

Iridium-Catalyzed Isomerization/Cycloisomerization/Aromatization of *N*-Allyl-*N*-sulfonyl-*o*-(λ^1 -silylethynyl)aniline Derivatives to Give Substituted Indole Derivatives

Jiawei Qiu, Makoto Sako, Tomoyuki Tanaka, Tsuyoshi Matsuzaki, Tsunayoshi Takehara, Takeyuki Suzuki, Shohei Ohno, Kenichi Murai, and Mitsuhiro Arisawa*

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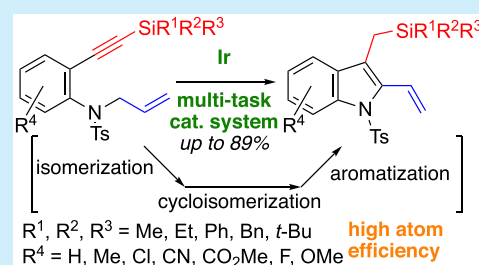
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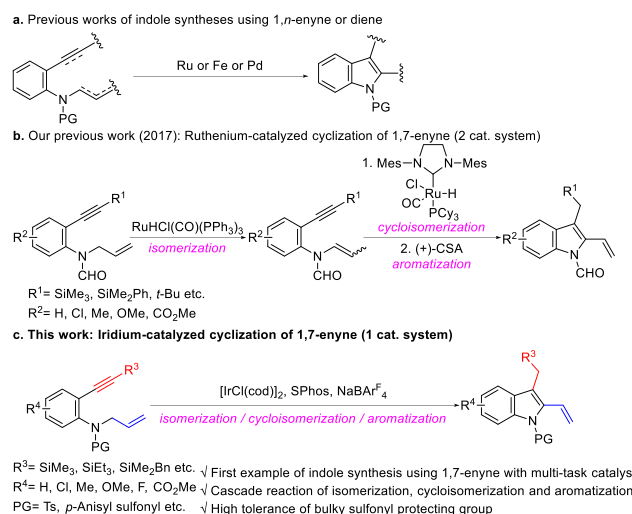
Supporting Information

ABSTRACT: We have developed a one-iridium-catalyst system that transforms *N*-allyl-*N*-sulfonyl-2-(silylalkynyl)aniline derivatives, which are 1,7-enynes in which both multiple bonds have a heteroatom, to the corresponding substituted indole derivatives via isomerization/cycloisomerization/aromatization. This strategy provides an atom-economical and straightforward synthetic approach to a series of valuable indoles having vinyl and silylmethyl groups at the 2- and 3-positions.



The substituted indole structure is a widespread heterocyclic skeleton in natural products, optoelectronic materials,^{1,2} and pharmaceutical agents (anticancer activity, antimicrobial activity, anti-HIV activity etc.).³ Classic methodologies for indole synthesis have been investigated very well.⁴ However, these methods are not only restricted to some harsh conditions in which strong acids (or bases) and heating are used for transformations but also applied to a narrow scope of substrates. On the other hand, recent transition-metal-catalyzed indole synthesis methods have been attractive because of their high efficiency, mild conditions, and wide substrate scope. Among them, transition-metal-catalyzed cyclization of enynes or dienes is one promising reaction because of the easy transformation from an uncomplicated acyclic structure to a multisubstituted cyclic structure.⁵ Especially, researchers envisioned that transition-metal-catalyzed cyclization of enynes or dienes could be utilized as a useful indole synthesis approach. Indeed, transition metal (Ru, Fe, Pd)-catalyzed cyclization of 1,7-dienes and 1,6-enynes, which are reactions between an enamide and a multiple bond without a heteroatom, have been reported to yield the corresponding indole derivatives, and further chemical transformations of them are rather difficult (Scheme 1a).^{6,7} However, transition-metal-catalyzed cyclization between an enamide and a multiple bond with a heteroatom, which gives indole derivatives with a heteroatom substituent, have not been developed except in our report of Ru-catalyzed cyclization of 1,7-enynes involving an aromatic enamide and a silylalkyne (Scheme 1b).⁸ Although it is an atom-economical and efficient method to yield 2-vinyl-3-(silylmethyl)indoles, which have chemical transferability, two kinds of Ru catalysts and one more extra camphorsulfonic acid for aromatization are

Scheme 1. Previous Works on Transition-Metal-Catalyzed Indole Syntheses Using 1,*n*-Enynes or -Dienes and This Work



necessary. Also, this method cannot tolerate a more stable and synthetically useful bulkier sulfonyl protective group on nitrogen very well.

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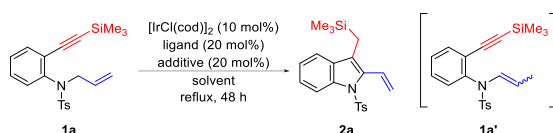
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Here we report the first example of indole synthesis using 1,7-enynes in which both multiple bonds have a heteroatom with just a single multitask catalyst, $[\text{IrCl}(\text{cod})_2]$.⁹ The catalytic system could promote isomerization/cycloisomerization/aromatization of *N*-allyl-*N*-sulfonyl-*o*-(λ^1 -silylethynyl)-aniline derivatives to give the corresponding 2-vinyl 3-silylmethylindole derivatives (Scheme 1c) and tolerates a bulkier protecting group (a sulfonyl group) on nitrogen.

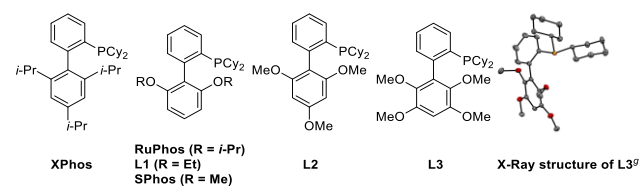
At first, we subjected starting material **1a** having trimethylsilylalkyne and allylsulfonylamide groups to several sets of reaction conditions using a variety of organometallic catalysts, ligands, and additives (Table 1). As a result, we

Table 1. Optimization of the Reaction Conditions



entry	ligand	additive	solvent (M)	yield (%) ^c
1	PCy ₃	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	22
2	P(<i>t</i> -Bu) ₃	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	0
3	XPhos	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	trace
4	RuPhos	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	72
5	L1	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	75
6	SPhos	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	78
7	L2	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	73
8	L3	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	trace
9	SPhos	AgOTf	(CH ₂ Cl) ₂ (0.1)	trace
10	SPhos	AgSbF ₆	(CH ₂ Cl) ₂ (0.1)	18
11 ^a	SPhos	NaBAR ^F ₄	(CH ₂ Cl) ₂ (0.1)	56
12 ^{b,c}	SPhos	NaBAR ^F ₄	C ₆ H ₅ CF ₃ (0.1)	88
13 ^{b,c}	SPhos	NaBAR ^F ₄	C ₆ H ₅ CF ₃ (0.05)	92 (89 ^f)
14 ^{b,c}	SPhos	NaBAR ^F ₄	C ₆ H ₅ CF ₃ (0.02)	80
15	SPhos	—	C ₆ H ₅ CF ₃ (0.1)	0
16 ^d	SPhos	—	C ₆ H ₅ CF ₃ (0.1)	trace

^a5 mol % $[\text{IrCl}(\text{cod})_2]$, 10 mol % SPhos, and 10 mol % NaBAR^F₄ (Ar^F = 3,5-bis(trifluoromethyl)phenyl). ^b4 mol % $[\text{IrCl}(\text{cod})_2]$, 8 mol % SPhos, and 8 mol % NaBAR^F₄. ^c12 h. ^d8 mol % $[\text{Ir}(\text{cod})_2]$ BAR^F₄, 8 mol % SPhos. ^eNMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. ^fThe isolated yield is shown in parentheses. ^gORTEP drawing of L3 at the 50% probability level (CCDC 2075648).

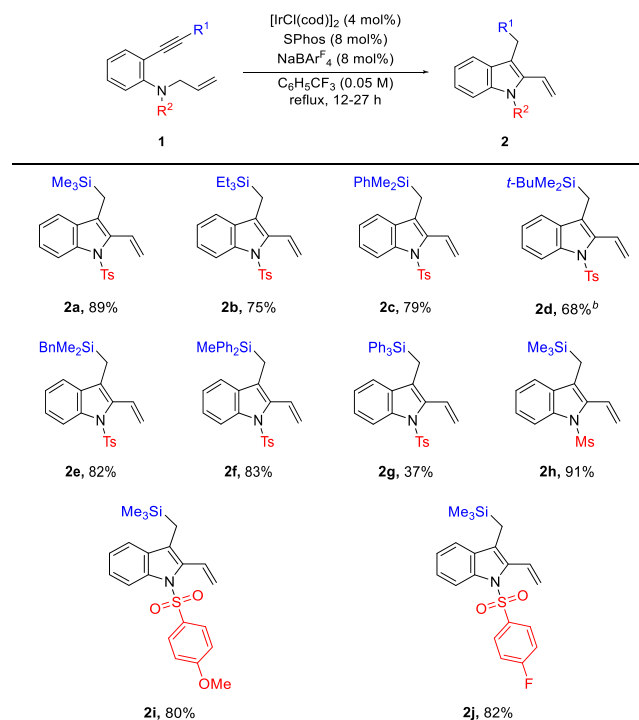


obtained the desired 2,3-disubstituted indole **2a** in 22% yield when we refluxed a dichloroethane solution of **1a**, $[\text{IrCl}(\text{cod})_2]$ (10 mol %), PCy₃ (20 mol %), and NaBAR^F₄ (20 mol %) (entry 1). Then, in order to improve the yield of **2a**, we screened a P(*t*-Bu)₃ ligand, which has a slightly bigger cone angle than PCy₃, along with other phosphine ligands that are sterically bulky (XPhos) or electron-rich (RuPhos, L1, and SPhos).¹⁰ The product **2a** was obtained in yields of 0%, trace, 72%, 75%, and 78%, respectively (entries 2–6). Furthermore, we designed L2 and L3, which have different steric configurations and more electron-donating groups on the biphenyl core, and tried to perform the same reaction as above.

However, the yield of **2a** was not improved (73% and trace; entries 7 and 8). On the basis of the ligand screening results, we fixed SPhos as the best ligand and continued the optimization, focusing on metal salt additives to activate the iridium catalyst species and promote the reaction. We chose silver salts (AgOTf and AgSbF₆) and added them to the above reaction mixtures.¹¹ As a result, the yield of **2a** sharply decreased to trace and 18%, respectively (entries 9 and 10). Next, the effects of the catalyst loading, solvent, and concentration were examined. At first, we decreased the catalyst loading of iridium to 5 mol % (entry 11). As a result, only a 56% yield of **2a** and a 28% yield of isomerized intermediate **1a'** were obtained, as confirmed by ¹H NMR spectroscopy. To perform the reaction at a higher temperature, α,α,α -trifluorotoluene was chosen because of its higher boiling point and same electrostatic constant as (CH₂Cl)₂. The yield of **2a** was improved to 88% (4 mol % $[\text{IrCl}(\text{cod})_2]$), even within 12 h (entry 12). We then examined the concentration of the reaction mixture (0.05 and 0.02 M) in this Ir-catalyzed cascade reaction, and **2a** was obtained in 92% and 80% yield, respectively (entries 13 and 14). In a control experiment in the absence of NaBAR^F₄, the reaction did not proceed at all (entry 15), and when $[\text{Ir}(\text{cod})_2]\text{BAR}^{\text{F}}_4$ was used in place of $[\text{IrCl}(\text{cod})_2]$ and NaBAR^F₄, only a trace yield of **2a** was obtained (entry 16). In addition, we confirmed that other metal catalyst systems ($[\text{Rh}(\text{cod})_2]\text{BF}_4$ and $\text{Ni}(\text{cod})_2$), which showed excellent cycloisomerization activities in the past,^{12,13} did not work well.

We next examined the effect of substituents on the alkyne or nitrogen (Scheme 2). Silylalkyne derivatives **1b**, **1c**, **1e**, and **1f** (with SiEt₃, SiMe₂Ph, SiMe₂Bn, and SiPh₂Me groups, respectively) gave the corresponding indoles in yields of 75% (**2b**), 79% (**2c**), 82% (**2e**), and 83% (**2f**). In contrast,

Scheme 2. Effect of Substituents on the Alkyne or Nitrogen^a

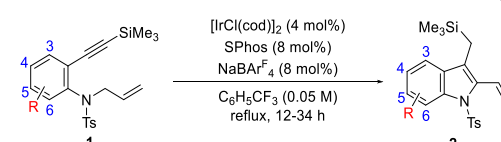


^aIsolated yields are shown. ^b6 mol % $[\text{IrCl}(\text{cod})_2]$, 12 mol % SPhos, 12 mol % NaBAR^F₄.

derivatives **1d** and **1g** having bulky silyl groups were converted to **2d** and **2g** in 68% and 37% yield, respectively. Carbon-substituted derivatives ($R^1 = \text{Me}$ (**S1a**), Ph (**S1b**)) were not transformed to the corresponding indoles, which implied the importance of the electron-donating silyl substituent on the alkyne in this Ir-catalyzed cyclization. To know the effect of the substituent on nitrogen, we also performed the same reaction using substrates **1h–j** with other sulfonyl protecting groups and obtained the corresponding indole derivatives in yields of 91% (**2h**), 80% (**2i**), and 82% (**2j**). In addition, we prepared formyl and benzoyl derivatives ($R^2 = \text{CHO}$ (**S1c**), Bz (**S1d**)) and subjected them to the optimized conditions, but only trace amounts of the corresponding products were obtained.

The effect of substituents on the benzene ring was investigated by subjecting substrates **1k–u** to the optimized reaction conditions (Table 2). The indole products **2k–m**, **2o**,

Table 2. Effect of Substituents on the Benzene Ring



entry	1	R	2	yield (%) ^a
1	1a	H	2a	89
2	1k	3-Cl	2k	59
3	1l	4-Cl	2l	39
4	1m	5-Cl	2m	82
5	1n	6-Cl	2n	0
6	1o	4-Me	2o	85
7	1p	5-Me	2p	79
8	1q	4,6-Me ₂	2q	0
9	1r	4-CN	2r	trace
10	1s	4-OMe	2s	80
11	1t	5-CO ₂ Me	2t	73
12	1u	5-F	2u	78

^aIsolated yields.

2p, and **2s–u** were obtained in high or moderate yields (entries 2, 3, 4, 6, 7, 10, 11, and 12). However, substrates **1n** and **1q**, having a substituent at the 6-position, did not adapt themselves to the reaction conditions, probably because of their steric hindrance toward the iridacycle intermediate (entries 5 and 8). Substrates **1r** and **1s** were converted to the corresponding cyclized indole products **2r** and **2s** in trace and 80% yield, respectively (entries 9 and 10). These results suggest that an electron-withdrawing group at the 4-position disturbed the key coordination of the silylalkyne to iridium metal.

We also examined the effect of the alkene substituent using **1v** and **1w** (Figure 1) and found that the cyclization of **1v** or **1w** to give the corresponding indoles did not proceed at all under the optimal reaction conditions, which means that a methyl substituent on the alkene impedes the reaction.

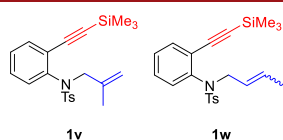
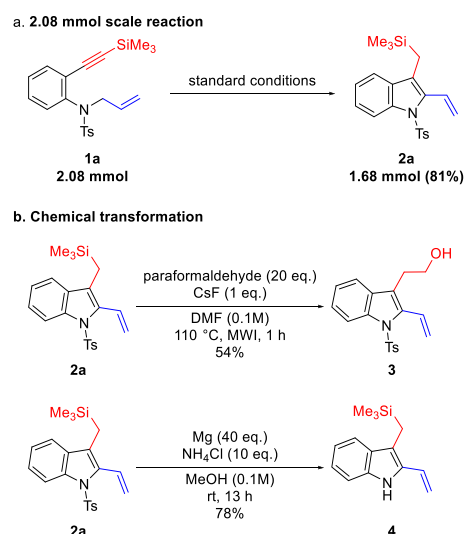


Figure 1. Structures of **1v** and **1w**.

The reaction was also tested on a 2.08 mmol scale (Scheme 3a). When we performed the reaction under standard

Scheme 3. Reaction on a 2.08 mmol Scale and Chemical Transformations



conditions using 2.08 mmol of **1a**, the corresponding product **2a** was obtained in 81% yield. Moreover, the obtained compound **2a** was applied to chemical transformations (Scheme 3b). When **2a** was treated with paraformaldehyde and CsF, the one-carbon extension product **3** was formed. Another fluoride reagent (e.g., *n*-Bu₄NF) decomposed the substrate and did not give the desired compound. In addition, we tried deprotection of **2a** under Mg/MeOH conditions and obtained product **4** in 78% yield.

To study the reaction mechanism, we used electrospray ionization mass spectrometry (ESI-MS) to obtain some information about the iridium species in this reaction. The reaction with a stoichiometric amount of iridium species (1 equiv) was performed within 5 min and then was analyzed. Consequently, we detected a peak for C₄₇H₅₈IrNO₄PSSi at *m/z* 984.3222 (see Figures S2 and S4), which possibly corresponds to intermediate C with further elimination of two hydrogens. Its exact mass (984.3222) is 2 fewer than the simulation mass (986.3374), probably because of the trend to keep a stable state (C' or C'') by elimination during ESI-MS analysis (Figure 2). Also, we found a peak for C₃₄H₄₇IrO₂P at *m/z* 711.2943 (see Figures S2 and S3), corresponding to the iridium complex [Ir]⁺ in Figure 2.

A plausible mechanism for the iridium-catalyzed cyclization is shown in Scheme 4. The cationic iridium complex reacts with the substrate to form the isomerized product **1a'**.¹⁴ Then the double bond and triple bond coordinate to the Ir species to form intermediate B. Iridacycle intermediate C is generated via

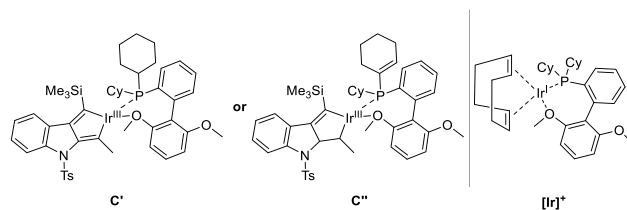
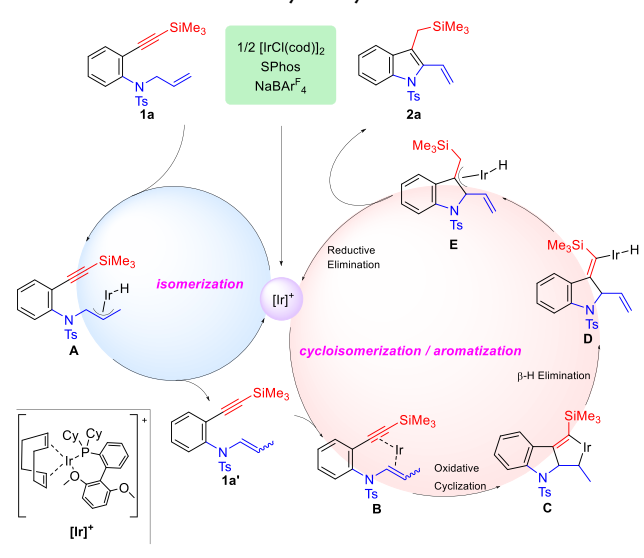


Figure 2. Structures of reaction intermediates predicted by ESI-MS.

Scheme 4. Plausible Catalytic Cycle



oxidative cyclization, and subsequent β -H elimination gives intermediate **D**. Finally, aromatization and reductive elimination proceed to give the corresponding 2,3-disubstituted indole **2a**.

In conclusion, we have found the first example of single-iridium-catalyst-catalyzed isomerization/cycloisomerization/aromatization of *N*-allyl-*N*-sulfonyl-*o*-(λ^1 -silylethynyl)aniline derivatives, in which both multiple bonds have a heteroatom, to give substituted indole derivatives. This methodology enabled the synthesis of a series of 2,3-disubstituted indoles having vinyl and silylmethyl groups at the 2- and 3-positions, respectively. In addition, some information about the iridium species in this reaction was obtained by ESI-MS.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01231>.

Experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2075648 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Mitsuhiro Arisawa – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan; orcid.org/0000-0002-7937-670X; Email: arisaw@phs.osaka-u.ac.jp

Authors

Jiawei Qiu – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

Makoto Sako – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan;

orcid.org/0000-0002-4268-7002

Tomoyuki Tanaka – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

Tsuyoshi Matsuzaki – Comprehensive Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan

Tsunayoshi Takehara – Comprehensive Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan; orcid.org/0000-0002-4113-7578

Takeyuki Suzuki – Comprehensive Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan; orcid.org/0000-0002-2137-0276

Shohei Ohno – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

Kenichi Murai – Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan;

orcid.org/0000-0002-1689-6492

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01231>

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996. (b) Bandari, C.; Scull, E. M.; Bavineni, T.; Nimmo, S. L.; Gardner, E. D.; Bensen, R. C.; Burgett, A. W.; Singh, S. FgaPT2, a biocatalytic tool for alkyl-diversification of indole natural products. *MedChemComm* **2019**, *10*, 1465–1475.
- (2) For a recent review, see: Urieta-Mora, J.; García-Benito, I.; Molina-Ontoria, A.; Martín, N. Hole transporting materials for perovskite solar cells: a chemical approach. *Chem. Soc. Rev.* **2018**, *47*, 8541–8571.
- (3) (a) Jordan, M. A.; Wilson, L. Microtubules as a target for anticancer drugs. *Nat. Rev. Cancer* **2004**, *4*, 253–265. (b) Smart, B. P.; Oslund, R. C.; Walsh, L. A.; Gelb, M. H. The first potent inhibitor of mammalian group X secreted phospholipase A2: elucidation of sites for enhanced binding. *J. Med. Chem.* **2006**, *49*, 2858–2860. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. *Chem. Rev.* **2010**, *110*, 4489–4497.
- (4) Taber, D. F.; Tirunahari, P. K. Indole synthesis: a review and proposed classification. *Tetrahedron* **2011**, *67*, 7195–7210.
- (5) Yamamoto, Y. Transition-metal-catalyzed cycloisomerizations of α,ω -dienes. *Chem. Rev.* **2012**, *112*, 4736–4769.
- (6) (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. Selective isomerization of a terminal olefin catalyzed by a ruthenium complex: the synthesis of indoles through ring-closing metathesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734. (b) Xia, X.; He, W.; Zhang, G.;

Wang, D. Iron-catalyzed reductive cyclization reaction of 1,6-enynes for the synthesis of 3-acylbenzofurans and thiophenes. *Org. Chem. Front.* **2019**, *6*, 342–346. (c) Zhang, P.; Wang, C.; Cui, M.; Du, M.; Li, W.; Jia, Z.; Zhao, Q. Synthesis of difluoroalkylated benzofuran, benzothiophene, and indole derivatives via palladium-catalyzed cascade difluoroalkylation and arylation of 1,6-enynes. *Org. Lett.* **2020**, *22*, 1149–1154.

(7) Ohno, S.; Arisawa, M. Cyclizations of benzo-fused substrates involving two multiple bonds, including heteroatom-substituted unsaturated bonds. *J. Org. Chem.* **2020**, *85*, 6831–6843.

(8) Takamoto, K.; Ohno, S.; Hyogo, N.; Fujioka, H.; Arisawa, M. Ruthenium-catalyzed 1,6-aromatic enamide–silylalkyne cycloisomerization: approach to 2,3-disubstituted indoles. *J. Org. Chem.* **2017**, *82*, 8733–8742.

(9) Inprung, N.; James, M. J.; Taylor, R. J. K.; Unsworth, W. P. A Thiol-Mediated Three-Step Ring Expansion Cascade for the Conversion of Indoles into Functionalized Quinolines. *Org. Lett.* **2021**, *23*, 2063–2068.

(10) (a) Milne, J. E.; Buchwald, S. L. An extremely active catalyst for the Negishi cross-coupling reaction. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032. (b) Jover, J.; Cirera, J. Computational assessment on the Tolman cone angles for P-ligands. *Dalton Trans* **2019**, *48*, 15036–15048.

(11) (a) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2006**, *25*, 4643–4647. (b) Cheng, H.; Yang, D. Iridium-catalyzed asymmetric ring-opening of oxabenzonorbornadienes with phenols. *J. Org. Chem.* **2012**, *77*, 9756–9765. (c) Feng, Y.; Li, Y.; Yu, Y.; Wang, L.; Cui, X. Iridium-catalyzed direct sulfamidation of quinazolinones. *RSC Adv.* **2018**, *8*, 8450–8454.

(12) Okamoto, R.; Okazaki, E.; Noguchi, K.; Tanaka, K. Rhodium-catalyzed olefin isomerization/enantioselective intramolecular alderene reaction cascade. *Org. Lett.* **2011**, *13*, 4894–4897.

(13) Ohno, S.; Qiu, J.; Miyazaki, R.; Aoyama, H.; Murai, K.; Hasegawa, J.; Arisawa, M. Ni-catalyzed cycloisomerization between 3-phenoxy acrylic acid derivatives and alkynes via intramolecular cleavage and formation of the C–O bond to give 2,3-disubstituted benzofurans. *Org. Lett.* **2019**, *21*, 8400–8403.

(14) Biswas, S.; Huang, Z.; Chohly, Y.; Wang, D. Y.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S. Olefin Isomerization by Iridium Pincer Catalysts. Experimental Evidence for an η^3 -Allyl Pathway and an Unconventional Mechanism Predicted by DFT Calculations. *J. Am. Chem. Soc.* **2012**, *134*, 13276–13295.