Tandem Catalysis

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Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides

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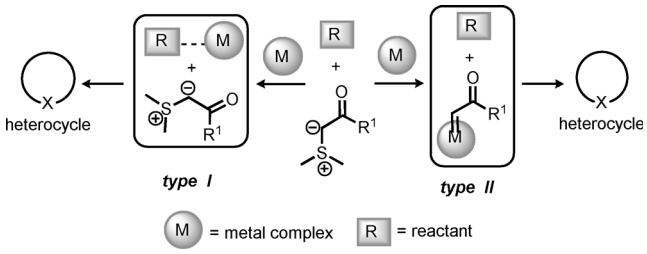
Abstract: *Metal carbenes can undergo a myriad of synthetic transformations. Sulfur ylides are potential safe precursors of metal carbenes. Herein, we report cascade reactions that involve carbenoids derived from sulfoxonium ylides for the efficient and regioselective synthesis of indoles and pyrroles. The tandem action of iridium and Brønsted acid catalysts enables rapid assembly of the heterocycles from unmodified anilines or readily accessible enamines under microwave irradiation. The key mechanistic steps are the catalytic transformation of the sulfoxonium ylide into an iridium–carbene complex, followed by N–H or C–H functionalization of an aniline or enamine, respectively, and a final acid-catalyzed cyclization. The present method was successfully applied to the synthesis of the densely functionalized pyrrole subunit of atorvastatin.*

Sulfur (sulfonium and sulfoxonium) ylides are versatile synthetic precursors for a diverse range of chemical transformations.[1] For example, they are widely used as methylene synthons in the formation of small rings, such as epoxides, aziridines, and cyclopropanes, from electrophilic substrates, such as aldehydes, imines, and enones. The cycloaddition of sulfur ylides to a variety of electrophilic metal-associated (Pd, Fe, Cu, Rh, or Au) intermediates has been explored for the synthesis of heterocycles (Scheme 1; type I).[2]

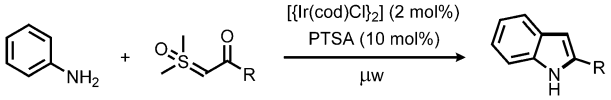


Scheme 1. Sulfur-ylide-based heterocycle synthesis via a metal-associated intermediate (type I) or a metal–carbene complex (type II).

Sulfur ylides can also function as precursors to transition-metal–carbene complexes.[3,4] However, this metal–carbene chemistry is currently limited to the insertion of X–H (X = N, O, S) bonds and cyclopropanation reactions.[5] The development of reactions involving sulfur-ylide-derived metal–carbene complexes for a wider range of applications is highly desirable,[6] as these intermediates can offer some advantages over diazocarbenes. Large-scale synthesis with diazo compounds can be challenging owing to safety issues resulting from rapid exothermic reactions.[7] Sulfoxonium ylides are safer to synthesize and give crystalline, bench-stable compounds that can serve as practical substitutes for diazo compounds in metal–carbene reactions.[5e] However, unlike diazocarbenes, sulfoxonium-ylide-based carbenes have not yet been explored in cascade transformations.[8] We became interested in studying the potential of metal-catalyzed reactions of sulfur ylides (Scheme 1; type II) in a cascade approach to the synthesis of heteroaromatic compounds, such as indoles and pyrroles.

The indole moiety is found in many natural products, pharmaceuticals, and agrochemicals,[9] and numerous methods for the synthesis of the indole scaffold have been developed. Most reported methods for the synthesis of indoles require modified anilines, such as N-substituted aniline derivatives or *ortho*-functionalized anilines;[10] in one approach, *N*-(*ortho*-chloromethyl)aryl amides were used with sulfur ylides as methylene synthons.[11] In 1881, Möhlau reported the synthesis of indoles from unmodified anilines and *ortho*-halo ketones.[12] This reaction has received little attention, perhaps owing to its poor regioselectivity, low yields, and harsh reaction conditions, and the frequent need for a two-step process.[13] An efficient procedure for the conversion of simple anilines into substituted indoles in one step is lacking. Herein, we report a highly regioselective one-step iridium-catalyzed indole synthesis from unmodified anilines and sulfur ylides (Scheme 2).

Initially, we investigated the microwave irradiation of aniline (2 equiv) with ylide **2a** (1 equiv) in the presence of [{Ir(cod)Cl}$_2$] (10 mol%) in dichloroethane (DCE) at 80 °C for 45 min. Interestingly, the reaction afforded a small amount of the unprecedented 2-substituted indole **4a** (5% yield) along with the expected N-alkylated aniline **3a** (73% yield;



Scheme 2. Sulfur-ylide-derived metal carbenes in indole synthesis. cod = 1,5-cyclooctadiene, μw = microwave irradiation.

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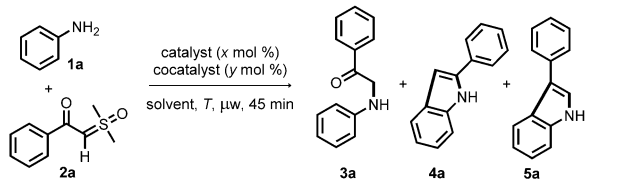
Table 1, entry 1). Other transition-metal (Ru, Rh) catalysts afforded the N-alkylated product **3a** in low yield (Table 1, entries 2–4). An increased amount of indole **4a** (12%) was observed when the iridium-catalyzed reaction was performed at 140 °C in toluene (Table 1, entry 5). No reaction was observed in the absence of the iridium catalyst (Table 1, entry 6), which is a notable indication of the stability of ylide **2a** under microwave heating conditions (140 °C). For comparison, α-diazoketones undergo either decomposition or Wolf rearrangement at high temperatures.[14] The use of triflic acid (TfOH, 20 mol%), polyphosphoric acid (PPA, 20 mol%), or *p*-toluenesulfonic acid (PTSA, 30 mol%) along with the iridium catalyst led to a mixture of 2- and 3-substituted indoles (Table 1, entries 7–9). The formation of 3-substituted indole **5a** can be explained by a Friedel–Crafts-type reaction of the N-alkylated aniline **3a** at increased acid concentrations.[15] Gratifyingly, a decrease in the concentration of PTSA from 30 to 10 mol% led to the formation of 2-substituted indole **4a** selectively in over 80% yield (Table 1, entry 11). The corresponding reaction at 110 °C without microwave irradiation for 16 h afforded **4a** in comparable yield (see the Supporting Information), while no cyclization was observed without heating, leading to **3a** in 86% yield (Table 1, entry 12). Partial formation of **5a** was also observed when the amount of aniline was decreased from 2 equivalents to 1 equivalent (Table 1, entry 13).

Having optimized the reaction conditions (Table 1, entry 11), we then examined the scope of this reaction (Scheme 3). A series of sulfoxonium ylide substrates **2** with electron-donating, electron-withdrawing, and halo substituents on the benzene ring underwent smooth cyclization to give indole products **4** in moderate to good yields. When a nitro group was introduced on the benzene ring of ylide **2**, the corresponding indole **4l** was formed in poor yield under the standard reaction conditions. This problem was addressed by carrying out the reaction in a 3:1 mixture of toluene and *N*,*N*-dimethylformamide (DMF); in this way, the yield of indole **4l** was improved to 54%.[16] The aliphatic ylide (R′ = Me) furnished indole **4q** in low yield (12%).

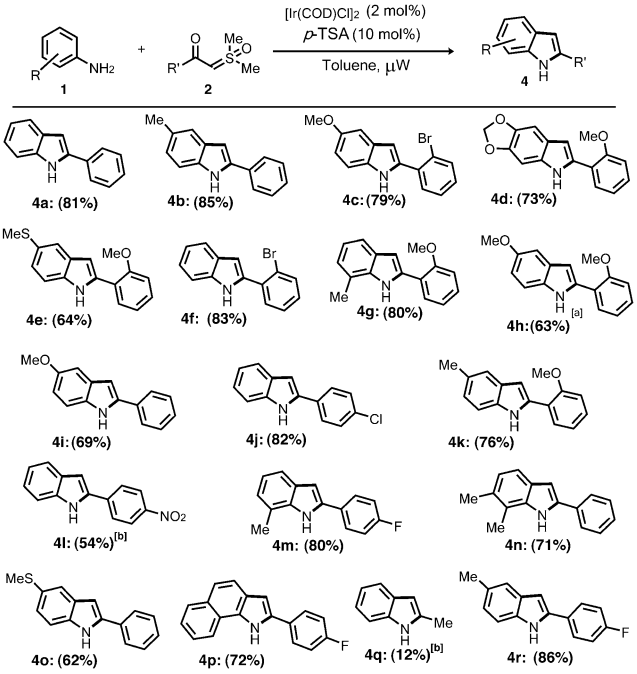
When examining the scope of the reaction with respect to the aniline derivative, we found that electron-donating substituents, such as methyl, methoxy, and methylthio groups, on the aniline ring were tolerated well (Scheme 3). The polycyclic indole **4p** was obtained from 1-aminonaphthalene in 72% yield. In the case of nonsymmetric 3,4-(methylenedioxy)aniline **1d**, the reaction was highly regioselective, and only isomer **4d** was obtained, in 73% yield. When halogen atoms and electron-withdrawing groups were introduced on the aniline ring, the reaction did not afford the indole products, but instead we observed the corresponding N-alkylated anilines **3**, thus showing that electron-poor aniline derivatives did not cyclize to the indoles.[17]

Table 1: Optimization of the reaction conditions.[a]



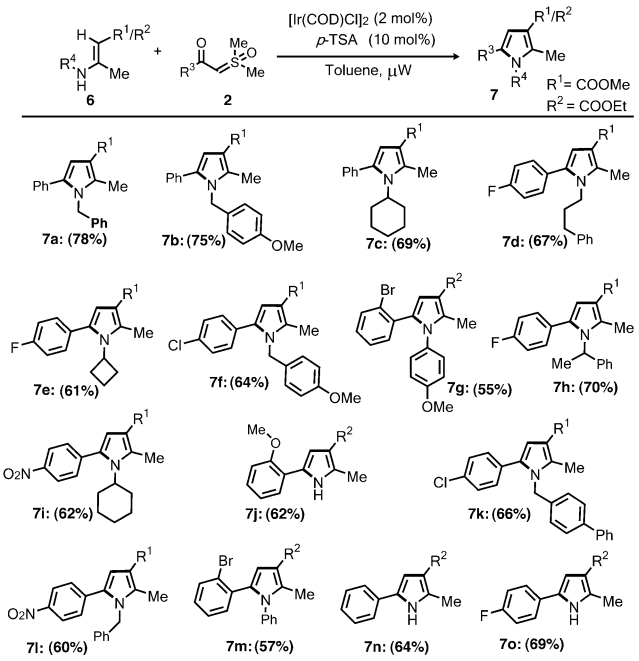
Entry	Catalyst (x mol%)	Cocatalyst (y mol%)	Solvent[b]	Yield [%][c] **3a/4a/5a**
1	[{Ir(cod)Cl}$_2$] (10)	–	DCE	73/5/–
2	[Rh$_2$(OAc)$_4$] (10)	–	DCE	12/–/–
3	[Cp*RuCl(cod)] (10)	–	DCE	10/–/–
4	[Rh(acac)cod] (10)	–	DCE	18/–/–
5	[{Ir(cod)Cl}$_2$] (10)	–	toluene	68/12/–
6	–	–	toluene	–/–/–
7	[{Ir(cod)Cl}$_2$] (2)	TfOH (20)	toluene	–/68/10
8	[{Ir(cod)Cl}$_2$] (5)	PPA (20)	toluene	–/30/27
9	[{Ir(cod)Cl}$_2$] (2)	PTSA (30)	toluene	–/55/10
10	[{Ir(cod)Cl}$_2$] (5)	LiClO$_4$ (20)	toluene	58/15/–
11	[{Ir(cod)Cl}$_2$] (2)	PTSA (10)	toluene	–/81/–
12[d]	[{Ir(cod)Cl}$_2$] (2)	PTSA (10)	toluene	86/–/–
13[e]	[{Ir(cod)Cl}$_2$] (2)	PTSA (10)	toluene	–/42/12
14	[{Ir(cod)Cl}$_2$] (10)	PTSA (10)	toluene	–/79/–
15	[{Ir(cod)Cl}$_2$] (2)	PTSA (10)	DCE	–/68/–
16	[Ir(cod)$_2$] BARF (2)	PTSA (10)	toluene	–/48/–
17	[{Ir(cod)Cl}$_2$] (2)	PTSA (5)	toluene	10/58/–

[a] Reactions were carried out with 2 mmol of **1a** and 1 mmol of **2a** in 3.0 mL of the solvent, unless otherwise specified. [b] Reactions in DCE were carried out at 80 °C, and reactions in toluene were carried out at 140 °C. [c] Yield of the isolated product. [d] The reaction was carried out at room temperature without microwave irradiation for 20 h. [e] The reaction was carried out with 1 mmol of **1a** and 1 mmol of **2a**.



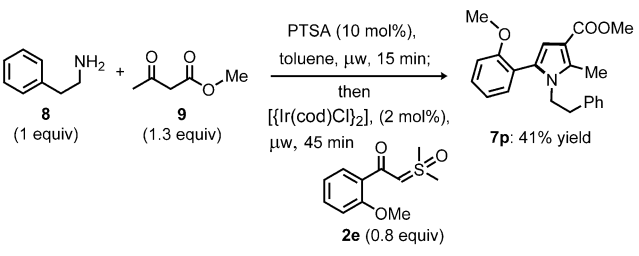
Scheme 3. Scope of the iridium-catalyzed synthesis of indoles. General reaction conditions: **1** (2 mmol), **2** (1 mmol), toluene (3.0 mL). Yields are for the isolated product. [a] The indole regioisomer **5h** was formed in 15% yield. [b] The reaction was carried out in toluene/DMF (3:1). [c] The N-alkylated product **3q** was formed in 40% yield.

Next, we envisioned that, in analogy with the indole synthesis, pyrroles[18] might be formed from the reaction of a sulfoxonium ylide with a β-enamino ester. The treatment of ylides **2** with β-enamino esters **6** in the presence of [{Ir(cod)Cl}$_2$] (2 mol%) and *p*-TSA (10 mol%) in toluene at 140 °C under microwave irradiation gave pyrroles **7** (Scheme 4). A series of electronically diverse ylides **2** underwent smooth cyclization with various β-enamino esters **6** (R^4 = benzylic, aliphatic or cyclic, aromatic) to provide the corresponding pyrrole derivatives in moderate to good yields (55–78%). Additionally, the one-pot three-component synthesis of a pyrrole was possible by the use of a sulfoxonium ylide and a β-enamino ester generated in situ from amine **8** and β-ketoester **9** (Scheme 5).[16]

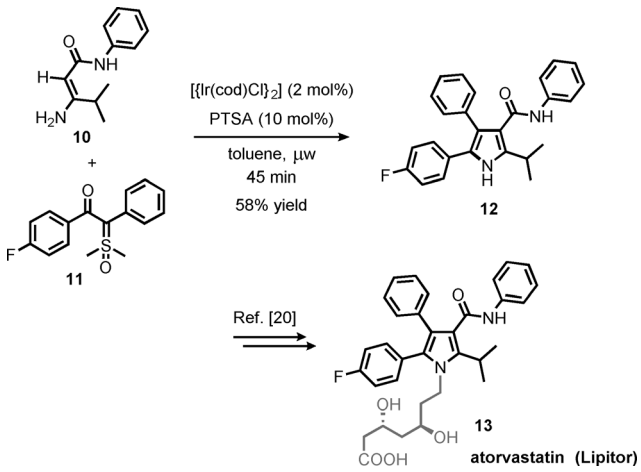


Scheme 4. Scope of the iridium-catalyzed synthesis of pyrroles. General reaction conditions: **6** (2 mmol), **2** (1 mmol), [{Ir(cod)Cl}$_2$] (2 mol%), PTSA (10 mol%), toluene (3.0 mL), 140 °C, microwave irradiation, 45 min. Yields are for the isolated product.

The applicability of our method was demonstrated by the synthesis of the pyrrole subunit of atorvastatin (Lipitor, **12**; Scheme 6), the world's largest-selling cholesterol-lowering drug in therapeutic use.[19] The cyclization of β-enamino amide **10** with sulfoxonium ylide **11** in the presence of [{Ir(cod)Cl}$_2$] (2 mol%) and *p*-TSA (10 mol%) gave the tetrasubstituted pyrrole **12**[20] in 58% yield.

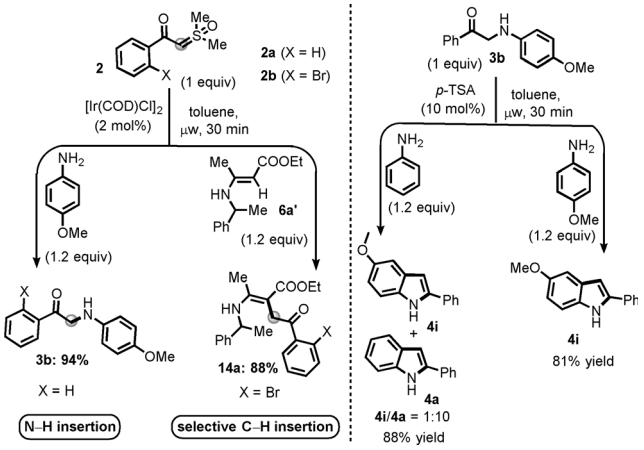


Scheme 5. One-pot reaction for pyrrole synthesis.



Scheme 6. Synthesis of the pyrrole subunit **12** of atorvastatin (**13**).

To gain insight into the reaction mechanisms, we carried out a series of control experiments. First, treatment of the ylide **2b** (X = Br) with iridium catalyst in the absence of an aniline or β-enamino ester resulted in dimerization of the ylide.[5b,16] Next, the reaction of ylide **2a** (X = H) and 4-methoxyaniline was evaluated in the absence of the Brønsted acid cocatalyst under microwave irradiation. Under these conditions, N–H insertion of the carbene occurred to afford **3b** (Scheme 7). Interestingly, the replacement of **1a′** with β-enamino ester **6a′** under the same reaction conditions resulted in selective C–H functionalization in the presence of a free N–H group to give **14a** in 88% yield. In previously reported reactions involving other metal carbenes, unselective N and C attack of acyclic β-enamino esters resulted in mixtures of pyrroles.[21] Iridium carbenoids generated from sulfoxonium ylides might be less reactive but more selective as compared to other metal carbenes.[5b]

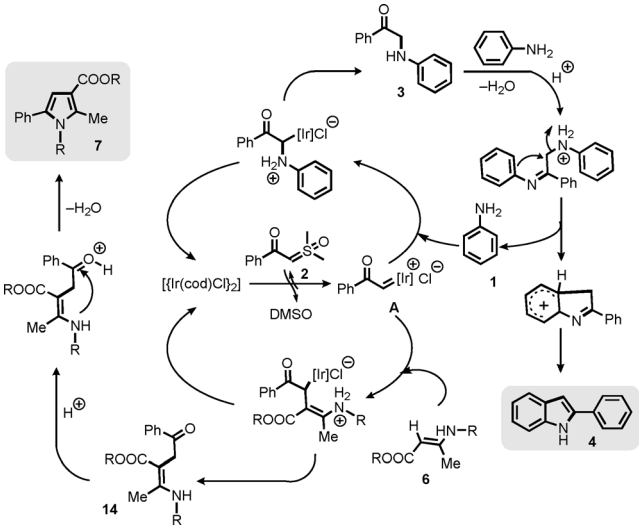


Scheme 7. Mechanistic investigations.

To evaluate the role of the acid, we treated **3b** (1 equiv) with aniline (1.2 equiv) and an acid catalyst and obtained

a mixture of 2-aryl indoles **4i** and **4a** in a 1:10 ratio, whereas the reaction of **3b** (1 equiv) with **1a′** (1.2 equiv) resulted in the formation of **4i** in 81% yield. This reaction resembles a Bischler–Möhlau indole synthesis, but the latter normally gives mixtures of regioisomers (**4** and **5**) owing to competition between imine formation and a Friedel–Crafts-type reaction[13a] and is performed with an excess amount of a base to trap the acid generated in situ. In the new method described herein, the regioselectivity can be controlled by a catalytic amount of an acid to give exclusively 2-substituted indoles (Table 1).

From these observations[16] (Scheme 7) and literature precedent,[5] we propose the following reaction mechanism (Scheme 8): Activation of the sulfoxonium ylide **2** by Ir^I

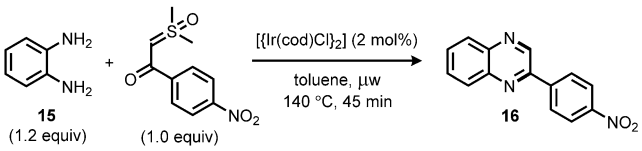


Scheme 8. Proposed mechanism for the synthesis of indoles and pyrroles from sulfoxonium ylides.

generates the iridium carbene complex **A**. This carbene is trapped by aniline to give **3**, which undergoes acid-catalyzed electrophilic cyclization to give indole **4**. Alternatively, metal carbene **A** can be trapped by a β-enamino ester **6** to give **14**, which cyclizes under acidic conditions to give a pyrrole **7**.

The reported method could also be extended to the synthesis of a quinoxaline scaffold **16** using *o*-phenylenediamine (**15**) and a sulfoxonium ylide (Scheme 9). Interestingly, for this transformation, the additional acid catalyst was not required.

In conclusion, we have demonstrated a novel synthetic strategy for the preparation of indoles (through a cascade involving carbene generation, N–H insertion, imine formation, substitution, and aromatization) and pyrroles (through C–H insertion of carbenes, followed by cyclization) from stable sulfoxonium ylides by the use of $[\{Ir(cod)Cl\}_2]$ and PTSA as catalysts. The new approach is operationally straightforward and enables the synthesis of a range of substituted pyrroles and indoles from readily accessible starting materials with commercially available catalysts.



Scheme 9. Iridium-catalyzed synthesis of quinoxaline **16**.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: heterocycles · indoles · metal carbenes · pyrroles · sulfur ylides

[1] a) A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341; b) V. K. Aggarwal, C. L. Winn, *Acc. Chem. Res.* **2004**, *37*, 611; c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301.

[2] a) T.-R. Li, F. Tan, L.-Q. Lu, Y. Wei, Y.-N. Wang, Y.-Y. Liu, Q.-Q. Yang, J.-R. Chen, D.-Q. Shi, W.-J. Xiao, *Nat. Commun.* **2014**, *5*, 5500; b) Q. Wang, X. Qi, L.-Q. Lu, T.-R. Li, Z.-G. Yuan, K. Zhang, B.-J. Li, Y. Lan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2016**, *55*, 2840; *Angew. Chem.* **2016**, *128*, 2890; c) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres, C. Bolm, *J. Am. Chem. Soc.* **2012**, *134*, 6924; d) S. Klimczyk, A. Misale, X. Huang, N. Maulide, *Angew. Chem. Int. Ed.* **2015**, *54*, 10365; *Angew. Chem.* **2015**, *127*, 10507; e) S. Kramer, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2012**, *51*, 4681; *Angew. Chem.* **2012**, *124*, 4759; f) V. K. Aggarwal, J. G. Ford, S. Fonquerna, H. Adams, R. V. H. Jones, R. Fieldhouse, *J. Am. Chem. Soc.* **1998**, *120*, 8328; g) X. Huang, S. Klimczyk, L. F. Veiros, N. Maulide, *Chem. Sci.* **2013**, *4*, 1105; h) V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Am. Chem. Soc.* **1996**, *118*, 7004; i) X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 8886; *Angew. Chem.* **2012**, *124*, 9016; j) J. Sabbatani, X. Huang, L. F. Veiros, N. Maulide, *Chem. Eur. J.* **2014**, *20*, 10636; k) S. Klimczyk, X. Huang, H. Kahlig, L. F. Veiros, N. Maulide, *J. Org. Chem.* **2015**, *80*, 5719.

[3] a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1964**, *86*, 1640; b) B. M. Trost, *J. Am. Chem. Soc.* **1966**, *88*, 1587.

[4] M. Gandelman, B. Rybtchinski, N. Ashkenazi, R. M. Gauvin, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 5372.

[5] a) J. E. Baldwin, R. M. Adlington, C. R. A. Godfrey, D. W. Gollins, J. G. Vaughan, *J. Chem. Soc. Chem. Commun.* **1993**, 1434; b) I. K. Mangion, I. K. Nwamba, M. Shevlin, M. A. Huffman, *Org. Lett.* **2009**, *11*, 3566; c) I. K. Mangion, M. Weisel, *Tetrahedron Lett.* **2010**, *51*, 5490; d) A. M. Phelps, V. S. Chan, J. G. Napolitano, S. W. Krabbe, J. M. Schomaker, S. Shekhar, *J. Org. Chem.* **2016**, *81*, 4158; e) A. C. B. Burtoloso, R. M. P. Dias, I. A. Leonarczyk, *Eur. J. Org. Chem.* **2013**, 5005.

[6] C. Molinaro, P. G. Bulger, E. E. Lee, B. Kosjek, S. Lau, D. Gauvreau, M. E. Howard, D. J. Wallace, P. D. O'Shea, *J. Org. Chem.* **2012**, *77*, 2299.

[7] a) J. A. Moore, D. E. Ree, *Org. Synth.* **1961**, *41*, 16; b) M. M. Bio, G. Javadi, Z. J. Song, *Synthesis* **2005**, 19; c) L. D. Proctor, A. J. Warr, *Org. Process Res. Dev.* **2002**, *6*, 884.
[8] M. Jia, S. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 9134; *Angew. Chem.* **2016**, *128*, 9280.
[9] a) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; c) S. Lal, T. J. Snape, *Curr. Med. Chem.* **2012**, *19*, 4828.
[10] a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195.
[11] Q.-Q. Yang, C. Xiao, L.-Q. Lu, J. An, F. Tan, B.-J. Li, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 9137; *Angew. Chem.* **2012**, *124*, 9271.
[12] R. Möhlau, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 171.
[13] a) Y. Vara, E. Aldaba, A. Arrieta, J. L. Pizarro, M. I. Arriortua, F. P. Cossio, *Org. Biomol. Chem.* **2008**, *6*, 1763; b) V. Sridharan, S. Perumal, C. Avendaño, J. C. Menéndez, *Synlett* **2006**, 0091.
[14] H. Meier, K.-P. Zeller, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32; *Angew. Chem.* **1975**, *87*, 52.
[15] a) K. Pchalek, A. W. Jones, M. M. T. Wekking, D. S. Black, *Tetrahedron* **2005**, *61*, 77; b) H. Galons, J.-F. Girardeau, C. C. Farnoux, M. Miocque, *J. Heterocycl. Chem.* **1981**, *18*, 561.
[16] For details, see the Supporting Information.
[17] L. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 12496; *Angew. Chem.* **2011**, *123*, 12704.
[18] a) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2003**, *42*, 3582; *Angew. Chem.* **2003**, *115*, 3706.
[19] A. P. Lea, D. McTavish, *Drugs* **1997**, *53*, 828.
[20] a) T. J. Donohoe, N. J. Race, J. F. Bower, C. K. A. Callens, *Org. Lett.* **2010**, *12*, 4094; b) P. Mathew, C. V. Asokan, *Tetrahedron* **2006**, *62*, 1708.
[21] M. N. Eberlin, C. Kascheres, *J. Org. Chem.* **1988**, *53*, 2084.

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Communications

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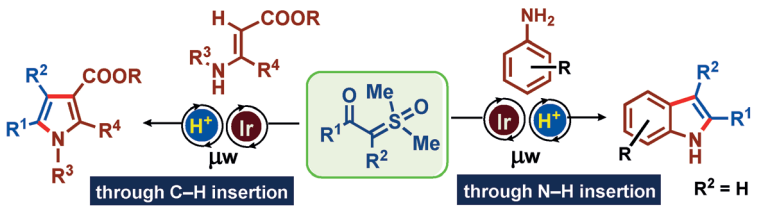
Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides



Take the shortcut: Substituted indoles and pyrroles, including the densely functionalized pyrrole subunit of atorvastatin, were assembled in one step from sulfoxonium ylides and unmodified anilines or readily accessible enamines through tandem catalysis by $[\{Ir(cod)Cl\}_2]$ and a Brønsted acid under microwave irradiation (see scheme). The transformation involves the formation of an iridium–carbene complex and an unprecedented C–H functionalization step.

