A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
GDCh
International Edition
www.angewandte.org

Title: Controlling Regioselectivity in the Enantioselective N-Alkylation of Indole Analogs Catalyzed by Dinuclear Zinc-ProPhenol

Authors: Barry M. Trost, Elumalai Gnanamani, and Chao-I (Joey) Hung

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201705315
Angew. Chem. 10.1002/ange.201705315

Link to VoR: http://dx.doi.org/10.1002/anie.201705315
http://dx.doi.org/10.1002/ange.201705315

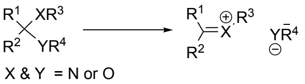
WILEY-VCH

Controlling Regioselectivity in the Enantioselective *N*-Alkylation of Indole Analogs Catalyzed by Dinuclear Zinc-ProPhenol

Barry M. Trost,* Elumalai Gnanamani, and Chao-I (Joey) Hung

Abstract: The enantioselective *N*-alkylation of indole and its derivatives with aldimines is efficiently catalyzed by a zinc-ProPhenol dinuclear complex under mild conditions to afford *N*-alkylated indole derivatives in good yield (up to 86%) and excellent enantiomeric ratio (up to 99.5: 0.5 e.r.). This protocol tolerates a wide array of indoles, as well as pyrrole and carbazole, to afford the corresponding *N*-alkylation products. The reaction can be run on gram scale with reduced catalyst loading without impacting the efficiency. The chiral aminals were further elaborated into various chiral polyheterocyclic derivatives. The surprising stability of the chiral *N*-alkylation products will open new windows for asymmetric catalysis and medicinal chemistry.

Acetals, hemiaminals and aminals share a structure possessing a carbon bearing two heteroatoms prone to undergo ionization as shown in eq 1.[1]



(eq. 1)

While they are broadly present both in synthetic and natural product chemistry, they are commonly constrained in ring systems to enhance their intrinsic stability.[2]

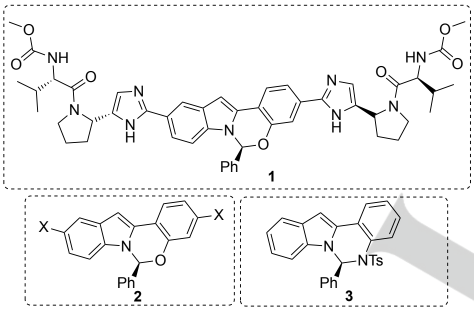
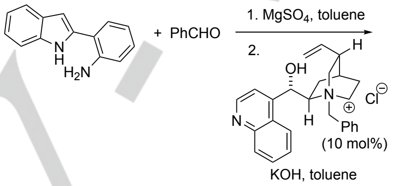


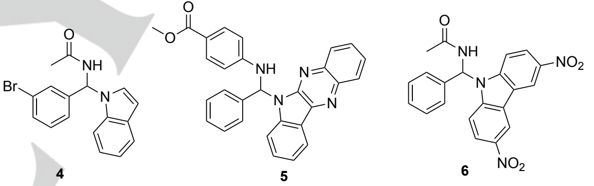
Figure 1. Elbasvir and related hemiaminals and aminals

An exciting recent illustration of this phenomenon is the development of a potentially sensitive hemiaminal, elbasvir **1** (see figure 1), which is a highly potent and selective NS5A inhibitor of the hepatitis C virus. The potential sensitivity of this structural unit is mitigated by its incorporation in a ring. Indeed, its stability is such that the synthetic intermediate **2** can be synthesized asymmetrically using a novel C-N coupling.[3] Indeed, this method extended to form the cyclic aminal **3** asymmetrically. Also there are many methods available for the synthesis of *N*,*O*-aminals and utilized for several organic transformations.[12] On the other hand, attempts to develop more traditional indole moieties containing asymmetric aminal syntheses as shown in eq. 2 have been less effective.[4] These results may derive from the sensitivity of the aminal. In fact, a recent study in the stability of cyclic aminals noted and synthesized asymmetrically, [5] "for the preparation and workup of these valuable intermediate and natural products, appropriate conditions have to be chosen and for application as drug molecules their sensitivity towards hydrolysis has to be taken into account."



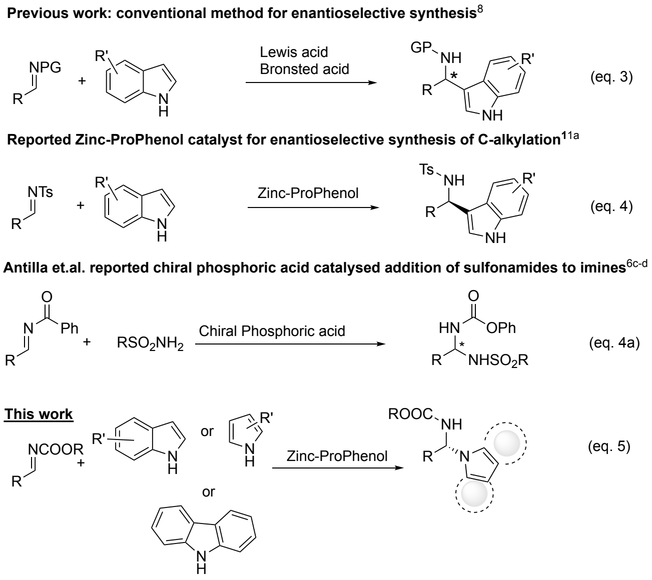
(eq. 2)

Figure 2. Non-cyclic aminals as antibiotics



4 5 6

Non-acyclic aminals make the challenge even more daunting. Recent studies have shown that aminals **4**-**6** have significant antibiotic properties (Figure 2).[6a-b] Indole and its derivatives have been extensively investigated as medicinally active molecules.[7]



Scheme 1. Enantioselective alkylation of Aldimines with indoles and sulfonamides

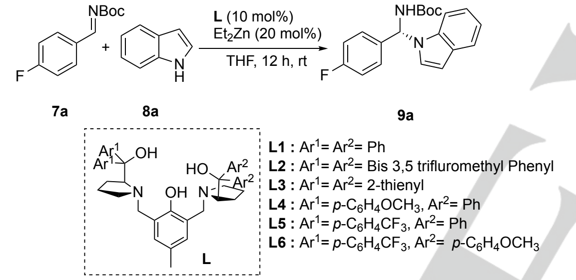
---

[a] Prof. Dr. B. M. Trost, Dr. E. Gnanamani, C.-I. Hung
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
E-mail: bmtrost@stanford.edu

Supporting information and the ORCID identification number(s) for the author(s) of this articale can be found under http:

Thus incorporating indoles into such aminals is made interesting. The only reports of asymmetric alkylation of indole are at C3 position.[8] There are only two reports of the alkylation of the indole nitrogen to form the acyclic aminal, but none asymmetrically.[9] Antilla et. al. reported the synthesis of chiral aminals by addition of sulfonamides and imide to imines with excellent enantioselectivity (Eqn 4a).[6c-d] Due to the lack of methods available for the asymmetric synthesis of *N*,*N*-acyclic aminals, these compounds have not been utilized to date. Indeed, the reported use of Zn-ProPhenol[10] led only to asymmetric C3-alkylation using the *N*-Ts imine as the aminoalkylating agent (Scheme 1).[11a] One explanation for this regioselectivity could be that attack at the indole *N* occurs reversibly, whereas attack at C3 was irreversible. Due to the increased synthetic versatility of carbamate-protected amines relative to sulfonamides, we were intrigued to see what type of behaviour would be observed with *N*-Boc and *N*-Cbz imines. We began our studies with imine **7a** and indole **8a** in the presence of our zinc-ProPhenol **L1** catalyst in THF at room temperature for 12 h. To our surprise, the *N*-alkylation product **9a** was obtained in 61% yield with 98.5:1.5 e.r., while the C3-alkylation product was observed in 11% yield with 77:33 e.r. Clearly, the carbamate-protected imines gave us access to the reaction pathway in which C3-alkylation is suppressed.

Table 1. Optimization of the reaction conditions[a,b]

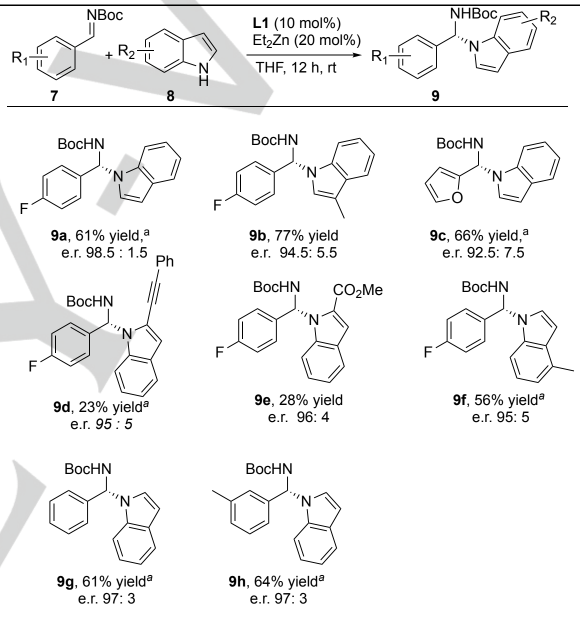


L1 : Ar^1= Ar^2= Ph
L2 : Ar^1= Ar^2= Bis 3,5 trifluromethyl Phenyl
L3 : Ar^1= Ar^2= 2-thienyl
L4 : Ar^1= *p*-$C_6H_4OCH_3$, Ar^2= Ph
L5 : Ar^1= *p*-$C_6H_4CF_3$, Ar^2= Ph
L6 : Ar^1= *p*-$C_6H_4CF_3$, Ar^2= *p*-$C_6H_4OCH_3$

entry	Solvent/ Ligand	*N*-alk. Yield	*N*-alk. e.r.	C3-alk. Yield	C3-alk. e.r.
1	PhMe/**L1**	15 %	81:19	60 %	57.5:42.5
2	DCM/**L1**	Trace	77:23	70 %	42:58
3	**THF/L1**	**61 %**	**98.5:1.5**	**11%**	**77:33**
4	PhH/**L1**	14 %	65:35	65 %	74:26
5	ACN/**L1**	12 %	90:10	70%	89.5:10.5
6	DME/**L1**	7%	96:4	42%	61.5:38.5
6	THF/**L2**	35 %	82:18 (-)	34 %	56:44(-)
7	THF/**L3**	Trace	70:30	14 %	68:32
8	THF/**L4**	17 %	98:2	54 %	85:15
9	THF/**L5**	35 %	98:2	14 %	64:36
10	THF/**L6**	37 %	96:4	30%	65.5:34.5

a Reaction conditions: 1 equiv of indole, 1.1 equiv of imine, 10 mol % of Zn-ProPhenol (Generated using 1M Et_2Zn in hexanes and ligand (2:1)) at rt in solvent (0.3 M) for 12 h. b Remaining starting material has been recovered.

Given the rarity of chiral aminals in the literature, as well as their potential applications, we were excited to explore this reaction further. Hoping to improve the selectivity for the *N*-alkylation product, a solvent screen was performed. Relative to THF, all of the solvents examined gave inferior yield and enantioselectivity of the desired *N*-alkylation product (Table 1). In fact, all of the other solvents screened gave the C3-alkylation adduct as the major product. Other ProPhenol catalysts **L2**-**L6** were also screened and the catalyst **L1** produced the best yield and enantioselectivity of *N*-alkylation product (Table 1). While we were unable to completely suppress the C3-alkylation, the *N*-alkylated compounds were typically the major product in THF, were formed with good yield and enantioselectivity and were easily separable from the C3-alkylation product. With optimized conditions in hand, we sought to explore the scope of the reaction by first varying the indole (See the scheme 2).

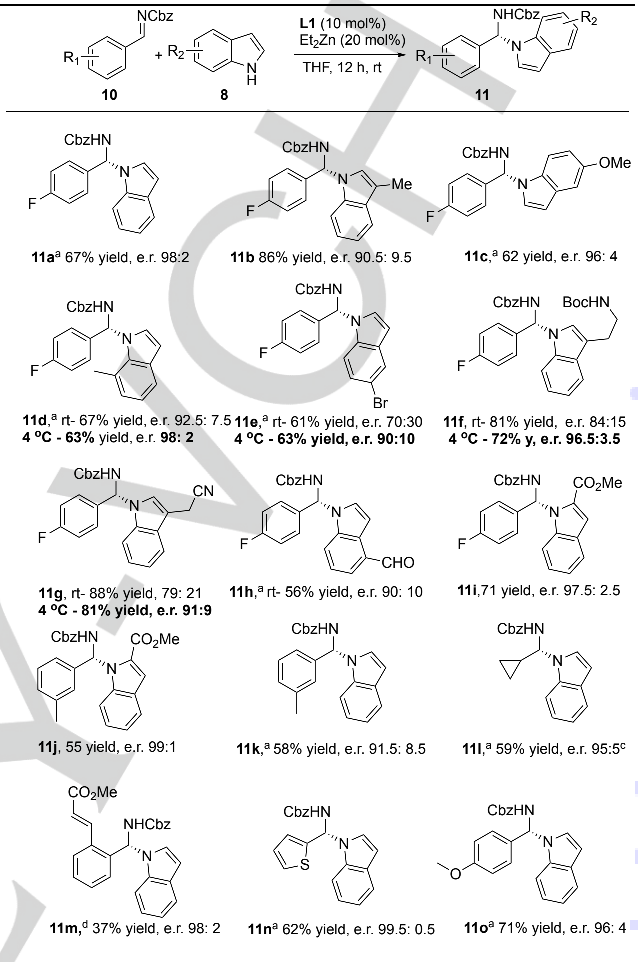


Scheme 2. Scope of the reaction with Boc imines. [a] <12% of C3-alkylation product obtained with low e.r. [b] Reaction conditions: 1 equiv of indole, 1.1 equiv of imine, 10 mol % of Zn-ProPhenol (Generated using 1M Et_2Zn in hexanes and ligand (2:1)), at rt, in THF (0.3 M) for 12 h.

When the indole C3 position was blocked, higher yields of the desired compounds were obtained. Skatole produced the *N*-alkylation product **9b** in 77% yield with e.r. of 94.5:5.5. A heterocyclic imine such as 2-furyl substituted **7c** gave the *N*-alkylation product **9c** in 66% yield with 92.5 : 7.5 e.r. (Scheme 2**)** To determine the effect of steric crowding of the nucleophilic site the reaction was screened with 2-substituted indoles. With an alkyne at the 2-position, the *N*-alkylated indole derivative **9d** was formed exclusively with excellent enantioselectivity (95:5 e.r.). Higher temperatures and longer reaction times did not improve the yield. Similarly, methyl indole-2-carboxylate also produced exclusively the *N*-alkylation product **9e** in 94:6 e.r. The scope of the reaction further extended to the other imines, such as phenyl imine **7g** and 3-methylphenyl imine **7h**; the desired products were obtained in 61% yield with 97:3 e.r. and 64% with 95:5 e.r., respectively.

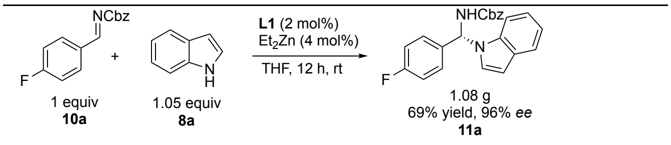
To further expand the substrate scope and to improve the yield of the reaction, Cbz imines were also examined. Due to decreased steric demands of the Cbz group relative to Boc, we anticipated that Cbz imines would be more reactive. Indeed, the reaction proceeded even at 4 °C, which allowed improvement in a number of examples. With methyl indole-2-carboxylate, the Cbz imine **10i** was quite differential and gave the desired product **11i** in 71% yield with 97.5:2.5 e.r., compared to 28% yield and 94:6 e.r. for the Boc *N*-alkylation product **9e**. This supports our hypothesis that the increased yield of these substrates is due to the decreased steric demand of the Cbz imines. Since indole-2-carboxylates are useful for the synthesis of polycyclic molecules, the reaction was also carried out with other imines, such as 3-methylphenyl imine **10j**, which gave the *N*-alkylation product **11j** in 55% yield (BRSM 87%) with excellent enantiomeric ratio (99:1). Skatole formed the *N*-alkylation product **11b** in good yield (86%) with 90.5:9.5 e.r. The 5-methoxyindole produced the desired *N*-alkylation product **11c** in 62% yield with 96:4 e.r. To explore the *peri* effect, the reaction was carried out with 7-methylindole. To our delight, the methyl group did not negatively affect the reaction, and the *N*-alkylation product **11d** was obtained in 63% yield with 98:2 e.r. even at 4 °C. The scope of the reaction was further analyzed with halogen substituted indoles. With 5-bromoindole, the corresponding *N*-alkylation product **11e** was obtained in 61% yield with 70:30 e.r. To improve these results, the reaction was carried out at 4 °C, which increased the selectivity up to e.r 90:10 with no loss of yield. The reaction tolerated a carbamate NH, which was not competitive with the indole nitrogen; the indole *N*-alkylation product **11f** was obtained in 85:15 e.r. at room temperature. Pleasingly, the enantioselectivity increased to 96:4 e.r. by reducing the temperature to 4 °C. The reaction even tolerated a nitrile-bearing indole, and the desired product **11g** formed in 81% yield with 91:9 e.r. This observation is noteworthy, as the Lewis basic nitrile could have acted as a poison for the Zn-ProPhenol catalyst. Due to the increased reactivity of imines relative to aldehydes in ProPhenol reactions, the reaction could even be applied to aldehyde-substituted indoles. With 4-indole carboxaldehyde, the *N*-alkylation product **11h** was obtained in 56% yield with 90:10 e.r (Scheme 3).

The scope of the reaction further extended to the 3-methyphenyl imine with indole, where the product **11k** was obtained in 58% yield with 91.5:8.5 e.r. Cyclopropyl imine were also tolerated, and the corresponding *N*-alkylated indole product **11l** was formed in 59% yield with 70:30 e.r. Because of the lower enantioselectivity, the reaction was screened with other ProPhenol ligands (see Supporting Information for details). To our delight, the electron rich 4-methoxyphenyl derived ProPhenol (L4) produced the product with a greatly enhanced enantomeric ratio of 95:5 with 59% yield. A sterically crowded imine bearing an alkene substituent at the 2-position was also a viable substrate, and the *N*-alkylation product **11m** was obtained in 37% yield with 98:2 e.r. An imine bearing a 2-thiophene group (**10n**) gave the *N*-alkylation product **11n** in 62% yield with excellent enantioselectivity (99.5: 0.5 e.r.). The 4-methoxyphenyl substituted imine **10o** with indole produced the *N*-alkylation product in 71% yield with 96:4 e.r. (Scheme 3).



Scheme 3. Scope of the reaction with Boc imines [a] less than 10% of C3-alkylation product obtained with low enantioselectivity. [b] Reaction conditions: 1 equiv of indole, 1.1 equiv of imine, 10 mol % of Zn-ProPhenol (Generated using 1M Et_2Zn in hexanes and ligand (2:1)), at rt, in THF (0.3 M) for 12 h. [c] **L4** ProPhenol ligand used (optimization table given in SI). [d] 40% of C3 alkylation product formed.

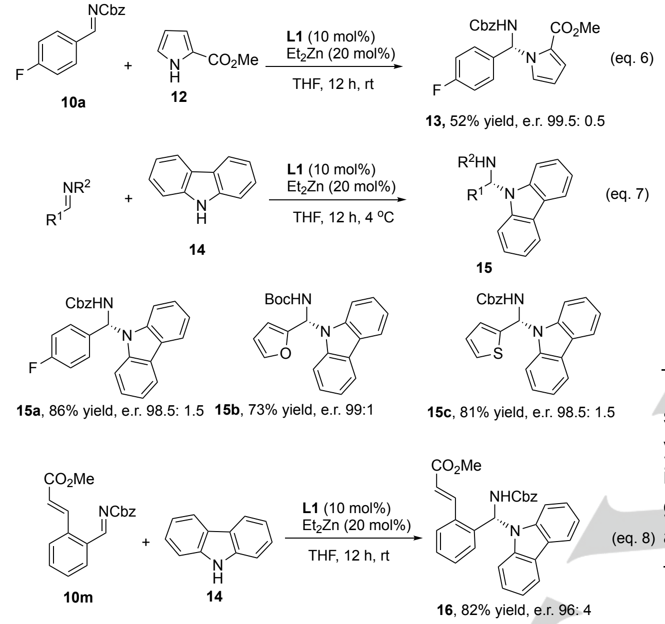
To demonstrate the scalability and practicality of this method we performed a gram scale reaction using **8a** and 1.05 equivalent of imine **10a**. Notably, we could reduce the catalyst loading from 10 mol % to 2 mol % without impacting the yield or enantioselectivity of the reaction (Scheme 4).[13]



Scheme 4. Gram Scale reaction[14]

Since indole derivatives were good substrates for this transformation, we sought to determine whether the reaction extended to other nitrogen-containing heterocycles. Pleasingly, methyl pyrrole-2-carboxylate with imine **10a** produced the *N*-

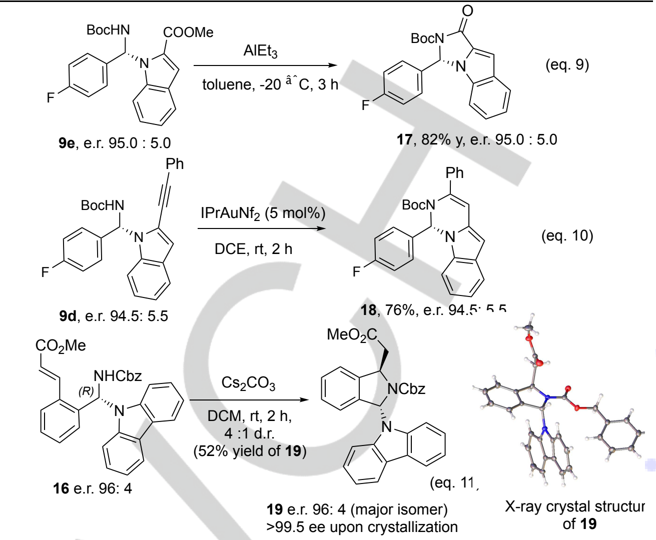
alkylation product **13** in 52% yield with 99.5:0.5 e.r (eq. 6). Carbazole with imine **10a** solely produced *N*-alkylation product **15a** in good yield with 98.5:1.5 e.r. at 4 °C. Similarly, 2-furyl imine **7c** and 2-thienyl imine **10n** both reacted with carbazole to give *N*-alkylation products **15b** and **15c** in 73 and 81% yield, respectively, with excellent enantioselectivity (eq. 7). As with indoles, a 2-substituted imine also reacted cleanly with carbazole, giving **16** in 82% yield and 96: 4 e.r (eq. 8, Scheme 5).



Scheme 5. Reaction with imines with other nucleophiles[14]

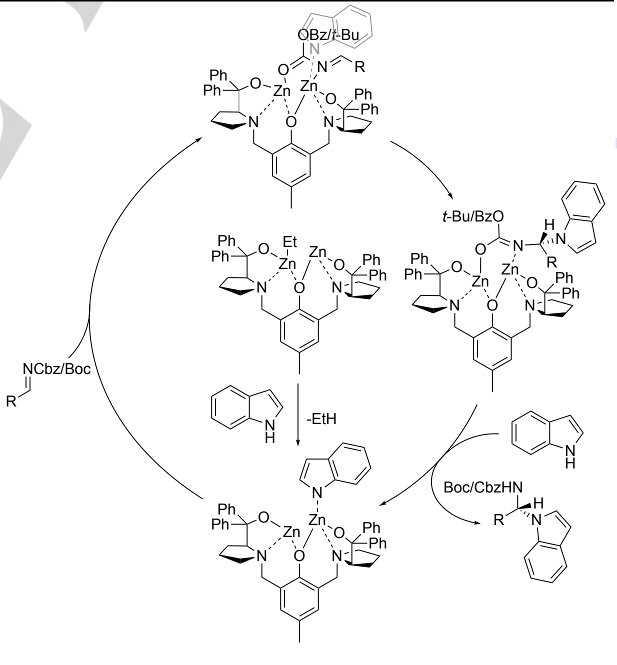
The *N*-alkylated products that are produced efficiently using our method provide an ideal platform to construct new classes of valuable chiral heterocycles (Scheme 6). For example, the compound (**9e**) was cyclized onto the pendant ester with AlEt$_3$ to form a 5-membered ring lactam **17** in 82% yield with no erosion of enantiopurity (eq. 9). To further utilize the unique grouping of functionality in these molecules, a gold-catalyzed 6-*endo*-dig cyclization was performed on amino alkyne **9d** to afford tetrahydropyrimidine **18** in 76% yield (eq. 10).

Furthermore, treatment of **16** with Cs$_2$CO$_3$ induced an *aza*-Michael addition to give rise to carbazole-substituted isoindoline derivative **19** in 52% isolated yield with no erosion of enantioselectivity (eq. 11). The structure of this molecule **19** was unambiguously determined through single crystal XRD analysis. The relative and absolute configurations were determined as 1*S*, 3*R* from the crystal structure of **19**. By analogy, the same configuration was assigned to all the aminals reported herein (see the crystal structure **19**). It should be noted that the assignment of *S* as the configuration of the aminal stereocenter in **19** corresponds to an assignment of *R* in the cyclization precursor. Thus, *R* is assigned to all the initial aminals.[11b] These cyclizations are noteworthy, as they provide the first synthetic route to chiral 1,3-disubstituted isoindoline derivatives.



Scheme 6. Synthetic applications

In conclusion, we have developed the first enantioselective synthesis of *N*-alkylated indoles, which proceeds with good yields with excellent enantioselectivities. Particularly noteworthy is the change in enantioselectivity with Zn-ProPhenol catalysts in going from the *N*-sulfonylimines (favoring C3) to the *N*-alkoxyacylimines. Scheme 7 offers a possible explanation.



Scheme 7. Proposed catalytic cycle for the *N*-alkylation

N-Sulfonylimines should bind *via* one-point coordination of the imine nitrogen to zinc. Thus, the complex is rather flexible, which allows attack from both the nitrogen and C3 of the indole nucleophile. Moreover, since the attack at the nitrogen is presumably more reversible than the reaction at C3, C3-

alkylation became the majority driven by thermodynamics. On the other hand, the *N*-alkoxyacyl imine undergoes two-point binding (Scheme 7). This more structurally rigid complex brings the nitrogen of the heterocycle and the carbon of imine to closer proximity, facilitating the observed asymmetric process. Exchange of the alkoxyacylimine with the bound product then liberates the adduct and initiates another cycle. This model predicts formation of the *R* enantiomer of the product as observed.

This methodology extended to pyrrole and carbazole derivatives, which afforded similarly desirable results. These chiral aminals are synthetically useful motifs that could be utilized for stereoselective lactam synthesis, and could also be transformed into a tetrahydropyrimidine. We also used these aminals—via an *aza*-Michael addition—to obtain the first reported examples of chiral 1,3-disubstituted isoindoline derivatives. It is noteworthy that all the transformations of the aminals occurred with no observable loss of e.r. Importantly this method for the first time opens the door for the utilization of the indole chiral *N*-alkylation products for further organic transformations and possible applications, notably for biological purposes as some aminals have already demonstrated antibiotic activity.

Acknowledgements

We thank the National Science Foundation (CHE-1360634) and the National Institute of Health (GM-033049) for their generous support of our programs. We thank Dr. Jana Maclaren (Stanford University) for X-ray crystallographic analysis and Christopher A. Kalnmals and Jacob S. Tracy (Stanford University) for NMR experiments. E.G. is grateful for a Fulbright Nehru post-doctoral fellowship, USIEF, India.

Keywords: *N*-alkylation • Asymmetric catalysis • Zn-ProPhenol • Indole addition with Boc and Cbz aldimines • chiral isoindoline derivatives

[1] a) J. Kimand, M. Movassaghi, *Acc. Chem. Res.* **2015**, *48*, 1159-1171; b) S. G. Davies, T. J. M. J. Donohoe, J. M. J. *Pure & Appl. Chem.,* **1992**, *64*, 379-386; c) M. Petrini, *Chem. Rev.* **2005**, *105*, 3949-3977; d) B. E. Maryanoff, H.-C. Zhang, J. H.Cohen, I. J.Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431-1628; d) M. Sugiura, S. Kobayashi, *Org. Lett.* **2001**, *3*, 477-480; e) Y.-Y. Huang, A. Chakrabarti, N. Morita, U. Schneider, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 11121-11124.

[2] a) G. R. Pettit, J.-P. Xu, J.-C. Chapuis, R. K. Pettit, L. P. Tackett, D. L. Doubek, J. N. A. Hooper, J. M. Schmidt, *J. Med. Chem.* **2004**, *47*, 1149-1152; b) Tanaka, J.-I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535–5538; c) Pavan, M.; Bo, G. *Physiol. Comp. Oecol.* **1953**, *3*, 307.

[3] a) C. A.Coburn, P. T. Meinke, W. Chang, C. M. Fandozzi, D. J. Graham, B. Hu, Q. Huang, S. Kargman, J. Kozlowski, R. Liu, J. A. McCauley, A. A. Nomeir, R. M. Soll, J. P. Vacca, D. Wang, H. Wu, B. Zhong, D. B. Olsen, S. W. Ludmerer, *ChemMedChem* **2013**, *8*, 1930-1940; b) H. Li. K. M. Belyk, J. Yin, Q. Chen, A. Hyde, Y. Ji, S. Oliver, M. T. Tudge, L. – C. Campeau, K. R. Campos, *J. Am. Chem. Soc.* **2015**, *137*, 13728-13731 (references therein).

[4] R. J. Armstrong, M. D'Ascenzio, M. Smith, *Synlett* **2016**, *27*, 6-10.

[5] a) E. Sawatzky, A. Drakopoulos, M. Rölz, C. Sotriffer, B. Engels, M. Decker, *Beilstein J. Org. Chem.* **2016,** *12,* 2280–2292. b) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc*. **2008**, *130*, 15786-15787.

[6] a) P. Nimavat, J. Vasoya, *J. Indian Chem. Soc.,* **2003**, *80*, 711-713; b) R. Tiwari, G. Chhabra, *Asian J. Chem.* **2010**, *22*, 5987-5992; c) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696-15697. d) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman, J. C. Antilla, *Chem. Commun.* **2007**, 4477- 4479.

[7] a) M. A. A. Radwan, E. A. Ragab, N. M. Sabry, S. M. E. Shenawy, *Bioorg Med Chem* **2007**, *15*, 3832 - 3841; b) V. Sharma, P. Kumar, D. Pathak, *J. Heterocyclic Chem.,* **2010**, *47*, 491-502 (references cited therein); c) Y. J. Wu New Indole-Containing Medicinal Compounds. In: Gribble GW, editor. *Heterocyclic Scaffolds II*. Berlin, Heidelberg: Springer; **2011**. pp. 1–29; d) J.J. Li, Indoles, oxindoles, and azaindoles. In: J. J. Li, editor. *Heterocyclic chemistry in drug discovery*. Hoboken, New Jersey: John wiley and Sons Inc; **2013**. pp. 54–11; e) P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley, Chichester, **2009**; f) *Comprehensive Natural Products Chemistry* (Ed.: D. H. R. Barton, K. Nakanishi, O. Meth-Cohn, J. W. Kelly), Pergamon, Oxford, **1999**; g) C. A.Coburn, P. T. Meinke, W. Chang, C. M. Fandozzi, D. J. Graham, B. Hu, Q. Huang, S. Kargman, J. Kozlowski, R. Liu, J. A. McCauley, A. A. Nomeir, R. M. Soll, J. P. Vacca, D. Wang, H. Wu, B. Zhong, D. B. Olsen, S. W. Ludmerer, *ChemMedChem* **2013**, *8*, 1930-1940

[8] a) M. Johannsen, *Chem. Commun.* **1999**, 2233-2234; b) Y. -Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, 128, 8156-8157; c) Y. -X. Jia, J.-H. Xie, H.-F. Duan, L.- X. Wang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1621-1624; d) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292-293; e) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484-1485; f) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609-2611; g) P. Yu, J. He, C. Guo, *Chem. Commun.* **2008**, 2355-2357; h) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem. Int. Ed.* **2008**, *47*, 5661-5665; i) Y. Qian, C. Jing, C. Zhai, W.-H. Hu, *Adv. Synth. Catal.* **2012**, *354*, 301-307; i) J. Feng, W. Yan, D. Wang, P. Li, Q. Sun, R. Wang, *Chem. Commun.* **2012**, *48*, 8003-8005.

[9] a) N. George, M. Bekkaye, A. Alix, J. Zhu, G. Masson *Chem. Eur. J.* **2014**, *20*, 3621- 3625. b) Base-promoted synthesis of such aminals in racemic form in good yield (G. Blay.; R. M. Girón, M. Montesinos-Magraner, J. R. Pedro, *Eur. J. Org. Chem.* **2013**, 3885 - 3895).

[10] a) B. M. Trost, M. J. Bartlett, *Acc. Chem. Res.* **2015**, *48*, 688-701; b) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003 – 12004; c) B. M. Trost, C. –I. Hung, D. C. Koester, Y. Miller, *Org. Lett.* **2015,** *17*, 3778 – 3781; d) B. M. Trost, F. Miege, *J. Am. Chem. Soc.* **2014**, *136*, 3016 – 3019; e) B. M. Trost, T. Saget, C. -I. Hung, *J. Am. Chem. Soc.* **2016**, *138*, 3659-3662.

[11] a) B. -L. Wang, N. -K. Li, J. -X. Zhang, G. -G.Liu, T. Liu, Q. Shen, X. -W. Wang, *Org. Biomol. Chem.* **2011**, *9*, 2614-2617; b) Note that the assignment of *S* to the aminal stereocenter in the cyclized product **19** corresponds to the *R* enantiomer in static acylic aminal **16**.

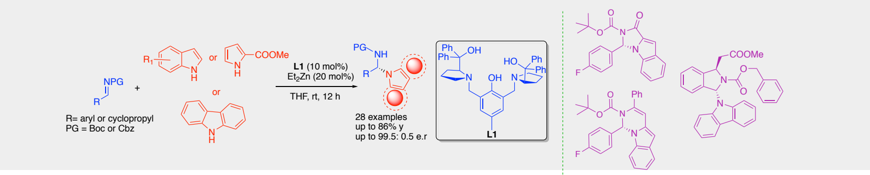
[12] Y. –Y. Huang, C. Cai, Z. Yang, Z. -C. Lv, U. Schneider, *ACS Catal*. **2016**, *6*, 5747- 5763.

[13] Notably we observed 10% of C3–alkylation product with e. r. of 75: 25. In many ProPhenol reactions, the effective catalyst loading can be further reduced by recovering the ProPhenol ligand using the procedure reported in: B. M. Trost, M. J. Bartlett *Acc. Chem. Res.* **2015**, *48*, 688-701.

[14] 10 mol% of Zn-ProPhenol was used for the reaction, which was generated using 1M Et_2Zn in hexanes and ligand (2:1).

Layout 2:

COMMUNICATION



Prof. Dr. Barry M. Trost, Elumalai Gnanamani, and Chao-I (joey) Hung*

Page No. – Page No.

Controlling Regioselectivity in the Enantioselective *N*-alkylation of Indole Analogs Catalysed by Dinuclear Zinc-ProPhenol