Indole Chemistry

DOI: 10.1002/anie.201107575

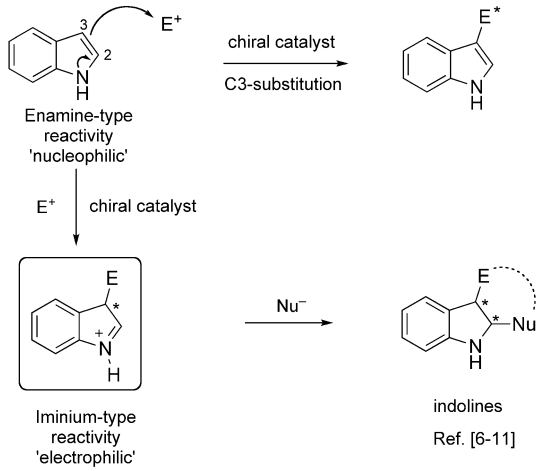
Exploiting the Electrophilic Properties of Indole Intermediates: New Options in Designing Asymmetric Reactions

*Charles C. J. Loh and Dieter Enders**

asymmetric catalysis · domino reactions · gold · indoles · organocatalysis

Indole has been one of the most intensively investigated aromatic heterocycles.[1] With the exponential growth of literature reports, especially in the two areas of organocatalysis and transition-metal catalysis, it might be challenging for organic chemists to adopt a holistic approach in designing reactions based on a substrate reactivity strategy, as compared to a functional-group activation approach. Moreover, while the nucleophilic Friedel–Crafts type reactivity of indoles has been extensively reviewed,[1] the electrophilic iminium type reactivity of the corresponding intermediates of indoles is rarely discussed (Scheme 1). Herein we critically examine this untapped potential of the indole heterocycle, restricting it mainly to enantioselective annulations of 1*H*-indoles and new frontier developments in this field.

In classical organic chemistry indole is classified as a π-excessive heterocycle which undergoes electrophilic substitutions, such as halogenations, Mannich and Michael reactions.[2] This nucleophilic property is attributed to the imbedded enamine in the indole framework which provides a nucleophilic character at the C3 position (Scheme 1). This characteristic enamine type reactivity, or broadly termed in the literature as a Friedel–Crafts type reaction, has been intensively exploited recently, especially in organocatalysis[3] and gold catalysis[4] by designing novel diastereo- and enantioselective reactions. In addition, there is an increasing tendency to explore the reactivity of the indole nitrogen atom in enantioselective cyclization reactions.[5] All these reactions require the synthesis to be planned around the nucleophilic properties of indoles.

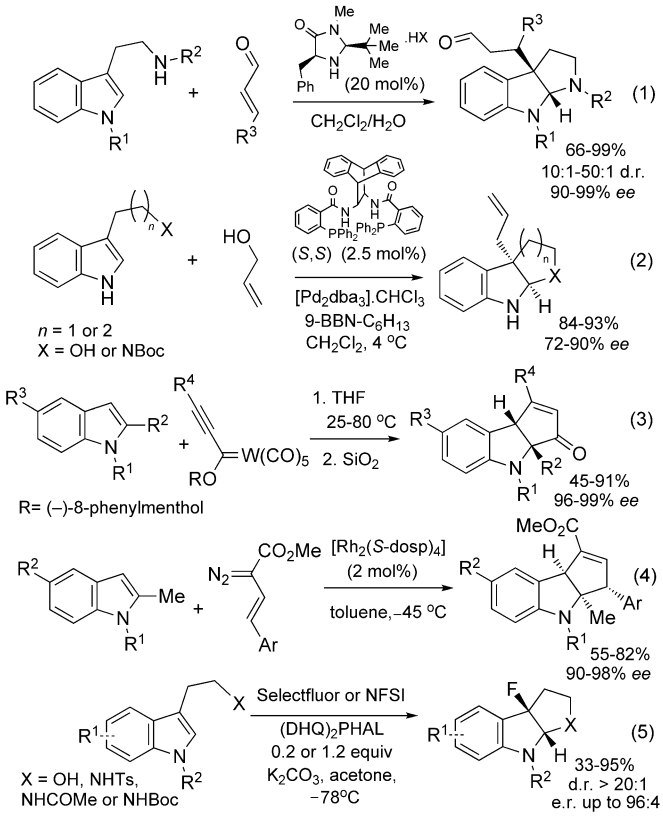


Scheme 1. Enamine versus iminium type reactivity of indole.

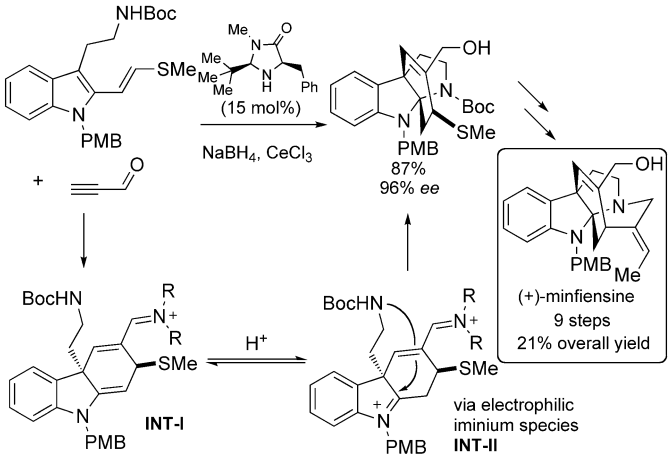
While the above mentioned enamine type reactivity allowed for nucleophilicity on C3, an enamine attack produces an iminium intermediate which confers a momentary electrophilic site on C2. If this incipient 'C2 electrophile' is trapped by an inbuilt nucleophile, indolines with new stereogenic centers are formed by dearomatization (Scheme 1).

This strategy was first adopted in the synthesis of tricyclic frameworks, such as pyrroloindolines, by MacMillan et al. By employing organocatalysis with an imidazolidinone, an enantioselective Friedel–Crafts type reaction of a tryptamine derivative with an α,β-unsaturated aldehyde was achieved. Subsequently, an amino group on the 3-substituent acts as a nucleophile to trap the incipient iminium electrophile with excellent diastereo- and enantioselectivies [Scheme 2, Eq. (1)].[6a] Subsequently, Trost et al. reported an enantioselective palladium-catalyzed C3-allylation strategy to effect the in-situ trapping of the iminium cation through a prefunctionalized amino or hydroxy group on the C3 substituent with very good to excellent enantioselectivities [Scheme 2, Eq. (2)].[6b] Barluenga et al. developed an enantioselective variant using tungsten Fischer carbenes containing a 8-phenylmenthol chiral auxiliary to achieve cyclopenta annulation through a C–C bond formation at the indole C2 [Scheme 2, Eq. (3)].[6c] Davies et al. also reported a rhodium-catalyzed enantioselective version of such a [3+2] indole annulation reaction [Scheme 2, Eq. (4)].[6d] Reisman et al. have recently published a (*R*)-BINOL·$SnCl_4$ catalyzed indole annulation variant.[6e] Very recently, Gouverneur et al. demonstrated an enantioselective approach to such tricyclic indolines by using fluorine electrophiles to quarternarize indole C3 and trapping the C2 iminium species by a C3-tethered nucleophile [Scheme 2, Eq. (5)].[6f]

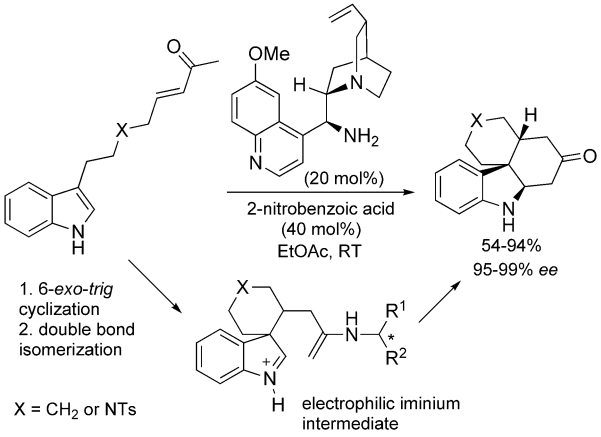
[*] C. C. J. Loh, Prof. Dr. D. Enders
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: enders@rwth-aachen.de



Scheme 2. Diastereo- and enantioselective indoline syntheses. dosp = *N*-(dodecylbenzenesulfonyl)prolinate, NFSI = *N*-fluorobenzenesulfonimide.



Scheme 3. Enantioselective synthesis of (+)-minfiensine.



Scheme 4. Enantioselective synthesis of densely fused indolines.

In addition, there is also very recent surge in using this iminium-trapping approach to synthesize tetracyclic indolic frameworks enantioselectively.

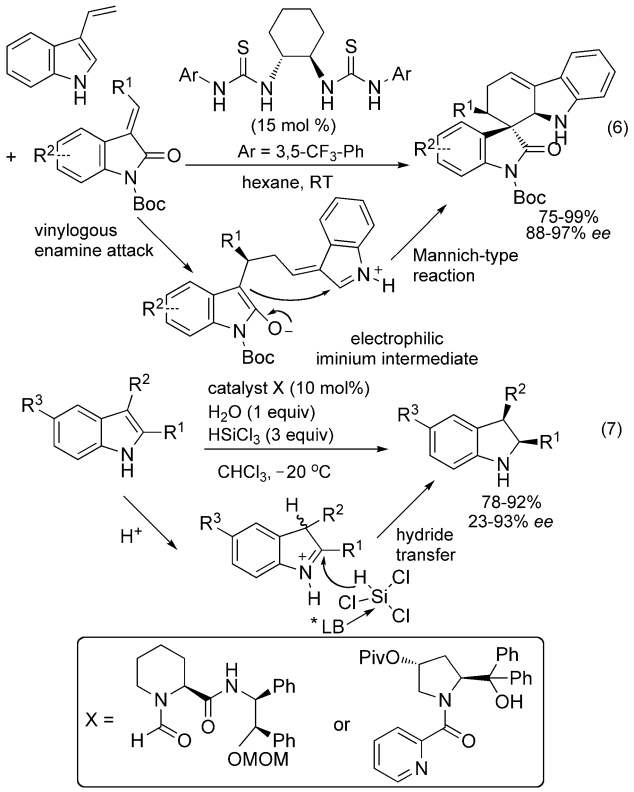
The first elegant example was demonstrated by MacMillan et al. in the enantioselective total synthesis of (+)-minfiensine through an iminium-activation controlled Diels–Alder cyclization step to generate the tetracyclic structure with excellent enantio- and diastereocontrol (Scheme 3).[7] The key step involved a protonation of **INT-I** leading to the electrophilic indolic **INT-II** which captures the nucleophilic amine to generate the core framework of (+)-minfiensine with 96% *ee*.

Very recently, Bandini et al. have reported a method using Au^I catalysis to access highly densely functionalized tetracyclic indoline structures containing a quarternary C3 diastereo- and regioselectively.[8] A similar approach was published almost concurrently by You et al.,[9] however, a Michael/Mannich organocascade with a quinine-derived primary amine catalyst and an iminium/enamine activation strategy was employed with excellent enantioselectivities and good to excellent yields of tetracyclic indolines (Scheme 4). The formation of a key electrophilic quarternary indolenine intermediate was necessary for the successful execution of this strategy. This route was also employed in the synthesis of an analogue of the natural product (+)-kresiginine, further eliciting the potential application of this method for biological purposes.

Barbas et al. also reported the enantioselective synthesis of carbazole spirooxindole derivatives in a Diels–Alder type reaction catalyzed by bifunctional thioureas. [Scheme 5, Eq. (6)].[10] While it is unclear whether this reaction proceeds in a concerted or a stepwise fashion, a possible pathway involves the indolenine intermediate generated from the vinylogous enamine to be intercepted in a Mannich-type reaction to form the desired spirocyclic products. This method was also carried out on a preparative gram scale to demonstrate its utility in scaling up.

Another recent report by Chen et al. also describes the cooperative use of a Lewis base organocatalyst and a Brønsted acid additive to effect an asymmetric hydrosilylation on C3- and C2-substituted indoles to form enantiopure indolines. [Scheme 5, Eq. (7)].[11] While the first proton addition step is suggested to be non-enantioselective, a dynamic kinetic resolution was proposed to explain the excellent yields and enantioselectivities of this method.

Furthermore, some additional advances by Zhao et al. and Xiao et al. should be mentioned where Diels–Alder type reactions of C2-substituted vinyl indoles have been used effectively to exploit the vinylogous electrophilicity mediated



Scheme 5. Synthesis of spirocycles and hydrosilylation.

by the indole iminium species towards highly enantioenriched functionalized tetrahydrocarbazoles.[12]

In addition, very recent advances in Au^I catalysis allowing an umpolung on indole C3 have been achieved by exploiting electrophilic gold carbenoid species as reported independently by Gagosz et al. and Zhang et al.[13,14] While no enantioselective variant is yet known, these reports demonstrate an unprecedented example where alkynyl–aryl azides could be used to generate an electrophilic gold carbenoid for nucleophile interception. This concept also opens up a plethora of opportunities for enantioselective reaction design in the future especially in combination with organocatalysis.[15]

In conclusion, recent advances in indole chemistry are highlighted focusing on the enantioselective synthesis of new molecular architectures utilizing the in-situ generated electrophilic iminium species generated after a Friedel–Crafts type reaction of indoles. We believe that this shift from a widely understood π-excessive nucleophilic indolic entity to an electrophilic (indolenine or gold carbenoid) entity is a concept that will see further advances in the design of enantioselective reactions on indole substrates, allowing chemists to achieve even more complex structures with high enantiocontrol.

Received: October 27, 2011
Published online: December 8, 2011

[1] For selected recent reviews of indole Friedel–Crafts type reactions, see: a) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; c) S. L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; d) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449.

[2] M. Bandini, A. Umani-Ronchi, *Catalytic Asymmetric Friedel–Crafts Alkylations*, Wiley-VCH, Weinheim, **2009**.

[3] For selected general reviews on organocatalysis, see: a) Special issue, *Chem. Rev.* **2007**, *107*, 5413; (guest editor B. List); b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; c) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; e) K. A. Jørgensen, S. Bertelsen, *Chem. Soc. Rev.* **2009**, *38*, 2178; f) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167.

[4] For selected general reviews on gold catalysis, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; c) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; e) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208; f) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232; g) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358.

[5] a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238; b) Q. Cai, C. Zheng, S. L. You, *Angew. Chem.* **2010**, *122*, 8848; *Angew. Chem. Int. Ed.* **2010**, *49*, 8666; c) D. Enders, C. Wang, G. Raabe, *Synthesis* **2009**, 4119; d) L. Hong, W. Sun, C. Liu, L. Wang, R. Wang, *Chem. Eur. J.* **2010**, *16*, 440.

[6] a) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; b) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; c) J. Barluenga, E. Tudela, A. Ballesteros, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 2096; d) Y. Lian, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 440; e) L. M. Repka, J. Ni, S. E. Reisman, *J. Am. Chem. Soc.* **2010**, *132*, 14418; f) O. Lozano, G. Bessley, T. Martinez Del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem.* **2011**, *123*, 8255; *Angew. Chem. Int. Ed.* **2011**, *50*, 8105.

[7] S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606.

[8] G. Cera, P. Crispino, M. Monari, M. Bandini, *Chem. Commun.* **2011**, *47*, 7803.

[9] Q. Cai, C. Zheng, J.-W. Zhang, S.-L. You, *Angew. Chem.* **2011**, *123*, 8824; *Angew. Chem. Int. Ed.* **2011**, *50*, 8665.

[10] B. Tan, G. Hernándes-Torres, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 12354.

[11] Y. C. Xiao, C. Wang, Y. Yao, J. Sun, Y.-C. Chen, *Angew. Chem.* **2011**, *123*, 10849; *Angew. Chem. Int. Ed.* **2011**, *50*, 10661.

[12] a) C. Zheng, Y. Lu, J. Zhang, X. Chen, Z. Chai, W. Ma, G. Zhao, *Chem. Eur. J.* **2010**, *16*, 5853; b) Y.-J. Cao, H.-G. Cheng, L.-Q. Lu, J.-J. Zhang, Y. Cheng, J.-R. Chen, W.-J. Xiao, *Adv. Synth. Catal.* **2011**, *353*, 617.

[13] A. Wetzel, F. Gagosz, *Angew. Chem.* **2011**, *123*, 7492–7496; *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.

[14] B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem.* **2011**, *123*, 8508–8512; *Angew. Chem. Int. Ed.* **2011**, *50*, 8358–8362.

[15] For a very recent example, see: C. C. J. Loh, J. Badorrek, G. Raabe, D. Enders, *Chem. Eur. J.* **2011**, *17*, 13409.

