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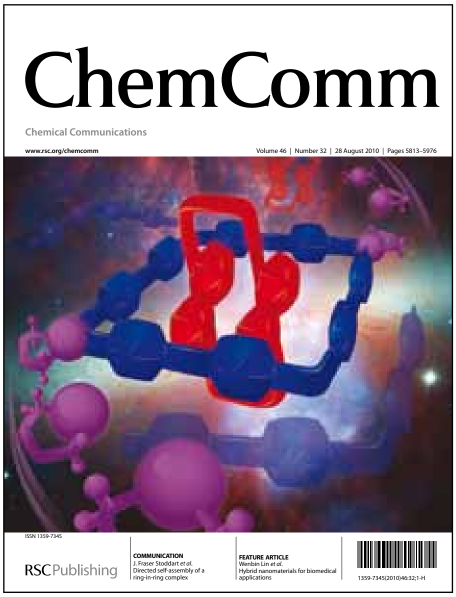

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ARTICLE TYPE

Heteroannulation of Arynes with *N*-Aryl-*α*-Aminoketones for the Synthesis of Unsymmetrical *N*-Aryl-2,3-Disubstituted Indoles: An Aryne Twist of Bischler-Möhlau Indole Synthesis

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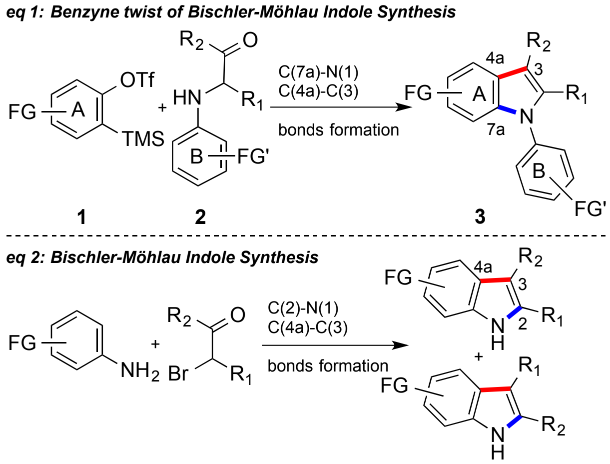
Reaction of 2-(trimethylsilyl)aryl triflates 1 with *N*-aryl-α-amino ketones 2 afforded *N*-aryl-2,3-disubstituted indoles in good to excellent yields with complete control of the substitution patterns. This methodology allowed for the first time a one-step synthesis of unsymmetric 2,3-dialkyl substituted indoles in a regiospecific manner.

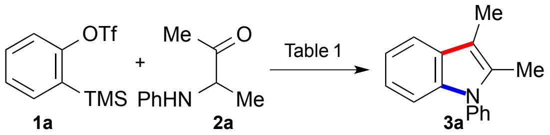
N-arylindoles are present in a large number of biologically and medicinally relevant compounds with proven utilities in pharmacology, agrochemistry and material science.[1] Despite a large number of existing methodologies that have been developed over the past century,[2] methods allowing direct access to *N*-arylindoles[3] remain scarce.



Scheme 1 Reaction of arynes with *N*-aryl-*α*-aminoketones to *N*-arylindoles

As a continuation of our research program aiming at developing efficient syntheses of indoles[4] and indole-containing natural products,[5] we became interested in developing a one-step synthesis of *N*-arylindoles by a new benzannulation reaction between arynes,[6,7] generated in situ from 2-(trimethylsilyl)aryl triflates **1**, and *N*-aryl-*α*-aminoketones **2** (Scheme 1, eq 1).[8,9] The advantage of the present transformation is that it should allow the regiospecific synthesis of 2,3-disubstituted indoles in contrast to the classic Bischler-Möhlau reaction, which inevitably afforded a mixture of two regioisomeric indoles (Scheme 1, eq 2).[10] In addition, it could provide a valuable solution to a one-step synthesis of unsymmetrical 2,3-dialkyl (non-methyl) substituted indoles, a longstanding and challenging problem in the field of indole synthesis.[11]

Table 1 Optimizations of reaction conditions[a]



Entry	Additive	Solvent	T (°C)	Yield[e]
1	--	CH_3CN	65	50
2	--	EtCN	65	61
3	--	*n*-PrCN	65	58
4	--	*i*-PrCN	65	62
5	--	*t*-BuCN	65	44
6	18-C-6[b]	*i*-PrCN/DCE (1/4)	rt	(72)[f]
7	18-C-6[b]	*i*-PrCN	rt	(52)[f]
8	18-C-6[b,c]	*i*-PrCN/DCE (1/4)	rt	(65)[f]
9	18-C-6[b], Cs_2CO_3[d]	*i*-PrCN/DCE (1/4)	rt	71(75)[f]

[a] All reactions were carried out under Ar using **2a** (1.0 equiv), **1a** (1.4 equiv), CsF (3.0 equiv), solvent (*c* 0.14 M); [b] 1.1 equiv of 18-C-6; [c] KF (3.0 equiv) was used as fluoride source; [d] 2.0 equiv of Cs_2CO_3; [e] Isolated yield; [f] Yield in parenthesis is calculated based on ^1H NMR spectrum using CH_2Br_2 as an internal standard; DCE = 1,2-dichloroethane.

We began our investigation using 2-(trimethylsilyl)phenyl triflate (**1a**)[12] and 3-(phenylamino)butan-2-one (**2a**) as test substrates for evaluating reaction conditions (Table 1). Performing the reaction in acetonitrile at 65 °C in the presence of CsF afforded the desired indole **3a** in 50% yield accompanied by a significant amount of **3aa** (32%) and **3ab** (9%, Scheme 2). Mechanistically, nucleophilic addition of amine **2a** to the *in situ* generated benzyne **A** would lead to intermediate **B** from which, three different reactions could take place leading to the observed products. Indole **3a** resulted from the cyclization of **B** followed by dehydration of 3-hydroxyindoline **C** as we expected (pathway *a*). Aniline **3aa** could be produced by an intramolecular proton transfer of intermediate **B** (pathway *b*).[13] This pathway, a side reaction to be avoided in our case, has been elegantly exploited for the synthesis of functionalized anilines.[14] The formation of

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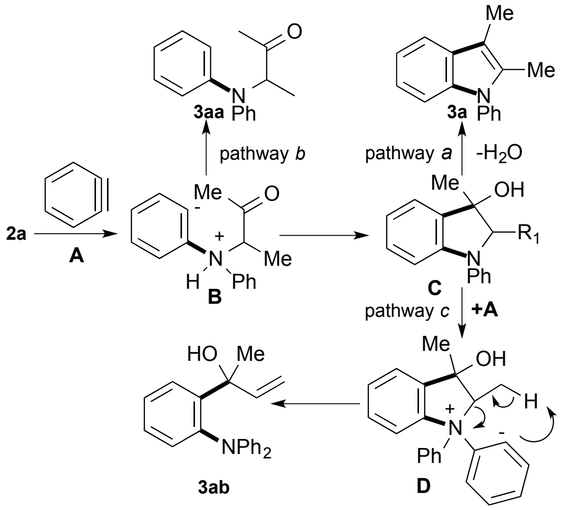
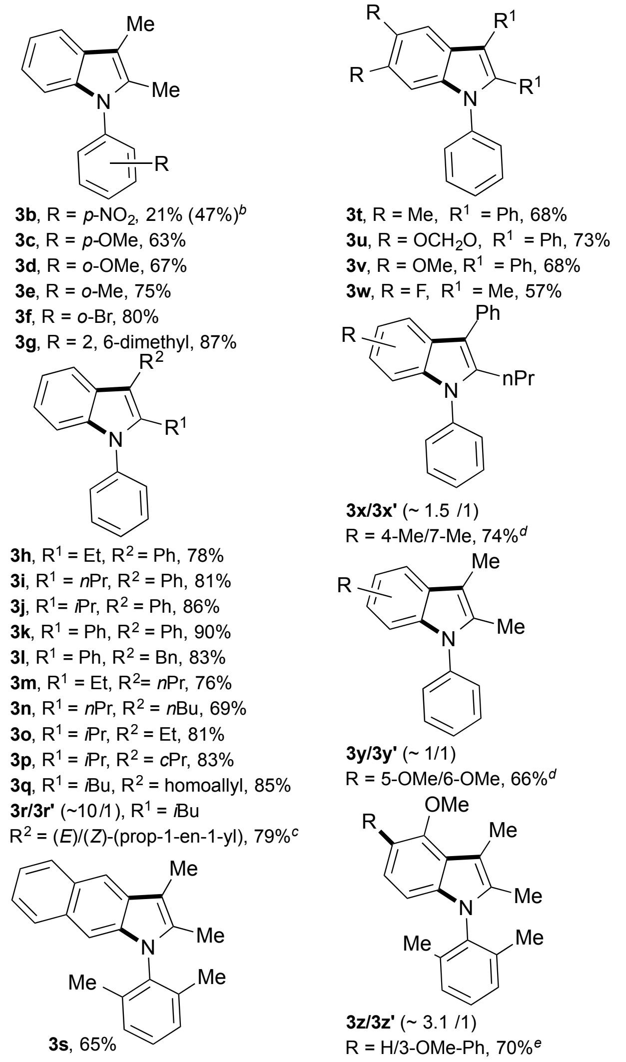
3ab was less evident and we assumed that it might go through the intermediate **D** resulting from the nucleophilic addition of tertiary amine **C** onto the benzyne **A**. Intramolecular proton transfer followed by β-elimination would then afford **3ab** (pathway *c*)[15] To channel the reaction into the pathway *a*, an extensive survey of reaction conditions was carried out varying the fluoride sources (CsF, KF, TBAF), the solvents, the temperature, the reaction time, the bases, and the additives. Some representative results are presented in Table 1. Addition of crown ether enabled the annulation to be realized at room temperature that effectively suppressed the formation of side product **3ab**. Overall, the optimized conditions consisted of performing the reaction in a solvent mixture (isopropionitrile/dichloroethane = 1/4) in the presence of CsF (3.0 equiv), Cs_2CO_3 (2.0 equiv) and 18-C-6 (1.1 equiv) at room temperature (entry 9).[16] Under these conditions, the indole **3a** was formed together with a variable amount of *N*-phenyl-2,3-dimethyl-3-hydroxy indoline **C** (Scheme 2). However, the latter readily underwent dehydration upon purification on silica gel column chromatography to provide indole **3a** in 71% overall yield.



Scheme 2 Possible reaction pathways leading to **3a**, **3aa** and **3ab**.

The generality of this reaction was subsequently explored by varying electronic and steric properties of both **1** and **2** under the optimal conditions. Since the dehydration of 3-hydroxyindoline **C** was not spontaneous in some cases, the crude annulation product was first treated with silica gel in $MeOH/CH_2Cl_2/AcOH$ (1/1/1, 40 °C) before purification. The results are summarized in Table 2. The effect of *N*-aryl substituents was studied first (see **3b-g**). Strong (OMe) and weak (Me) electron donating groups were tolerated in the *ortho* and *para* positions. The presence of an *ortho* substituent in the *N*-aryl group had a positive effect on the reaction outcome (**3a** *vs* **3e** *vs* **3g**). Weak electron withdrawing group (Br, **3f**) was well tolerated. However, strong electron-withdrawing group (NO_2) in *para* position reduced significantly the reaction efficiency furnishing **3b** in only 21% yield. The reduced nucleophilicity of the *p*-nitroaniline could account for this observation. Fortunately, by performing the reaction in EtCN at 65 °C in the absence of 18-C-6, **3b** can be isolated in 47% yield. Variation of substituents at position 2 and 3 of indole was next examined (**3h-3r**). It was noticed that the efficiency of the reaction increased as the size of the R^1 substituent increased (**3h-k**). Most importantly, the unsymmetrical 2,3-dialkyl (non-methyl) substituted indoles (**3m** – **3r**) can be synthesized in good yields without scrambling of the R^1 and R^2 substituents. To the best of our knowledge, this represented the first examples of one-step synthesis of this type of indoles with complete control of regiochemistry.[17]

Table 2 Reaction Scope[a]



3b, R = *p*-NO_2, 21% (47%)[b]
3c, R = *p*-OMe, 63%
3d, R = *o*-OMe, 67%
3e, R = *o*-Me, 75%
3f, R = *o*-Br, 80%
3g, R = 2, 6-dimethyl, 87%

3h, R^1 = Et, R^2 = Ph, 78%
3i, R^1 = *n*Pr, R^2 = Ph, 81%
3j, R^1= *i*Pr, R^2 = Ph, 86%
3k, R^1 = Ph, R^2 = Ph, 90%
3l, R^1 = Ph, R^2 = Bn, 83%
3m, R^1 = Et, R^2= *n*Pr, 76%
3n, R^1 = *n*Pr, R^2 = *n*Bu, 69%
3o, R^1 = *i*Pr, R^2 = Et, 81%
3p, R^1 = *i*Pr, R^2 = *c*Pr, 83%
3q, R^1 = *i*Bu, R^2 = homoallyl, 85%
3r/3r' (~10/1), R^1 = *i*Bu
R^2 = (*E*)/(*Z*)-(prop-1-en-1-yl), 79%[c]

3s, 65%

3t, R = Me, R^1 = Ph, 68%
3u, R = OCH_2O, R^1 = Ph, 73%
3v, R = OMe, R^1 = Ph, 68%
3w, R = F, R^1 = Me, 57%

3x/3x' (~ 1.5 /1)
R = 4-Me/7-Me, 74%[d]

3y/3y' (~ 1/1)
R = 5-OMe/6-OMe, 66%[d]

3z/3z' (~ 3.1 /1)
R = H/3-OMe-Ph, 70%[e]

[a] All reactions were carried out under Ar using *N*-aryl-*α*-aminoketone **2** (0.21 mmol, 1.0 equiv), **1** (0.29 mmol, 1.4 equiv), CsF (0.63 mmol, 3.0 equiv), Cs_2CO_3 (0.42 mmol, 2.0 equiv), 18-C-6 (0.23 mmol, 1.1 equiv), *i*-PrCN/DCE (1/4) (1.5 mL, *c* 0.14 M) at RT for 2-6 h then $MeOH/CH_2Cl_2/AcOH$ (1/1/1), silica gel, 40 °C; [b] EtCN (*c* 0.14 M), 65 °C; [c] the starting material was 2-methyl-5-(phenylamino)oct-7-en-4-one; [d] inseparable mixture; [e] the two compound were separated.

Finally, substituted 2-(trimethylsilyl)aryl triflates **1** were examined. Electron rich and poor symmetric arynes all reacted well with *N*-aryl *α*-aminoketones to furnish *N*-arylindoles in moderate to good yields (**3s-w**). As expected, a mixture of two regioisomers were produced (**3x**/**3x'**, **3y**/**3y'**) when 3-methyl-2-(trimethylsilyl)phenyl triflate, and 4-methoxy-2-(trimethylsilyl)phenyl triflate were used as aryne precursors. However, a single regioisomer **3z** was produced with 3-methoxy-

2-(trimethylsilyl)phenyl triflate in accordance with the literature precedents.[18] An arylation product **3z'** (R = 3-methoxy phenyl, 17%) was also isolated resulting from the nucleophilic addition of **3z** (R = H) to benzyne in this case.

Conclusions

In summary, we developed a novel heteroannulation reaction between benzynes and *N*-aryl α-aminoketones for the synthesis of *N*-aryl-2,3-disubstituted indoles **3** with a wide application scope. The reaction allowed, for the first time, a one-step synthesis of unsymmetrical 2,3-dialkyl (non methyl) substituted indoles with complete control of regioseletivity.

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Notes and references

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Scheme for TOC

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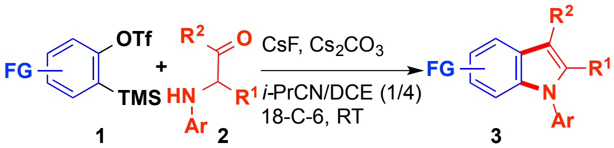

5 A new indole synthesis was developed allowing preparation of unsymmetrical 2,3-dialkyl substituted *N*-aryl indoles in one-step with complete regio control.