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

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Direct alkylation of indoles with a wide variety of tertiary propargylic alcohols under Brønsted acid catalysis conditions has been studied. A general and environmentally friendly method for the synthesis of 3-propargylated indoles with quaternary carbon atoms at their propargylic positions has been developed. The reactions are highly regioselective with regard both to the indole and to the alkynol components. Only with *N*-unsubstituted 2-arylindoles do competitive S_N' reactions take place to afford 3-dienyl- or 3-allenylindoles, depending on the alkynol moiety. The reactions were carried out in air with undried solvents, and water was the only side product.

Introduction

The indole nucleus is one of the most ubiquitous heterocyclic structures found in nature, and it is a fundamental constituent of a number of natural and synthetic products displaying biological activity.[1] The synthesis and functionalization of indoles has therefore 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 3-position is a fundamental synthetic task in the preparation of relevant molecules containing indole nuclei.[3]

Indoles are electron-rich heteroaromatic systems that react with electrophiles much more rapidly than most benzene derivatives. The position in indole most reactive towards electrophilic substitution is the 3-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 in which carbocations are generated under relatively mild conditions are likely to be successful. The Friedel–Crafts reaction (i.e., electrophilic attack of carbocations or related electrophiles onto 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, etc.). 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] whereas the well-known Pd-catalyzed allylic substitution (Tsuji–Trost reaction) also represents a useful approach.[11] Moreover, enantioselective Friedel–Crafts reactions between indoles and readily available prochiral electrophilic starting materials constitute a simple strategy for the preparation of optically active indole derivatives.[12]

As mentioned above, alkylation of indoles is usually carried out with typical electrophiles. However, 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] (benzylic, propargylic, allylic) has led to the development of new catalytic methodologies for Friedel–Crafts reactions. In this field, several reports in which different Lewis acids[14] and late transition metal salts/complexes[15] have been used as catalysts for direct alkylations of indoles with alcohols, including few examples of intramolecular cycloalkylations,[16] have appeared in recent

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years. However, the use of expensive, toxic, and/or moisture-sensitive catalysts in some of these methods limits their practical usefulness in large-scale syntheses. Much more appealing is the use of Brønsted acids as catalysts in these processes as simple alternatives to some toxic and precious metals.[17]

Among π-activated alcohols, propargylic alcohols are appropriate substrates for catalyzed propargylic substitution reactions, which have emerged as useful synthetic tools.[18] However, the risk of competing allene formation due to the nature of propargylic cations, which are better represented by the corresponding allenium species, as well as the tendency to undergo competitive elimination, are issues that need to be considered mainly in the case of tertiary propargylic alcohols (Figure 1). In most reports of catalyzed propargylation reactions, secondary benzylic propargylic alcohols (1-arylprop-2-yn-1-ol derivatives) are therefore usually employed as alkylating agents.

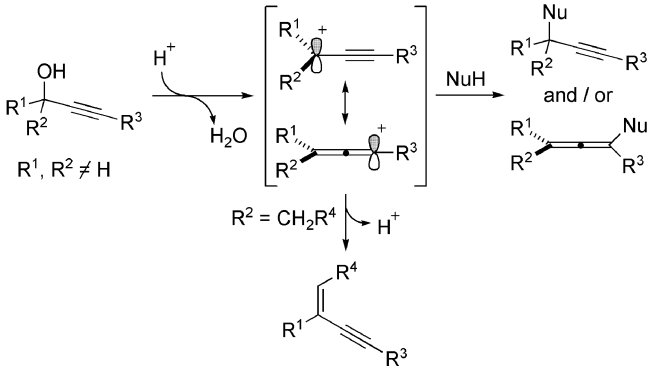


Figure 1. Propargylic cations from tertiary propargylic alcohols.

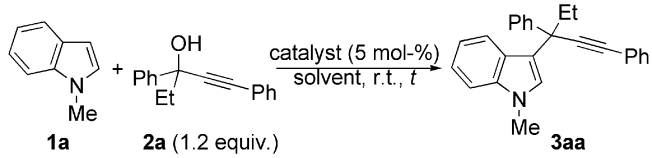
Although some methods for the preparation of 3-propargylindoles have been reported,[14c,14e,14g,14h] no preparatively useful synthesis of such compounds with quaternary centers at their propargylic positions had been described until our preliminary reports.[19,20] Moreover, it should be noted that few general methods for the direct introduction of quaternary carbon atoms at the 3-position of indoles are known.[21] In addition, the usefulness of 3-propargylindoles for subsequent gold-catalyzed transformations involving 1,2-indole migration has also been pointed out by our research group.[22] In an extension of our interest in the development of strategies for catalytic direct nucleophilic substitutions with alcohols,[23] we wish to report our studies in this field with indoles as nucleophiles and tertiary propargylic alcohols as electrophiles.

Results and Discussion

Optimization Studies

We initially selected the reaction between *N*-methylindole (**1a**) and the tertiary alkynol **2a** as a model system to assess the catalytic activities of several Brønsted and Lewis acids and to determine the optimum reaction conditions. The alkynol **2a** was chosen because it is an ideal substrate for testing nucleophilic substitution vs. competitive elimination, as well as for checking 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) took place to afford the desired alkylated indole derivative **3aa** in good yields and with 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 would be expected, the substitution reaction did not take place in the absence of catalyst (Entry 7), whereas 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 – originating from an elimination process in **2a**. It is also interesting to note the complete regioselectivity observed for this process with regard both to the nucleophile (only 3-attack takes place) and to the alkynol (exclusive substitution at the α-position of the propargylic moiety is observed). The absence of formation of allenic products is significant because the use of tertiary propargylic alcohols or their derivatives in nucleophilic substitution reactions usually affords mixtures of regioisomers or mainly the allenyl derivatives.[24]

Table 1. Evaluation of Brønsted and Lewis acid catalysts for the alkylation of *N*-methylindole (**1a**) with the 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** as determined by GC–MS analysis. [b] Isolated yield of **3aa** after column chromatography. [c] Reaction performed at reflux under N_2. [d] The elimination product (ca. 15%) was also formed.

We selected PTSA as the catalyst for screening of different solvents, due to its ready availability and ease of handling. Although the alkylation process was also efficient in CH_2Cl_2 and $MeNO_2$, no significant improvements in yield or reactivity with respect to our initial experiment with MeCN (Entries 8–9) were observed. We therefore settled on PTSA as catalyst and MeCN as solvent at room temperature as the best reaction conditions for exploring the scope and limitations of this Friedel–Crafts alkylation of indoles with alkynols.

Alkylation of 2-Unsubstituted Indoles

Reactions with the Benzylic Alkynols 2

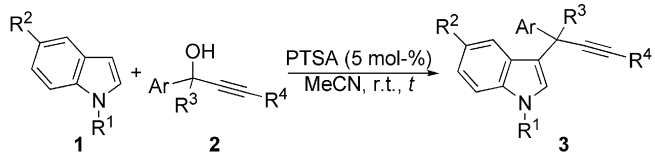
The results obtained from the reactions between a series of 2-unsubstituted indoles **1** and the benzylic tertiary alkynols **2**, catalyzed by PTSA (5 mol-%) under the optimized reaction conditions, are summarized in Table 2. *N*-Methylindole (**1a**) was successfully coupled with different benzylic alkynols bearing either aromatic (Entries 1–7), heteroaromatic (Entry 8), or alkyl substitution (Entries 9–12) at their terminal positions (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 positions (R^3). In all cases the corresponding 3-propargylated indoles are obtained regioselectively, 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 the hindered alkynols **2m** and **2n**, each bearing a substituent at the *ortho*-position of this aromatic group, no conversion was observed under the standard conditions. In these cases it was necessary to heat the mixture in MeCN at reflux for 24 h in order to obtain the corresponding functionalized indoles **3**. Significantly, we were able to reduce the reaction times dramatically by performing the processes under microwave irradiation conditions (Entries 13–14). The indoles **3am** and **3an** were isolated in moderate yields.

Not only *N*-methylindole (**1a**), but also *N*-unsubstituted indoles (Entries 15–25), including those with electron-withdrawing substituents at C-5 (consequently less nucleophilic; Entries 20–25) were successfully coupled. Again, the 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 monitored and analyzed by GC–MS, and we did not observe the presence of any byproduct in significant amounts. The moderate yields obtained in some cases are probably due to decomposition of the final indole derivative **3** under the reaction or purification conditions.

Reactions with the Dialkyl-Substituted Alkynols 4

We next examined the alkylation of the 2-unsubstituted indoles **1** with the alkynols **4**, each bearing two aliphatic substituents at the propargylic position (Table 3). Under the conditions described in Table 2 the reactions were slow, and

Table 2. Alkylation of the indoles **1** with the benzylic alkynols **2**; synthesis of the 3-(1-arylpropargyl)indoles **3** (2-Th = 2-thienyl, 3-Th = 3-thienyl).[a]



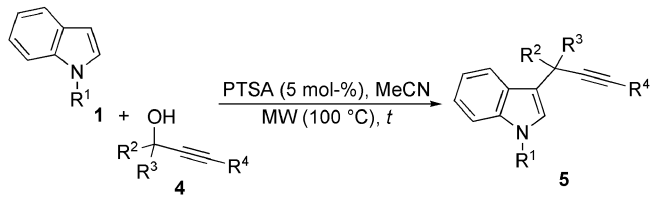
Entry	**1**	R^1	R^2	**2**	Ar	R^3	R^4	*t* [h]	**3**	Yield [%][b]
1	**1a**	Me	H	**2a**	Ph	Et	Ph	2	**3aa**	78
2	**1a**	Me	H	**2b**	Ph	Me	Ph	2	**3ab**	81
3	**1a**	Me	H	**2c**	Ph	*n*Pr	Ph	2	**3ac**	60
4	**1a**	Me	H	**2d**	Ph	*i*Pr	Ph	0.5	**3ad**	80
5[c]	**1a**	Me	H	**2e**	Ph	cC_3H_5	Ph	0.5	**3ae**	89
6	**1a**	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	cC_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 room temp. [b] Isolated yield of **3** after column chromatography. [c] Carried out at 100 °C under microwave irradiation conditions (see the Supporting Information for details). [d] Isolated along with **1a**.

heating in MeCN at reflux was required to achieve reasonable conversions. The difference in reactivity between the alkynols **2** and the alkynols **4a–e** is not surprising, because the stabilities of the propargylic carbocations proposed as intermediates for the substitution reactions should be significantly decreased when an aryl group at the propargylic position is changed for an alkyl group (see Figure 1). Once again, as in the reactions of the hindered alkynols **2m** and **2n**, 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 in the former case, probably due to its higher nucleophilicity. With regard to the alkynol counterpart, both linear (Entries 1–2, 4–7) and cyclic (Entry 3) aliphatic substituents are tolerated at the propargylic positions. In addition, the triple bond can variously bear 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 3-propargylated indoles **5** were obtained only in moderate yields in all cases.

Because the lower reactivities of the dialkyl-substituted alkynols **4** relative to the benzylic alkynols **2** are probably due to the inferior stabilities of the positively charged intermediates, and in view of the known ability of the cyclopropyl group to stabilize carbocations,[26] we envisaged that the cyclopropyl-substituted alkynols **6** might be appropriate substrates for nucleophilic substitutions with the indoles **1** under mild conditions. Gratifyingly, we found out that reactions between different 2-unsubstituted indoles **1** and a series of cyclopropylalkynols **6** took place in short times at room temperature to afford the corresponding alkylated indoles **7** in high yields (Table 4).

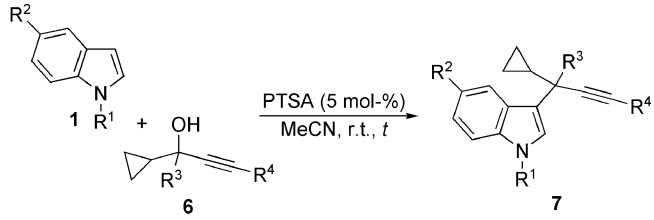
Table 3. Alkylation of the indoles **1** with the dialkyl-substituted alkynols **4a–e**; synthesis of the 3-(1,1-dialkylpropargyl)indoles **5** (cC_6H_9 = cyclohex-1-enyl).[a]



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	nC_5H_{11}	50	**5ad**	36[c]
5	**1a**	Me	**4e**	Me	Me	cC_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 °C under microwave irradiation conditions (see the 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**.

Table 4. Alkylation of the indoles **1** with the cyclopropyl-substituted alkynols **6**; synthesis of the 3-(1-cyclopropylpropargyl)indoles **7** (2-Th = 2-thienyl, 3-Th = 3-thienyl, cC_6H_9 = cyclohex-1-enyl).[a]



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	cC_3H_5	2	**7ac**	73
4	**1a**	Me	H	**6d**	Me	*n*Bu	13	**7ad**	77
5	**1a**	Me	H	**6e**	Me	cC_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	$(CH_2)_2Ph$	2	**7ag**	79
8	**1a**	Me	H	**6h**	Me	$SiMe_3$	0.5	**7ah**	60
9	**1a**	Me	H	**6i**	Me	$2\text{-}PhC_6H_4$	1	**7ai**	82
10	**1a**	Me	H	**6j**	cC_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	$(CH_2)_2Ph$	3	**7bg**	62
14	**1b**	H	H	**6l**	Me	*t*Bu	14	**7bl**	50
15	**1d**	H	CO_2Me	**6i**	Me	$2\text{-}PhC_6H_4$	24	**7di**	87

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at room temp. [b] Isolated yield of **7** after column chromatography.

Furthermore, the process is broadly general, and so both *N*-methylindole (**1a**, Entries 1–11) and *N*-unsubstituted indoles such as **1b** (Entries 12–14), as well as those with electron-withdrawing substituents at the benzenoid moiety (Entry 15), are suitable nucleophiles for the coupling. With regard to the cyclopropyl-substituted alkynol component, 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 systems (Entry 3), and also silyl (Entry 8) groups, are well tolerated at the terminal positions of the triple bonds, 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 involving the cyclopropyl-substituted alkynol. No products arising from a competitive ring-opening pathway, as occurs in other related catalyzed nucleophilic substitution processes,[27] were observed.

Alkylation of 2-Substituted NH-Indoles

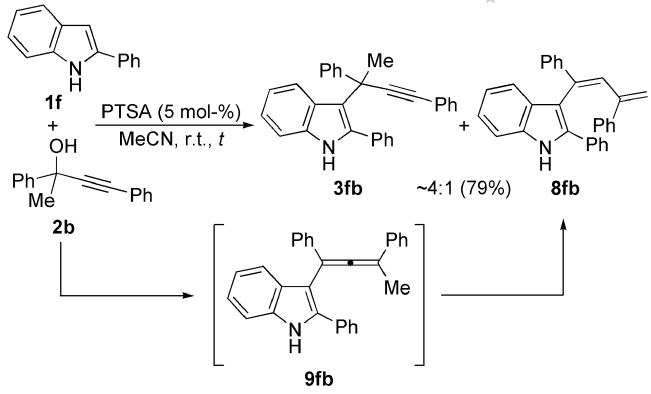
Once we had established the scope of the propargylation of 2-unsubstituted indoles, we turned our attention to the alkylation of 2-substituted ones. We were interested in evaluating the effects that the additional groups could have in the substitution reactions and in the possibility of synthesizing 2,3-disubstituted indoles by the developed methodology. We first decided to use 2-arylindoles, because aromatic substituents at C-2 significantly increase the nucleophilic character of the indole nucleus.

Alkylation of N-Unsubstituted 2-Arylindoles

a) Reactions with the Benzylic Alkynols **2**

We started our studies by treating the commercially available 2-phenylindole (**1f**) with the tertiary alkynol **2b** under the conditions previously established as optimal for 2-unsubstituted indoles (Scheme 1). Although the expected 3-propargylated indole **3fb** was obtained as major product, we found that in this case the reaction was not completely selective, and a significant amount of the 3-dienyl derivative **8fb** was also isolated. The generation of **8fb** could be explained in terms of a competitive S_N' substitution reaction leading to an allene derivative such as **9fb**, which could undergo 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 now reaches from the phenyl group at the 2-position of the indole to the terminal alkene.

We reasoned that the allenylation pathway should be favored if the steric hindrance at the propargylic position in the starting alkynol were increased, and so we performed the reaction between **1f** and the alkynol **2a**, bearing a bulkier substituent than **2b** (Et instead of Me). In this case the 3-dienylindole **8fa** was exclusively obtained in good yield,



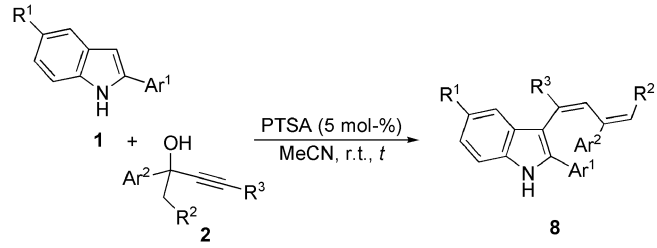
Scheme 1. Reaction between 2-phenylindole (**1f**) and the alkynol **2b** under PTSA catalysis conditions.

thus confirming our hypothesis (Table 5, Entry 1). There are no known methods for the direct synthesis of 3-dienylindole derivatives from unfunctionalized starting indole compounds,[28] so we decided to evaluate the scope of this procedure for the synthesis of 3-dienylindoles. It should be noted that these compounds have been used as precursors for the synthesis of alkaloids through Diels–Alder cyclizations.[29]

We first studied the reactions between the different 2-arylindole derivatives **1f**–**l** and tertiary benzylic alkynols **2** possessing linear substituents sterically more demanding than methyl ($R^2 \neq H$) at their propargylic positions (Table 5). When the alkynol **2a** was tested against 2-phenylindoles containing electron-donating (Entry 2) or electron-withdrawing (Entry 3) groups on their benzenoid moieties, the corresponding dienylindole derivatives **8** were exclusively obtained in good yields.[30] In addition, aryl groups with different electronic natures and substitution patterns (Entries 6–8, 12) as well as a heteroaryl group (Entry 9), are tolerated well at C-2 of the indole, also exclusively yielding 3-dienyl derivatives. With regard to the substituent at the terminal position of the triple bond, it was found that the alkynol **2i**, bearing an alkyl group at this position, mainly afforded the 3-propargylated derivative **3fi** (Entry 5). This seems to indicate that an aryl group is required at the terminal position of the acetylene moiety in order to favor the formation of 3-dienylindoles over that of 3-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.

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

Table 5. Alkylation of the 2-arylindoles **1f–l** with the benzylic α-monosubstituted alkylalkynols **2**; synthesis of the 3-dienylindoles **8**[a] (2-Th = 2-thienyl).



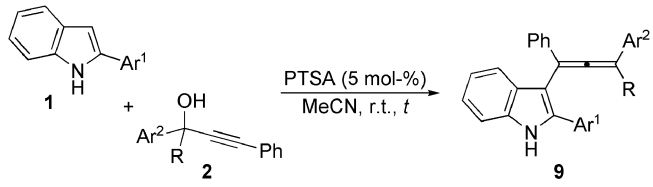
Entry	1	R^1	Ar^1	2	Ar^2	R^2	R^3	*t* [h]	8	Yield [%][b]
1	**1f**	H	Ph	**2a**	Ph	Me	Ph	0.5	**8fa**	70
2	**1g**	OMe	Ph	**2a**	Ph	Me	Ph	1	**8ga**	69
3	**1h**	Cl	Ph	**2a**	Ph	Me	Ph	1	**8ha**	67
4	**1f**	H	Ph	**2c**	Ph	Et	Ph	0.5	**8fc**	66
5	**1f**	H	Ph	**2i**	Ph	Et	*n*Bu	1.5	–[c]	–
6	**1i**	H	4-FC_6H_4	**2a**	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 room temp. [b] Isolated yield of **8** after column chromatography. [c] The 3-propargylindole **3fi** was the major isomer in the crude reaction mixture, and it was isolated in 65% yield.

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

In view of the potential interest of 3-allenylindoles and the fact that no direct route to these compounds had been described previously, we decided to synthesize a collection of allene derivatives **9** through PTSA-catalyzed reactions

Table 6. Alkylation of 2-arylindoles of type **1** with benzylic (branched alkyl)alkynols of type **2**; synthesis of the 3-allenylindoles **9** (2-Th = 2-thienyl).[a]

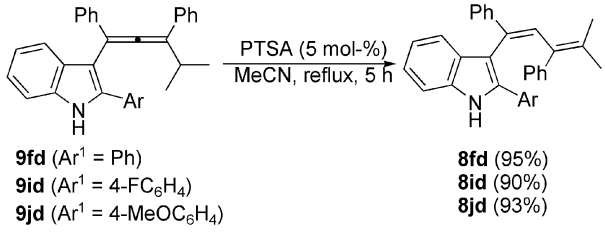


Entry	1	Ar^1	2	Ar^2	R	*t* [h]	9	Yield [%][b]
1	**1f**	Ph	**2d**	Ph	*i*Pr	1	**9fd**	65
2	**1i**	4-FC_6H_4	**2d**	Ph	*i*Pr	1	**9id**	67
3	**1j**	4-$MeOC_6H_4$	**2d**	Ph	*i*Pr	1	**9jd**	82[c]
4	**1l**	2-Th	**2d**	Ph	*i*Pr	2	**9ld**	70[d]
5	**1f**	Ph	**2t**	4-$MeOC_6H_4$	*c*C_3H_5	4	**9ft**	75[c]
6	**1j**	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 room temp. [b] Isolated yield of **9**. [c] PTSA (20 mol-%, 0.1 mmol). [d] The corresponding 3-propargylindole **3ld** (ca. 10%) was also detected.

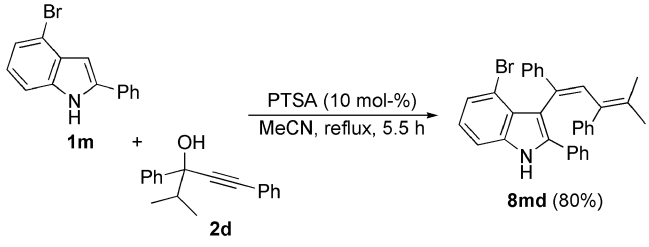
between 2-arylindoles of type **1**[31] and a series of benzylic (branched alkyl)alkynols (Table 6). Indoles with different aryl substituents at their 2-positions, including electron-withdrawing (Entry 2), electron-donating (Entry 3), and heteroaromatic (Entry 4) groups, were efficiently coupled with the alkynol **2d** to yield the corresponding allene derivatives **9**. Furthermore, it is not only the isopropyl group that is tolerated at the propargylic position: cyclopropyl- (Entries 5–7), cyclobutyl- (Entry 8), cyclopentyl- (Entries 9, 12, 14), and cyclohexyl-substituted alkynols (Entries 10, 11, 13) also behave in the same way to afford the 3-allenylindoles **9** in good yields and with short reaction times. In most cases, the 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, in which cases larger amounts of PTSA (20 mol-%) had to be added to ensure completion of the reaction.

In addition, the acid-catalyzed isomerization of the allenes **9** to the dienes **8** was also examined. The 3-allenylindoles **9fd**, **9id**, and **9jd** were transformed into the corresponding 3-dienylindoles **8** (Scheme 2) in almost quantitative yields on heating of acetonitrile solutions of the allenyl derivatives at reflux in the presence of PTSA (5 mol-%). These results provide further evidence for the mechanism outlined in Scheme 1, supporting the intermediacy of the allenes **9** in the formation of the dienes **8**.



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

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

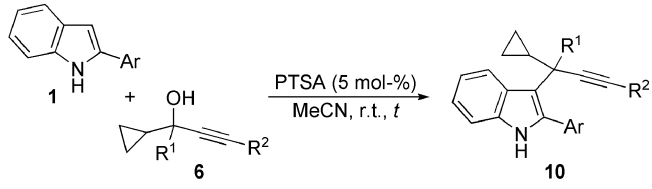


Scheme 3. Synthesis of the 4-bromo-3-dienylindole **8md**.

b) Reactions with the Cyclopropyl-Substituted Alkynols ***6***

Once we had established the reactivity of 2-arylindoles with the tertiary benzylic alkynols **2**, we turned our attention to their behavior towards the tertiary cyclopropyl-substituted alkynols **6**, bearing no aromatic groups at their propargylic positions (Table 7). Different cyclopropyl-substituted alkynols **6** were coupled under the standard conditions with indoles bearing either an aryl (Entries 1, 3–5) or a heteroaryl (Entry 2) group at C-2, to yield the 2-aryl-3-propargylindoles **10** in good yields. Even in the cases of the alkynols **6j** and **6m**, bearing groups sterically more demanding than methyl at their other propargylic positions, the direct substitution pathway was preferred (Entries 4–5). These direct propargylation reactions contrast with the allenylation pathway observed for the 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. Reactions between 2-arylindoles of type **1** and cyclopropyl-substituted alkynols of type **6**; synthesis of the 2-aryl-3-(1-cyclopropyl)propargylindoles **10** (2-Th = 2-thienyl).[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	cC_3H_5	1	**10c**	80
4	**1f**	Ph	**6j**	cC_3H_5	Ph	1	**10d**	76
5	**1f**	Ph	**6m**	Et	Ph	2	**10e**	75

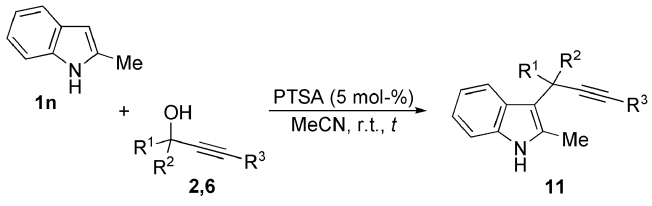
[a] Reaction conditions: **1** (1 mmol), **6** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at room temp. [b] Isolated yield of **10** after column chromatography.

Alkylation of 2-Methylindole (1n)

At this point, we wondered if 2-alkylindoles would follow the same behavior as observed for 2-arylindoles or if, in contrast, the regioselectivity of the substitution would also be controlled by the nature of the substituent at C-2 in the indole component. To this end, we started by performing a reaction, under the standard conditions, between the commercially available 2-methylindole (**1n**) and the benzylic alkynol **2b**, bearing a methyl group at the propargylic position. As in the alkylation of 2-phenylindole (**1f**), the corresponding 3-propargylated derivative **11a** was obtained in good yield (Table 8, Entry 1). However, a distinctive outcome was observed for the alkynols **2a** and **2d**, possessing a larger linear substituent (Entry 2) or a larger branched substituent (Entry 3) at their propargylic positions. Whereas the 3-allenylindoles **9** had been obtained with 2-phenyl-

indole (**1f**), the 3-propargylindoles **11** were now formed as major products in the reactions of 2-methylindole (**1n**). Not surprisingly, the direct substitution pathway is also preferred for alkynols with alkyl groups at the terminal positions of their triple bonds (Entries 4 and 5) and those bearing two alkyl groups at their propargylic positions (Entry 6).

Table 8. Reactions between 2-methylindole (**1n**) and the benzylic alkynols **2** or the cyclopropyl-substituted alkynol **6a**; synthesis of the 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]

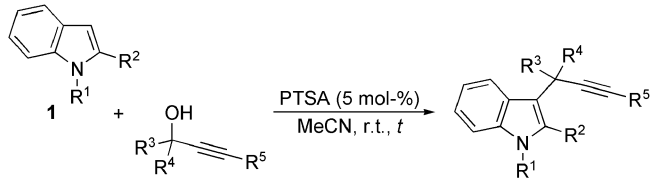
[a] Reaction conditions: **1n** (1 mmol), **2** or **6** (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at room temp. [b] Isolated yield of **11** after column chromatography. [c] The corresponding 3-dienylindole **8na** was also isolated (14%) and characterized. [d] Isolated along with trace amounts of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

Alkylation of 1,2-Disubstituted Indoles

Because only the alkylation of 2-substituted indoles with a free NH moiety had so far been discussed, we next evaluated the influence of substitution at the nitrogen atom. Coupling between 1,2-dimethylindole (**1o**) and tertiary propargylic alcohols with different selected substitution patterns thus led in all cases to the 3-propargylindoles **12** in moderate to good yields (Table 9, Entries 1–6).

We next studied the reaction behavior 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 their propargylic positions and aryl groups at the terminal positions of their triple bonds (Entries 7 and 10). In contrast, when coupled with 2-phenylindole (**1f**), these alkynol derivatives had exclusively led to the corresponding allene or diene derivatives **8** or **9** (Tables 5 and 6). In these cases, the higher nucleophilicity of this indole **1p** probably accounts for the high obtained yields of the corresponding 1-methyl-2-phenyl-3-propargylindoles **13**. It therefore seems that the presence of a

Table 9. Reactions between the 1,2-disubstituted indoles **1o**–**q** and the alkynols **2**, **4**, and **6**; synthesis of the 1,2-disubstituted 3-propargylindoles **12**–**14** (2-Th = 2-thienyl).[a]



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

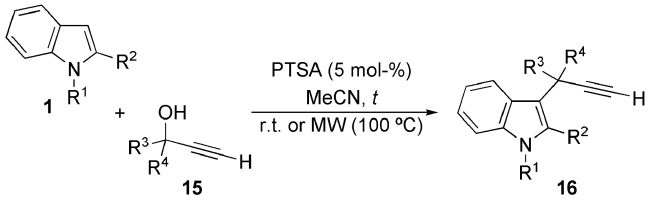
[a] Reaction conditions: **1** (1 mmol), alkynol (1.2 mmol), PTSA (0.05 mmol) in MeCN (2 mL) at room temp. [b] Isolated yield of **12**–**14** after column chromatography. [c] The 3-dienylindole **8oa** was also isolated (20%). [d] Carried out under microwave irradiation conditions at 100 °C (see the 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**.

substituent at the nitrogen atom favors the S_N reaction over the S_N' reaction. This hypothesis was further confirmed when the reaction with 1,2-diphenylindole (**1q**) was examined and the 3-propargylindoles **14a** and **14b** were exclusively obtained in high yields (Table 9, Entries 16 and 17), thus confirming that substitution at the nitrogen atom, either with an aryl or an alkyl group, suppresses the allenylation (S_N') pathway.

Alkylation of Indoles with the Tertiary Terminal Propargylic Alcohols 15

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

Table 10. Reactions between the indoles **1** and the 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	cC_3H_5	1	**16aa**	74
2	**1f**	H	Ph	**15a**	Ph	cC_3H_5	1	**16fa**	77
3[c]	**1f**	H	Ph	**15b**	Ph	Et	0.5	**16fb**	51
4	**1n**	H	Me	**15a**	Ph	cC_3H_5	1	**16na**	70
5[c]	**1n**	H	Me	**15b**	Ph	Et	0.5	**16nb**	53
6	**1o**	Me	Me	**15a**	Ph	cC_3H_5	1	**16oa**	69

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

Regardless of the structure of the indole, we isolated the 3-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 by microwave irradiation to obtain good conversions in short reaction times.

Conclusions

The scope and limitations of Brønsted acid catalyzed direct alkylation reactions between indoles and tertiary propargylic alcohols have been studied. The effects of the nature of the substituents both on the indole and on the alcohol components have been analyzed. Direct substitution leading to 3-propargylated indoles was found to be the preferred reaction pathway in most cases, and only with *N*-unsubstituted 2-arylindoles does a competitive S_N' reaction take place to afford 3-dienyl- or 3-allenylindoles. Mild conditions were generally used, and reaction times were kept short. Moreover, reactions were performed with undried solvents under air, and water was the only side product. We can therefore conclude that a general, operationally simple, and environmentally friendly procedure with wide scope for the synthesis of 3-propargylated indoles with quaternary carbon atoms at their propargylic positions has been established.

Experimental Section

General Procedure for the Syntheses of the 3-Propargyl-1*H*-indoles 3, 7, 10–14, and 16 and of the 3-Dienyl-1*H*-indoles 8: PTSA (5 mol-%) was added to a mixture of the corresponding alkynol (1.2 equiv.) and the indole derivative (1 equiv.) in analytical-grade MeCN (2 mL mmol^{-1}). The reaction mixture was stirred at room temperature until the indole had been consumed, as determined by GC–MS and/or TLC. The crude mixture was neutralized by the addition of concd. NaOH (2 drops); H_2O (20 mL) and EtOAc (15 mL) were added. The separated aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous 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): This compound (Table 2, Entry 4) was produced 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) with PTSA (19 mg, 0.1 mmol) as catalyst. The reaction mixture was stirred at room temp. 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 from 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, 3 H, CH_3CHCH_3], 1.39 [d, ^3J(H,H) = 6.5 Hz, 3 H, CH_3CHCH_3], 2.97 [sept, ^3J(H,H) = 6.5 Hz, 1 H, $CH(CH_3)_2$], 3.79 (s, 3 H, NCH_3), 7.07 [t, ^3J(H,H) = 7.5 Hz, 1 H, Ar*H*], 7.15–7.23 (m, 2 H, Ar*H*), 7.25 (s, 1 H, NC*H*), 7.26–7.47 (m, 6 H, Ar*H*), 7.55–7.68 (m, 2 H, Ar*H*), 7.77 [d, ^3J(H,H) = 7.5 Hz, 2 H, Ar*H*], 7.87 [d, ^3J(H,H) = 8.1 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2950, 1486, 1324, 763, 745, 721, 696 cm^{-1}. LRMS (70 eV, EI): *m*/*z* (%) = 320 (100) [M – C_3H_7]$^+$. HRMS (70 eV, EI): calcd. for $C_{27}H_{25}N$ 363.1987; found 363.1990. $C_{27}H_{25}N$ (363.2): calcd. 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): This compound (Table 4, Entry 2) was produced 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) with PTSA (9.5 mg, 0.05 mmol) as catalyst. The reaction mixture was stirred at room temp. 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, 2 H, CH(C*H*H)$_2$],

0.77–0.88 [m, 2 H, CH(CH*H*)$_2$], 1.46–1.60 [m, 1 H, C*H*(CH$_2$)$_2$], 1.96 (s, 3 H, C*H*$_3$), 3.81 (s, 3 H, NC*H*$_3$), 7.15–7.17 (m, 1 H, Ar*H*), 7.18 (s, 1 H, Ar*H*), 7.21–7.30 (m, 2 H, Ar*H*), 7.31–7.37 (m, 1 H, Ar*H*), 7.40 [d, ^3J(H,H) = 8.1 Hz, 1 H, Ar*H*], 7.44 [dd, ^3J(H,H) = 2.9, 1.1 Hz, 1 H, Ar*H*], 8.13 [d, ^3J(H,H) = 8.0 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 305 (59) [M]$^+$, 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): This compound (Table 5, Entry 2) was produced 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) with PTSA (5 mg, 0.025 mmol) as catalyst. The reaction mixture was stirred at room temp. for 30 min, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et$_2$O 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, 3 H, C*H*$_3$], 3.68 (s, 3 H, OC*H*$_3$), 5.48 [dq, ^3J(H,H) = 6.9, 1.1 Hz, 1 H, C*H*CH$_3$], 6.49 [d, ^3J(H,H) = 2.3 Hz, 1 H, Ar*H*], 6.73–6.80 (m, 3 H, Ar*H*), 6.85 [dd, ^3J(H,H) = 6.7, 3.0 Hz, 2 H, Ar*H*], 7.01 [d, ^3J(H,H) = 8.7 Hz, 1 H, Ar*H*], 7.13 (s, 1 H, Ar*H*), 7.47–7.20 (m, 9 H, Ar*H*), 7.62 [dd, ^3J(H,H) = 7.8, 1.6 Hz, 2 H, Ar*H*], 7.76 (br. s, 1 H, N*H*) ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 441 (24) [M]$^+$, 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): This compound (Table 7, Entry 2) was produced 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) with PTSA (9.5 mg, 0.05 mmol) as catalyst. The reaction mixture was stirred at room temp. for 1 h, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et$_2$O 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, 1 H, C*H*HCHCH$_2$), 0.47–0.53 (m, 1 H, CH$_2$CHC*H*H), 0.72–0.86 [m, 2 H, CH(CH*H*)$_2$], 1.38–1.52 [m, 1 H, C*H*(CH$_2$)$_2$], 1.86 (s, 3 H, C*H*$_3$), 7.08 [dd, ^3J(H,H) = 5.1, 3.6 Hz, 1 H, Ar*H*], 7.14–7.38 (m, 9 H, Ar*H*), 7.42 [dd, ^3J(H,H) = 5.1, 1.0 Hz, 1 H, Ar*H*], 7.95 (br. s, 1 H, N*H*), 8.33 [d, ^3J(H,H) = 8.0 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 367 (53) [M]$^+$, 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): This compound (Table 8, Entry 4) was produced 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) with PTSA (9.5 mg, 0.05 mmol) as catalyst. The reaction mixture was stirred at room temp. for 3 h, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et$_2$O, 7:1) to afford **11d** (251 mg, 73%) as a yellow foam. R_f = 0.41 (hexane/Et$_2$O, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.05 [m, 6 H, (CH$_2$)$_2$C*H*$_3$ and (CH$_2$)$_3$C*H*$_3$], 1.44–1.68 [m, 6 H, CH$_2$C*H*$_2$CH$_3$ and CH$_2$(C*H*$_2$)$_2$CH$_3$], 2.28–2.44 [m, 6 H, C*H*HCH$_2$CH$_3$, C*H*$_2$(CH$_2$)$_2$CH$_3$ and NCC*H*$_3$], 2.63 [td, ^3J(H,H) = 12.3, 4.5 Hz, 1 H, CH*H*CH$_2$CH$_3$], 6.98–7.05 (m, 1 H, Ar*H*), 7.11 [td, ^3J(H,H) = 9.3 Hz, 1 H, Ar*H*], 7.18–7.25 (m, 2 H, Ar*H*), 7.27–7.34 (m, 2 H, Ar*H*), 7.54–7.60 (m, 3 H, Ar*H*), 7.73 (br. s, 1 H, N*H*) ppm. ^{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) ppm. IR (KBr): $\tilde{\nu}$ = 3396, 2955, 2926, 1699, 1682 cm^{-1}. LRMS (70 eV, EI): *m*/*z* (%) = 343 (11) [M]$^+$, 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): This compound (Table 9, Entry 3) was produced 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) with PTSA (9.5 mg, 0.05 mmol) as catalyst. The reaction mixture was stirred at room temp. for 4 h, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et$_2$O, 20:1) to afford **12c** (218 mg, 61%) as a yellow foam. R_f = 0.46 (hexane/Et$_2$O, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 [t, ^3J(H,H) = 7.2 Hz, 3 H, (CH$_2$)$_n$C*H*$_3$], 1.13 [t, ^3J(H,H) = 7.4 Hz, 3 H, (CH$_2$)$_n$C*H*$_3$], 1.51–1.80 [m, 6 H, CH$_2$C*H*$_2$CH$_3$ and CH$_2$(C*H*$_2$)$_2$CH$_3$], 2.43 (s, 3 H, NCC*H*$_3$), 2.47 [t, ^3J(H,H) = 7.0 Hz, 2 H, C*H*$_2$(CH$_2$)$_2$CH$_3$], 2.53 [td, ^3J(H,H) = 12.2, 4.7 Hz, 1 H, C*H*HCH$_2$CH$_3$], 2.81 [td, ^3J(H,H) = 12.2, 4.2 Hz, 1 H, CH*H*CH$_2$CH$_3$], 3.68 (s, 3 H, NC*H*$_3$), 7.15 [t, ^3J(H,H) = 7.5 Hz, 1 H, Ar*H*], 7.25 [d, ^3J(H,H) = 8.1 Hz, 1 H, Ar*H*], 7.31 [d, ^3J(H,H) = 7.1 Hz, 1 H, Ar*H*], 7.34–7.43 (m, 3 H, Ar*H*), 7.67 [d, ^3J(H,H) = 7.5 Hz, 2 H, Ar*H*], 7.85 [d, ^3J(H,H) = 8.0 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 357 (41) [M]$^+$, 314 (100), 300 (17), 145 (30). HRMS (70 eV, EI): calcd. for $C_{26}H_{31}N$ 357.2456; found 357.2455. $C_{25}H_{29}N$ (343.5): calcd. 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): This compound (Table 9, Entry 14) was produced according to the General 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 mixture was stirred at room temp. for 2 h, and the residue was purified by column chromatography on silica gel (eluent: hexane/Et$_2$O, 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 to 0.05 (m, 1 H, C*H*HCHCH$_2$), 0.16–0.31 (m, 1 H, CH$_2$CHC*H*H), 0.48–0.64 [m, 2 H, CH(CH*H*)$_2$], 0.82–0.94 [m, 1 H, C*H*(CH)$_2$], 1.18 [s, 9 H, C(C*H*$_3$)$_3$], 1.55 (s, 3 H, C*H*$_3$), 3.33 (s, 3 H, NC*H*$_3$), 7.14 [t, ^3J(H,H) = 7.4 Hz, 1 H, Ar*H*], 7.25 [d, ^3J(H,H) = 7.1 Hz, 1 H, Ar*H*], 7.29 [d, ^3J(H,H) = 5.5 Hz, 1 H, Ar*H*], 7.32–7.46 (m, 5 H, Ar*H*), 8.33 [dd, ^3J(H,H) = 8.1, 0.6 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 355 (30) $[M]^+$, 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. $C_{26}H_{29}N$ (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): This compound (Table 10, Entry 1) was produced 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) with PTSA (9.5 mg, 0.05 mmol) as catalyst. The reaction mixture was stirred at room temp. 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, 1 H, C*H*HCHCH$_2$), 0.69–0.78 (m, 1 H, CH$_2$CHC*H*H), 0.80–0.90 [m, 2 H, CH(CH*H*)$_2$], 1.60–1.75 [m, 1 H, C*H*(CH$_2$)$_2$], 2.45 (s, 1 H, C≡CC*H*), 3.84 (s, 3 H, NC*H*$_3$), 6.92–7.05 (m, 1 H, Ar*H*), 7.17–7.38 (m, 7 H, Ar*H*), 7.57–7.65 (m, 2 H, Ar*H*) ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 285 (78) $[M]^+$, 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 the 3-(1,1-Dialkylpropargyl)-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 °C with stirring for the required time (see Table 3) until the alkynol had disappeared, as determined by GC–MS and/or TLC. The reaction mixture was allowed to cool to room temperature and neutralized by the addition of 2 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): This compound (Table 3, Entry 1) was produced 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) with PTSA (19 mg, 0.1 mmol) as catalyst. The reaction mixture was stirred under microwave irradiation conditions (50 W) at 100 °C 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, 6 H, 2×C*H*$_3$), 3.84 (s, 3 H, NC*H*$_3$), 7.18 (s, 1 H, NC*H*), 7.41–7.53 (m, 6 H, Ar*H*), 7.67–7.73 (m, 2 H, Ar*H*), 8.30 [d, ^3J(H,H) = 7.9 Hz, 1 H, Ar*H*] ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 273 (23) $[M]^+$, 258 (100). HRMS (70 eV, EI): calcd. for $C_{20}H_{19}N$ 273.1517; found 273.1513.

Typical Procedure for the Synthesis of the 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. PTSA (5 mg, 0.025 mmol) was added 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). The reaction mixture was stirred at room temp. for 1 h (completion of the reaction was monitored by GC-MS and TLC), after which a solid had precipitated. This 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, 3 H, C*H*$_3$CHCH$_3$], 1.23 [d, ^3J(H,H) = 6.5 Hz, 3 H, CH$_3$CHC*H*$_3$], 2.83–2.97 [m, 1 H, C*H*(CH$_3$)$_2$], 6.94 [t, ^3J(H,H) = 8.4 Hz, 2 H, Ar*H*], 7.10 [t, ^3J(H,H) = 7.4 Hz, 1 H, Ar*H*], 7.16–7.35 (m, 9 H, Ar*H*), 7.38–7.57 (m, 6 H, Ar*H*), 8.19 (br. s, 1 H, N*H*) ppm. ^{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, 1 C], 206.3 (C) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 443 (16) $[M]^+$, 400 (100), 366 (19), 322 (42). HRMS (70 eV, EI): calcd. for $C_{32}H_{26}FN$ 443.2049; found 443.2061. $C_{32}H_{26}FN$ (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 the 3-(Buta-1,3-dienyl)-1*H*-indoles 8 from the 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): PTSA (6 mg, 0.03 mmol) was added 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). The reaction mixture was stirred at reflux for 5 h (until the isomerization reaction was complete, 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 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3 H, C*H*$_3$), 1.75 (s, 3 H, C*H*$_3$), 6.60–6.75 (m, 5 H, Ar*H*), 6.94 [ddd, ^3J(H,H) = 7.9, 6.6, 1.2 Hz, 1 H, Ar*H*], 7.02 [d, ^3J(H,H) = 7.9 Hz, 1 H, Ar*H*], 7.13 [ddd, ^3J(H,H) = 8.1, 6.6, 1.4 Hz, 1 H], Ar*H*, 7.16–7.22 (m, 1 H, Ar*H*), 7.27–7.38 (m, 7 H, Ar*H*), 7.50 [dd, ^3J(H,H) = 8.2, 1.5 Hz, 2 H, Ar*H*], 7.58 [dd, ^3J(H,H) = 8.0, 1.7 Hz, 2 H, Ar*H*], 7.89 (br. s, 1 H, N*H*) ppm. ^{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) ppm. LRMS (70 eV, EI): *m*/*z* (%) = 425 (45) $[M]^+$, 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 for compound **8md**.

Acknowledgments

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[33] In addition, the reaction between the dialkyl-substituted alkynol **4a** and 2-phenylindole (**1f**) also afforded the 3-propargylindole derivative, although it could not be completely purified.

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