Heterocycles

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Formation of Enehydrazine Intermediates through Coupling of Phenylhydrazines with Vinyl Halides: Entry into the Fischer Indole Synthesis**

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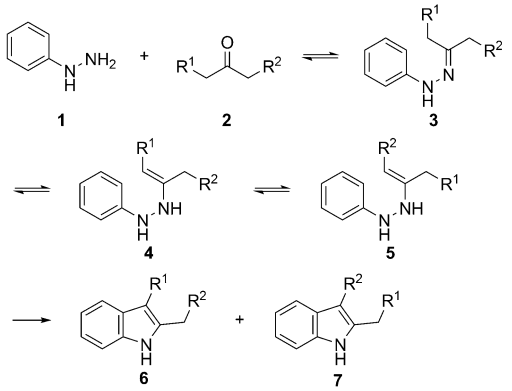
Indoles, one of the most abundant heterocycles in nature, constitute the essential functional cores in the structures of various fragrances, dyes, agricultural chemicals, and pharmaceuticals.[1] The synthesis of indoles has been an active research field because of their structural diversity as well as the numerous applications of natural and synthetic indole derivatives. Over the last century, a wide array of approaches have been developed,[2] and among them the Fischer indole synthesis is probably the most well-known method because of its fascinating combination of experimental simplicity and mechanistic complexity.[3] Although it was established over a century ago in 1883, the Fischer indole synthesis still remains a popular research topic[4] and substantial efforts have been made to explore its applications or to overcome its drawbacks.[5]

A major drawback recognized in the classic Fischer indole synthesis is its lack of regioselectivity resulting from the use of unsymmetrical ketones (**2**, Scheme 1) in the reaction.[4a] When phenylhydrazine (**1**) reacts with an unsymmetrical ketone (**2**) under acidic conditions, it leads to the hydrazone **3**, which then tautomerizes to an enehydrazine before the [3,3] sigmatropic rearrangement occurs.[4a] However, because of the unsymmetrical nature of **3**, a pair of regioisomers, **4** and **5** (presumably in equilibrium), could be formed, and thus lead to the isomeric indole products **6** and **7**, respectively. This regioselectivity issue in the Fischer indolization has largely limited its application to the total synthesis of complex natural products such as *Aspidosperma* and *Strychnos* indole alkaloids.[6]



Scheme 1. Regioselectivity issue in the classic Fischer indole synthesis.

A potential solution to the regioselectivity issue was conceived in our attempt to make the aforementioned indole alkaloids by applying the Fischer indole synthesis. The strategy involves direct formation of enehydrazines through the coupling of phenylhydrazines with vinyl halides. Herein, we report our study on this strategy and its synthetic applications to the synthesis of indole alkaloids.

Our study commenced with selecting the right type of substrates and catalyst systems for the coupling reaction. Given that the use of hydrazine derivatives in C–N coupling reactions has been such an active research area over the past decade,[5a,7] it is surprising to find few reports on the application of the coupling reactions to phenylhydrazines and vinyl halides or vinyl pseudohalides for the Fischer indole synthesis. To the best of our knowledge, the only example was a palladium-catalyzed coupling reaction between N-Boc phenylhydrazine and 1-iodocyclohex-1-ene to produce the enehydrazine intermediate in 45% yield, as reported by Cho and co-workers.[8] However, they did not report other parallel reactions or any follow-up studies on this topic.[9] Our extensive survey of substrates and catalyst systems allowed us to find that a combination of CuI, DMEDA, and K_2CO_3 in toluene[10] worked well with the substrate *N*-methyl-*N*′-acetyl phenylhydrazine (**8**) and a vinyl bromide (**9**; Table 1).[11]

Under optimal reaction conditions, the coupling of **8** with **9** proceeded smoothly to produce the sensitive enehydrazine **10**, which generated the tricyclic indole **11** upon treatment with $ZnCl_2$.[12] Notably, the methyl group installed on N in the phenylhydrazine is essential for high yields. By contrast, *N*′-acetyl phenylhydrazine without the methyl group only afforded the corresponding enehydrazine intermediate in less than 40% yield. When comparing different substrates, we noticed that phenylhydrazines bearing both deactivating groups (**8b**, **8c**, and **8d**) and activating groups (**8e** and **8f**) were readily coupled with cyclic vinyl bromides (**9a**, **9b**, **9c**, and **9d**) of different ring sizes to produce the tricyclic indoles **11** in good to excellent yield. Interestingly, we also found that the phenyl bromide **8d** did not interfere with the coupling

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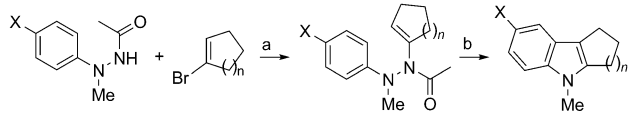
Table 1: Efficient variants of the Fischer indole synthesis through copper-catalyzed coupling reaction between protected phenylhydrazines and cyclic vinyl bromides.[a]



8 **9** **10** **11**

Entry	8	9	11	Yield [%][b]
1	**8a** (X = H)	**9a** (*n* = 1)	**11aa**	61
2	**8a**	**9b** (*n* = 2)	**11ab**	93
3	**8a**	**9c** (*n* = 3)	**11ac**	90
4	**8a**	**9d** (*n* = 4)	**11ad**	91
5	**8b** (X = F)	**9a** (*n* = 1)	**11ba**	80
6	**8b**	**9b** (*n* = 2)	**11bb**	92
7	**8b**	**9c** (*n* = 3)	**11bc**	89
8	**8b**	**9d** (*n* = 4)	**11bd**	90
9	**8c** (X = Cl)	**9a** (*n* = 1)	**11ca**	73
10	**8c**	**9b** (*n* = 2)	**11cb**	89
11	**8c**	**9c** (*n* = 3)	**11cc**	92
12	**8c**	**9d** (*n* = 4)	**11cd**	91
13	**8d** (X = Br)	**9b** (*n* = 2)	**11db**	82
14	**8d**	**9c** (*n* = 3)	**11dc**	79
15	**8d**	**9d** (*n* = 4)	**11dd**	81
16	**8e** (X = Me)	**9a** (*n* = 1)	**11ea**	65
17	**8e**	**9b** (*n* = 2)	**11eb**	82
18	**8e**	**9c** (*n* = 3)	**11ec**	82
19	**8e**	**9d** (*n* = 4)	**11ed**	86
20	**8f** (X = OMe)	**9b** (*n* = 2)	**11fb**	86
21	**8f**	**9c** (*n* = 3)	**11fc**	79
22	**8f**	**9d** (*n* = 4)	**11fd**	82

[a] Reaction conditions: a) CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 110°C; b) $ZnCl_2$ (2.2 equiv), toluene, 90°C. [b] The combined yield of two operations without isolation of **10**. DMEDA = *N*,*N*′-dimethyl-1,2-ethanediamine.

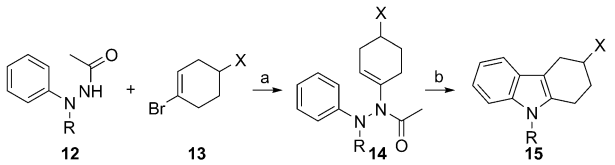
reaction (Table 1, entries 13–15) and generated products (**11db**, **11dc**, and **11dd**) eligible for further modifications to produce indoles of higher structural complexity.

Considering that methyl-protected indoles are difficult to convert into synthetically more useful free indoles, we further tested our approach using *N*-allyl-*N*′-acetyl phenylhydrazine (**12a**) and *N*-benzyl-*N*′-acetyl phenylhydrazine (**12b**) as the coupling partners (Table 2). Gratifyingly, both of them were suitable substrates, thereby allowing preparation of synthetically more versatile allyl- or benzyl-protected indoles (**15**). Notably, the coupling reaction not only tolerated the ester functional groups in **13c** and **13d** (Table 2, entries 3, 4, and 7), but it was also compatible with the free hydroxy group in **13b** to produce **15ab** and **15bb** in good yields (entries 2 and 6).[13]

Although encouraged by the successful indolizations, we were still intrigued by one key question which could not be answered by using the cyclic vinyl bromides **9** and **13** as substrates: is there equilibration between the two regioisomeric enehydrazine intermediates (**4** and **5**, Scheme 1) which would scramble the double bond under the reaction conditions?

To address this question, we chose the linear vinyl bromide **16**[14] (Table 3) as a substrate and characterized the distribution of the potential products **18a** and **19a**. Among a panel of Lewis acids assessed, both $AlCl_3$ and $FeCl_3$ were

Table 2: Preparation of allyl- and benzyl-protected indoles **15**.[a]

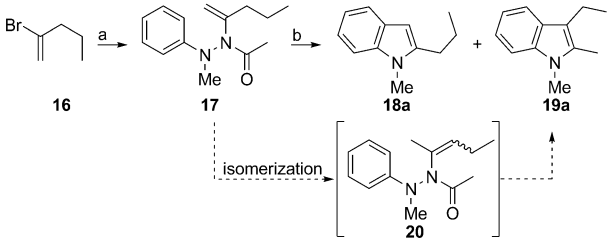


12 **13** **14** **15**

Entry	12	13	15	Yield [%][b]
1	**12a** (R = allyl)	**13a** = **9b** (X = H)	**15aa**	88
2	**12a**	**13b** (X = OH)	**15ab**	78
3	**12a**	**13c** (X = OBz)	**15ac**	86
4	**12a**	**13d** (X = OAc)	**15ad**	55[c]
5	**12b** (R = Bn)	**13a** = **9b** (X = H)	**15ba**	89
6	**12b**	**13b** (X = OH)	**15bb**	82
7	**12b**	**13c** (X = OBz)	**15bc**	83

[a] Reaction conditions: a) CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 110°C; b) $ZnCl_2$ (2.2 equiv), toluene, 90°C. [b] The combined yield of two operations without isolation of **14**. [c] With 35% recovery of **12a**. Bn = benzyl; Bz = benzoyl.

Table 3: The effect of selected Lewis acids on isomerization of the enehydrazine intermediate **17**.[a]



16 **17** **18a** **19a** **20**

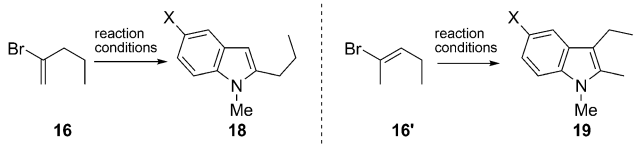
Entry	Lewis acid	Equiv	*T*	*t*	Yield [%][b] 18a	19a
1	$AlCl_3$	1.1	RT	20 min	4.3	92.7
2	$FeCl_3$	1.1	RT	1.0 h	4.5	62.5
3	$ZnCl_2$	1.1	RT	3.0 h	0	0
4	$ZnCl_2$	1.1	90°C	2.0 h	89	0
5	$ZnCl_2$	2.2	90°C	1.0 h	92	0
6	$Zn(OTf)_2$	1.1	RT	3.0 h	0	0
7	$Zn(OTf)_2$	1.1	90°C	1.5 h	93	0

[a] Reaction conditions: a) **8a**, CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 110°C; b) Lewis acid, toluene. [b] The combined yield of two operations without isolation of **17** or **20**. Tf = trifluoromethanesulfonyl.

able to catalyze the indolization after a short time even at room temperature, and produced **19a** as the predominant product. We speculate **19a** came from the enehydrazine **20**, which indicates **17** equilibrated to the more stable trisubstituted regioisomer **20** under the reaction conditions. In comparison, $ZnCl_2$ and $Zn(OTf)_2$ did not catalyze the cyclization after 3 hours at room temperature, but at an elevated temperature, both of them gave **18a** as the exclusive product in excellent yield without isomerizing **17** into **20**.

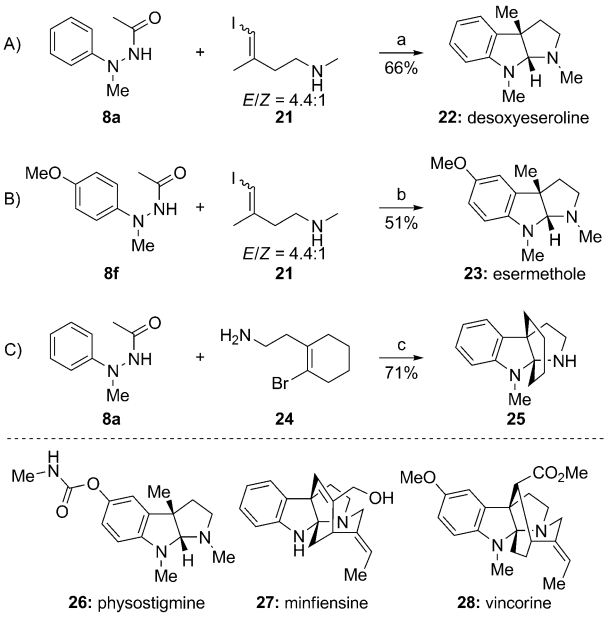
We sought to demonstrate the stereospecific nature of our method by using the regioisomeric vinyl bromides **16** and **16′**[15] as substrates (Table 4). Unlike the classic Fischer indole synthesis which would form both regioisomeric products **18** and **19** from *N*-methyl phenylhydrazine and 2-pentanone,[16]

Table 4: Selective synthesis of the regioisomers **18** and **19** from specific precursors **16** and **16′**.[a]



Entry	8	Vinyl bromide	Product	Yield [%][b]
1	**8a** (X = H)	**16**	**18a**	92
2	**8a**	**16′**	**19a**	91
3	**8b** (X = F)	**16**	**18b**	95
4	**8b**	**16′**	**19b**	86
5	**8c** (X = Cl)	**16**	**18c**	92
6	**8c**	**16′**	**19c**	85
7	**8d** (X = Br)	**16**	**18d**	82
8	**8e** (X = Me)	**16**	**18e**	89
9	**8e** (X = Me)	**16′**	**19e**	78
10	**8f** (X = OMe)	**16**	**18f**	86
11	**8f**	**16′**	**19f**	79

[a] Reaction conditions: **8**, CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 110°C; then $ZnCl_2$ (2.2 equiv), toluene, 90°C. [b] The combined yield of two operations without isolation of the enehydrazine intermediate.



Scheme 2. Synthesis of the complex carbon skeletons in indole alkaloids through interrupted indolizations. a) CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 100°C, 30 h; $ZnCl_2$ (2.0 equiv), toluene, 90°C, 1 h. b) CuI (5 mol%), DMEDA (10 mol%), K_2CO_3 (2 equiv), toluene, 80°C, 40 h; then $ZnCl_2$ (2.0 equiv), toluene, 90°C, 1 h. c) CuI (5 mol%), 1,10-phenanthroline (10 mol%), K_2CO_3 (2 equiv), toluene, 110°C, 40 h; then $ZnCl_2$ (2.0 equiv), toluene, 90°C, 1 h.

our approach was able to generate one isomerically pure product just by choosing a specific vinyl bromide. Under the standard reaction conditions, **18** and **19** were produced in good to excellent yields from **16** and **16′**, respectively.

The unique advantage of our new approach was further demonstrated by its application to the synthesis of complex carbon framework in indole alkaloids. Remarkably, treatment of **8a** and **8f** with the vinyl iodide **21**[17] produced the natural products desoxyeseroline[18] (**22**) and esermethole[19] (**23**), respectively, in good yields (Scheme 2A and B). It is noteworthy that the free secondary amine in **21** did not interfere with the reaction owing to the high chemoselectivity of the coupling chemistry between phenylhydrazine and **21**. Moreover, the excellent chemoselectivity guaranteed the success of the interrupted Fischer indolizations[20] and fulfilled one-step divergent preparations of indole alkaloids **22** and **23** from the same vinyl iodide **21**. Notably, desoxyeseroline and esermethole are in the same family of alkaloids as physostigmine (**26**), which is a commercial API known to treat myasthenia gravis, glaucoma, Alzheimer's disease, and delayed gastric emptying.[21] Either of the alkaloids can be readily converted into the drug molecule according to well-established procedures.[22] In addition, we found the coupling chemistry was also compatible with the primary amine in the vinyl bromide **24**.[23] Although our standard reaction conditions did not work well with this challenging substrate, tuning of the ligand from DMEDA to 1, 10-phenanthroline[24] led to efficient production of **25** in 71% yield (Scheme 2C). Therefore, our coupling chemistry provided a new way for quick construction of the tetracyclic pyrrolidinoindoline scaffold **25**, which is the key structural motif in the *Strychnos* alkaloid minfiensine[25] (**27**) and the *Akuammiline* alkaloid vincorine[26] (**28**).

In summary, we created a new entry into the Fischer indole synthesis and it overcomes the regioselectivity problem with the classic Fischer indolization. Our approach is based on direct formation of the enehydrazine intermediate through copper-catalyzed coupling of phenylhydrazines and vinyl halides. The chemistry tolerates ester functional groups, free hydroxy groups, and free amines. It allowed us to not only fulfill selective synthesis of isomeric indoles but also to develop interrupted indolizations to conveniently synthesize the pyrrolidinoindoline framework. Therefore, our approach is expected to have great potential in quick construction of complex carbon skeletons in indole alkaloids, especially those bearing quaternary carbon centers. What is worth pointing out is that the formation of the enehydrazine intermediate, without scrambling the double bond, opens a new avenue for the challenging asymmetric synthesis of indoles and indolines, which presumably could be achieved through either substrate or reagent control of the [3,3] sigmatropic rearrangement in the Fischer indole synthesis.[27] Relevant studies on this strategy and its synthetic applications are underway in our laboratory.

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[1] a) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**; b) A. Rahman, *Indole Alkaloids*, Harwood Academic Publisher, Amsterdam, **1998**; c) "Indole and its Derivatives": A. Joule in *Science of Synthesis: Methods of Molecular Transformations*

(Houben-Weyl), *Cat. 2*, *Vol. 10* (Eds.: E. J. Thomas), Thieme, Stuttgart, **2000**, p. 361; d) T. Eicher, S. Hauptmann in *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed., Wiley-VCH, Weinheim, **2003**.

[2] For recent reviews on indole synthesis, see: a) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195 – 7210; b) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. React.* **2012**, *76*, 281 – 534.

[3] For seminal studies of the Fischer indole synthesis, see: a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241 – 2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559 – 568.

[4] For recent reviews on the Fischer indole synthesis, see: a) D. L. Hughes, *Org. Prep. Proced. Int.* **1993**, *25*, 607 – 632; b) R. S. Downing, P. J. Kunkeler in *The Fischer Indole Synthesis* (Eds.: R. A. Sheldon, H. Bekkum), Wiley-VCH, New York, **2001**; c) J.-Z. Jiang, Y. Wang, *Chin. J. Org. Chem.* **2006**, *26*, 1025 – 1030.

[5] For representative modifications on the Fischer indole synthesis, see: a) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621 – 6622; b) B. P. Bondzić, P. Eilbracht, *Org. Lett.* **2008**, *10*, 3433 – 3436; c) I.-K. Park, S.-E. Suh, B.-Y. Lim, C.-G. Cho, *Org. Lett.* **2009**, *11*, 5454 – 5456; d) B. A. Haag, Z.-G. Zhang, J.-S. Li, P. Knochel, *Angew. Chem.* **2010**, *122*, 9703 – 9706; *Angew. Chem. Int. Ed.* **2010**, *49*, 9513 – 9516; e) N. T. Patil, A. Konala, *Eur. J. Org. Chem.* **2010**, 6831 – 6839; f) M. Inman, C. J. Moody, *Chem. Commun.* **2011**, *47*, 788 – 790; g) D. McAusland, S. Seo, D. G. Pintori, J. Finlayson, M. F. Greaney, *Org. Lett.* **2011**, *13*, 3667 – 3669; h) I.-K. Park, J. Park, C.-G. Cho, *Angew. Chem.* **2012**, *124*, 2546 – 2549; *Angew. Chem. Int. Ed.* **2012**, *51*, 2496 – 2499; i) S. Gore, S. Baskaran, B. König, *Org. Lett.* **2012**, *14*, 4568 – 4571.

[6] For examples on regiochemistry of the Fischer indolization in synthetic studies on *Aspidosperma* alkaloids, see: a) S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628 – 4641; b) G. Lawton, J. E. Saxton, A. J. Smith, *Tetrahedron* **1977**, *33*, 1641 – 1653, and references therein; for an example on regiochemistry of the Fischer indolization in synthetic study on *Strychnos* alkaloids, see: c) J. Bonjoch, N. Casamitjana, J. Quirante, M. Rodriguez, J. Bosch, *J. Org. Chem.* **1987**, *52*, 267 – 275.

[7] For selected examples of using hydrazine derivatives in C–N coupling reactions, see: a) H. Suzuki, A. Yamamoto, *J. Chem. Res. Synop.* **1992**, 280 – 281; b) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2249 – 2252; *Angew. Chem. Int. Ed.* **1998**, *37*, 2090 – 2092; c) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727 – 7729; d) S. Cacchi, G. Fabrizi, A. Goggiamani, E. Licandro, S. Maiorana, D. Perdicchia, *Org. Lett.* **2005**, *7*, 1497 – 1500; e) J. Barluenga, P. Moriel, F. Aznar, C. Valdes, *Org. Lett.* **2007**, *9*, 275 – 278; f) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542 – 4546; g) A. Reichelt, J. R. Falsey, R. M. Rzasa, O. R. Thiel, M. M. Achmatowicz, R. D. Larsen, D. Zhang, *Org. Lett.* **2010**, *12*, 792 – 795; h) R. J. Lundgren, M. Stradiotto, *Angew. Chem.* **2010**, *122*, 8868 – 8872; *Angew. Chem. Int. Ed.* **2010**, *49*, 8686 – 8690; i) X. Xiong, Y. Jiang, D. Ma, *Org. Lett.* **2012**, *14*, 2552 – 2555; j) S. J. Welsch, C. Kalinski, M. Umkehrer, G. Ross, J. Kolb, C. Burdack, L. A. Wessjohann, *Tetrahedron Lett.* **2012**, *53*, 2298 – 2301; For other approaches to indoles employing hydrazines for hydroaminations, see: k) Y. Li, Y. Shi, A. L. Odom, *J. Am. Chem. Soc.* **2004**, *126*, 1794 – 1803; l) A. Tillack, H. Jiao, I. G. Castro, C. G. Hartung, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2409 – 2420.

[8] Y.-K. Lim, C.-G. Cho, *Tetrahedron Lett.* **2004**, *45*, 1857 – 1859.

[9] Instead, they reported a variety of applications of palladium-catalyzed coupling reactions between aryl hydrazide and aryl halides, see: a) S.-E. Suh, I.-K. Park, B.-Y. Lim, C.-G. Cho, *Eur. J. Org. Chem.* **2011**, 455 – 457; b) H.-Y. Kim, W.-J. Lee, H.-M. Kang, C.-G. Cho, *Org. Lett.* **2007**, *9*, 3185 – 3186; c) H.-M. Kang, Y.-K. Lim, I.-J. Shin, H.-Y. Kim, C.-G. Cho, *Org. Lett.* **2006**, *8*, 2047 – 2050; d) Y.-K. Lim, K.-S. Lee, C.-G. Cho, *Org. Lett.* **2003**, *5*, 979 – 982.

[10] For use of a combination of CuI, DMEDA, K_2CO_3, and toluene in C–N coupling, see: a) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421 – 7428; b) L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667 – 3669.

[11] See the Supporting Information for the synthesis of **8a**–**8f** and **9a**–**9d**.

[12] For the first use of $ZnCl_2$ in the Fischer indole synthesis, see: E. Fischer, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1567.

[13] See the Supporting Information for the synthesis of **12a**, **12b**, and **13b**–**13d**.

[14] L. K. Sydnes, K. F. S. Alnes, N. Erdogan, *Monatsh. Chem.* **2005**, *136*, 1737 – 1749.

[15] H. Kim, S.-K. Lee, D. Lee, J. K. Cha, *Synth. Commun.* **1998**, *28*, 729 – 735.

[16] D. L. Hughes, D. Zhao, *J. Org. Chem.* **1993**, *58*, 228 – 233.

[17] See the Supporting Information for the synthesis of **21**.

[18] a) P. L. Julian, J. Pikl, K. Boggess, *J. Am. Chem. Soc.* **1934**, *56*, 1797 – 1801; b) P. L. Julian, J. Pikl, *J. Am. Chem. Soc.* **1935**, *57*, 539 – 544.

[19] a) F. E. King, R. Robinson, *J. Chem. Soc.* **1932**, 326 – 336; b) B. K. Blount, R. Robinson, *J. Chem. Soc.* **1932**, 1429 – 1433; c) F. E. King, R. Robinson, *J. Chem. Soc.* **1932**, 1433 – 1438; d) F. E. King, R. Robinson, *J. Chem. Soc.* **1933**, 270 – 273; e) F. E. King, M. Liguori, R. Robinson, *J. Chem. Soc.* **1934**, 1416 – 1419.

[20] For examples of interrupted Fischer indolizations, see: a) I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, T. A. Ivanova, *Dokl. Akad. Nauk SSSR* **1967**, *176*, 583 – 585; b) A. Z. Britten, W. G. Bardsley, C. M. Hill, *Tetrahedron* **1971**, *27*, 5631 – 5639; c) I. I. Grandberg, G. P. Tokmakov, *Khim. Geterotsikl. Soedin.* **1975**, 207 – 210; d) P. Rosenmund, E. Sadri, *Liebigs Ann. Chem.* **1979**, 927 – 943; e) P. Rosenmund, S. Gektidis, H. Brill, R. Kalbe, *Tetrahedron Lett.* **1989**, *30*, 61 – 62; f) S. Takano, M. Moriya, Y. Iwabuchi, K. Ogasawara, *Chem. Lett.* **1990**, 109 – 112; g) R. Tsuji, M. Nakagawa, A. Nishida, *Heterocycles* **2002**, *58*, 587 – 593; h) B. W. Boal, A. W. Schammel, N. K. Garg, *Org. Lett.* **2003**, *5*, 3667 – 3669; i) A. Nishida, S. Ushigome, A. Sugimoto, S. Arai, *Heterocycles* **2005**, *66*, 181 – 185; j) A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron* **2010**, *66*, 4687 – 4695; k) L. Zu, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877 – 8879; l) C. Bunders, J. Cavanagh, C. Melander, *Org. Biomol. Chem.* **2011**, *9*, 5476 – 5481; m) A. W. Schammel, G. Chiou, N. K. Garg, *J. Org. Chem.* **2012**, *77*, 725 – 728; n) A. W. Schammel, G. Chiou, N. K. Garg, *Org. Lett.* **2012**, *14*, 4556 – 4559.

[21] a) J. Jobst, O. Hesse, *Ann. Chem. Pharm.* **1864**, *129*, 115 – 121; b) S. J. Traub, L. S. Nelson, R. S. Hoffman, *J. Toxicol. Clin. Toxicol.* **2002**, *40*, 781 – 787.

[22] M. G. Kulkarni, A. P. Dhondge, A. S. Borhade, D. D. Gaikwad, S. W. Chavhan, Y. B. Shaikh, V. B. Ningdale, M. P. Desai, D. R. Birhade, M. P. Shinde, *Tetrahedron Lett.* **2009**, *50*, 2411 – 2413.

[23] See the Supporting Information for the synthesis of **24**.

[24] For the use of 1, 10-phenanthroline in copper-catalyzed coupling of hydrazides with aryl iodides, see: M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803 – 3805.

[25] G. Massiot, P. Thepenier, M. J. Jacquier, L. Le Men-Olivier, C. Delaude, *Heterocycles* **1989**, *29*, 1435 – 1438.

[26] J. Mokrý, L. Dúbravková, P. Šefčovič, *Experientia* **1962**, *18*, 564 – 565.

[27] For a recent report on catalytic asymmetric Fischer indolization, see: S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537.

