CH_2(CH_2)_2CH_3$), 2.43 (s, 3H, $NCCH_3$), 2.47 (t, ^3J(H,H) = 7.0 Hz, 2H, $CH_2(CH_2)_2CH_3$), 2.53 (td, ^3J(H,H) = 12.2, 4.7 Hz, 1H, $CHHCH_2CH_3$), 2.81 (td, ^3J(H,H) = 12.2, 4.2 Hz, 1H, $CHHCH_2CH_3$), 3.68 (s, 3H, NCH_3), 7.15 (t, ^3J(H,H) = 7.5 Hz, 1H, Ar*H*), 7.25 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.31 (d, ^3J(H,H) =7.1 Hz, 1H, Ar*H*), 7.34–7.43 (m, 3H, Ar*H*), 7.67 (d, ^3J(H,H) =7.5 Hz, 2H, Ar*H*), 7.85 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.1 (CH_3), 13.8 (CH_3), 14.5 (CH_3), 18.9 (CH_2), 19.3 (CH_2), 22.2 (CH_2), 29.3 (CH_3), 31.3 (CH_2), 45.7 (CH_2), 46.0 (C), 84.6 (C), 85.2 (C), 108.7 (CH), 114.9 (C), 118.8 (CH), 120.0 (CH), 120.7 (CH), 125.9 (CH), 126.8 (C), 127.1 (2 × CH), 127.8 (2 × CH), 134.7 (C), 136.4 (C), 148.0 (C); LRMS (70 eV, EI): *m/z* (%) 357 (M^+, 41), 314 (100), 300 (17), 145 (30); HRMS (70 eV, EI): calcd for $C_{26}H_{31}N$, 357.2456; found, 357.2455; elemental analysis: calcd (%) for $C_{25}H_{29}N$ (343.5): C, 87.41; H, 8.51; N, 4.08. Found: C, 87.29; H, 8.56; N, 4.05.

Synthesis of 3-(2-Cyclopropyl-5,5-dimethylhex-3-yn-2-yl)-1-methyl-2-phenyl-1*H*-indole (13h; Table 9, entry 14). According to the typical procedure from 2-cyclopropyl-5,5-dimethylhex-3-yn-2-ol **6l** (200 mg, 1.2 mmol) and 1-methyl-2-phenyl-1*H*-indole **1p** (207 mg, 1 mmol). The reaction was stirred at r.t. for 2 h and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 20/1) to afford **13h** (284 mg, 80%) as a white solid: m.p. 122–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = −0.08–0.05 (m, 1H, $CHHCHCH_2$), 0.16–0.31 (m, 1H, CH_2CHCHH), 0.48–0.64 (m, 2H, $CH(CHH)_2$), 0.82–0.94 (m, 1H, $CH(CH)_2$), 1.18 (s, 9H, $C(CH_3)_3$), 1.55 (s, 3H, CH_3), 3.33 (s, 3H, NCH_3), 7.14 (t, ^3J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.25 (d, ^3J(H,H) = 7.1 Hz, 1H, Ar*H*), 7.29 (d, ^3J(H,H) = 5.5 Hz, 1H, Ar*H*), 7.32–7.46 (m, 5H, Ar*H*), 8.33 (dd, ^3J(H,H) = 8.1, 0.6 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 2.6 (CH_2), 4.3 (CH_2), 21.9 (CH), 27.5 (C), 30.2 (CH_3), 31.3 (3 × CH_3), 32.1 (CH_3), 37.5 (C), 81.3 (C), 90.8 (C), 109.1 (CH), 117.9 (C), 118.6 (CH), 121.5 (CH), 122.6 (CH), 126.8 (C), 127.80 (CH), 127.84 (CH), 128.4 (CH), 131.5 (CH), 131.7 (CH), 135.0 (C), 135.8 (C), 136.7 (C); LRMS (70 eV, EI): *m/z* (%) 355 (M^+, 30), 340 (100), 327 (79), 314 (41), 298 (18), 282 (15), 268 (15), 233 (13), 220 (13); HRMS (70 eV, EI): calcd for $C_{26}H_{29}N$, 355.2300; found, 355.2294; elemental analysis: calcd (%) for $C_{26}H_{29}N$ (355.5): C, 87.84; H, 8.22; N, 3.94; found: C, 87.71; H, 8.25; N, 3.92.

Synthesis of 3-(1-Cyclopropyl-1-phenylprop-2-ynyl)-1-methyl-1*H*-indole (16aa; Table 10, entry 1). According to the general procedure from 1-cyclopropyl-1-phenylprop-2-yn-1-ol **15a** (207 mg, 1.2 mmol) and 1-methylindole **1a** (131 mg, 1 mmol) in MeCN (2 mL) under PTSA (9.5 mg, 0.05 mmol) catalysis. The reaction was stirred at r.t. for 1 h and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 10/1) to afford **16aa** (211 mg, 74%) as a white solid: m.p. 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.56–0.66 (m, 1H, $CHHCHCH_2$), 0.69–0.78 (m, 1H, CH_2CHCHH), 0.80–0.90 (m, 2H, $CH(CHH)_2$), 1.60–1.75 (m, 1H, $CH(CH_2)_2$), 2.45 (s, 1H, $C{\equiv}CCH$), 3.84 (s, 3H, NCH_3), 6.92–7.05 (m, 1H, Ar*H*), 7.17–7.38 (m, 7H, Ar*H*), 7.57–7.65 (m, 2H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 2.5 (CH_2), 3.8 (CH_2), 21.2 (CH), 32.9 (CH_3), 45.5 (C), 72.7 (CH), 84.6 (C), 109.3 (CH), 118.9 (CH), 119.3 (C), 121.2 (CH), 121.7 (CH), 126.0 (C), 126.6 (CH), 127.2 (2 × CH), 127.3 (CH), 128.1 (2 × CH), 137.8 (C), 145.2 (C); LRMS (70 eV, EI): *m/z* (%) 285 (M^+, 78), 270 (21), 257 (100), 244 (90), 202 (22), 157 (43), 144 (82); HRMS (70 eV, EI): calcd for $C_{21}H_{19}N$, 285.1517; found, 285.1511.

General Procedure for the Synthesis of 3-(1,1-Dialkyl)propargyl-1*H*-indoles 5. In a heavy-walled 10 mL vial, PTSA (5 mol-%) was added to a mixture of the corresponding alkynol (2.4 mmol) and indole derivative (2 mmol) in MeCN (2 mL). The reaction vessel was sealed and subjected to microwave irradiation (50 W) at 100 ºC under stirring for the required time (see Table 3) until the alkynol disappeared, as determined by GC-MS and/or TLC. The reaction mixture was cooled to room temperature and neutralized by the addition of two drops of concd NaOH. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford the corresponding 3-propargylindoles.

Synthesis of 1-Methyl-3-(2-methyl-4-phenylbut-3-yn-2-yl)-1*H*-indole (5aa; Table 3, entry 1). According to the general procedure from 2-methyl-4-phenylbut-3-yn-2-ol **4a** (384 mg, 2.4 mmol) and *N*-methylindole **1a** (262 mg, 2 mmol) in MeCN (2 mL) under PTSA (19 mg, 0.1 mmol) catalysis. The reaction was stirred at 100 °C under microwave irradiation (50 W) for 20 min and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 15/1) to afford **5aa** (219 mg, 40%) as a yellow foam; R_f = 0.30 (hexane/Et_2O, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.08 (s, 6H, 2 × CH_3), 3.84 (s, 3H, NCH_3), 7.18 (s, 1H, NC*H*), 7.41–7.53 (m, 6H, Ar*H*), 7.67–7.73 (m, 2H, Ar*H*), 8.30 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 30.8 (2 × CH_3), 31.2 (CH_3), 32.5 (C), 80.4 (C), 97.2 (C), 109.5 (CH), 118.8 (CH), 120.9 (C), 121.0 (CH), 121.5 (CH), 124.1 (C), 124.7 (CH), 125.9 (C), 127.6 (CH), 128.2 (2 × CH), 131.7 (2 × CH), 137.8 (C); LRMS (70 eV, EI): *m/z* (%) 273 (M^+, 23), 258 (100); HRMS (70 eV, EI): calcd for $C_{20}H_{19}N$, 273.1517; found, 273.1513.

Typical Procedure for the Synthesis of 3-(Propa-1,2-dienyl)-1*H*-indoles 9: Synthesis of 2-(4-Fluorophenyl)-3-(4-methyl-1,3-diphenylpenta-1,2-dienyl)-1*H*-indole (9id; Table 6, entry 2). To a mixture of 4-methyl-1,3-diphenylpent-1-yn-3-ol **2d** (130 mg, 0.52 mmol) and 2-(4-fluorophenyl)-1*H*-indole **1i** (106 mg, 0.5 mmol) in analytical grade MeCN (2 mL), PTSA (5 mg, 0.025 mmol) was added. The reaction was stirred at r.t. for 1 h (the completion of the reaction was monitored by GC-MS and TLC) whereas a solid precipitated, which was filtered to afford **9id** (149 mg, 67%) as a pale yellow solid: m.p. 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (d, ^3J(H,H) = 6.5 Hz, 3H, CH_3CHCH_3), 1.23 (d, ^3J(H,H) = 6.5 Hz, 3H, CH_3CHCH_3), 2.83–2.97 (m, 1H, $CH(CH_3)_2$), 6.94 (t, ^3J(H,H) = 8.4 Hz, 2H, Ar*H*), 7.10 (t, ^3J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.16–7.35 (m, 9H, Ar*H*), 7.38–7.57 (m, 6H, Ar*H*), 8.19 (bs, 1H, N*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 22.2 (CH_3), 22.5 (CH_3), 29.6 (CH), 104.7 (C), 109.3 (C), 110.9 (CH), 115.6 (CH), 115.8 (d, ^2J(C,F)= 25.4 Hz, 2 × CH), 120.4 (d, ^3J(C,F)= 3.8 Hz, 2 × CH), 122.7 (CH), 126.5 (2 × CH), 126.9 (CH), 127.1 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 128.78 (C), 127.82 (C), 129.6 (CH), 129.7 (CH), 134.5 (C), 136.0 (C), 136.5 (C), 137.2 (C), 162.5 (d, ^1J(C,F) = 247.6 Hz, C), 206.3 (C); LRMS (70 eV, EI): *m/z* (%) 443 (M^+, 16), 400 (100), 366 (19), 322 (42); HRMS (70 eV, EI): calcd for $C_{32}H_{26}FN$, 443.2049; found, 443.2061; elemental analysis: calcd (%) for $C_{32}H_{26}FN$ (443.6): C, 86.65; H, 5.91; N, 3.16; found: C, 86.80; H, 5.93; N, 3.13.

Typical Procedure for the Synthesis of 3-(Buta-1,3-dienyl)-1*H*-indoles 8 from 3-(Propa-1,2-dienyl)-1*H*-indoles 9: Synthesis of 3-((*Z*)-4-Methyl-1,3-diphenylpenta-1,3-dienyl)-2-phenyl-1*H*-indole (8fd). To a mixture of 3-(4-methyl-1,3-diphenylpenta-1,2-dienyl)-2-phenyl-1*H*-indole **9fd** (128

mg, 0.3 mmol) in analytical grade MeCN (1 mL) was added PTSA (6 mg, 0.03 mmol). The reaction mixture was stirred at reflux for 5 h (until the isomerization reaction was completed, as determined by GC-MS). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et_2O, 10/1) to afford **8fd** (121 mg, 95%) as a pale yellow solid: m.p. 53–55 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.55 (s, 3H, C*H*$_3$), 1.75 (s, 3H, C*H*$_3$), 6.60–6.75 (m, 5H, Ar*H*), 6.94 (ddd, ^3J(H,H) = 7.9, 6.6, 1.2 Hz, 1H, Ar*H*), 7.02 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.13 (ddd, ^3J(H,H) = 8.1, 6.6, 1.4 Hz, 1H), Ar*H*, 7.16–7.22 (m, 1H, Ar*H*), 7.27–7.38 (m, 7H, Ar*H*), 7.50 (dd, ^3J(H,H) = 8.2, 1.5 Hz, 2H, Ar*H*), 7.58 (dd, ^3J(H,H) = 8.0, 1.7 Hz, 2H, Ar*H*), 7.89 (bs, 1H, N*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6 (CH_3), 22.2 (CH_3), 110.2 (CH), 113.5 (C), 119.3 (CH), 120.7 (CH), 122.0 (CH), 124.6 (CH), 126.3 (2 × CH), 126.8 (2 × CH), 127.0 (2 × CH), 127.1 (CH), 127.2 (CH), 128.29 (2 × CH), 128.33 (2 × CH), 128.6 (2 × CH), 129.4 (C), 132.1 (CH),132.8 (C), 134.25 (C),134.30 (C), 135.31 (C), 135.34 (C), 135.7 (C),141.3 (C), 142.7 (C); LRMS (70 eV, EI): *m/z* (%) 425 (M^+, 45), 410 (12), 348 (100), 293 (23), 293 (69); HRMS (70 eV, EI): calcd for $C_{32}H_{27}N$, 425.2143; found, 425.2155.

Supporting Information (see footnote on the first page of this article): Complete experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all the compounds, COSY and NOESY spectra of **8fa** and **8ga** and ORTEP diagram from compound **8md**.

Acknowledgments

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[31] a) Indoles **1h-l** were prepared by Fisher indole synthesis, see: D. L. Hughes, *Org. Prep. Proc. Int.* **1993**, *25*, 607–632. b) Indole **1g** was obtained by a modified Madelung synthesis, see: W. J. Houlihan, V. A. Parrino, Y. Uike, *J. Org. Chem.* **1981**, *46*, 4511–4515.

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[33] In addition, the reaction of dialkyl-substituted alkynol **4a** with 2-phenylindole **1f** also afforded the 3-propargylindole derivative though it could not be completely purified.

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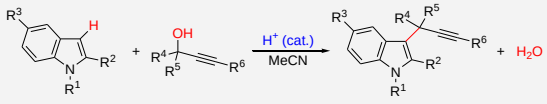
Entry for the Table of Contents

((Indole Alkylation))



R^1, R^2 = H, Alk, Ar R^4, R^6 = Ar, HetAr, Alk
R^3 = H, Br, CO_2Me R^5 = Alk

Treatment of indoles with tertiary propargylic alcohols under Brønsted acid-catalysis provides an efficient access to 3-propargylindoles bearing a quaternary center at the propargylic position. In addition, 3-dienyl and 3-allenylindoles could also be obtained with convenient substitution at both the indole and alkynol counterparts. Reactions are performed without special precautions, and water is the only side product

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Brønsted Acid-Catalyzed Alkylation of Indoles with Tertiary Propargylic Alcohols: Scope and Limitations

Keywords: ((Indoles / Alkylation / Brønsted acids / Alcohols / Nucleophilic Substitution))