Asymmetric Catalysis

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PyBidine/Copper Catalyst: Asymmetric *exo*′-Selective [3+2] Cycloaddition using Imino Ester and Electrophilic Indole**

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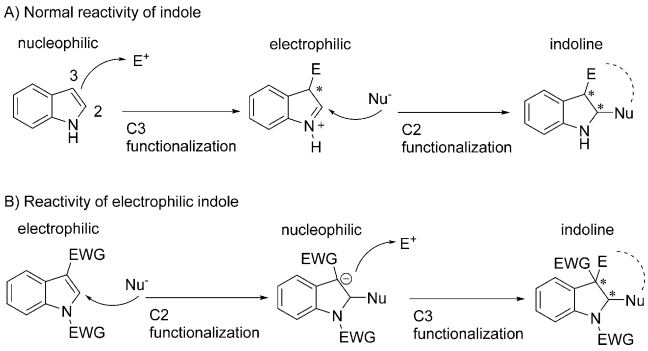
Abstract: *Electrophilic indoles having two electron-withdrawing groups undergo nucleophilic attack at C2 and electrophilic functionalization at C3. This is the first enantioselective formal [3+2] cycloaddition using electrophilic indoles. The PyBidine/Cu catalyst smoothly promoted highly enantio- and exo′-selective [3+2] cycloaddition using imino esters and 3-nitroindoles. This reaction provides a method for the preparation of diverse and complex chiral pyrroloindoline compounds.*

The indole skeleton is found in numerous biologically active compounds and pharmaceutical drugs.[1] Reactions involving indoles generally occur through nucleophilic attack at the C3-position, such as a Friedel–Crafts reaction.[2] Nucleophilic reaction at the C3-position acts as a trigger, thus trapping the iminium intermediate, which provides an elegant synthetic route for indoline derivatives (Scheme 1 A).[3] However, an indole containing two electron-withdrawing groups can behave as an electrophilic alkene.[4] These indoles undergo nucleophilic functionalization at the C2-position and attack electrophiles at the C3-position in an inverse manner (Scheme 1 B). The inverse reaction using electrophilic indoles provides highly functionalized indolines which are different from those indolines made using electron-enriched indoles. An example of a racemic reaction using electrophilic indoles was reported by Gribble and co-workers, who succeeded in synthesizing nonchiral pyrrolo[2,3-b]indole by an unusual Barton–Zard reaction of 3-nitroindoles with isocyanoacetate.[4a] Mancini et al. applied electrophilic indoles to a Diels–Alder reaction.[4d,g] Recently, Piettre et al. reported a [3+2] cycloaddition of an azomethine ylide with 3-nitroindoles.[4m] However, no example of a catalytic asymmetric reaction using electrophilic indoles has been reported.



Scheme 1. Reactivity of indole substrates.

In a study on catalytic asymmetric [3+2] cycloaddition reactions,[5] the bis(imidazolidine)pyridine (PyBidine)[6] and imidazoline aminophenol (IAP) ligands[7] were developed. The PyBidine/Cu complex catalyzed the *endo*-selective asymmetric [3+2] cycloaddition of nitroalkenes with imino esters.[6a] An *exo*′-selective enantioselective cyclization also has been achieved using a chiral IAP/Ni catalyst.[7a,b,8] We present herein a catalytic asymmetric [3+2] cycloaddition between imino esters and electrophilic indoles for diversity-oriented asymmetric catalysis (DOAC).[9,10] This strategy allows synthesis of pyrrolo[3,4-b]indole derivatives,[11,12] having a quaternary carbon center, which are structural isomers of cyclotryptamines.[13]

Initially, the effect of chiral catalysts on the [3+2] cycloaddition using 1-tosyl-3-nitroindole was first investigated (Table 1). The IAP/Ni catalyst gave the desired product with moderate enantioselectivity and lower diastereoselectivity. However, the IAP/Cu catalyst did not promote [3+2] cycloaddition. In contrast, the PyBidine/Cu catalyst smoothly catalyzed the reaction to give high diastereo- and enantioselectivity (entry 3). X-ray crystallographic analysis confirmed that the major isomer was of the *exo*′ form (see the Supporting Information).[14] Some of the chiral ligands examined (entries 4–7)[15] resulted in reduced catalyst activity, while the binap/Ag catalyst promoted *exo* selectivity. The use of Cs_2CO_3 as the base improved enantioselectivity (entry 9), and the catalyst loading was reduced to 5 mol% to obtain results similar to those shown in entry 3 (entry 10). The highly *exo*′-selective reaction is easily scaled up and maintains the excellent enantioselectivity (entry 11).

After optimization of the reaction conditions, the substrate scope for catalytic asymmetric [3+2] cycloaddition was investigated. Variously substituted N-Ts-protected 3-indoles provided products with excellent stereoselectiveties (Table 2, entries 1–5). Cycloaddition of the 5-chloro-3-nitroindole compound was conducted at 25 °C in 1,4-dioxane to ensure dissolution of the substrate (entry 2). 6-Methyl- and 7-chloro-3-nitroindoles required a longer reaction time (entries 6 and 7). Another sulfonyl protecting group, such as *p*-nitro- or *p*-methoxybenzenesulfonyl, was also compatible in the PyBi-

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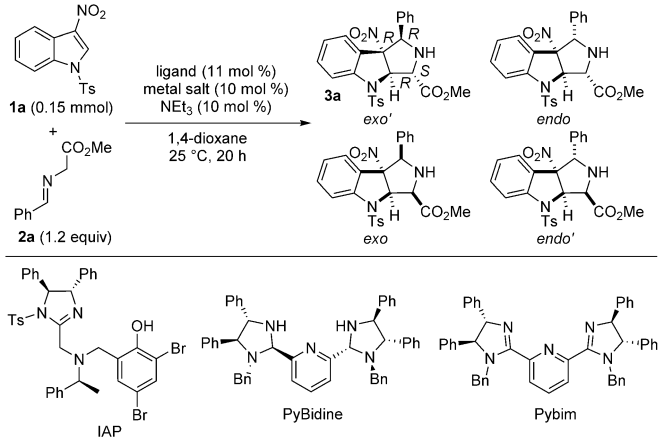
Table 1: Optimization of reaction conditions.



No.	Ligand	Metal salt	*t* [h]	Yield [%][a]	*exo′*/*exo*/*endo* (or *endo′*)[b]	*ee* [%] (*exo′*)
1	IAP	$Ni(OAc)_2$	20	61	56:44:n.d.	62
2	IAP	$Cu(OTf)_2$	20	trace	–	–
3	PyBidine	$Cu(OTf)_2$	20	75	>99:n.d.:n.d.	98
4	Pybim	$Cu(OTf)_2$	20	trace	–	–
5	(*S*,*S*)-*t*Bu-box[c]	$Cu(OTf)_2$	20	54	24:55:21	4
6	(*R*)-binap	$Cu(OTf)_2$	20	99	69:24:7	79
7	(*R*)-binap	$AgClO_4$	5	92	33:49:18	−55
8[c]	PyBidine	$Cu(OTf)_2$	8	78	>99:n.d.:n.d.	98.9
9[c,d]	PyBidine	$Cu(OTf)_2$	20	97	>99:n.d.:n.d.	99.6
10[c,d,e]	PyBidine	$Cu(OTf)_2$	48	91	>99:n.d.:n.d.	98
11[c,f]	PyBidine	$Cu(OTf)_2$	20	86	99:n.d.:n.d.	99

[a] Combined yield of diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Cs_2CO_3 was used instead of NEt_3. [d] Conducted at 10 °C. [e] 5 mol % catalyst and Cs_2CO_3 were used. [f] 1 mmol scale (427 mg of *exo′*-pyrroloindoline product were obtained). binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, (*S*,*S*)-*t*Bu-box = 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], Ts = 4-toluenesulfonyl, Tf = trifluoromethanesulfonyl.

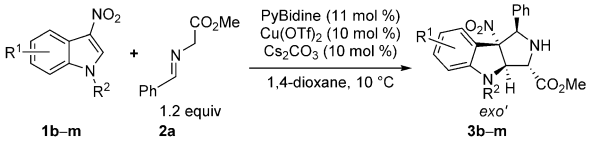
dine/Cu-catalyzed reaction. The N-acetylated or alkoxycarbonylated 3-nitroindoles gave chiral pyrroloindolines with satisfactory selectivity (entries 10–12).

Various imino esters gave products with good diastereoselectivity, and the major products possessed high enantioselectivity (Table 3, entries 1–5). Although the *o*-bromo substituent decreased enantioselectivity, an *o*-methyl group showed high enantiomeric excess (entries 6 and 7). Imino esters with a bicyclic skeleton also were converted into their corresponding *exo′* products (entries 8 and 9).

Chemical transformation of the indoline product is shown in Scheme 2. The nitro functionality on the quaternary carbon center was reduced to the amine **4a** using zinc powder and TMSCl.[16] The radical denitration proceeded selectively to produce **5a** in 72 % yield without loss of diastereoselectivity.[17] Enantiomeric excess was retained in these transformations.

The X-ray crystallographic analysis of **3a** revealed the (*S*,*S*)-diphenylethylene-diamine-derived PyBidine/$Cu(OTf)_2$ complex gave the *exo′*-(*R*,*S*,*R*,*R*)-cycloadduct as described in Table 1 (see the Supporting Information). The *exo′*-selective cycloaddition can be explained by a double *anti*-selective

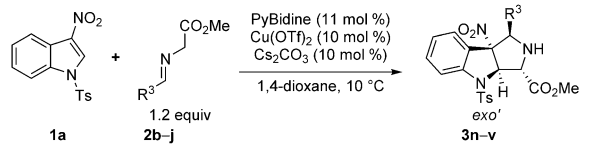
Table 2: Substrate scope of 3-nitroindoles.



No.	**1** (R^1, R^2)	*t* [h]	**3**	Yield [%][a]	*exo′*/*exo*/*endo* (or *endo′*)[b]	*ee* [%] (*exo′*)
1	**1b** (5-Br, Ts)	48	**3b**	99	97:3:n.d.	99
2[c]	**1c** (5-Cl, Ts)	40	**3c**	78	93:7:n.d.	96
3	**1d** (5-F, Ts)	19	**3d**	97	>99:n.d.:n.d.	99
4	**1e** (5-CN, Ts)	19	**3e**	99	>99:n.d.:n.d.	99
5	**1f** (5-BzO, Ts)	21	**3f**	82	>99:n.d.:n.d.	99
6	**1g** (6-Me, Ts)	46	**3g**	93	>99:nd:nd	99
7	**1h** (7-Cl, Ts)	48	**3h**	91	>99:n.d.:n.d.	99
8	**1i** (H, Nos)	24	**3i**	82	>99:n.d.:n.d.	99
9	**1j** (H, Mbs)	22	**3j**	99	90:10	91
10[c]	**1k** (H, Ac)	17	**3k**	98	>99:n.d.:n.d.	98
11	**1l** (H, CO_2Et)	22	**3l**	94	>99:n.d.:n.d.	97
12[c]	**1m** (H, Boc)	18	**3m**	82	>99:n.d.:n.d.	97

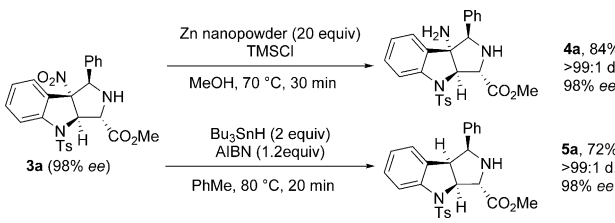
[a] Combined yield of diastereomers. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Conducted at 25 °C. Boc = *tert*-butoxycarbonyl, Mbs = *p*-methoxybenzenesulfonyl, Nos = *p*-nitrobenzenesulfonyl.

Table 3: Substrate scope of imino esters.



No.	**2** (R^3)	*t* [h]	**3**	Yield [%][a]	*exo′*/*exo*/*endo* (or *endo′*)[b]	*ee* [%] (*exo′*)
1	**2b** (4-BrC_6H_4)	20	**3n**	99	>99:n.d.:n.d.	99
2	**2c** (4-FC_6H_4)	27	**3o**	84	>99:n.d.:n.d.	96
3	**2d** (4-MeC_6H_4)	20	**3p**	92	>99:n.d.:n.d.	98
4	**2e** (4-$MeOC_6H_4$)	26	**3q**	81	>99:n.d.:n.d.	99
5	**2f** (3-ClC_6H_4)	24	**3r**	77	>99:n.d.:n.d.	98
6[c]	**2g** (2-BrC_6H_4)	24	**3s**	73	86:14:n.d.	65
7	**2h** (2-MeC_6H_4)	27	**3t**	90	95:5:n.d.	96
8	**2i** (3,4-(OCH_2O)-C_6H_3)	24	**3u**	92	>99:n.d.:n.d.	99
9	**2j** (1-naphthyl)	30	**3v**	80	92:8:n.d.	97

[a] Combined yield of diastereomers. [b] Determined by ^{1}H NMR analydis of the crude reaction mixture. [c] Conducted at 25 °C.



Scheme 2. Transformation of reaction products. AIBN = 2,2′-azobis(2-methylpropionitrile).

Michael/Mannich reaction (see a proposed transition state and the catalytic cycle in the Supporting Information).[18,19]

Although the PyBidine/Cu catalyst gave the *endo* product in the [3+2] cycloaddition of an imino ester with *trans*-β-nitrostyrene,[6a] the enantioface selection of the first Michael reaction is the same in both cases.

In summary, the PyBidine/Cu complex catalyzed an enantioselective formal [3+2] cycloaddition using imino esters and 3-nitroindoles. The highly enantiomerically enriched pyrrolindoline compounds were obtained with *exo′* selectivity. This reaction represents the first report of the catalytic asymmetric formal [3+2] cycloaddition using electrophilic indoles. This reaction provides an efficient method for constructing diverse and complex chiral pyrroindoline compounds. Research into further applications of this enantioselective [3+2] cycloaddition with 3-nitroindoles is in progress.

Experimental Section

Procedure for the catalytic asymmetric [3+2] cycloaddtion of imino ester with 3-nitroindoles (entry 11, Table 1): PyBidine (0.110 mmol) and $Cu(OTf)_2$ (0.100 mmol) were added to a two-necked round-bottomed flask containing a stir bar under Ar. 1,4-Dioxane (5 mL) was added to the flask and the mixture was stirred for 2 h. To the resulting solution, imino ester (1.20 mmol), and Cs_2CO_3 (0.100 mmol) were added subsequently at RT, then 3-nitroindole (1.00 mmol) was added at 25 °C. After being stirred for 20 h, the reaction mixture was quenched by water. The organic layer was extracted with chloroform. The collected organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the resulting crude reaction mixture was subjected to short column chromatography (Hex/AcOEt = 2:1) to remove decomposed imino esters. Column chromatography (Hex/AcOEt = 5:1) gave the product as white solid (427 mg). The enantiomeric excesses of the products were determined by chiral-phase HPLC using a Daicel Chiralpak IA column. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 8.1$ Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.23–7.18 (m, 6H), 7.04 (d, $J = 7.4$ Hz, 2H), 7.41 (dd, $J = 7.4$, 7.9 Hz, 1H), 6.00 (d, $J = 7.9$ Hz, 1H), 5.68 (s, 1H), 4.91 (s, 1H), 4.57 (s, 1H), 3.93 (s, 3H), 2.73 (br, 1H), 2.32 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.8$, 145.0, 143.9, 135.1, 132.6, 131.6, 129.9, 129.0, 128.7, 128.1, 127.9, 127.4, 123.3, 122.8, 114.8, 101.3, 72.7, 69.8, 66.0, 53.1, 21.5 ppm; HRMS calcd for $C_{25}H_{24}N_3O_6$ $[M+H]^+$: 494.1380, found: m/z 494.1370; Enantiomeric excess was determined by HPLC with a Chiralpak IA column (80:20 hexane:2-propanol, 1.0 mL min^{-1}, 254 nm); minor enantiomer $t_r = 11.1$ min, major enantiomer $t_r = 21.2$ min; $[\alpha]_D^{25} = +100.9$ ($c = 1.0$, $CHCl_3$, 99 % *ee*).

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[1] J. S. Bindra, *The Alkaloids*, *Vol. 14* (Eds: R. H. F. Manske), Academic Press, New York, **1973**, pp. 84–121.

[2] Selected reviews of Friedel–Crafts type reactions, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550; b) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199; c) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903; d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; e) S. L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; f) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449.

[3] For review, see: a) C. C. J. Loh, D. Enders, *Angew. Chem.* **2012**, *124*, 46; *Angew. Chem. Int. Ed.* **2012**, *51*, 46; b) M. Bandini, *Org. Biomol. Chem.* **2013**, *11*, 5206; c) L. M. Repka, S. E. Reisman, *J. Org. Chem.* **2013**, *78*, 12314; for a recent review of dearomatization reaction: d) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem.* **2012**, *124*, 12834; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; e) S. P. Roche, J. A. Porco, Jr., *Angew. Chem.* **2011**, *123*, 4154; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.

[4] a) E. T. Pelkey, L. Chang, G. W. Gribble, *Chem. Commun.* **1996**, 1909; b) E. T. Pelkey, G. W. Gribble, *Chem. Commun.* **1997**, 1873; c) E. T. Pelkey, G. W. Gribble, *Tetrahedron Lett.* **1997**, *38*, 5603; d) B. Biolatto, M. Kneeteman, P. M. E. Mancini, *Tetrahedron Lett.* **1999**, *40*, 3343; e) E. T. Pelkey, G. W. Gribble, *Synlett* **1999**, *7*, 1117; f) I. Chataigner, E. Hess, L. Toupet, S. R. Piettre, *Org. Lett.* **2001**, *3*, 525; g) B. Biolatto, M. Kneeteman, E. Paredes, P. M. E. Mancini, *J. Org. Chem.* **2001**, *66*, 3906; h) T. L. S. Kishbaugh, G. W. Gribble, *Tetrahedron Lett.* **2001**, *42*, 4783; i) A. Chrétien, I. Chataigner, N. L′Hélias, S. R. Piettre, *J. Org. Chem.* **2003**, *68*, 7990; j) S. Roy, T. L. S. Kishbaugh, J. P. Jasinski, G. W. Gribble, *Tetrahedron Lett.* **2007**, *48*, 1313; k) I. Chataigner, C. Panel, H. Gérard, S. R. Piettre, *Chem. Commun.* **2007**, 3288; l) I. Chataigner, S. R. Piettre, *Org. Lett.* **2007**, *9*, 4159: m) S. Lee, S. Diab, P. Queval, M. Sebban, I. Chataigner, S. R. Piettre, *Chem. Eur. J.* **2013**, *19*, 7181; n) C. Beemelmanns, S. Gross, H.-U. Reissig, *Chem. Eur. J.* **2013**, *19*, 17801; see also: o) M.-L. Teyssot, A.-T. Lormier, I. Chataigner, S. R. Piettre, *J. Org. Chem.* **2007**, *72*, 2364; p) N. Chopin, H. Gérard, I. Chataigner, S. R. Piettre, *J. Org. Chem.* **2009**, *74*, 1237; q) S. Lee, I. Chataigner, S. R. Piettre, *Angew. Chem.* **2011**, *123*, 492; *Angew. Chem. Int. Ed.* **2011**, *50*, 472.

[5] Reviews of catalytic asymmetric [3+2] cycloaddition: a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863; b) G. P. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484; c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235; e) S. Kanemasa, *Heterocycles* **2010**, *82*, 87; f) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784.

[6] a) T. Arai, A. Mishiro, N. Yokoyama, K. Suzuki, H. Sato, *J. Am. Chem. Soc.* **2010**, *132*, 5338; b) T. Arai, M. Mishiro, E. Matsumura, A. Awata, M. Shirasugi, *Chem. Eur. J.* **2012**, *18*, 11219.

[7] a) T. Arai, N. Yokoyama, A. Mishiro, H. Sato, *Angew. Chem.* **2010**, *122*, 8067; *Angew. Chem. Int. Ed.* **2010**, *49*, 7895; b) A. Awata, T. Arai, *Chem. Eur. J.* **2012**, *18*, 8278; c) A. Awata, M. Wasai, H. Masu, S. Kado, T. Arai, *Chem. Eur. J.* **2014**, *20*, 2470.

[8] Examples of enantioselective *exo′*-selective cyclization: a) S. Filippone, E. E. Maroto, A. Martin-Domenech, M. Suarez, N. Martin, *Nat. Chem.* **2009**, *1*, 578; b) Q.-H. Li, L. Wei, X. Chen, C.-J. Wang, *Chem. Commun.* **2013**, *49*, 6277; c) R. Narayan, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldman, *Angew. Chem.* **2013**, *125*, 13130; *Angew. Chem. Int. Ed.* **2013**, *52*, 12892.

[9] T. Arai, Y. Yamamoto, *Org. Lett.* **2014**, *16*, 1700.

[10] a) R. A. Stavenger, S. L. Schreiber, *Angew. Chem.* **2001**, *113*, 3525; *Angew. Chem. Int. Ed.* **2001**, *40*, 3417; b) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldman, *Nat. Chem.* **2010**, *2*, 735; c) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldman, *Angew. Chem.* **2012**, *124*, 9650; *Angew. Chem. Int. Ed.* **2012**, *51*, 9512; d) V. Eschenbrenner-Lux, P. Küchler, S. Ziegler, K. Kumar, H. Waldman, *Angew. Chem.* **2014**, *126*, 2166; *Angew. Chem. Int. Ed.* **2014**, *53*, 2134; also see, ref. [8c].

[11] For biological evaluations of pyrrolo[3,4-b]indole derivatives, see: a) A. V. Ivachtchenko, E. B. Frolov, O. D. Mitkin, S. E. Tkachenko, A. V. Khvat, *Chem. Heterocycl. Compd* **2010**, *46*, 170; b) M. R. Schrimpf, C.-H. Lee, T. Li, G. A. Gfesser, K. H.

Mortell, R. Faghih, D. L. Nersesian, K. B. Sippy, W. H. Bunnelle, M. Scanio (Abbot Labratories), WO 2010/036998A2, **2010**; c) A. A. Ivashchenko, A. V. Ivashchenko, S. Y. Tkachenko, I. M. Okun, N. F. Savchuk (Alla Chem. LLC), WO 2008/060190A2, **2008**; d) A. A. Ivashcn. henko, Y. B. Frolov, S. Y. Tkachenko, A. V. Khvat, S. V. Malyarchuk, O. D. Mitkin, I. M. Okun, A. S. Kyselev, N. F. Savchuk, A. V. Ivanshchenk (Alla Chem. LLC), WO 2008/026965A1, **2008**; e) Y. L. Chen (Pfizer Inc), EP 441517A2, **1991**.

[12] For synthesis of pyrrolo[3,4-b]indole derivatives, see: a) C.-K. Sha, J.-F. Yang, C.-J. Chang, *Tetrahedron Lett.* **1996**, *37*, 3487; b) G. W. Gribble, H. L. Fraser, J. C. Badenock, *Chem. Commun.* **2001**, 805; c) C. H. Wang, S. Alluri, A. K. Ganguly, *Tetrahedron Lett.* **2009**, *50*, 1879; d) H. Liu, C. Zhang, S.-L. You, *J. Org. Chem.* **2014**, *79*, 1047; and see Ref. [4].

[13] a) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Alvarez, *Chem. Eur. J.* **2011**, *17*, 1388; b) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; c) M. A. Schmidt, M. Movassaghi, *Synlett* **2008**, 313; also see, Ref. [3c].

[14] The stereochemistry is depicted by a Cossio's classification, see: M. Ayerbe, A. Arrieta, F. P. Cossio, *J. Org. Chem.* **1998**, *63*, 1795; also see, Ref. [18c].

[15] For recent reviews on bis(imidazoline)or bis(oxazoline)ligands, see: a) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284.

[16] F. Tan, L.-Q. Lu, Q.-Q. Yang, W. Guo, Q. Bian, J.-R. Chen, W.-J. Xiao, *Chem. Eur. J.* **2014**, *20*, 3415.

[17] A. Voituriez, J. Moulinas, C. Kouklovsky, Y. Langlois, *Synthesis* **2003**, 1419; also see ref. [4j].

[18] a) A. de Cózar, F. P. Cossío, *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858; b) E. Conde, D. Bello, Abel de Cózar, M. Sánchez, M. A. Vánquez, F. P. Cossío, *Chem. Sci.* **2012**, *3*, 1486; c) L. M. Castelló, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Org. Lett.* **2013**, *15*, 2902; d) E. E. Maroto, S. Filippone, M. Suárez, R. Martínez-Álvarez, A. de Cózar, F. P. Cossío, N. Martín, *J. Am. Chem. Soc.* **2014**, *136*, 705.

[19] The stepwise nature of the reaction was also supported by experimental results. See: a) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691; b) Y. H. Kim, L.-Y. Li, S. Kim, K. Oh, *J. Am. Chem. Soc.* **2011**, *133*, 20750; c) K. Imae, T. Konno, K. Ogata, S. Fukuzawa, *Org. Lett.* **2012**, *14*, 4410; also see, Ref. [7a,b].

