Advanced Synthesis & Catalysis

Accepted Article

Title: Facile Synthesis of 2-(Arylthio)indolenines via Chemoselective Arylation of Thio-oxindoles with Arynes

Authors: Adi Saputra, Rong Fan, Tuanli Yao, Jian Chen, and Jiajing Tan

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202000308

Link to VoR: https://doi.org/10.1002/adsc.202000308

10.1002/adsc.202000308

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of 2-(Arylthio)indolenines via Chemoselective Arylation of Thio-oxindoles with Arynes

Adi Saputra,[a] Rong Fan,[a] Tuanli Yao,[b]* Jian Chen,[a] and Jiajing Tan[a]*

[a] Department of Organic Chemistry, College of Chemistry, Beijing University of Chemical Technology, Beijing 100029, China.
E-mail: tanjj@mail.buct.edu.cn

[b] College of Chemistry and Chemical Engineering, Shaanxi University of Science and Technology, 6 Xuefu Road, Weiyang District, Xi'an, Shaanxi 710021, China.
E-mail: yaotuanli@sust.edu.cn

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

A chemoselective *S*-arylation reaction of thio-oxindoles with arynes is presented. The reaction was performed under mild conditions and provided a straightforward synthesis of 2-(arylthio)indolenines in good to excellent yields. Besides, this simple operational protocol is not only scalable but also has good functional group compatibilities and substrate scope. Thus, our protocol should allow for the expansion of chemical space via developing new scaffolds of thioimidates that are difficult to synthesize otherwise.

Keywords: Chemoselective *S*-arylation; thio-oxindoles; Aryne; 2-(Arylthio)indolenines; Chemical space

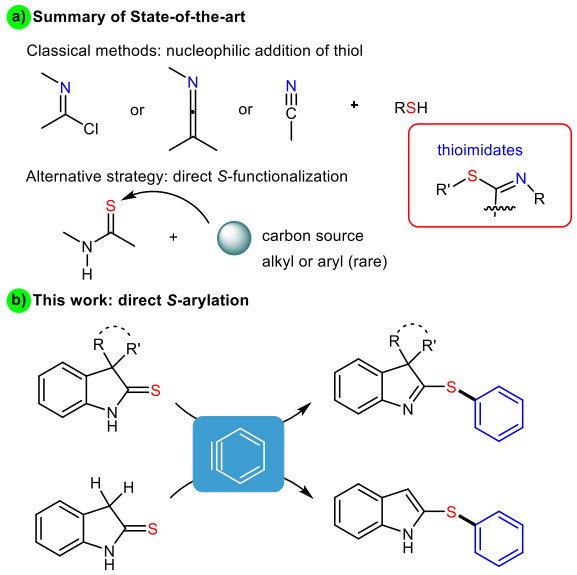
Introduction

Thioimidates are not only widespread in bioactive molecules, but also important synthetic intermediates toward various nitrogen and sulfur-containing compounds.[1] Classical methods to prepare such structural units relied on reactions of sulfur nucleophiles with C-N multiple bonds containing components including imidoyl chlorides, ketenimines or nitriles (Scheme 1a).[2] An alternative strategy was to react carbon source with thioamide derivatives. Although many advances have been witnessed on S-alkylation reactions to access alkyl thioimidates,[3] synthesis of aryl thioimidates via chemoselective *S*-arylation continues to be underdeveloped.[4] A critical challenge would be the side *N*-arylation reaction, as thioamides are bidentate nucleophiles containing both thio-carbonyl and N-H groups.[1-2] Only until recently, Olofsson and co-workers reported an efficient *S*-arylation reaction of acrylic secondary thioamides using diaryliodonium salts, whereas cyclic substrates gave less satisfying selectivities.[5] To the best of our knowledge, the *S*-arylation of cyclic thioamides remained to be an unsolved task in chemical literatures, which was probably due to the poor conjugation of nitrogen lone pair in thioamide moiety and resulting lower nucleophilicity of sulfur.[6]

Among cyclic thioamide motifs, we were particularly interested in thio-oxindoles. It's well-known that indoles, indolenines, oxindoles, and their derivatives are endowed with diverse applications in pharmaceutical chemistry.[7] For instance, the indole motifs bearing C2-thioether scaffolds, although less explored from synthetic perspectives, have displayed promising applications as potential anti-HIV, anti-cancer, anti-inflammatory, and anti-bacterial agents.[8] In fact, the expansion of chemical space through the generation of structural diversity still represented the key piece in discovering new drugs.[9] Given their importance along with abovementioned gap in technology, our aim of this project was to identify an efficient *S*-arylation process that was capable of delivering divergent sulfur-containing indolenines and explore the reactivities of these moieties.

The past decades have witnessed the renaissance of innovative aryne chemistry.[10-11] Under mild conditions, aryne species could undergo a variety of unique transformations (including insertion, cycloaddition, multicomponent reaction, *etc.*) to build molecular complexity in high efficacy.[10-11] Given our group's long-standing interests in aryne and organosulfur chemistry,[12] the authors questioned whether it would be feasible to employ arynes to achieve the direct *S*-arylation of thioamides. We hypothesized that polarizable aryne species with their low-lying LUMO should offer enough "soft" electrophilic nature, and might pair reactivity with the "soft" sulfur center of thioamides to enable the chemoselective *S*-arylation (Scheme 1b).[13-14] As such,

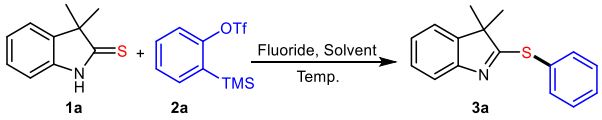
we herein would like to report our recent efforts in developing the chemoselective arylation reaction of thio-oxindoles with arynes to provide direct access to structurally diverse 2-(arylthio)indolenine derivatives.



Scheme 1. Synthesis of Thioimidates.

Results and Discussion

Table 1. Optimization of the Reaction Conditions.[a, b]

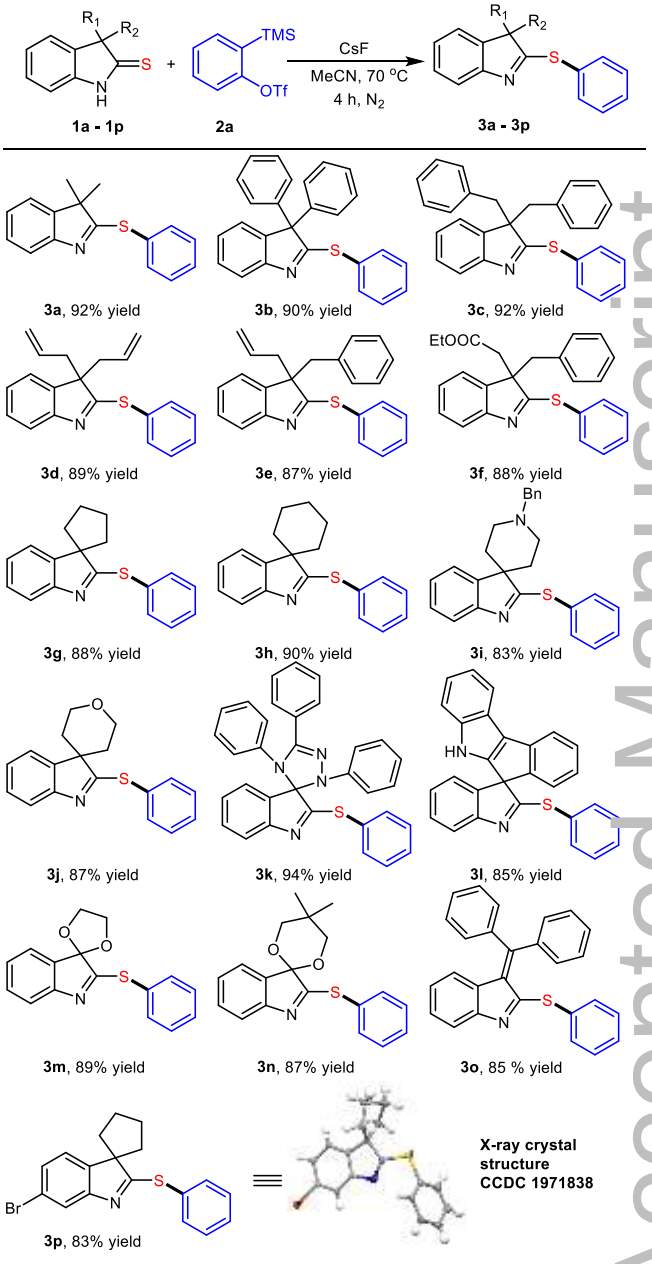


Entry	"F⁻"/Base	Solv.	Temp. (°C)	Yield (%)
1	CsF	MeCN	25	69
2	KF/18-Crown-6	THF	25	60
3	TBAF	THF	25	48
4	Cs_2CO_3/18-Crown-6	THF	25	28
5	CsF	MeCN	0	trace
6	CsF	MeCN	50	85
7	CsF	MeCN	70	92(92)[c]
8[d]	CsF	MeCN	70	75
9[e]	CsF	MeCN	70	90

[a] **1a** (0.11 mmol), **2a** (0.13 mmol) and F^- source (0.33 mmol) solvent (2.0 mL) for 4 h. [b] Determined by ^1H NMR using an internal standard. [c] Isolated yield. [d] CsF (2.0 equiv.). [e] 1.0 equiv. of **2a** used.

We commenced our investigations with 3,3-dimethyldihydroin-dole-2-thione (**1a**) and 2-(trimethylsilyl)-phenyl trifluoromethanesulfonate (**2a**) as model substrates (Table 1). To our delight, the reaction proceeded in the presence of cesium fluoride (CsF) under N_2 atmosphere, gave the *S*-arylation product **3a** exclusively in 69% yield (entry 1). Various aryne formation conditions were then investigated, and none of them increased the chemical yields (entries 2-4). To further improve the reaction efficiency, the temperature effect was evaluated. Lowering the reaction temperature to 0 °C only led to a trace amount of **3a** (entry 5), while increasing it to 70 °C gave the desired product in a 92% isolated yield (entry 7). Finally, decreasing the amount of CsF or switching the reactant ratio failed to improve the overall reaction outcomes (entries 8-9).

Table 2. Substrate Scope for Thio-oxindoles.[a]



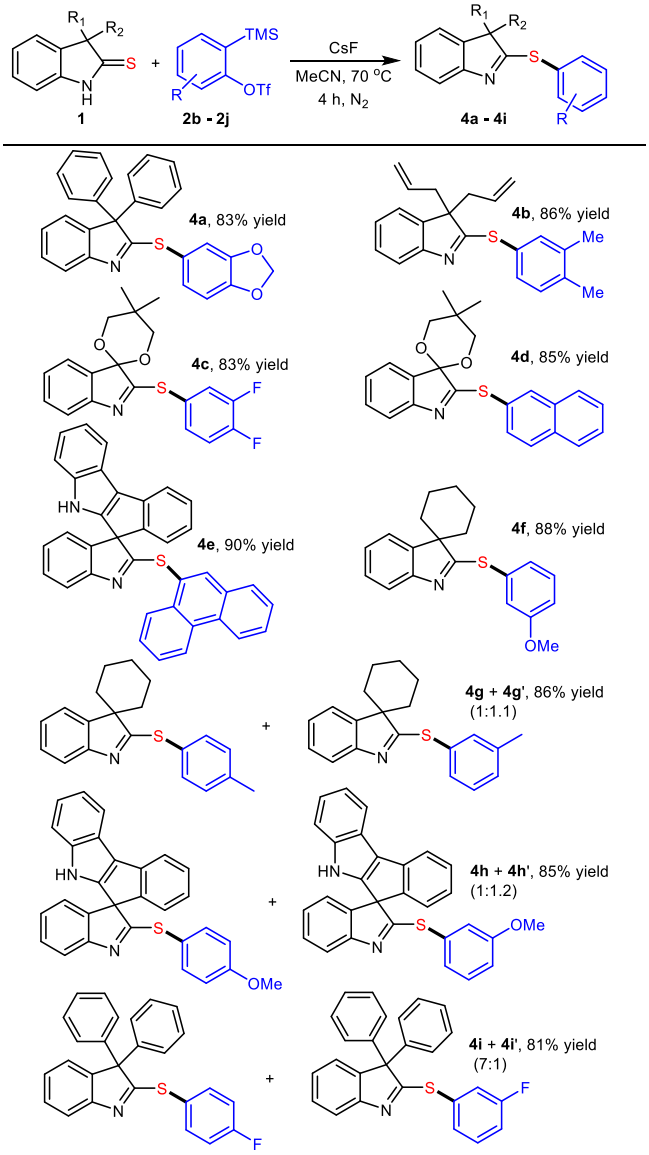
[a] Standard reaction conditions: **1a-1p** (0.28 mmol, 1.0 equiv.), **2a** (0.34 mmol, 1.2 equiv.), CsF (3.0 equiv.) in MeCN (3 mL) at 70 °C for 4 h under N_2.

With optimal conditions in hands, we next explored the substrate scope of 2-indolinethiones (Table 2). A variety of substituent groups were well-tolerated to offer the desired products (**3a-3o**) in good yields. First, we examined 2-indolinethiones containing several acyclic substituent groups on 3 and 3' positions, all of which were successful coupling partners (**3a-3f**, 87-

10.1002/adsc.202000308

92% yields). Substrates bearing spirocyclic motifs were also amenable, providing good yields of the desired products (**3g-3j**). Interestingly, the heterocyclic fragments, which were well known to react with arynes, proved to be tolerated under standard reaction conditions (**3k-3l**).[15] Substrates containing acetal groups as latent synthetic handles at the 3-position also proceeded smoothly to give corresponding products **3m** and **3n** in 89% and 87% yields, respectively. Moreover, the Diels-Alder product was not observed, when the substrate with hetero-diene moiety was employed (**3o**). Finally, 6-bromo-substituted thio-oxindole **1p** was utilized, and the absolute configuration of corresponding product **3p** was unambiguously determined by X-ray diffraction studies.[16] It should be noted that complete chemoselectivity for bond formation at the sulfur was observed for all substrates.

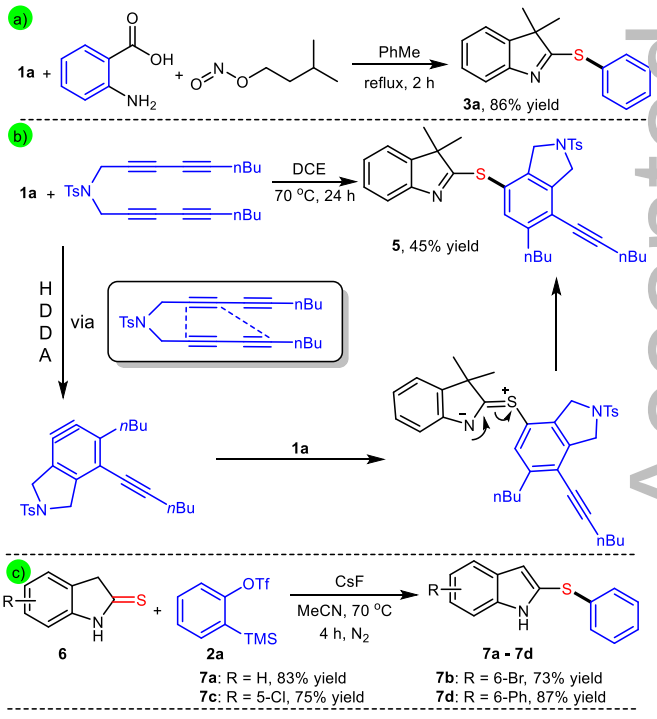
Table 3. Substrate Scope for Aryne Precursors.[a]



[a] Standard reaction conditions: **1** (0.28 mmol, 1.0 equiv.), **2b-2j** (0.34 mmol, 1.2 equiv), CsF (3.0 equiv.) in MeCN (3 mL) at 70 °C for 4 h under N_2.

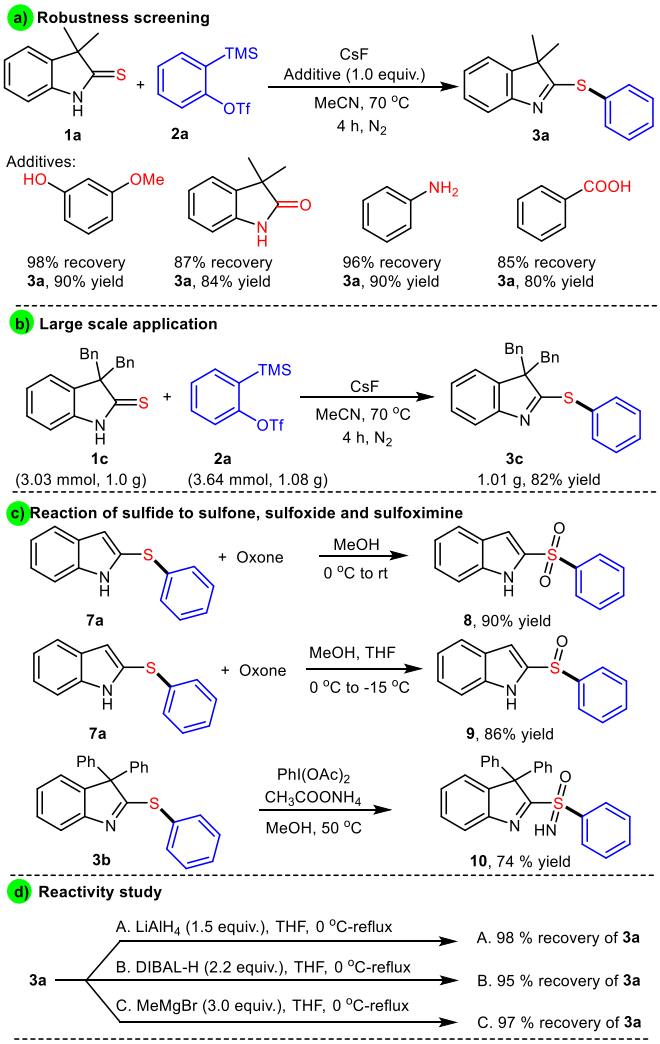
Variation of the aryne species was evaluated next (Table 3). A series of functionalized thio-oxindoles readily reacted with symmetrical arynes to afford the coupled products in 83-90% yields (**4a-4e**). 3-methoxybenzyne also underwent the reaction smoothly to give **4f** with significant regioselectivity, which is in accordance with the distortion/interaction model reported by Houk, Garg and *et al*.[17] Generally, the electronic effects of the substituent groups on arynes had no significant impacts on reaction outcomes. Furthermore, when unsymmetrical arynes were reacted with thio-oxindoles, the desired products (**4g-4i**) were obtained as regioisomeric mixtures.

Further studies to gain insights into the reactivities of **1a** with other aryne precursors were performed (Scheme 2). We reacted **1a** with benzyne that was generated from aprotic diazotization of anthranilic acid followed by thermal decomposition of the diazonium carboxylate, gave **3a** with 86% isolated yield. Treating **1a** with aryne that was thermally generated via hexadehydro-Diels-Alder gave product **5** in 45% yield.[18] Given that the transformation occurred under base-free conditions, it should offer great synthetic flexibility. Next, we investigated the reactivity of indoline-2-thiones with three possible nucleophilic sites. In all cases, the aromatization products were obtained (**7a-7d**, 73-87% yields), which offered a complement method to direct sulfenylation of indoles that usually proceeded at 3-positions.



Scheme 2. Reaction with Other Substrates.

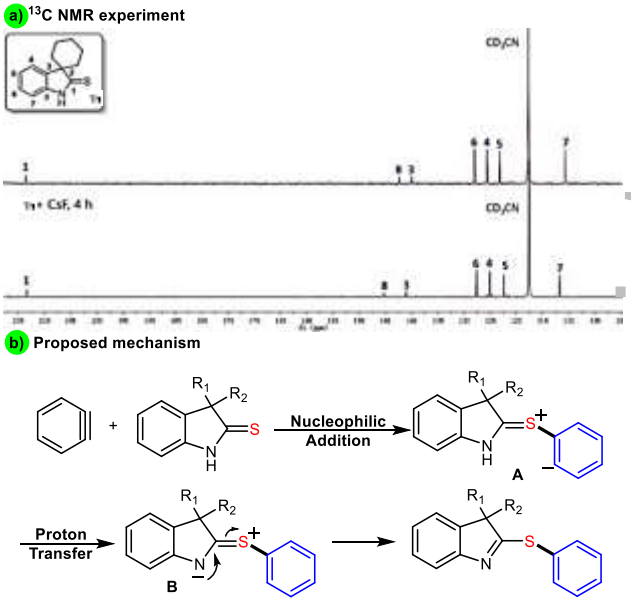
The synthetic utilities of our strategy toward expanding the chemical space have been demonstrated in various aspects (Scheme 3). First, an additive-based robustness screen was undertaken.[19] The experiments were performed in the presence of one equivalent of additives, and **3a** was still obtained in good yields under otherwise same conditions. Meanwhile, the additives were mostly recovered, suggesting that our protocol be potentially well-suited for complex substrates. Undeniably, the observed functional group tolerance and preservation attributed to the inherent nucleophilic scale differentiation.[20] Second, we used **1c** (1.0 gram) with a slight excess of the aryne precursor **2a**, and the desired product **3c** was obtained in 82% yield (1.01 gram) at gram scale.



Scheme 3. Synthetic Applications.

Moreover, sulfide **7a** could be readily oxidized to sulfone **8** and sulfoxide **9** in 90% and 86% yields, respectively. Product **3b** could be also converted to sulfoximine **10** in 74% yield via *N* and *O*-transfer. Finally, when **3a** was reacted with excess reductants or Grignard reagents, it remained stable even at reflux conditions with 95-98% recovery yields of **3a**.

To probe the reaction mechanism, the NMR experiment was performed (Scheme 4). When **1h** was treated with CsF at 70 °C, we observed no changes in the chemical shift of C-S double bond in ^{13}C NMR spectrum.[21] Based on this finding along with experimental results in Scheme 2, a plausible mechanism was proposed. Initially, the nucleophilic addition of **1** to *in-situ* formed aryne species gave the key zwitterionic intermediate **A**. The proton transfer eventually generated the final product.



Scheme 4. NMR Experiments and Proposed Mechanism.

Conclusion

In summary, we have reported a chemoselective *S*-arylation reaction of thioamides under transition-metal free conditions. This mild protocol has been applied to a range of structurally diverse building blocks as well as being scaled effectively to gram scale. The robustness screen and derivatization studies further demonstrated its potentials in exploring chemical space for medicinal chemistry use. We thus strongly believe that the operational simplicity and broad functional group tolerance of our protocol should make it suitable for target synthesis projects in both academic and industrial settings.

Experimental Section

Preparation of Compounds 3 and 4: In an oven-dried 10 mL schlenk tube, a mixture of thio-oxindole (0.28 mmol, 1.0 equiv.), CsF (3.0 equiv.), in acetonitrile (3 mL) was added aryne precursor (0.34 mmol, 83 µL, 1.2 equiv.) under N_2. The resulting mixture was stirred at 70 °C for 4 hours. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (10 mL). The organic layer was washed with water (10 mL, three times). The combined organic layers were dried over with Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography to afford the desired products.

Acknowledgements

JJT is grateful for the support of the National Natural Science Foundation of China (21702013) and the Fundamental Research Funds for the Central Universities (XK1802-6, buctrc201721). T. L. Yao thanks Shaanxi University of Science and Technology for financial support of this research (BJ15-33).

References

[1] a) O.V. Solod, K. N. Zelenin, V. V. Pinson, *Chem. Heterocycl. Compd*. **1996**, *32*, 1-11; b) T. S. Jagodziński, *Chem. Rev*. **2003**, *103*, 197-228; c) M. Koketsu, H. Ishihara, *Curr. Org. Synth*. **2007**, *4*, 15-29; d) W.-S. Guo, L.-R. Wen, M. Li, *Org. Biomol. Chem*. **2015**, *13*, 1942-1953; e) Y. Minami, H. Kuniyasu, A. Sanagawa, N. Kambe, *Org. Lett*. **2010**, *12*, 3744-3747; f) K. Shvydenko, K. Nazarenko, T. Shvydenko, Y. Vlasenko, A. Tolmachev, A. Kostyuk, *Tetrahedron* **2015**, *71*, 7567-7574; g) N. Mahanta, D. M. Szantai-Kis, E. J. Peterson, D. A. Mitchel, *ACS Chem. Biol*. **2019**, *14*, 142-163.

[2] a) W. Kantlehner, In *Comprehensive Organic Synthesis*, Eds. I. Fleming, Pergamon, Oxford, **1991**, 485; b) R. Smith, T. Livinghouse, *Synth. Commun.* **1984**, *14*, 639-646; c) N. Nakajima, M. Ubukata, *Sci. Synth*. **2005**, *22*, 361-366; d) A. N. Kolontsova, M. N. Ivantsova, M. I. Tokareva, M. Mironov, *Mol. Diversity.* **2010**, *14*, 543-550; e) T. Murai, (Eds) *Chemistry of Thioamides*. Springer, Singapore, **2019**.

[3] a) H. Nishiyama, H. Nagase, K. Ohno, *Tetrahedron Lett*. **1979**, *20*, 4671-4674; b) M. A. Casadei, B. Di Rienzo, F. Micheletti Moracci, *Synth. Commun*. **1983**, *13*, 753-759; c) J. Sawada, K. Okamoto, T. Yamamoto, T. Kanbara, *Tetrahedron Lett*. **2007**, *48*, 8603-8606.

[4] a) I. I. Kandror, I. Bragina, O. *Russ. Chem. Bull*. **1982**, *31*, 1873-1876; b) I. I. Kandror, B. V. Kopylova, R. K. Freidlina, *Sulfur Rep*. **1984**, *3*, 289-316.

[5] P. Villo, G. Kervefors, B. Olofsson, *Chem. Commun*. **2018**, *54*, 8810-8813.

[6] K. B. Wiberg, *Acc. Chem. Res.* **1999**, *32*, 922-929.

[7] a) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev*. **2010**, *39*, 4449-4465; b) Y. Zhu, H. V. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 111-114; c) S. P. Roche, J.-J. Youte Tendoung, B. Treguier, *Tetrahedron*. **2015**, *71*, 3549-3591; d) M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J*. **2016**, *22*, 2856-2881; e) M. Kaur, M. Singh, N. Chadha, O. Silakari, *Eur. J. Med. Chem*. **2016**, *123*, 858-894.

[8] a) K. S. Feldman, D. B. Vidulova, A. G. Karatjas, *J. Org. Chem*. **2005**, *70*, 6429-6440; b) K. S. Feldman, A. G. Karatjas, *Org. Lett*. **2006**, *8*, 4137-4140; c) V. Boyarskikh, A. Nyong, D. J. Rainer, *Angew. Chem. Int. Ed*. **2008**, *47*, 5374-5377.

[9] a) S. Dandapani, L. A. Marcaurelle, *Nat. Chem. Biol*. **2010**, *6*, 861-863; b) L. Batiste, A. Unzue, A. Dolbois, F. Hassler, X. Wang, N. Deerain, J. Zhu, D. Spiliotopoulos, C. Nevado, A. Caflisch, *ACS Cent. Sci*. **2018**, *4*, 180-188.

[10] For selected reviews on aryne chemistry, see: a) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev*. **2012**, *41*, 3140-3152; b) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550-3577; c) T. R. Hoye, B. Baire, D. W. Niu, P. H. Willoughby, B. P. Woods, *Nature* **2012**, *490*, 208-212; d) S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res*. **2016**, *49*, 1658-1670; e) J.-R. Shi, Y.-Y. Li, Y. Li, *Chem. Soc. Rev*. **2017**, *46*, 1707-1779; f) T. Roy, A. T. Biju, *Chem. Commun*. **2018**, *54*, 2580-2594; g) T. Matsuzawa, S. Yoshida, T. Hosoya, *Tetrahedron Lett*. **2018**, *59*, 4197-4208; h) D. B. Werz, A. T. Biju, *Angew. Chem. Int. Ed*. **2020**, *59*, 3385-3398.

[11] For selected reports on aryne chemistry, see: a) U. N. Rao, E. Biehl, *J. Org. Chem.* **2002**, *67*, 3409-3411; b) M. Pawliczek, L. K. B. Garve, D. B. Werz, *Org. Lett*. **2015**, *17*, 1716-1719; c) J. Wallbaum, P. G. Jones, D. B. Werz, *J. Org. Chem*. **2015**, *80*, 3730-3734; d) D. L. Chen, Y. Sun, M. Y. Chen, X. J. Li, L. Zhang, X. Huang, Y. H. Bai, F. Luo, B. Peng, *Org. Lett.* **2019**, *21*, 3986-3989; e) V. Palani, J. H. Chen, T. R. Hoye, *Org. Lett*. **2016**, *18*, 6312; f) R. Samineni, C. R. C. Bandi, P. Srihari, G. Mehta, *Org. Lett*. **2016**, *18*, 6184-6187; g) C. J. Lv, C. W. Wan, S. Liu, Y. Lan, Y. Li, *Org. Lett.* **2018**, *20*, 1919-1923; h) T. L. Yao, D. He, *Org. Lett.* **2017**, *19*, 842-845; i) T. L. Yao, B. G. Ren, B. Wang, Y. N. Zhao, *Org. Lett.* **2017**, *19*, 3135-3138; j) X. J. Li, Y. Sun, X. Huang, L. Zhang, L. C. Kong, B. Peng, *Org. Lett.* **2017**, *19*, 838-841; k) F. I. M. Idiris, C. E. Majesté, G. B. Craven, C. R. Jones, *Chem. Sci*. **2018**, *9*, 2873-2878; l) H. Xu, J. He, J. R. Shi, L. Tan, D. C. Qiu, X. H. Luo, Y. Li, *J. Am. Chem. Soc*. **2018**, *140*, 3555-3559; m) R. N. Gaykar, S. Bhattacharjee, A. T. Biju, *Org. Lett.* **2019**, *21*, 737-740; n) S. Mukherjee, S. Shee, T. Poisson, T. Besset, A. T Biju, *Org. Lett.* **2018**, *20*, 6998-7002; o) H. Tanaka, H. Kuriki, T. Kubo, I. Osaka, H. Yoshida, *Chem. Commun.* **2019**, *55*, 6503-6506; p) T.-Y. Zheng, J.-J. Tan, R. Fan, S.-S. Su, B.-B. Liu, C. Tan, K. Xu, *Chem. Commun.* **2018**, *54*, 1303-1306; q) S.-J. Li, Y. Wang, J.-K. Xu, D. Xie, S.-K. Tian, Z.-X. Yu, *Org. Lett.* **2018**, *20*, 4545-4548; r) X. Xiao, T. R. Hoye, *J. Am. Chem. Soc.* **2019**, *141*, 9813-9818; s) W. H. Wang, H. W. Wan, G. F. Du, B. Dai, L. He, *Org. Lett.* **2019**, *21*, 3496-3500; t) S. Arora, J. Zhang, V. Pogula, T. R. Hoye, *Chem. Sci.* **2019**, *10*, 9069-9076; u) H. Tanaka, I. Osaka, H. Yoshida, *Chem. Lett*. **2019**, *48*, 1032-1034; v) M. Pawliczek, L. K. B. Garve, D. B. Werz, *Chem. Commun.* **2015**, *51*, 9165-9168.

[12] a) J.-J. Tan, T.-Y. Zheng, K. Xu, C.-Y. Liu, *Org. Biomol. Chem*. **2017**, *15*, 4946-4950; b) J.-J. Tan, B.-B. Liu, S.-S. Su, *Org. Chem. Front*. **2018,** *5*, 3093-3097; c) L. Liu, C. Tan, R. Fan, Z. H. Wang, H. G. Du, K. Xu, J.-J. Tan, *Org. Biomol. Chem*. **2019**, *17*, 252-256; d) R. Fan, B.-B. Liu, T.-Y. Zheng, K. Xu, C. Tan, T.-L. Zeng, S.-S. Su, J.-J. Tan, *Chem. Commun*. **2018**, *54*, 7081-7084.

[13] Y. W. Zeng, J. B. Hu, *Synthesis*, **2016**, *48*, 2137-2150.

[14] a) K. Biswas, M. F. Greaney, *Org. Lett*. **2011**, *13*, 4946-4949; b) J. R. Hwu, Y. C. Hsu, *Chem. Eur. J*. **2011**, *17*, 4727-4731; c) J.-R. Shi, D. C. Qiu, J. Wang, H. Xu, Y.

Li, *J. Am. Chem. Soc*. **2015**, *137*, 5670-5673; d) V. G. Pandya, S. B. Mhaske, *Org. Lett*., **2014**, *16*, 3836-3839; e) X. Peng, C. Ma, C.-H. Tung, Z. Xu, *Org. Lett*. **2016**, *18*, 4154-4157; f) P. Garg, A. Singh, *Org. Lett.* **2018**, *20*, 1320-1323; g) M. M. Ahire, M. B. Thoke, S. B. Mhaske, *Org. Lett.* **2018**, *20*, 848-851.

[15] For selected reports, see: (a) J. J. Li, *Heterocyclic Chemistry in Drug Discovery*, Ed. J. J. Li, John Wiley & Sons, Hoboken, NJ, **2013**; (b) J. Tan, Y. Chen, H. Li, N. Yasuda, *J. Org. Chem.* **2014**, *79*, 8871-8876. and reference therein

[16] CCDC-1971838 (**3p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] J. M. Medina, J. L. Mackey, N. K. Garg, K. H. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798-15805.

[18] a) J. Chen, V. Palani, T. R. Hoye, *J. Am. Chem. Soc.* **2016**, *138*, 4318-4321; b) V. Palani, J. Chen, T. R. Hoye, *Org. Lett.* **2016**, *18*, 6312-6315.

[19] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597-601; b) K. D. Collins, A. Rühling, F. Glorius, *Nat. Protoc*. **2014**, *9*, 1348-1353.

[20] a) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584-595; b) R. Loos, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2003**, *125*, 14126-14132.

[21] The chemical shift changes of C7 and C8 might be caused by the hydrogen bonding interaction between **1h** with CsF.

10.1002/adsc.202000308

FULL PAPER

Synthesis of 2-(Arylthio)indolenines via Chemoselective Arylation of Thio-oxindoles with Arynes

Adv. Synth. Catal. **2020**, *Volume*, Page – Page

Adi Saputra,[a] Rong Fan,[a] Tuanli Yao,[b]* Jian Chen,[a] and Jiajing Tan [a]*