Organic Syntheses

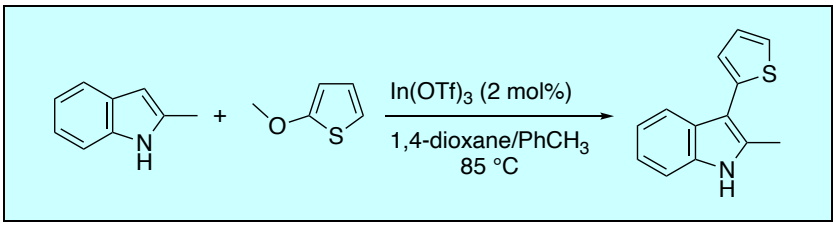
Discussion Addendum for:

Indium-Catalyzed Heteroaryl–Heteroaryl Bond Formation through Nucleophilic Aromatic Substitution: Preparation of 2-Methyl-3-(thien-2-yl)-1*H*-indole

Teruhisa Tsuchimoto*[1]

Department of Applied Chemistry, School of Science and Technology, Meiji University, Higashimita, Tama-ku, Kawasaki 214-8571, Japan

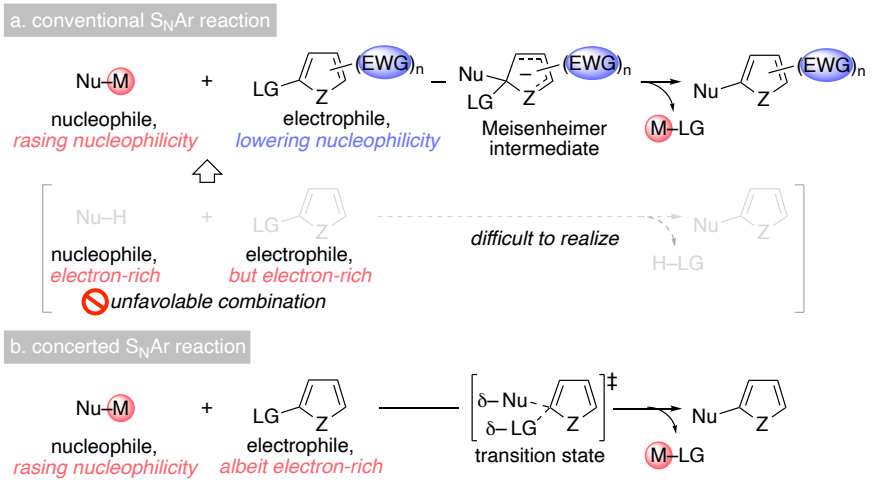
Original Article: Nagase, Y.; Tsuchimoto, T. Org. Synth. ***2014****, 91, 273–282.*



Due to their importance in, for instance, natural products,[2] bioactive molecules,[3] pharmaceuticals,[4] nutrients (vitamins),[5] agrochemicals,[6] dyes,[7] liquid crystals,[8] and functional polymers,[9] heteroaryl units have been recognized as essential structural motifs in various realms. The significance has motivated organic chemists to develop new methods and strategies for more efficiently constructing bonds on heteroaryl scaffolds. One of the most frequently utilized strategies for this purpose is transition metal catalysis, where diverse types of bonds can now be constructed on heteroaryl rings.[10] Another option for functionalizing heteroaryl rings is the nucleophilic aromatic substitution (S_NAr) reaction; however, this reaction has often been unsatisfactory. Despite its long history of use, the negative impression seems to be ascribed to critical limitations. Aromatic compounds are intrinsically electron-rich due to their $(4n + 2)\pi$ electrons but must react with electron-rich nucleophiles in the S_NAr process (Scheme 1a). This demand has narrowed the scope of substrates. Thus, anionic nucleophiles with highly electropositive metals and/or electron-poor heteroaryl electrophiles with one or more

DOI: 10.15227/orgsyn.100.0287 Published on the Web 09/20/2023

electron-withdrawing groups have been utilized (Scheme 1a).[11] This substrate combination appears most frequently in the conventional S_NAr reaction via an addition–elimination sequence where a Meisenheimer intermediate is involved. This mechanism can be viewed as the cause of the negative image of the conventional S_NAr reaction. However, the appearance of the concerted S_NAr reaction has triggered a major breakthrough.[12] The key feature thereof is that heteroaryl electrophiles without EWGs can serve as substrates, while metal nucleophiles are still needed in most cases (Scheme 1b).[12,13] The expanded scope of the heteroaryl electrophile is due presumably to an alternate mechanism involving a single transition state that does not require the disruption of aromaticity by way of the Meisenheimer intermediate, thereby lowering the activation energy of the process.



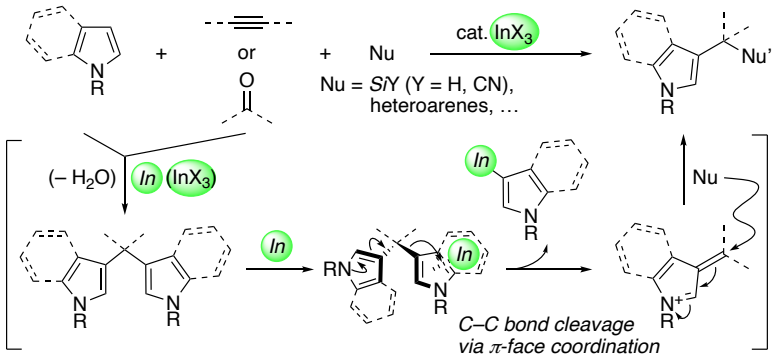
M = Li, Na, K, MgX, …; LG = leaving group; Z = NR, O, S, N=CH, …;
EWG = electron-withdrawing group (CF_3, NO_2, CN, CO_2R, …).

Scheme 1. Conventional and concerted S_NAr reactions

Our research group has been engaged in developing new Lewis-acid-catalyzed reactions, of which indium Lewis acids serve as the genesis of our study.[14,15] In 2000, we reported for the first time that indium salts are suited for activating the C≡C bond of alkynes;[16] the inspiration of our indium chemistry stems from the unique carbophilic nature of allylindium reagents, which can survive under aqueous conditions without undergoing hydrolysis and thus cleavage of the C–In bond, and can successfully add to carbonyl compounds.[17] Since our initial report, we have been continuing the use of

indium salts as π-Lewis acid catalysts for the activation of C≡C and C=C bonds,[18] and the resulting indium-activated carbon electrophiles have been mainly utilized for the S_EAr ($_E$ = electrophilic) reaction using (hetero)aryl nucleophiles.[14f,19] Even a C–C bond, albeit requiring the assistance of a directly connecting heteroaryl ring, can be cleaved by indium salts.[19b,e,f,g,h,20] A series of these studies are based on our research project: "*Activation of Hydrocarbon Functional Groups Classified into C≡C, C=C, C–C, and C–H*[21] *mainly by Indium Lewis Acids*".[22]

The C–C bond cleavage, described above, is observed during the indium-catalyzed three-component alkylation of pyrroles or indoles with alkynes or carbonyl compounds and nucleophiles (Nu) (Scheme 2). We considered at the time that the coordination of the heteroaryl ring to the indium salt (InX_3 = *In*) would be crucial to trigger the C–C bond cleavage. Furthermore, it was anticipated that the coordination should occur on the π-face rather than the heteroatom of the heteroaryl ring, due to the carbophilicity of *In*. We therefore envisioned that utilizing this coordination mode could enable the direct activation of the heteroaryl ring itself. Some findings obtained by investigations performed based on the working hypothesis are discussed and summarized in the ensuing sections.

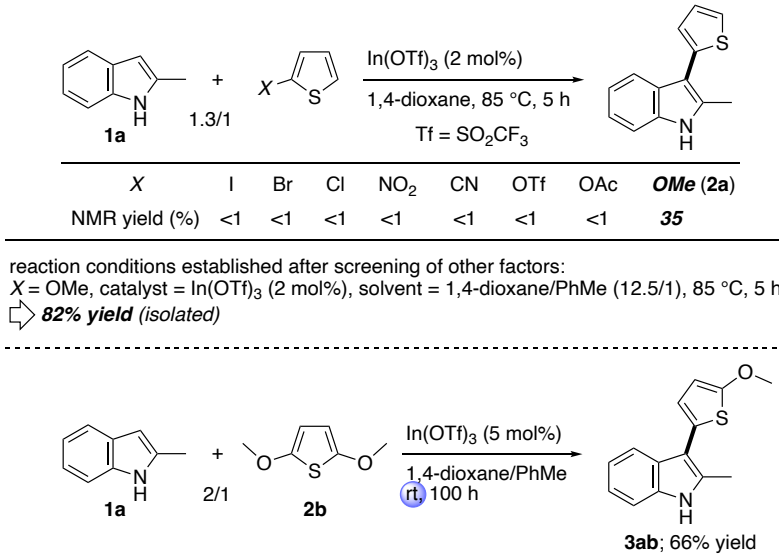


Scheme 2. C–C Bond cleavage triggered by the π-face coordination of the heteroaryl ring to the indium salt

Heteroaryl–Heteroaryl Bond-Forming Reaction

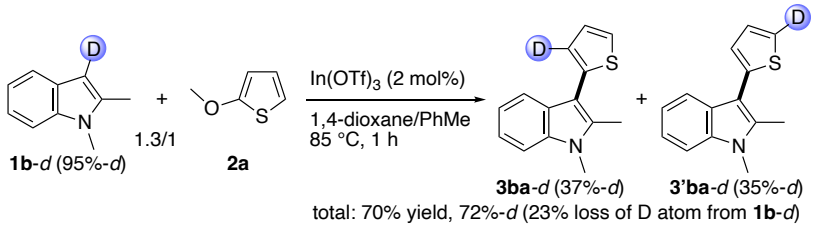
The first achievement is the S_NAr-based heteroaryl–heteroaryl bond-forming reaction[23] presented in the original article.[24] The topics that have not been discussed in the original article and that are crucial for this Discussion

Addendum are addressed here. Interestingly, only the electron-donating OMe group serves as a leaving group (Scheme 3; Ac = acetyl), in marked contrast to the typical S_NAr reaction where EWGs like Cl and NO_2 act as leaving groups. With the more electron-rich 2,5-dimethoxythiophene (**2b**), the reaction occurs even at room temperature (rt).



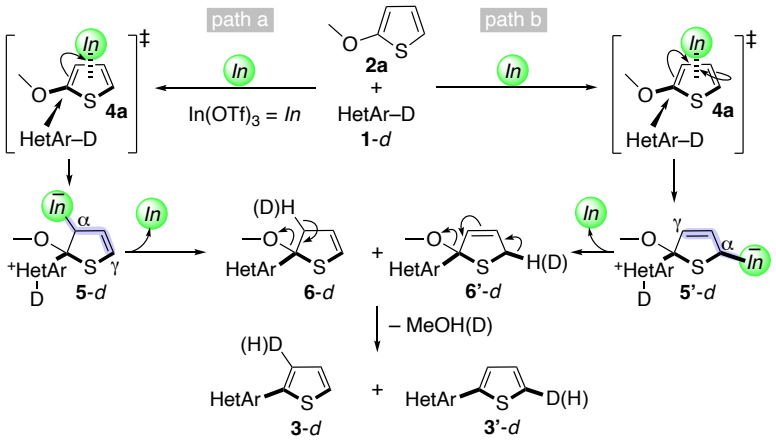
Scheme 3. Effect of leaving groups

Compounds **2** are electrophiles that react with electron-rich **1a**. However, **2** is clearly more favorable with higher π-electron density. The behavior of **2** might at first seem unusual but provides a useful insight into a reaction mechanism. The result of Scheme 4, giving **3ba**-*d* and **3'ba**-*d* from deuterated 1,2-dimethylindole (**1b**-*d*), is also crucial for mechanistic considerations.



Scheme 4. Indium-catalyzed S_NAr reaction of 2-methoxythiophene with 1,2-dimethylindole-*d*

Proposed reaction mechanisms that take the above observations into account are shown in Scheme 5 by the reaction of HetAr–D **1**-*d* with **2a**. First up is the π-face coordination of **2a** to *In* to give complex **4a**, in which *In* serves as a transient EWG to make **2a** electrophilic enough and thus to induce the nucleophilic attack of **1**-*d* via path a and/or b, giving allylindium-type intermediates **5**-*d* and/or **5′**-*d*, respectively. Subsequent D^+ transfer to their α and/or γ sites to give **6**-*d* and **6′**-*d*[25] followed by the aromatizing elimination of MeOH(D) yields **3**-*d* and **3′**-*d*. This reaction mechanism nicely explains the results of Schemes 3 and 4. Thus, the role of the MeO group is to enhance the π-electron density of the thiophene ring and facilitate the complexation of **2a** with electrophilic *In*. The 23% loss of the D atom observed should be attributed to the final step that can release both MeOH and MeOD. Moreover, the formation of **3**-*d* and **3′**-*d* due to the proposed deuteration of the C–*In* bond supports the probability of π-face coordination mode **4a** in which the carbon atoms of **2a** directly interact with *In*.

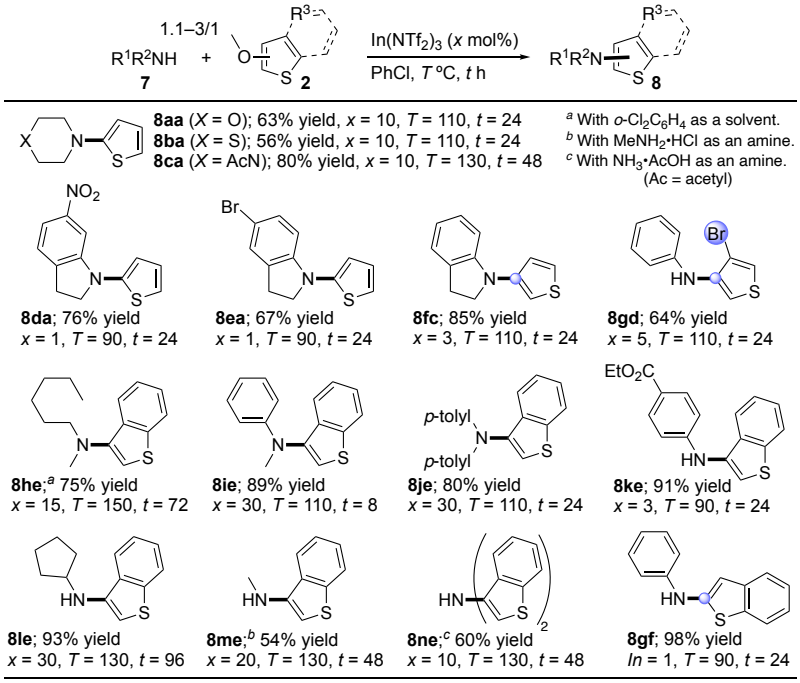


Scheme 5. Proposed reaction mechanisms

Worthy of note is that neither heteroaryl-metal nucleophiles nor EWGs-substituted heteroaryl electrophiles are necessary for this strategy. Moreover, the S_NAr reaction between two electron-rich heteroarenes is unique.[26] To the best of our knowledge, no catalytic S_NAr reaction involving heteroarene–metal π-complexs[27] has been presented other than reports based on our strategy (*vide infra*).[26] Next, we envisioned that electron-rich compounds other than **1** could be suitable for the indium-catalyzed S_NAr reaction.

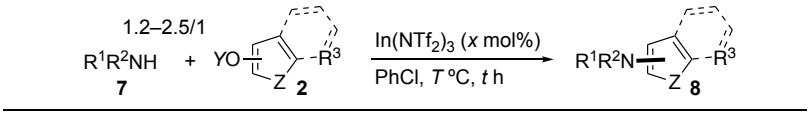
The electron-rich compound that we next focused on is an amine, thereby allowing the synthesis of a broad range of heteroarylamines.[28] Representative results obtained when using MeO–(benzo)thiophenes **2** are presented in Table 1. $In(NTf_2)_3$ is more effective than $In(OTf)_3$ for these reactions. As nucleophiles **7**, primary and secondary alkyl/aryl amines with cyclic/acyclic structures can be used. With 3-bromo-4-methoxythiophene (**2d**), the MeO-selective amination uniquely occurs, thus leaving the Br group intact in product **8gd**. If low-boiling amines are desired as nucleophiles, their salts, **7m** and **7n**, are good choices (**8me** and **8ne**). This reaction features high functional group compatibility: besides functional groups listed in Table 1, C(sp^2)–I, –CF_3, –CN, –OH, C(sp^3)–OH, pyridyl, thiazolyl, benzyl, and C=C are all tolerated.

Table 1. Indium-catalyzed S_NAr amination of MeO–(benzo)thiophenes



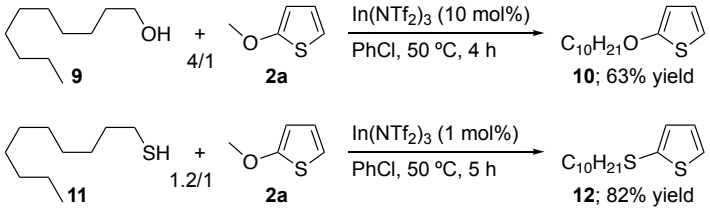
Heteroaryl electrophiles **2** besides MeO–(benzo)thiophenes are also capable of participating in the reaction (Table 2).

Table 2. Indium-catalyzed S_NAr amination with (benzo)furyl-, pyrrolyl-, and indolyl-based electrophiles



8ig; 65% yield	**8fh**; 97% yield	**8ai**; 60% yield	**8fj**; 69% yield
Y = Me, *x* = 2	*Y* = Me, *x* = 1	*Y* = Me, *x* = 10	*Y* = Ac, *x* = 5
T = 110, *t* = 2	*T* = 50, *t* = 24	*T* = 90, *t* = 46	*T* = 100, *t* = 4

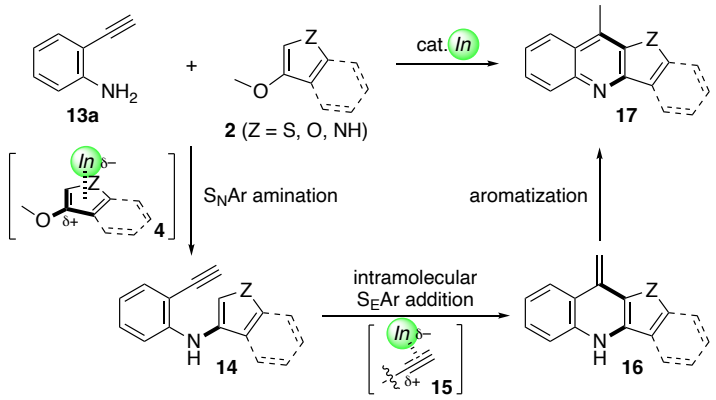
Furthermore, alcohols and thiols can be used instead of amines in this strategy,[29] and Scheme 6 displays representative examples.



Scheme 6. Indium-catalyzed S_NAr alkoxylation and thiolation

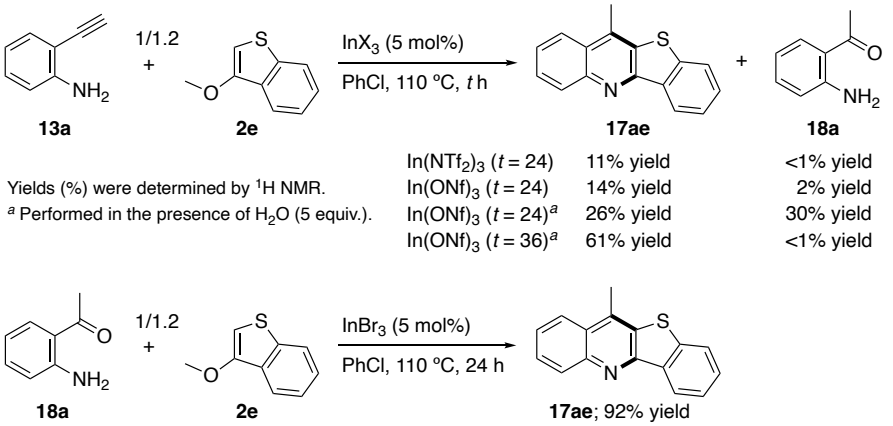
Nitrogen–Heteroaryl Bond-Forming Reaction Followed by Carbon–Heteroaryl Bond-Forming Annulation

We expected that combining two of our indium-catalyzed reactions, one of which is the S_NAr amination[28] and the other is the addition of heteroarenes to a C≡C bond,[19] could provide expedient access to heteroaryl[*b*]quinolines (HA[*b*]Qs).[30] A working hypothesis is illustrated in Scheme 7. The initial step would be the S_NAr amination of **2** by **13a** via π-coordination **4** to afford **14**. The C≡C bond of **14** would then be activated as in **15** to induce the intramolecular S_EAr addition of the heteroaryl ring, thereby providing **16**. Aromatization of **16** would result in the generation of HA[*b*]Qs **17**.



Scheme 7. A working hypothesis for constructing HA[*b*]Qs

To verify the working hypothesis, the annulation of *o*-ethynylaniline (**13a**) with 3-methoxybenzothiophene (**2e**) shown in Scheme 8 was tested.

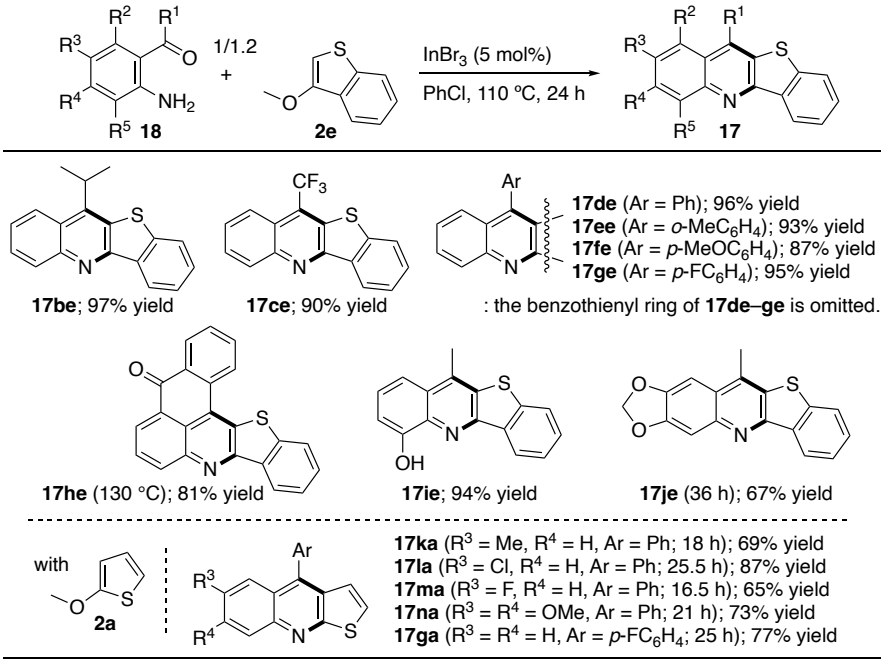


Scheme 8. Indium-catalyzed annulation of *o*-ethynylaniline or *o*-acetylaniline with 3-methoxybenzothiophene

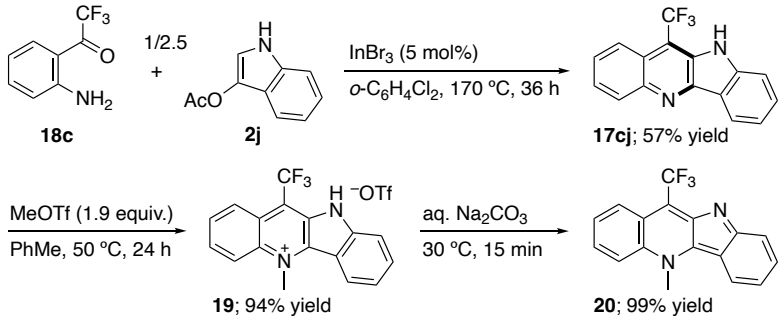
The treatment of **13a** and **2e** with 5 mol% of $In(NTf_2)_3$ under the heating conditions delivered the desired benzothieno[3,2-*b*]quinoline **17ae**, albeit in a low yield of 11%. Switching the catalyst to $In(ONf)_3$ (Nf = $SO_2C_4F_9$) gave not only **17ae** but also a small amount of *o*-acetylaniline (**18a**). The carbonyl group in **18a** was assumed to be formed by indium-catalyzed hydration of the C≡C bond with H_2O present in the reaction mixture. Hence, it was proposed that **17ae** could be formed via the S_NAr amination of **2e** with **18a** followed by

intramolecular nucleophilic addition of the benzothienyl ring to the carbonyl group and dehydration. Based on this proposal, the reaction of **13a** with **2e** was carried out with added H_2O, and as anticipated, the yields of both **17ae** and **18a** were raised. Prolonging the reaction time from 24 h to 36 h further improved the yield of **17ae** to 61% with the complete consumption of **18a**. Due to these results, we conducted the direct annulation of **18a** with **2e** and obtained **17ae** in 92% yield by using catalyst $InBr_3$, as also shown in Scheme 8. These results show that InX_3 activates the benzothienyl ring of **2e** and the carbonyl group of **18a**. The ability for both the π- and σ-electron-welcoming characteristics of InX_3 presents diverse opportunities for reactions.[18b] We have utilized this reactivity[19c,d,i,j,20,31] and further demonstrate indium's utility as a two-way activator. Representative results mainly focusing on the scope of **18** are thus collected in Table 3. For example, 2-propyl (**18b**), CF_3 (**18c**), and a series of aryl (**18d–h**) groups are available as R^1. The carbonyl group between two aryl rings (**18h**), the OH group (**18i**), and the acetal moiety (**18j**) remained untouched. Various thieno[2,3-*b*]quinolines **17ka–ga** can be also obtained from **2a** instead of **2e**.[32]

Table 3. Indium-catalyzed synthesis of HA[*b*]Qs



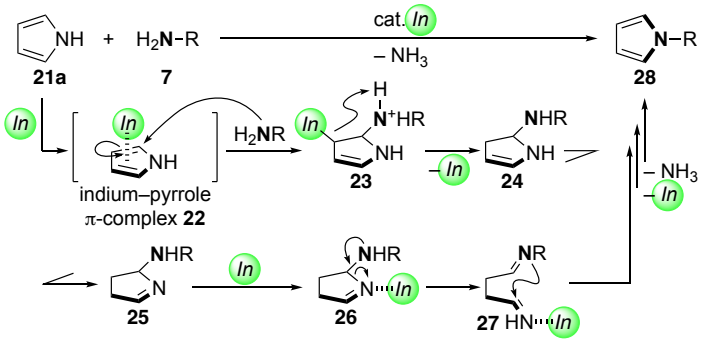
This method followed by a two-step transformation enables to synthesize cryptolepine derivatives, which represent a significant structural motif with anti-malarial and -cancer activities.[33] Thus, for instance, the indium-catalyzed annulation of **18c** with **2j** can be used to construct **17cj**, which, when followed by the methylation and treatment with aq. Na_2CO_3, delivers **20** (Scheme 9).



Scheme 9. Application to synthesis of a cryptolepine derivative

Formal N-Arylation and N-Alkylation of Pyrroles

The chemistry of the indium–heteroarene π-complex can be further applied to a distinct type of reaction: indium-catalyzed formal N-arylation and N-alkylation of pyrroles.[34] This transformation involves a unique nitrogen–nitrogen exchange strategy, or in other words, a pyrrole-ring opening–closing strategy. A working hypothesis that was developed before embarking on this study is depicted in Scheme 10.

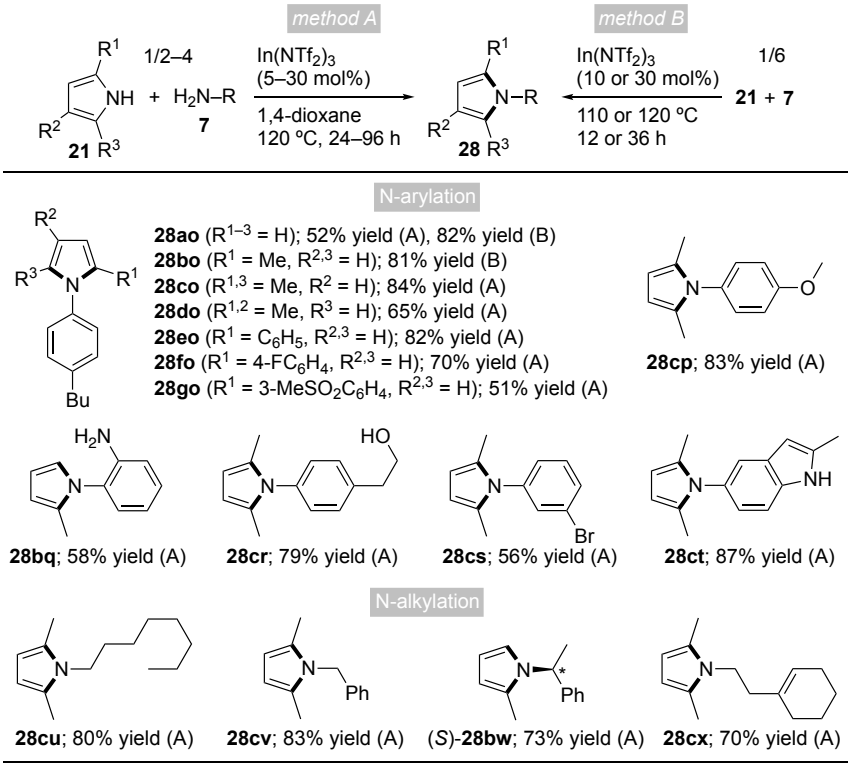


Scheme 10. A working hypothesis for formal N-arylation and N-alkylation of pyrroles

Upon the treatment of pyrrole (**21a**) and amine **7** with an indium catalyst (*In*), we expected the sequence of reaction steps illustrated in Scheme 10. Thus, coordination of **21a** to *In* would make **21a** electrophilic and promote reaction with **7**, giving the enamine intermediate **24** via **23**. Isomerization of **24** to imine **25** and coordination of its nitrogen atom to *In* would generate **26**, which could participate in ring opening and closing to produce **28** that incorporates the nitrogen atom of **7**. This sequence can be regarded as a variation on the Paal–Knorr pyrrole synthesis.[35] The bond formation when preparing *N*-aryl- and *N*-alkylpyrroles from pyrroles is usually made directly on the nitrogen atom. Accordingly, this indium-catalyzed process is totally distinct from the general approach and thus unique.[36]

The N-arylation and N-alkylation of pyrroles are carried out by two methods: method A with solvent 1,4-dioxane and method B with no solvent. Representative results are summarized in Table 4.

Table 4. Indium-catalyzed formal N-arylation and N-alkylation of pyrroles



The synthesis of **28ao–go** indicates the scope of pyrroles **21** that can be formed in the reaction, and the other products found in Table 4 demonstrate the scope of amines **7**. When 1,2-phenylenediamine (**7q**) is used, only one amino group reacted with 2-methylpyrrole (**21b**) to yield **28bq**. With 5-amino-2-methylindole (**7t**), the N-arylation chemoselectively occurred on the pyrrole ring, and the indolyl N–H thus remained unmodified, producing **28ct** in a high yield. No racemization was observed in the reaction of (*S*)-1-phenylethylamine (**7w**), suggesting that no pyrrolyl-N–C bond-forming step is involved in this reaction.

Although the results of mechanistic studies are not provided herein, it was demonstrated that the mechanistic proposal of Scheme 10 is plausible.[34]

Closing Remarks

This Discussion Addendum started with a brief history of the indium π-Lewis acid that is crucial in promoting our original chemistry and influencing a subsequent series of studies utilizing the indium–heteroarene π-complex (Figure 1). Since the first discovery of the heteroaryl–heteroaryl bond-forming reaction in which the π-complex between *In* and the MeO-substituted heteroarene participates, we have developed a number of new reactions: the nitrogen–, oxygen–, and sulfur–heteroaryl bond-forming reactions as well as the annulation reaction through the nitrogen–heteroaryl bond formation followed by the intramolecular carbon–heteroaryl bond formation. These reactions are unique because of occurring catalytically on electron-rich heteroaryl rings and should thus be classified as a distinct type of S_NAr reaction from the conventional and concerted ones.[37] Moreover, the π-complex has been demonstrated to be applicable to the formal N-arylation and N-alkylation of pyrroles.

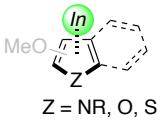


Figure 1. Indium–heteroarene π-complex

We are continuing to dedicate our efforts to the chemistry of the indium–heteroarene π-complex, with the anticipation of presenting our new findings in upcoming articles.

References

1. Department of Applied Chemistry, School of Science and Technology, Meiji University, Higashimita, Tama-ku, Kawasaki 214-8571, Japan. e-mail: tsuchimo@meiji.ac.jp
   Financial support by Meiji University is gratefully acknowledged.
2. For a selected review, see: Smolyar, I. V.; Yudin, A. K.; Nenajdenko, V. G. *Chem. Rev*. **2019,** *119*, 10032–10240.
3. For a selected review, see: St. Jean, D. J., Jr.; Fotsch, C. *J. Med. Chem*. **2012**, *55*, 6002–6020.
4. For example, see: Gonçalves, P. V. B.; de Lima Moreira, F.; de Lima Benzi, J. R.; Cavalli, R. C.; Duarte, G.; Lanchote, V. L. *J. Clin. Pharmacol.* **2020**, *60*, 1527–1529.
5. For example, see: Erkens, G. B.; Majsnerowska, M.; ter Beek, J.; Slotboom, D. J. *Biochemistry* **2012**, *51*, 4390–4396.
6. For selected reports, see: (a) Chang, F.; Dutta, S.; Becnel, J. J.; Estep, A. S.; Mascal, M. *J. Agric. Food Chem*. **2014**, *62*, 476–480. (b) Jeschke, P.; Lösel, P.; Hellwege, E.; Dietz, M.; Herrmann, S.; Gutbrod, O. *J. Agric. Food Chem.* **2022**, *70*, 11097–11108.
7. For a selected review, see: Ren, H.; Yang, P.; Winnik, F. M. *Polym. Chem*. **2020**, *11*, 5955–5961.
8. For example, see: Yeh, M.-C.; Su, Y.-L.; Tzeng, M.-C.; Ong, C. W.; Kajitani, T.; Enozawa, H.; Takata, M.; Koizumi, Y.; Saeki, A.; Seki, S.; Fukushima, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 1031–1034.
9. For a review, see: Oaki, Y.; Sato, K. *Nanoscale Adv*. **2022**, *4*, 2773–2781.
10. For selected reviews, see: (a) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 548–561. (b) Correa, A.; Cornella, J.; Martin, R. *Angew. Chem. Int. Ed*. **2013**, *52*, 1878–1880. (c) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal*. **2014**, *356*, 17–117. (d) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev*. **2016**, *116*, 12564–12649. (e) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem. Int. Ed*. **2017**, *56*, 16136–16179. (f) Ribaucourt, A.; Cossy, J. *ACS Catal*. **2020**, *10*, 10127–10148. (g) Wright, J. S.; Scott, P. J. H.; Steel, P. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 2796–2821. (h) Cook, X. A. F.; de Gombert, A.; McKnight, J.; Pantaine, L. R. E.; Willis, M. C. *Angew. Chem. Int. Ed*. **2021**, *60*, 11068–11091. (i) Xu, M.-Y.; Xiao, B. *Chem. Commu*n. **2021**, *57*, 11764–11775. (j) Hore, S.; Singh, R. P. *Org. Biomol. Chem.* **2022**, *20*, 498–537.
11. For a book, see: Terrier, F. *Modern Nucleophilic Aromatic Substitution*;

Wiley-VCH: Weinheim, Germany, 2013.
12. For a review, see: Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew. Chem. Int. Ed*. **2019**, *58*, 16368–16388.
13. For selected recent articles, see: (a) Ong, D. Y.; Tejo, C.; Xu, K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed*. **2017**, *56*, 1840–1844. (b) Luo, H.; Li, Y.; Zhang, Y.; Lu, Q.; An, Q.; Xu, M.; Li, S.; Li, J.; Li, B. *J. Org. Chem*. **2022**, *87*, 2590–2600.
14. Unlike rather rare indium, we have also disclosed that Lewis acids of earth-abundant zinc uniquely act as catalysts for dehydrogenative coupling, see: (a) Tsuchimoto, T.; Fujii, M.; Iketani, Y.; Sekine, M. *Adv. Synth. Catal*. **2012**, *354*, 2959–2964. (b) Tsuchimoto, T.; Iketani, Y.; Sekine, M. *Chem. Eur. J*. **2012**, *18*, 9500–9504. (c) Tsuchimoto, T.; Utsugi, H.; Sugiura, T.; Horio, S. *Adv. Synth. Catal*. **2015**, *357*, 77–82. (d) Tani, T.; Sawatsugawa, Y.; Sano, Y.; Hirataka, Y.; Takahashi, N.; Hashimoto, S.; Sugiura, T.; Tsuchimoto, T. *Adv. Synth. Catal*. **2019**, *361*, 1815–1834. (e) Kai, Y.; Oku, S.; Tani, T.; Sakurai, K.; Tsuchimoto, T. *Adv. Synth. Catal*. **2019**, *361*, 4314–4323. (f) Tani, T.; Sohma, Y.; Tsuchimoto, T. *Adv. Synth. Catal*. **2020**, *362*, 4098– 4108.
15. Considering the growing demand for sustainability, lately, our concern has gradually extended to organo-Lewis acid catalysis without using a metal catalyst. For a recent achievement, see: Andoh, H.; Nakamura, K.; Nakazawa, Y.; Ikeda-Fukazawa, T.; Okabayashi, S.; Tsuchimoto, T. *Adv. Synth. Catal*. DOI: 10.1002/adsc.202300423.
16. Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun*. **2000**, 1573–1574.
17. Li, C. J.; Chan, T. H. *Tetrahedron Lett*. **1991**, *32*, 7017–7020.
18. Other research groups have presented reviews on this concept, thus exhibiting that indium salts as π-Lewis acids have been attracting much attention, see: (a) Pathipati, S. R.; van der Werf, A.; Selander, N. *Synthesis* **2017**, *49*, 4931–4941. (b) Sestelo, J. P.; Sarandeses, L. A.; Martínez, M. M.; Alonso-Marañón, L. *Org. Biomol. Chem*. **2018**, *16*, 5733–5747.
19. (a) Tsuchimoto, T.; Kamiyama, S.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Chem. Commun*. **2003**, 852–853. (b) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun*. **2003**, 2454–2455. (c) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed*. **2005**, *44*, 1336–1340. (d) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc*. **2008**, *130*, 15823–15835. (e) Tsuchimoto, T.; Ainoya,

T.; Aoki, K.; Wagatsuma, T.; Shirakawa, E. *Eur. J. Org. Chem*. **2009**, 2437–2440. (f) Tsuchimoto, T.; Wagatsuma, T.; Aoki, K.; Shimotori, J. *Org. Lett*. **2009**, *11*, 2129–2132. (g) Tsuchimoto, T. *Chem. Eur. J.* **2011**, *17*, 4064–4075 (as a Concept article). (h) Tsuchimoto, T.; Kanbara, M. *Org. Lett*. **2011**, *13*, 912–915. (i) Nagase, Y.; Shirai, H.; Kaneko, M.; Shirakawa, E.; Tsuchimoto, T. *Org. Biomol. Chem*. **2013**, *11*, 1456–1459. (j) Nagase, Y.; Miyamura, T.; Inoue, K.; Tsuchimoto, T. *Chem. Lett*. **2013**, *42*, 1170–1172.

20. (a) Tsuchimoto, T.; Igarashi, M.; Aoki, K. *Chem. Eur. J*. **2010**, *16*, 8975–8979. (b) Nomiyama, S.; Hondo, T.; Tsuchimoto, T. *Adv. Synth. Catal*. **2016**, *358*, 1136–1149. (c) Nomiyama, S.; Ogura, T.; Ishida, H.; Aoki, K.; Tsuchimoto, T. *J. Org. Chem*. **2017**, *82*, 5178–5197.
21. Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed*. **2004**, *43*, 4231–4233.
22. For accounts, see: (a) Tsuchimoto, T. *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 752–765. (b) Tsuchimoto, T. *J. Synth. Org. Chem., Jpn.* **2011**, *69*, 889–903.
23. Tsuchimoto, T.; Iwabuchi, M.; Nagase, Y.; Oki, K.; Takahashi, H. *Angew. Chem. Int. Ed*. **2011**, *50*, 1375–1379.
24. Nagase, Y.; Tsuchimoto, T. *Org. Synth.* **2014**, *91*, 273–282.
25. Allylindum species are deuterated with less electrophilic D_2O, see: Haddad, T. D.; Hirayama, L. C.; Singaram, B. *J. Org. Chem*. **2010**, *75*, 642–649.
26. Whereas using *N*-tosyl(EWG)-substituted 3-metoxyindoles formed in situ, selective synthesis of 3,3′-biindolyls by the same strategy has been lately reported, see: Hirao, S.; Yamashiro, T.; Kohira, K.; Mishima, N.; Abe, T. *Chem. Commun*. **2020**, *56*, 5139–5142.
27. For a recent review including catalytic S_NAr reaction by η^6-arene–met (met = Ru, Rh) complexes, see: (a) Takemoto, S.; Matsuzaka, H. *Tetrahedron Lett.* **2018**, *59*, 697–703. For reports that are not included in the review, see: (b) Houghton, R. P.; Voyle, M.; Price, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 925–931. (c) Goryunov, L. I.; Litvak, V. V.; Shteingarts, V. D. *Zh. Org. Khim*. **1987**, *28*, 1230–1237. (d) Goryunov, L. I.; Steingarts, V. D. *Russ. J. Org. Chem*. **1998**, *34*, 1640–1645. (e) Goryunov, L. I.; Nikitin, Y. M.; Steingarts, V. D. *Russ. J. Org. Chem*. **1998**, *34*, 1646–1654. (f) Goryunov, L. I.; Steingarts, V. D. *Russ. J. Org. Chem*. **1999**, *35*, 246–251. (g) Kang, Q.-K.; Lin, Y.; Li, Y.; Shi, H. *J. Am. Chem. Soc*. **2020**, *142*, 3706–3711. (h) Kang, Q.-K.; Lin, Y.; Li, Y.; Xu, L.; Li, K.; Shi, H. *Angew. Chem. Int. Ed*. **2021**, *60*, 20391–20399. (i) Su, J.; Chen, K.; Kang, Q.-K.; Shi, H. *Angew. Chem. Int. Ed*. **2023**, *62*, e202302908.

28. Yonekura, K.; Yoshimura, Y.; Akehi, M.; Tsuchimoto, T. *Adv. Synth. Catal*. **2018**, *360*, 1159–1181.
29. Although heteroaryl electrophiles are limited to 3-MeO– and 3,4-$(MeO)_2$–thiophenes, their TfOH-catalyzed anilination and alkoxylation have been reported, see: Mishra, A. K.; Verma, A.; Biswas, S. *J. Org. Chem.* **2017**, *82*, 3403–3410.
30. Yonekura, K.; Shinoda, M.; Yonekura, Y.; Tsuchimoto, T. *Molecules* **2018**, *23*, 838 (as an invited contribution).
31. Tsuchimoto, T.; Johshita, T.; Sambai, K.; Saegusa, N.; Hayashi, T.; Tani, T.; Osano, M. *Org. Chem. Front.* **2021**, *8*, 2882–2892.
32. Sakata, T.; Tsuchimoto, T., unpublished results. Reaction conditions for the synthesis of **17ka–ga** and thus their yields have not been adjusted yet.
33. For selected reviews, see: (a) Ansah, C.; Mensah, K. B. *Ghana Med. J.* **2013**, *47*, 137–147. (b) Tudu, C. K.; Bandyopadhyay, A.; Kumar, M.; Radha; Das, T.; Nandy, S.; Ghorai, M.; Gopalakrishnan, A. V.; Proćków, J.; Dey, A. *Naunyn Schmiedebergs Arch. Pharmacol.* **2023**, *396*, 229–238.
34. Yonekura, K.; Oki, K.; Tsuchimoto, T. *Adv. Synth. Catal*. **2016**, *358*, 2895–2902.
35. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem*. **1991**, *56*, 6924–6931.
36. Only one study probably by a similar type of reaction had been reported before presenting our study. However, its scope is limited to the reactions of 2,5-dimethylpyrrole with benzyl- and arylamines, see: Zamora, R.; Hidalgo, F. J. *Synlett* **2006**, 1428–1430.
37. To the best of our knowledge, the S_NAr reactions of heteroarenes directly activated by (Lewis) acids have been reported but limited to those of electron-deficient pyridines, see: (a) Campos, J. M.; Núñez, M. C.; Sánchez, R. M.; Gómez-Vidal, J. A.; Rodríguez-González, A.; Báñez, M.; Gallo, M. A.; Lacal, J. C.; Espinosa, A. *Bioorg. Med. Chem*. **2002**, *10*, 2215–2231. (b) Abou-Shehada, S.; Teasdale, M. C.; Bull, S. D.; Wade, C. E.; Williams, J. M. J. *ChemSusChem* **2015**, *8*, 1083–1087. (c) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, *362*, 799–804. (d) Boyle, B. T.; Hilton, M. C.; McNally, A. *J. Am. Chem. Soc.* **2019**, *141*, 15441–15449.

Teruhisa Tsuchimoto was born in 1970 in Tajimi, Gifu, Japan. He received his Ph.D. in 1997 from Tokyo Institute of Technology under the direction of Prof. Tamejiro Hiyama. After working with Prof. Peter Wipf at the University of Pittsburgh, he returned to Japan in 1998 to join Prof. Shirakawa's group at JAIST as an Assistant Professor. In 2006, he moved to Meiji University as an Associate Professor and was appointed as a Full Professor in 2016. His research interests mainly focus on the development of new acid catalysis featuring heteroarenes and unsaturated hydrocarbons, as well as on the transformation of organoboron compounds.