COMMUNICATION

A Regiodivergent Truce-Smiles Rearrangement: A Strategy for the Synthesis of Arylated Indoles promoted by $KN(SiMe_3)_2$

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Fan Zhou,[ab] Huimin Jin,[ab] Zhenhua Xiang,[ab] Patrick J. Walsh*[c] & Jie Li,*[ab]

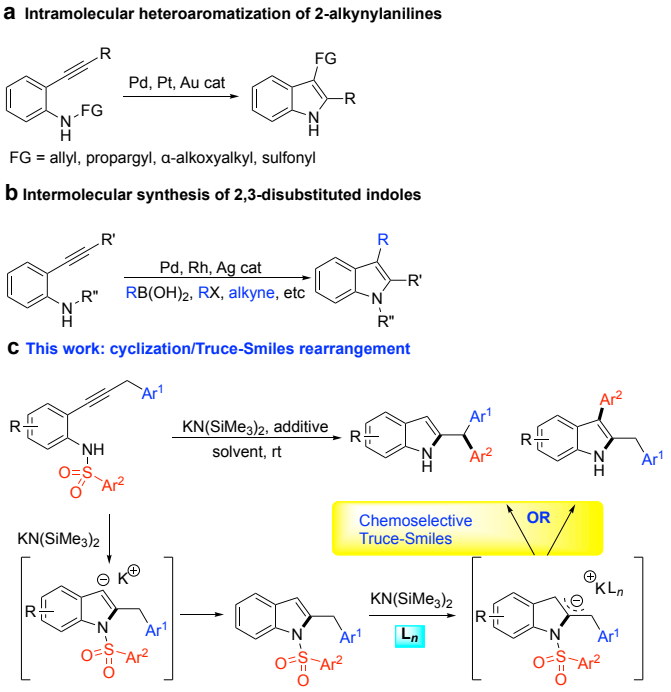
A chemo- and regioselective synthesis of 2-benzhydryl and 2,3-disubstituted indoles *via* cyclization and regiocontrolled Truce-Smiles (T-S) rearrangement is disclosed. A cascade 5-*endo*-*dig* cyclization of 2-amino diphenylacetylenes mediated by $KN(SiMe_3)_2$ is followed by a regiocontrolled T-S reaction. This system provides the first example of T-S regioselectivity and is controlled by ligands on K^+.

Introduction

Non-fused benzenoid rings are found in most approved small molecule medications.[1-3] Contributing to their observed prevalence is the utility and dependability of the Suzuki-Miyaura cross-coupling reaction[4] for the installation of benzenoid rings. Despite its utility, the Suzuki-Miyaura reaction has drawbacks, like the use of transition metals and prefunctionalized coupling partners. To address some of these limitations, chemists have turned to transition metal catalyzed C–H arylation reactions to increase generality and atom economy.[5] The need for transition metals in these processes persists, rendering them less sustainable and producing metal-containing waste, which can be difficult to separate from desired products.[6, 7] Thus, the demand for greener, general transition metal-free arylation reactions that enable control of regioselectivity remains high.[8-10]

To design greener processes, several research teams have recently been attracted to the Truce-Smiles (T-S) reaction[11-14] to deliver an aryl group to a carbon-based radical center. The rearrangement process itself does not require a transition metal, although metals are often used to generate radicals and then set up the rearrangement. Recent years have witnessed the introduction of enantioselective versions of the radical T-S arylation reaction.[15] The T-S rearrangement[11] can also proceed arylated products *via* a 2-electron pathway and is similar to S_NAr reactions. While Truce-Smiles rearrangement reactions generally require electron-withdrawing groups, the original work by Truce[16] and recent studies by Clayden[17, 18] and others[19, 20] have demonstrated that electron-withdrawing groups are not always needed.

Arylated indole derivatives, represent one of the most important classes of heterocyclic compounds that are found in bioactive molecules, pharmaceuticals and natural products.[21-26] Consequently, the development of efficient approaches for the construction and functionalization of these privileged heterocyclic compounds remains important.[27-41] For several years, members of our team have been interested in the preparation of indoles under transition metal free conditions.[42, 43] This interest springs from our long-standing goal: to generate and functionalize carbanions derived from weakly acidic pronucleophiles under mild conditions.[44-52]



Scheme. 1 Synthesis of multifunctional indoles from 2-alkynylaniline derivatives.

[a] *Department of Pharmacy, School of Medicine, Hangzhou City University, No. 48, Huzhou Road, Hangzhou 310015, P. R. China. E-mail: lijie@zucc.edu.cn*
[b] *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P. R. China*
[c] *Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, USA. E-mail: pwalsh@sas.upenn.edu*

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

In combining our interest in indoles with transition metal-free arylations, we focused on cyclization of 2-alkynylaniline derivatives (Scheme 1). Both intra and intermolecular cyclization of 2-alkynylaniline derivatives have become popular strategies for indole synthesis and functionalization.[53, 54] The approach typically starts with aminometallation of the C≡C bond, usually with the aid of a transition metal catalyst. It can be followed by a 1,3-migration of functional groups from the metalated indole nitrogen, including allyl,[55, 56] propargyl,[57] sulfonyl,[58] and *α*-alkoxyalkyl[59] moieties (Scheme 1a). On the other hand, cyclization of a metallated *ortho*-amino group on the alkyne forms an indolylmetal intermediate that can be trapped by external electrophiles, for example, *via* the Heck reaction,[60] Sonogashira reaction,[61] or Suzuki reaction,[62, 63] among others (Scheme 1b).[64-74]

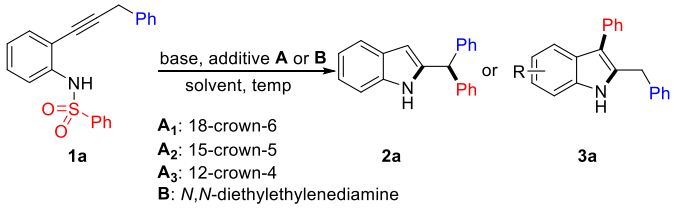
In the current study (Scheme. 1c), we employ 2-arylpropargyl anilines with weakly acidic benzylic sp^3 C–H bonds. Thus, base initiated deprotonation-nucleophilic attack of the sulfonamido nitrogen on the alkynyl moiety results in cyclization and produces a reactive sp^2-hybridized carbanion. This carbanion will be protonated to give the 2-benzyl indole. Deprotonation of the weakly acidic benzylic position produces the key resonance stabilized anionic intermediate. We envisioned that this carbanion could undergo a polar T-S rearrangement with the *N*-aryl sulfonamide to form arylated products. The goal of this study was to control the regiodivergent desulfonylated rearrangement[75-77] to chemoselectively furnish either 2,3-disubstituted indoles or 2-benzhydryl indoles. Our strategy was to judiciously choose ligands for K$^+$ to steer the regioselectivity. Herein, we outline the development of this transition metal-free regioselective T-S rearrangement and the isolation of 2,3-disubstituted indoles and 2-benzhydryl indoles (58 examples, up to 95% yield). To our knowledge, this report represents the first example of control of regioselectivity in a T-S rearrangement. It is also noteworthy that the T–S rearrangement herein occurs even with electronically neutral migrating aryl groups.

Results and discussion

Control of the regioselective T-S rearrangement. We initially focused on the T-S rearrangement in the presence of MN(SiMe$_3$)$_2$ and crown ethers to generate solvent separated cations. In general, arylation at the benzylic position took place to afford benzhydryl indoles. The benzhydryl group[78] is a common structural motif in many biologically active compounds, including indoles, and are contained in triarylmethanes.[79] Thus, 2-phenylpropargyl-*N*-phenylsulfonylaniline **1a** was combined with KN(SiMe$_3$)$_2$ and 18-crown-6 (18-C-6) at 60^o C to search for a suitable solvent. Of those examined [toluene, THF, cyclopentyl methyl ether (CPME), dioxane and DME, Table 1], THF (60% yield) was the most promising for the T-S rearrangement leading to 2-benzhydrylindole **2a** (entries 1, 3–5 *vs* 2). Lower temperatures were next examined. Comparable conversions to indole **2a** were observed at 40 °C (entry 6, 61% yield) and room temperature (entry 7, 66% yield). Fortunately, increasing the amount of KN(SiMe$_3$)$_2$ from 2 equiv to 3 equiv. provided 78% isolated yield (entry 8). Combinations of silyl amide bases and crown ethers were next examined. The combination of NaN(SiMe$_3$)$_2$/15-crown-5 gave indole **2a** in 51% isolated yield (entry 9), whereas LiN(SiMe$_3$)$_2$/12-crown-4 produced the product in only 27% yield (entry 10). Interestingly, it was found that only 5% yield of **2a** was obtained with KN(SiMe$_3$)$_2$ but without 18-crown-6, while the 2,3-disubstituted indole product **3a** was observed in 8% yield (entry 11). Clearly, the crown ether plays a crucial role in the process.

Changing the ligand on K$^+$ changed the regioselectivity of the T-S rearrangement. For example, the 3-phenyl indole **3a** was obtained as the sole product when the reaction was conducted at 80 °C in the presence of *N*,*N*-diethylethylenediamine (enEt$_2$) (entry 12, 43% yield). Of the five solvents screened (toluene, THF, CPME, dioxane and DME), to optimize the regiochemistry of the T-S rearrangement, CPME was the best for the generation of **3a** (61% yield, entry 13 vs. 26–55% for the others). Notably, this transformation was favored under more dilute reaction conditions in CPME (entry 17, 74% yield in 0.42 M *vs.* entry 13, 61% yield in 0.71 M). In addition, an excess of the combination KN(SiMe$_3$)$_2$/enEt$_2$ was critical for high yields and regioselectivities. Reducing the molar equivalence of KN(SiMe$_3$)$_2$/enEt$_2$ from 4 : 12 to 3 : 9 led to decreased yield (entry 18, 51%). Further elevation of the reaction temperature to 100 °C increased the product **3a** yield to 80% (entry 19), while only 51% of the product was obtained at 60 °C (entry 20). Overall, the optimized T-S rearrangement conditions for the chemoselective synthesis of both products were established (entry 8 for 2-benzhydryl indole **2a** and entry 19 for 3-phenyl indole derivative **3a**).

Table 1. T-S Regioselectivity Optimization[a]



1a 2a 3a

entry	solvent	MN(SiMe$_3$)$_2$	ligand	T (°C)	2a[b]	3a[b]
1	toluene	KN(SiMe$_3$)$_2$	A$_1$	60	48	–
2	THF	KN(SiMe$_3$)$_2$	A$_1$	60	60	–
3	CPME	KN(SiMe$_3$)$_2$	A$_1$	60	49	–
4	dioxane	KN(SiMe$_3$)$_2$	A$_1$	60	40	–
5	DME	KN(SiMe$_3$)$_2$	A$_1$	60	49	–
6	THF	KN(SiMe$_3$)$_2$	A$_1$	40	61	–
7	THF	KN(SiMe$_3$)$_2$	A$_1$	rt	66	–
8[c]	THF	KN(SiMe$_3$)$_2$	A$_1$	rt	78	–
9[c]	THF	NaN(SiMe$_3$)$_2$	A$_2$	rt	51	–
10[c]	THF	LiN(SiMe$_3$)$_2$	A$_3$	rt	27	–
11[c]	THF	KN(SiMe$_3$)$_2$	–	rt	5	8
12[d]	THF	KN(SiMe$_3$)$_2$	B	80	–	43
13[d]	CPME	KN(SiMe$_3$)$_2$	B	80	–	61
14[d]	DME	KN(SiMe$_3$)$_2$	B	80	–	26

15[d]	dioxane	$KN(SiMe_3)_2$	B	80	–	53
16[d]	toluene	$KN(SiMe_3)_2$	B	80	–	55
17[d,e]	CPME	$KN(SiMe_3)_2$	B	80	–	74
18[f]	CPME	$KN(SiMe_3)_2$	B	80	–	51
19[d,e]	CPME	$KN(SiMe_3)_2$	B	100	–	80
20[d,e]	CPME	$KN(SiMe_3)_2$	B	60	–	51

[a]Reactions were conducted with **1a** (0.1 mmol), $MN(SiMe_3)_2$ (0.2 mmol), ligand (0.4 mmol) solvent (1 mL), 12 h. [b]Isolated yields. [c]0.3 mmol of base, 0.6 mmol of ligand. [d]0.4 mmol of base, 1.2 mmol of ligand. [e]2 mL of solvent. [f]0.3 mmol of base, 0.9 mmol of ligand.

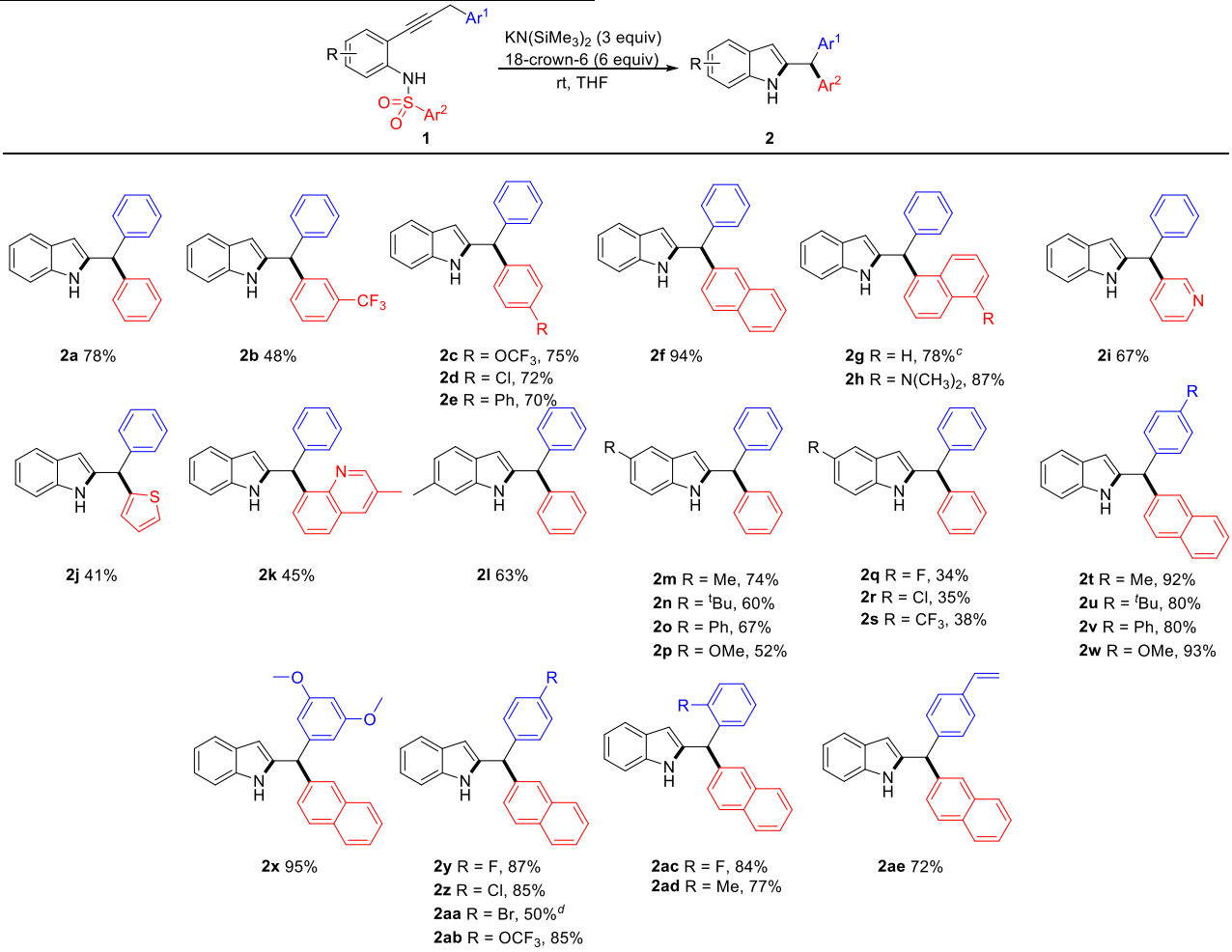


Fig. 1 Scope of the chemoselective synthesis of 2-benzhydryl indoles. [a]Reaction conditions: **1** (0.1 mmol), $KN(SiMe_3)_2$ (0.3 mmol), 18-crown-6 (0.6 mmol), THF (1 mL), rt, 12 h. [b]Isolated yield. [c]60 °C. [d]DME (1 mL).

Scope of the benzylic T-S rearrangement. The scope of the T-S rearrangement to the benzylic position is presented in **Fig. 1**. All reactions were conducted at room temperature apart from one example, which was performed at 60 ℃. Various migrating aryl groups were first examined. 2-Arylpropargyl sulfonylanilines bearing aryl sulfonamides with electron withdrawing or electronegative groups, such as 3-CF_3, 4-OCF_3, and 4-Cl, gave the desired products (**2b**, **2c**, **2d**) in 48%, 75%, and 72% yield. Biphenyl, 2-naphthyl, and 1-naphthyl sulfonamides provided **2e–2g** in 70–94% yields. A 1-naphthylsulfamide bearing an electron donating 5-NMe_2 also showed high conversion in this protocol, affording the cyclization/rearrangement product in 87% yield. Interestingly, sulfonamides possessing 3-pyridinyl, 2-thiofuranyl, and 8-(3-methyl-quinolyl) (**2i**, **2j**, **2k**) groups were all suitable substrates, affording the desired heterocyclic products in 43–67% yields.

Next, substitution on the aniline aromatic moiety was explored. 2-Arylpropargyl sulfonylanilines bearing alkyl (5-Me, 4-Me, 4-^{t}Bu) and phenyl groups on the aniline-based ring reacted readily under the optimal reaction conditions giving the 2-benzhydryl indole products **2l–2o** in 60–74% yields. In addition, both electron donating (4-OMe, **2p**), electronegative and electron withdrawing groups (4-F, **2q**; 4-Cl, **2r**; 4-CF_3, **2s**) on the aromatic ring of 2-arylpropargyl sulfonylanilines gave T–S rearrangement products in this reaction, albeit electron poor substrates were less efficient (34–38% for **2q–2s** *vs.* 52% for **2p**).

The scope of arylpropargyl groups on the T-S rearrangement was next investigated. As shown in **Fig. 1**, a variety of aryl-substituted propargyl derivatives were compatible with the T-S rearrangement (**2t–2ae**), producing the products in 50–95% yields. To avoid the duplication of the products above, 2-naphthalenesulfonamides were employed, resulting in a 2-naphthyl undergoing the T-S rearrangement. 2-Arylpropargyl 2-naphthyl-substituted sulfonylanilines bearing alkyl (4-Me, **2t**; 4-^{t}Bu, **2u**), phenyl (**2v**), or OMe (4-OMe, **2w**; 3,5-diOMe, **2x**) groups on the aryl ring of the aryl

propargyl group were successfully employed, furnishing the 2-benzhydryl indoles in excellent yields (80–95%). Additionally, this tandem reaction proceeded smoothly with substrates bearing electronegative substituents on the arylpropargyl group, including 4-F (**2y**), 4-Cl (**2z**), 4-Br (**2aa**), and 4-OCF_3 (**2ab**) (50–87% yields). Aryl groups bearing *ortho*-substituents, such as 2-F (**2ac**) and sterically hindered 2-Me (**2ad**) on the arylpropargyl group did not interfere with the T-S rearrangement, affording products in 77–84% yields. A substrate possessing a vinyl moiety on the arylpropargyl group was tolerated, providing the 2-benzhydryl indole **2ae** in 72% yield. Unfortunately, aniline derivatives with Ar^2 = 4-C_6H_4–I, 4-C_6H_4–F and 4-C_6H_4–Me were poor substrates that gave less than 35% yield. Not surprisingly, when replacing the sulfonamide *S*-Ar with *S*-alkyl , no T-S products were obtained.

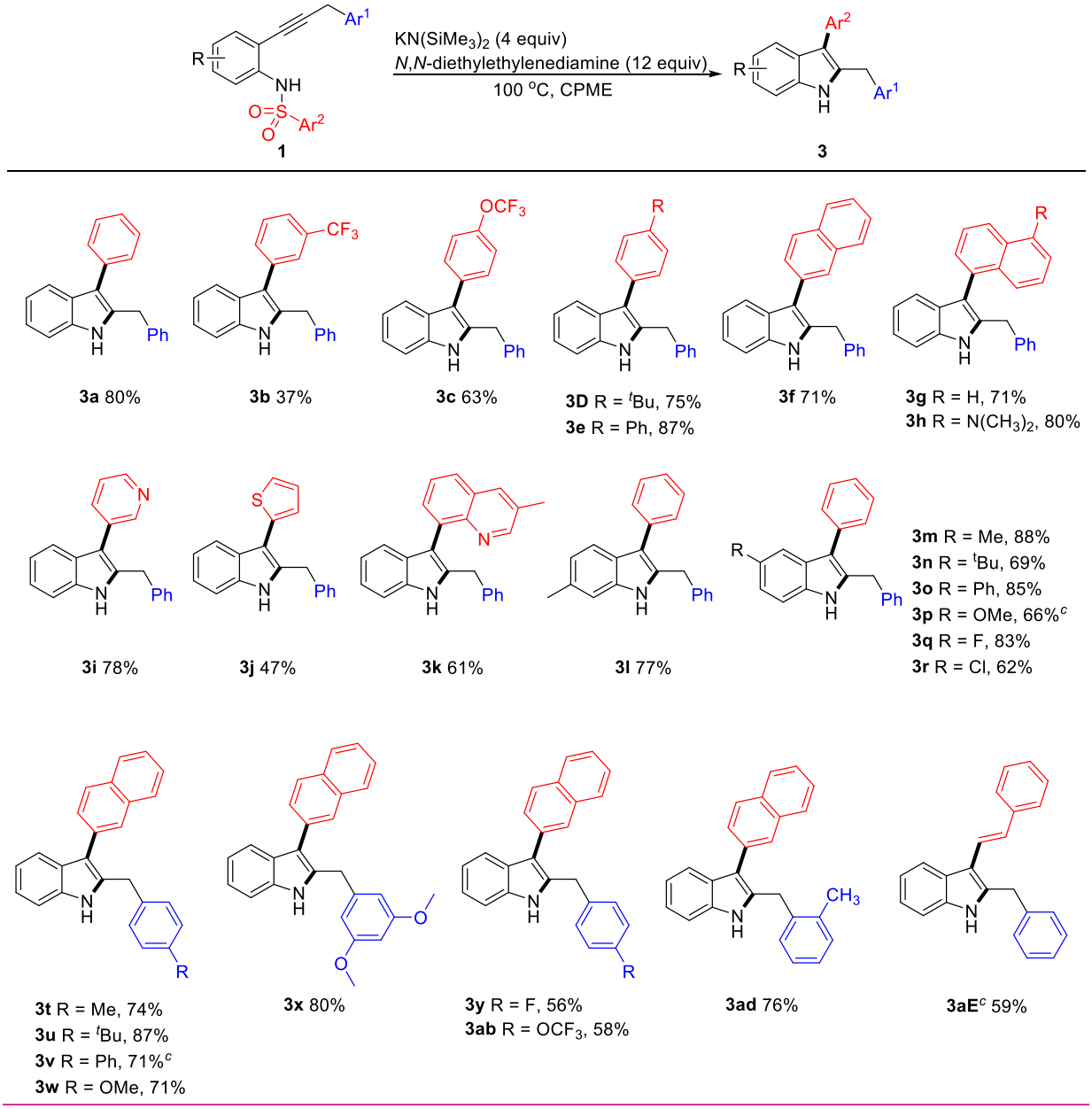


Fig. 2 Scope of the chemoselective synthesis of 2,3-disubstituted indoles. [a]Reaction conditions: **1** (0.1 mmol), $KN(SiMe_3)_2$ (0.4 mmol), *N,N*-diethylethylenediamine (1.2 mmol), CPME (2 mL), 100 °C, 12 h. [b]Isolated yield. [c]Toluene (2 mL).

T-S rearrangement to the indole 3-position. Next, we focused on the chemoselective T-S rearrangement to the indole skeleton to provide 2,3-disubstituted indoles. As presented in **Fig. 2**, substrates bearing diverse aryl-substituted sulfonyl groups exhibited fair to excellent reactivity. Aryl groups with electron withdrawing (3-CF_3, **3b**, 37% yield; 4-OCF_3, **3c**, 63% yield) and electron neutral alkyl (4-^{t}Bu, **3d**, 75% yield), and 4-phenyl (**3e**, 87% yield) gave the T-S rearranged products. Moreover, substrates possessing 2-naphthyl (**3f**), 1-naphthyl (**3g**), and 4-NMe_2-1-naphthyl (**3h**) substituents on the sulfonyl group were also well-tolerated in the T-S rearrangement, providing the product in 71–80% yields. Of note, heterocyclic 3-pyridyl (**3i**), 2-thiofuranyl (**3j**), and 8-(3-methyl-

quinolyl) (**3k**) substituents were all compatible with this transformation, assembling the desired products in 47−78% yields.

The diversity of the substituents on the aniline ring was next explored. In general, good to excellent yields of 2,3-disubstituted indoles were observed, regardless of the electronic nature of the aniline substituents. Thus, alkyl (5-Me, **3l**, 77% yield; 4-Me, **3m**, 88% yield; 4-^{t}Bu, **3n**, 69% yield), phenyl (**3o**, 85% yield), electron donating (4-OMe, **3p**, 66% yield) and electronegative substituents (4-F, **3q,** 83% yield; 4-Cl, **3r**, 62% yield) were all compatible with the cyclization/T-S rearrangement.

An exploration of the benzylic Ar^1 in Figure 2 was undertaken. 2-Arylpropargyl sulfonylanilines bearing Ar^1 groups with alkyl (4-Me, **3t**, 74% yield; 4-^{t}Bu, **3u**, 87% yield), 4-phenyl (**3v**, 71% yield), methoxy (4-OMe, **3w**, 71% yield; 3,5-diOMe, **3x**, 80% yield), and electron withdrawing (4-F, **3y**, 56% yield; 4-OCF_3, **3ab**, 58% yield) could be readily converted into the desired T-S rearrangement products. It is noteworthy that the sterically hindered Ar^1 = 2-Tol was successful in this reaction, giving the corresponding product **3ad** in 76% yield.

To our knowledge, there are only a few examples of T-S rearrangements wherein a vinyl group undergoes the migration.[80-82] To exam the ability of the styrenyl group to participate in this process, we prepared the β-styrenyl sulfenyl-containing substrate. When exposed to reaction conditions with $KN(SiMe_3)_2$ and diamine ligand, indole formation was followed by T-S β-styrenyl group transfer producing the vinyl-containing product **3aE** in 59% yield. Here again, sulfonamides with Ar^2 = 4-C_6H_4–Cl and 4-C_6H_4–Me were poor substrates giving none of the desired products.

Overall, a variety of 2,3-disubstituted indoles were readily prepared by tandem cyclization/T-S rearrangement of 2-arylpropargyl sulfonylanilines under transition metal-free conditions.

To illustrate the practicality of this protocol, we conducted the cyclization/T-S rearrangement of substrate **1w** on a 3 mmol scale. The corresponding product **2w** was isolated in 91% yield (0.995 g, Fig. 3a). In addition, 2,3-disubstituted indole **3x** was isolated in 43% yield (0.676 g) on scale up of the reaction (4 mmol).

Interestingly, in the case of substrate **1ac** (Fig. 3b) bearing a 2-fluoro phenyl, after the T-S rearrangement the reaction took an unexpected turn and the product **4** was formed in 60% yield under the standard reaction conditions. We hypothesize that the polycyclic indole **4** arises from formation of the expected 2,3-disubstituted indole, which then undergoes deprotonation at the indole nitrogen. A key mechanistic step to illustrate the initiation of the flow of electrons is shown in Fig. 3b, right. Once the new C–C bond is formed, the S_NAr is completed by loss of the fluoride. At this stage, we cannot rule out a mechanism involving base-promoted elimination of HF to generate a benzyne intermediate.

To gain insight into the reaction mechanisms of the indole formation/T-S rearrangements, we set out to isolate key intermediates in the process. We envisioned that replacement of $KN(SiMe_3)_2$ with a weaker base, K_2CO_3, might allow the tandem reaction to be halted at the indole stage (pre-T-S rearrangement). As shown in Fig. 3c, in the presence of K_2CO_3, **1a** underwent cyclization to form indole **5** without initiating the T-S rearrangement. Subjecting indole **5** to the $KN(SiMe_3)_2$ and the selectivity-controlling ligand in the T-S rearrangement gave 2-benzhydryl indole **2a** when the ligand was 18-crown-6 in 79% yield and the 2,3-disubstituted indole **3a** in 72% yield when $KN(SiMe_3)_2$ was used with excess *N*,*N*-diethylethylene diamine. These results point to the formation of the common intermediate indole **5**.

Finally, we wished to probe the T-S rearrangement to understand if any of the observed products might emerge from an intermolecular pathway in the presence of the crown and diamine ligands. Thus, crossover experiments were carried out as depicted in Fig. 3d. In the event, upon use of a combination of alkynes **1a** and **1x**, only two products (**2a** and **2x** in 75 and 86% yields, respectively) were detected when the reaction was conducted under the influence of 18-crown-6 (Fig. 1 conditions). Likewise, using alkynes **1a** and **1x** with $KN(SiMe_3)_2$ and in the presence of *N*,*N*-diethylethylene diamine led exclusively to the formation of the 2,3-disubstituted indoles **3a** and **3x** in 74–77% yields). Thus, only intramolecular T-S processes were observed for both divergent reaction pathways. These results are consistent with a 5-*endo*-*dig* cyclization to give the indole core and a subsequent T-S rearrangement.

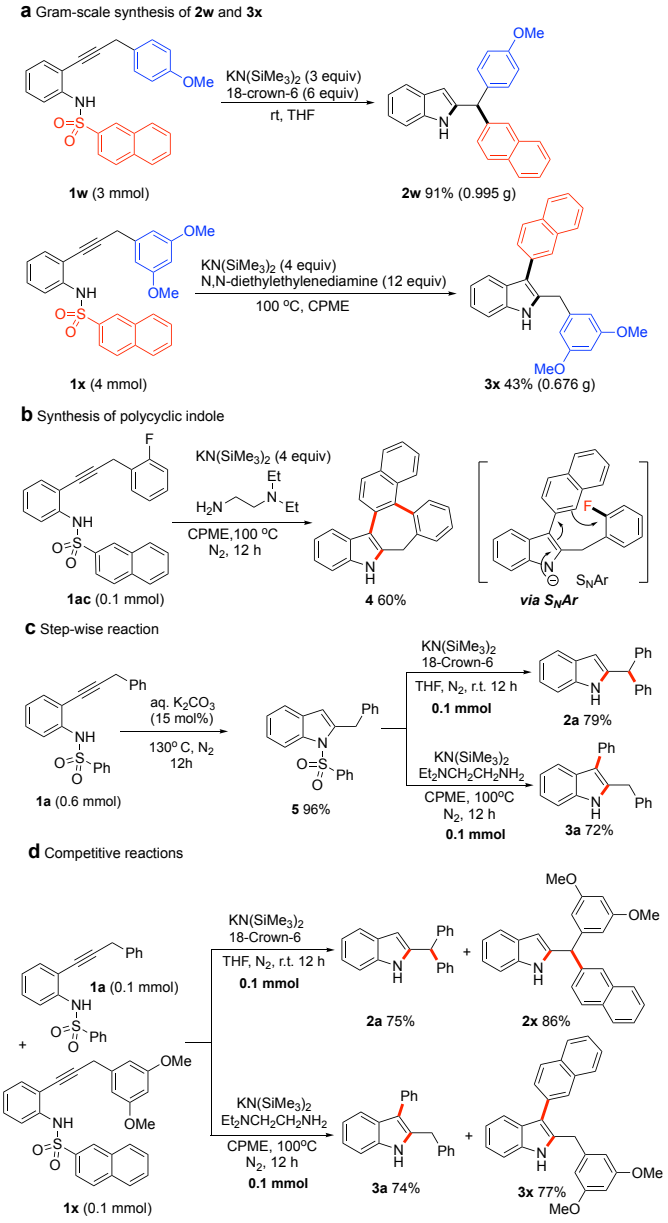


Fig. 3 Scale up reactions and control experiments. **a** Scale up synthesis of **2w** and **3x**. **b** Synthesis of polycyclic indole **4** ,possibly through an S_NAr. **c** Isolation of a common pre-Truce-Smiles intermediate. **d** Cross-over experiments.

The key advance in this study is the ability to control the chemoselectivity of the Truce-Smiles rearrangement by simply employing different ligands for K^+. It is known from gas phase studies that dimethoxy ethane binds to K^+ with a higher association constant than ethylene diamine (en).[83] The same study also reported that the interaction of the third ethylene diamine with $K^+(en)_2$ to give $K^+(en)_3$ has a "much lower" binding constant than the first two en molecules.[84] Of course, Pederson's[85] 18-crown-6 has a very high binding affinity for K^+.[80] Thus, we hypothesize that the benzylic C–H of the indole is readily deprotonated by the $KN(SiMe_3)_2$ in the presence of either 18-crown-6 (18-C-6) or *N,N*-diethylethylenediamine ($enEt_2$), as outlined in Scheme. 1c. In the case of $KN(SiMe_3)_2$/18-C-6, the K^+ is sequestered to give a solvent separated ion pair with K^+•(18-C-6) or perhaps K^+•(18-C-6) interacting with the aromatic pi-system of the deprotonated benzyl group or indole.[86] In this situation, we envision unhindered access of the carbanion to the SO_2–Ar group *ipso*-carbon for the T-S rearrangement. As a result, the T-S reaction readily takes place at room temperature with a low barrier to the benzylic position. Note that in the *absence* of the crown ether, it is anticipated that the K^+ will be associated with the anionic indole. Such an interaction will hinder the T-S rearrangement, which is consistent with the 5% yield of benzhydryl indole observed under crown-free conditions (Table 1, entry 11). In the case of the diamine additive, it is likely that the $K^+(enEt_2)_n$ has a stronger electrostatic interaction with the deprotonated benzylic site and neighboring aryl ring, because the weaker binding of the diamine. We propose that this tighter interaction hinders the T-S attack of the benzylic anion on the SO_2–Ar group ipso-carbon. More forcing conditions (100 °C) are required for attack by the anionic indole 3-position on the SO_2–Ar group ipso-carbon. Given the drive to more sustainable chemistry, including arylation reactions, we envision that this approach to steering the Truce-Smiles rearrangement by choice of ligands for cationic metals will be applicable to other arylation strategies.

Data availability

The authors declare that all the data supporting the findings of this study are available within the paper and its supplementary information files, or from the corresponding author upon request. For the experimental procedures and spectroscopic and physical data of compounds, see Supplementary Methods. For ^1H and $^{13}C\{^1H\}$ NMR spectra of compounds, see Supplementary Figures.

Author Contributions

F.Z., H.J., and Z.X. performed the experiments. J.L., P.J.W. and F.Z. conceived the study, directed the project and wrote the manuscript with the assistance of all of the authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

JL thanks Zhejiang Provincial Natural Science Foundation of China (LY20C020003) and National Natural Science Foundation of China (31670357). PJW thanks the US National Science Foundation (CHE-2154593).

Notes and references

1. R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in drugs, *J. Med. Chem.*, 2014, **57**, 5845-5859.
2. M. Aldeghi, S. Malhotra, D. L. Selwood and A. W. E, Two- and three-dimensional rings in drugs Chan, *Chem Biol Drug Des.*, 2014, **83**, 450-461.
3. A. Nilova, L.-C. Campeau, E. C. Sherer and D. R. Stuart,

Analysis of benzenoid substitution patterns in small molecule active pharmaceutical ingredients, *J. Med. Chem.*, 2020, **63**, 13389-13396.
4. N. Miyaura and A. Suzuki, The palladium-catalyzed cross-coupling reaction of 9-organothio-9-borabicyclo[3.3.1]nonanes with organic electrophiles: Synthesis of unsymmetrical sulfides, *Chem. Rev.*, 1995, **96**, 2457-2483.
5. T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson and L. Ackermann, C–H activation, *Nat. Rev. Methods Primers*, 2021, **1**, 43.
6. C. E. Garrett and K. Prasad, The art of meeting palladium specifications in active pharmaceutical ingredients produced by Pd-catalyzed reactions, *Adv. Synth. Catal.*, 2004, **346**, 889-900.
7. D. Barbaras, J. Brozio, I. Johannsen and T. Allmendinger, Removal of heavy metals from organic reaction mixtures: preparation and application of functionalized resins, *Org. Process Res. Dev.*, 2009, **13**, 1068-1079.
8. C. L. Sun and Z. J. Shi, Transition-metal-free coupling reactions, *Chem. Rev.*, 2014, **114**, 9219-9280.
9. V. P. Mehta and B. Punji, Recent advances in transition-metal-free direct C–C and C–heteroatom bond forming reactions, *RSC Advances*, 2013, **3**, 11957-11986.
10. M. Li, S. Berritt, L. Matuszewski, G. Deng, A. Pascual-Escudero, G. B. Panetti, M. Poznik, X. Yang, J. J. Chruma and P. J. Walsh, Transition-metal-free radical C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) coupling enabled by 2-azaallyls as super-electron-donors and coupling-partners, *J. Am. Chem. Soc.*, 2017, **139**, 16327-16333.
11. T. J. Snape, A truce on the Smiles rearrangement: revisiting an old reaction—the Truce–Smiles rearrangement, *Chem. Soc. Rev.*, 2008, **37**, 2452-2458.
12. B. Prüger, G. E. Hofmeister, C. B. Jacobsen, D. G. Alberg, M. Nielsen and K. A. Jørgensen, Transition-metal-free formal Sonogashira coupling and α-carbonyl arylation reactions, *Chem.-Eur. J.*, 2010, **16**, 3783-3790.
13. P. T. G. Rabet, S. Boyd, and M. F. Greaney, Metal-free intermolecular aminoarylation of alkynes, *Angew. Chem. Int. Edit.* 2017, **56**, 4183-4186.
14. A. R. P. Henderson, J. R. Kosowan and T. E. Wood, The Truce–Smiles rearrangement and related reactions: a review, *Can. J. Chem.*, 2017, **95**, 483-504.
15. C. Hervieu, M. S. Kirillova, T. Suárez, M. Müller, E. Merino and C. Nevado, Asymmetric, visible light-mediated radical sulfinyl-Smiles rearrangement to access all-carbon quaternary stereocentres, *Nat. Chem.*, 2021, **13**, 327-334.
16. W. E. Truce, W. J. Ray, O. L. Norman and D. B. Eickemeyer, Rearrangements of Aryl Sulfones. I. The Metalation and Rearrangement of Mesityl Phenyl Sulfone1, *J. Am. Chem. Soc.*, 1958, **80**, 3625-3629.
17. R. Abrams, M. H. Jesani, A. Browning and J. C. Clayden, Triarylmethanes and their medium-ring analogues by unactivated Truce–Smiles rearrangement of benzanilides, *Angew. Chem. Int. Edit.*, 2021, **60**, 11272-11277.
18. S. M. Wales, R. K. Saunthwal and J. Clayden, C(sp^3)-arylation by conformationally accelerated intramolecular nucleophilic aromatic substitution (SNAr), *Acc. Chem. Res.,* **2022**, *55*, 1731-1747.
19. Y. Wang, W. Pan, Y. Zhang, L. Wang and J. Han, Truce-Smiles rearrangement of diaryliodonium salts in ionic liquids, *Angew. Chem. Int. Edit.,* 2023, **62**, e202304897.
20. Y. Weng, Y. Zhang, A. Turlik, X. Wu, H. Li, F. Fei, Y. Yao, C. Wang, Z. Guo, J. Qu, K. N. Houk and Y. Chen, Nickel-catalysed regio- and stereoselective acylzincation of unsaturated hydrocarbons with organozincs and CO, *Nat. Synth.*, 2023, **2**, 261-274.
21. D. A. Horton, G. T. Bourne and M. L. Smythe, The combinatorial synthesis of bicyclic privileged structures or privileged substructures, *Chem. Rev.*, 2003, **103**, 893-930.
22. M. Somei and F. Yamada, Simple indole alkaloids and those with a non-rearranged monoterpenoid unit, *Nat. Prod. Rep.*, 2005, **22**, 73-103.
23. T. Kawasaki and K. Higuchi, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, *Nat. Prod. Rep.*, 2005, **22**, 761-793.
24. K. Higuchi and T. Kawasaki, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, *Nat. Prod. Rep.*, 2007, **24**, 843-868.
25. A. J. Kochanowska-Karamyan and M. T. Hamann, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, *Chem. Rev.*, 2010, **110**, 4489-4497.
26. T. V. Sravanthi and S. L. Manju, Indoles – A promising scaffold for drug development, *Eur. J. Pharm. Sci.*, 2016, **91**, 1-10.
27. G. Zeni and R. C. Larock, Synthesis of heterocycles *via* palladium π-olefin and π-alkyne chemistry, *Chem. Rev.*, 2004, **104**, 2285-2309.
28. S. Cacchi and G. Fabrizi, Synthesis and functionalization of indoles through palladium-catalyzed reactions, *Chem. Rev.*, 2005, **105**, 2873-2920.
29. G. R. Humphrey and J. T. Kuethe, Practical methodologies for the synthesis of indoles, *Chem. Rev.*, 2006, **106**, 2875-2911.
30. L. Ackermann, Catalytic arylations with challenging substrates: From air-stable HASPO preligands to indole syntheses and C-H-bond functionalizations, *Synlett*, 2007, 8, 507-526.
31. N. T. Patil and Y. Yamamoto, Coinage metal-assisted synthesis of heterocycles, *Chem. Rev.*, 2008, **108**, 3395-3442.
32. M. Bandini and A. Eichholzer, Catalytic functionalization of indoles in a new dimension, *Angew. Chem. Int. Edit.*, 2009, **48**, 9608-9644.
33. S. Cacchi and G. Fabrizi, Update 1 of: Synthesis and functionalization of indoles through palladium-catalyzed reactions, *Chem. Rev.*, 2011, **111**, PR215-PR283.
34. F. W. Patureau and F. Glorius, Oxidizing directing groups enable efficient and innovative C – H activation reactions, *Angew. Chem. Int. Edit.*, 2011, **50**, 1977-1979.
35. M. Shiri, Indoles in multicomponent processes (MCPs), *Chem. Rev.*, 2012, **112**, 3508-3549.
36. K. Kruger, A. Tillack and M. Beller, Catalytic synthesis of indoles from alkynes, *Adv. Synth. Catal.*, 2008, **350**, 2153-2167.
37. R. Vicente, Recent advances in indole syntheses: New routes for a classic target, *Org. Biomol. Chem.*, 2011, **9**, 6469-6480.
38. M. Platon, R. Amardeil, L. Djakovitch and J. C. Hierso, Progress in palladium-based catalytic systems for the sustainable synthesis of annulated heterocycles: a focus on indole backbones, *Chem. Soc. Rev.*, 2012, **41**, 3929-

3968.
39. M. Inman and C. J. Moody, Indole synthesis – something old, something new, *Chem. Sci.*, 2013, **4**, 29-41.
40. I. V. Seregin and V. Gevorgyan, Direct transition metal-catalyzed functionalization of heteroaromatic compounds, *Chem. Soc. Rev.*, 2007, **36**, 1173-1193.
41. J. S. S. Neto and G. Zeni, Recent advances in the synthesis of indoles from alkynes and nitrogen sources, *Org. Chem. Front.*, 2020, **7**, 155-210.
42. J. Mao, Z. Wang, X. Xu, G. Liu, R. Jiang, H. Guan, Z. Zheng and P. J. Walsh, Synthesis of indoles through domino reactions of 2-fluorotoluenes and nitriles, *Angew. Chem. Int. Edit.*, 2019, **58**, 11033-11038.
43. S. Kou, J. Huo, Y. Wang, S. Sun, F. Xue, J. Mao, J. Zhang, L. Chen and P. J. Walsh, Synthesis of indoles *via* domino reactions of 2-methoxytoluene and nitriles, *J. Org. Chem.*, 2022, **8**, 5147–5152.
44. G. Q. Liu, P. J. Walsh and J. Y. Mao, Alkaline-metal-catalyzed one-pot aminobenzylation of aldehydes with toluenes, *Org. Lett.*, 2019, **21**, 8514-8518.
45. J. Y. Mao, Z. T. Wang, X. Y. Xu, G. Q. Liu, R. S. Jiang, H. X. Guan, Z. P. Zheng and P. J. Walsh, Synthesis of indoles through domino reactions of 2-fluorotoluenes and nitriles, *Angew. Chem. Int. Edit.*, 2019, **58**, 11033-11038.
46. H. Jiang, S. C. Sha, S. A. Jeong, B. C. Manor and P. J. Walsh, Ni(NIXANTPHOS)-catalyzed mono-arylation of toluenes with aryl chlorides and bromides, *Org. Lett.*, 2019, **21**, 1735-1739.
47. J. D. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher and P. J. Walsh, Palladium-catalyzed C(sp^3)–H arylation of diarylmethanes at room temperature: Synthesis of triarylmethanes *via* deprotonative-cross-coupling processes, *J. Am. Chem. Soc.*, 2012, **134**, 13765-13772.
48. J. D. Zhang, A. Bellomo, N. Trongsiriwat, T. Z. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. L. Yin, J. R. Robinson, E. J. Schelter and P. J. Walsh, NiXantphos: A deprotonatable ligand for room-temperature palladium-catalyzed cross-couplings of aryl chlorides, *J. Am. Chem. Soc.*, 2014, **136**, 6276-6287.
49. X. Y. Cao, S. C. Sha, M. Y. Li, B. S. Kim, C. Morgan, R. D. Huang, X. D. Yang and P. J. Walsh, Nickel-catalyzed arylation of heteroaryl-containing diarylmethanes: exceptional reactivity of the Ni(NIXANTPHOS)-based catalyst, *Chem. Sci.*, 2016, **7**, 611-618.
50. J. Li, C. Wu, B. H. Zhou and P. J. Walsh, Nickel-catalyzed C(sp^3)–H arylation of diarylmethane derivatives with aryl fluorides, *J. Org. Chem.*, 2018, **83**, 2993-2999.
51. F. Yang, D. Zou, S. G. Chen, H. Wang, Y. C. Zhao, L. Y. Zhao, L. L. Li, J. Li and P. J. Walsh, Transition metal-free aroylation of diarylmethanes with *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles, *Adv. Synth. Catal.*, 2020, **362**, 3423-3430.
52. F. Gao, B. S. Kim and P. J. Walsh, Chemoselective palladium-catalyzed deprotonative arylation/[1,2]-Wittig rearrangement of pyridylmethyl ethers, *Chem. Sci.*, 2016, **7**, 976-983.
53. V. F. Vavsari, A. Nikbakht and S. Balalaie, Annulation of 2-alkynylanilines: The versatile chemical compounds, *Asian J. Org. Chem.*, 2022, **11**, 37.
54. A. A. Festa, P. V. Raspertov and L. G. Voskressensky, 2-(Alkynyl)anilines and derivatives – versatile reagents for heterocyclic synthesis, *Adv. Synth. Catal.*, 2022, **364**, 466-486.
55. A. Furstner and P. W. Davies, Heterocycles by $PtCl_2$-catalyzed intramolecular carboalkoxylation or carboamination of alkynes, *J. Am. Chem. Soc.*, 2005, **127**, 15024-15025.
56. M. G. Rong, T. Z. Qin and W. W. Zi, Rhenium-catalyzed intramolecular carboalkoxylation and carboamination of alkynes for the synthesis of C3-substituted benzofurans and indoles, *Org. Lett.*, 2019, **21**, 5421-5425.
57. Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, Gold-catalyzed cascade cyclization of 2-alkynyl-*N*-propargylanilines by rearrangement of a propargyl group, *Angew. Chem. Int. Edit.*, 2015, **54**, 7862-7866.
58. I. Nakamura, U. Yamagishi, D. C. Song, S. Konta and Y. Yamamoto, Gold- and indium-catalyzed synthesis of 3- and 6-sulfonylindoles from *ortho*-alkynyl-*N*-sulfonylanilines, *Angew. Chem. Int. Edit.*, 2007, **46**, 2284-2287.
59. I. Nakamura, T. Sato and Y. Yamamoto, Gold-catalyzed intramolecular carbothiolation of alkynes: synthesis of 2,3-disubstituted benzothiophenes from (α-alkoxy alkyl)(*ortho*-alkynyl phenyl) sulfides, *Angew. Chem. Int. Edit.*, 2006, **45**, 4473-4475.
60. R. Alvarez, C. Martinez, Y. Madich, J. G. Denis, J. M. Aurrecoechea and A. R. de Lera, A general synthesis of alkenyl-substituted benzofurans, indoles, and isoquinolones by cascade palladium-catalyzed heterocyclization/oxidative Heck coupling, *Chem.-Eur. J.*, 2010, **16**, 12746-12753.
61. B. Yao, Q. Wang and J. P. Zhu, palladium-catalyzed coupling of *ortho*-alkynylanilines with terminal alkynes under aerobic conditions: Efficient synthesis of 2,3-disubstituted 3-alkynylindoles, *Angew. Chem. Int. Edit.*, 2012, **51**, 12311-12315.
62. A. Arcadi, S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti and F. Marinelli, 2-Substituted 3-arylindoles through palladium-catalyzed arylative cyclization of 2-alkynyltrifluoroacetanilides with arylboronic acids under oxidative conditions, *Org. Biomol. Chem.*, 2013, **11**, 545-548.
63. Y. P. He, H. Wu, Q. Wang and J. P. Zhu, Palladium-catalyzed enantioselective Cacchi reaction: asymmetric synthesis of axially chiral 2,3-disubstituted indoles, *Angew. Chem. Int. Edit.*, 2020, **59**, 2105-2109.
64. Y. P. He, J. Cao, H. Wu, Q. Wang and J. P. Zhu, Catalytic enantioselective aminopalladation–Heck cascade, *Angew. Chem. Int. Edit.*, 2021, **60**, 7093-7097.
65. T. A. Jin, S. Suzuki, H. E. Ho, H. Matsuyama, M. Kawata and M. Terada, Pd-Catalyzed indolization/peri-C–H annulation/N-dealkylation cascade to cyclopenta-fused acenaphtho[1,2-b]indole scaffold, *Org. Lett.*, 2021, **23**, 9431-9435.
66. S. J. Guo, R. Pan, Z. Guan, P. P. Li, L. B. Cai, S. W. Chen, A. J. Lin and H. Q. Yao, Synthesis of indole-fused polycyclics *via* rhodium-catalyzed undirected C–H activation/alkene insertion, *Org. Lett.*, 2019, **21**, 6320-6324.
67. G. Wang, J. C. Li, Y. G. Zhou and Z. S. Ye, Enantioselective synthesis of indole-fused bicyclo[3.2.1]octanes *via* palladium(II)-catalyzed cascade reaction, *Org. Lett.*, 2021, **23**, 802-807.
68. S. Zhang, H. M. Ma, H. E. Ho, Y. Yamamoto, M. Bao and T. A. Jin, Pd-Catalyzed cascade cyclization of o-alkynylanilines via C–H/C–N bond cleavage leading to

dibenzo[a,c]carbazoles†, *Org. Biomol. Chem.*, 2018, **16**, 5236-5240.
69. J. Zhang, S. Q. Shi, W. J. Hao, G. Y. Dong, S. J. Tu and B. Jiang, Tunable electrocatalytic annulations of o-arylalkynylanilines: Green and switchable syntheses of skeletally diverse indoles, *J. Org. Chem.*, 2021, **86**, 15886-15896.
70. L. Yang, Y. H. Ma, F. J. Song and J. S. You, Silver-catalyzed one-pot cyclization/fluorination of 2-alkynylanilines: highly efficient synthesis of structurally diverse fluorinated indole derivatives, *Chem. Commun.*, 2014, **50**, 3024-3026.
71. J. Sheng, S. Y. Li and J. Wu, Synthesis of 3-((trifluoromethyl)thio)indoles *via* a reaction of 2-alkynylaniline with trifluoromethanesulfanylamide, *Chem. Commun.*, 2014, **50**, 578-580.
72. N. Isono and M. Lautens, Rhodium(I)-catalyzed cyclization reaction of o-alkynyl phenols and anilines. Domino approach to 2,3-disubstituted benzofurans and indoles, *Org. Lett.*, 2009, **11**, 1329-1331.
73. R. Karmakar, A. Suneja and V. K. Singh, Ag(I)-Catalyzed indolization/C3-functionalization cascade of 2-ethynylanilines *via* ring opening of donor–acceptor cyclopropanes, *Org. Lett.*, 2016, **18**, 2636-2639.
74. W. L. Yuan, X. J. Li, Z. S. Qi and X. W. Li, Palladium-catalyzed synthesis of functionalized indoles by acylation/allylation of 2-alkynylanilines with three-membered rings, *Org. Lett.*, 2022, **24**, 2093-2098.
75. D. M. Whalley and M. F. Greaney, Recent advances in the Smiles rearrangement: New opportunities for arylation, *Synthesis*, 2022, **54**, 1908-1918.
76. C. M. Holden and M. F. Greaney, Modern aspects of the Smiles rearrangement, *Chem.-Eur. J.*, 2017, **23**, 8992-9008.
77. I. Allart-Simon, S. Gerard and J. Sapi, Radical Smiles rearrangement: An update, *Molecules*, 2016, **21**, 11.
78. M. Nambo and C. M. Crudden, Recent advances in the synthesis of triarylmethanes by transition metal catalysis, *ACS catal.*, 2015, **5**, 4734-4742.
79. D. Roy and G. Panda, Benzhydryl amines: Synthesis and their biological perspective, *ACS Omega*, 2020, **5**, 19-30.
80. T. M. Monos, R. C. McAtee and C. R. J. Stephenson, Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylationk, *Science*, 2018, **361**, 1369-1373.
81. J. J. Douglas, H. Albright, M. J. Sevrin, K. P. Cole and C. R. J. Stephenson, A visible-light-mediated radical Smiles rearrangement and its application to the synthesis of a difluoro-substituted spirocyclic ORL-1 antagonist, *Angew. Chem. Int. Edit.*, 2015, **54**, 14898-14902.
82. Y. Wei, H. Zhang, X. Wu and C. Zhu, Alkene difunctionalization triggered by a stabilized allenyl radical: Concomitant installation of two unsaturated C−C bonds, *Angew. Chem. Int. Ed.*, 2021, **60**, 20215-20219.
83. W. R. Davidson and P. Kebarle, Binding energies and stabilities of potassium ion complexes with ethylene diamine and dimethoxyethane (glyme) from measurements of the complexing equilibria in the gas phase, *Can. J. Chem.*, 1976, **54**, 2594-2599.
84. C. J. Pedersen, Cyclic polyethers and their complexes with metal salts, *J. Am. Chem. Soc.*, 1967, **89**, 7017-7036.
85. H. K. Frensdorff, Stability constants of cyclic polyether complexes with univalent cations, *J. Am. Chem. Soc.*, 1971, **93**, 600-606.
86. E. S. Meadows, S. L. De Wall, L. J. Barbour and G. W. Gokel, Alkali metal cation−π interactions observed by using a Lariat ether model system, *J. Am. Chem. Soc.*, 2001, **123**, 3092-3107.