Convenient Synthesis of 1*H*-Indol-1-yl Boronates *via* Palladium(0)-Catalyzed Borylation of Bromo-1*H*-indoles with 'Pinacolborane'

by **Josef F. Stadlwieser*** and **Markus E. Dambaur**

Discovery Resarch, *ALTANA Pharma AG*, Byk-Gulden-Strasse 2, D-78467 Konstanz,
(e-mail: josef.stadlwieser@altanapharma.com)

An atom-economic Pd^0-catalyzed synthesis of a series of pinacol-type indolylboronates **3** from the corresponding bromoindole substrates **2** and pinacolborane (pinBH) as borylating agent was elaborated. The optimal catalyst system consisted of a 1:2 mixture of $[Pd(OAc)_2]$ and the *ortho*-substituted biphenylphosphine ligand **L-3** (*Scheme 4*, *Table*). Our synthetic protocol was applied to the fast, preparative-scale synthesis of 1-substituted indolylboronates **3a**–**h** in the presence of different functional groups, and at a catalyst load of only 1 mol-% of Pd.

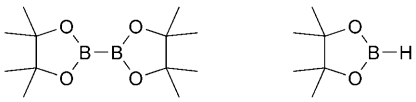
1. Introduction. – Arylboronic acids and their esters [1][2] have emerged as widely used nucleophiles in Pd^0-catalyzed carbon–carbon bond formation. They exhibit improved chemical stabilities compared to the corresponding Mg and Zn compounds, as well as lower toxicities relative to nucleophilic organostannanes commonly used in cross-coupling reactions [3][4].

Dealing with the high-throughput synthesis of compounds containing pharmaceutically relevant structural moieties, we were particularly interested in the efficient synthesis of diverse indolylboronates. Indolylboronic acids and their esters are often prepared by transmetalation (see, *e.g.*, [5]). However, the requirement of highly reactive lithiated intermediates prevents the presence of a range of versatile functional groups and, therefore, limits the applicability of this methodology to the synthesis of pharmacologically interesting building blocks.

Recently, the borylation of indole by Ir-catalyzed C–H activation was reported [6–8]. This elegant and atom-economic method was demonstrated to allow the preparation of indol-2-yl- or indol-3-yl-boronates from indoles with the aid of the reagents bis(pinacolato)diboron (pin_2B_2) or, alternatively, pinacolborane (pinBH)[1]) at ambient temperature [9][10].

The Pd^0-catalyzed borylation with pin_2B_2, first reported by *Miyaura* and co-workers [11], is an additional interesting methodology due to the wide range of tolerated functional groups [12–17]. However, the use of bromoindoles as substrates requires high loads of catalyst, judicious choice of reaction conditions [13][14], or microwave heating [15] to obtain good yields of 1*H*-indol-1-yl boronates. Borylation of 4-chloroindole was

[1]) Systematic name: 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.



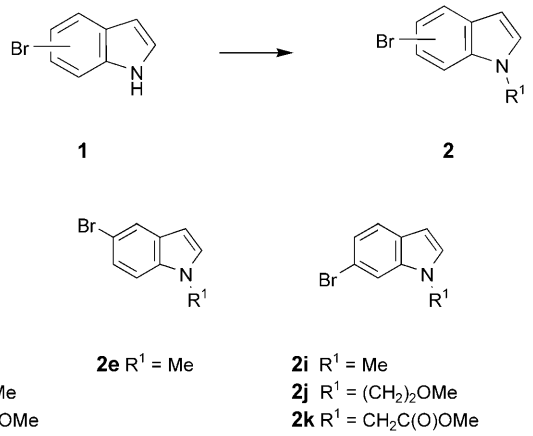
pin_2B_2 pinBH

achieved with the aid of a combination of $[Pd(dba)_2]$[2]) and tricyclohexylphosphane, $(C_6H_{11})_3P$, as catalyst [16].

In this communication, we describe the development of an upscalable and widely applicable Pd-catalyzed borylation of bromoindoles with pinBH as borylating agent under conditions allowing the presence of a range of functional groups.

2. Results and Discussion. – 2.1. *Preparation of Substrates.* The model substrates 5-bromo-1-(triisopropylsilyl)-1*H*-indole (**2a**) and 1-(triisopropylsilyl)-1*H*-indole (**4**) were prepared according to literature procedures [18][19]. The bromoindoles **2b** [20][21], **2c**–**d**, **2e** [18], **2h**–**j**, **2k** [22], and **2l** were prepared by alkylation of the commercially available bromoindoles **1a**–**d** using an appropriate alkylating agent and NaH as base. The reactions were performed at ambient temperature in 1,2-dimethoxyethane (DME) containing 10% of DMSO (*Scheme 1*).

Scheme 1



1 **2**

2b R^1 = Me
2c R^1 = $(CH_2)_2OMe$
2d R^1 = $CH_2C(O)OMe$

2e R^1 = Me

2i R^1 = Me
2j R^1 = $(CH_2)_2OMe$
2k R^1 = $CH_2C(O)OMe$

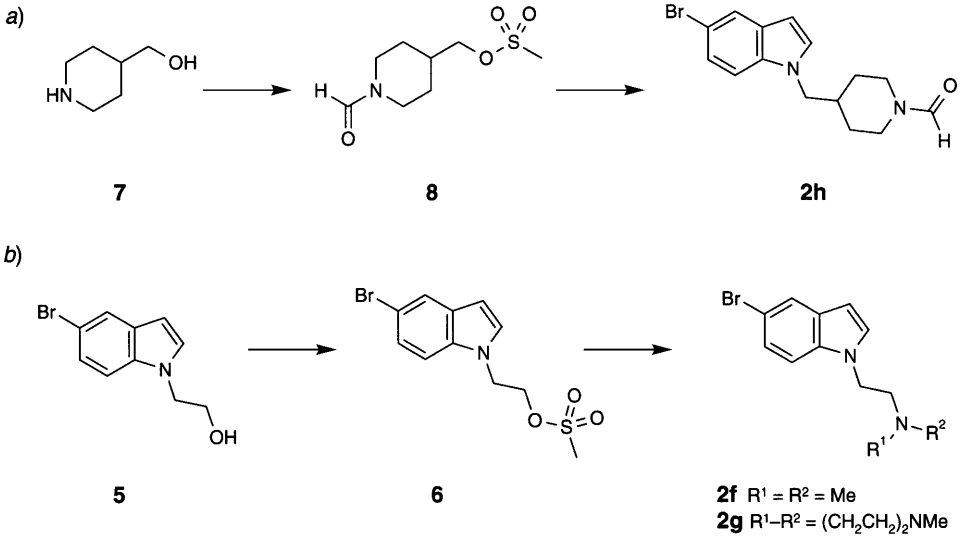
2l R^1 = Me

The alkylating agent **8** was prepared by selective *N*-formylation of commercially available (piperidin-4-yl)methanol (**7**) with HCO_2Me and subsequent reaction of the crude intermediate with methanesulfonyl chloride (MsCl) in the presence of Et_3N (overall yield: 88%; *Scheme 2*,*a*). Finally, the bromoindoles **2f** and **2g** were prepared in 92 and 93% yield, respectively, by mesylation of the alcohol **5** [23], followed by reaction of **6** with 5 equiv. of Me_2NH or 1-methylpiperazine (*Scheme 2*,*b*).

2.2. *Catalyst Screening.* In a first attempt based on *Masuda*'s protocol [24][25], we used **2a** as a substrate, and the Pd complexes $[Pd(dppf)Cl_2]$[3]) and $[Pd(PPh_3)_4]$ as cata-

[2]) The term 'dba' refers to 'dibenzylideneacetone'.
[3]) The term 'dppf' refers to diphenylphosphinoferrocen.

Scheme 2



lysts (*Scheme 3*). We observed the formation of the desired compound **3a**, along with a minor amount of the debrominated compound **4** at a poor conversion, even after prolonged heating (*Table*, *Entries 1* and *2*). Interestingly, when $[Pd(OAc)_2]$ was used as the catalyst in the *absence* of ligand, but under otherwise identical conditions, slow formation of **4** was the only observed reaction (*Entry 3*).

Assuming that Pd catalysts with electron-rich ligands facilitate oxidative addition to bromoindoles [16], we next studied the borylation of **2a** in the presence of commercially available $[Pd\{P(C_6H_{11})_3\}_2Cl_2]$. Unfortunately, **3a** was only formed in trace amounts after prolonged heating. On the other hand, unwanted **4** was not detected (HPLC) in the reaction mixture (*Entry 4*). The catalyst prepared from $[Pd(OAc)_2]$ and the imidazolium salt **L-1** in the presence of Et_3N – a system reported for microwave-assisted borylation of electron-poor aryl chlorides [26] – also proved inefficient to catalyze the transformation of **2a** into **3a**. Compound **4** was formed as the major product in a sluggish reaction (*Entry 5*).

Next, we investigated the combination of $[Pd(OAc)_2]$ with electron-rich and bulky *ortho*-(dialkylphosphino)biphenyl ligands. Such ligands have been extensively applied by *Buchwald* and co-workers in Pd-catalyzed coupling reactions (see, *e.g.*, [27]). A catalyst generated from $[Pd(dba)_2]$ and **L-2** was also disclosed to facilitate the borylation of 4-chlorobenzaldehyde with pin_2B_2 [16]. Noteworthy, the combination of $[Pd(dba)_2]$ with **L-2** or **L-3** was reported to lead to debromination when applied to the borylation of 3-bromo-2-nitrothiophene with pinBH [28]. For other substrates like *ortho*-substituted bromobenzenes, an efficient borylation with pinBH in the presence of $[Pd(OAc)_2]$ and **L-3** requires an exceptionally high catalyst load [29].

In our hands, the catalyst prepared from $[Pd(OAc)_2]$ and **L-2** (*Entry 6*) did not efficiently catalyze the transformation of **2a**. Besides minor amounts of desired **3a**, compound **4** was formed as the main product (48%). Fortunately, when the less-bulky

Scheme 3

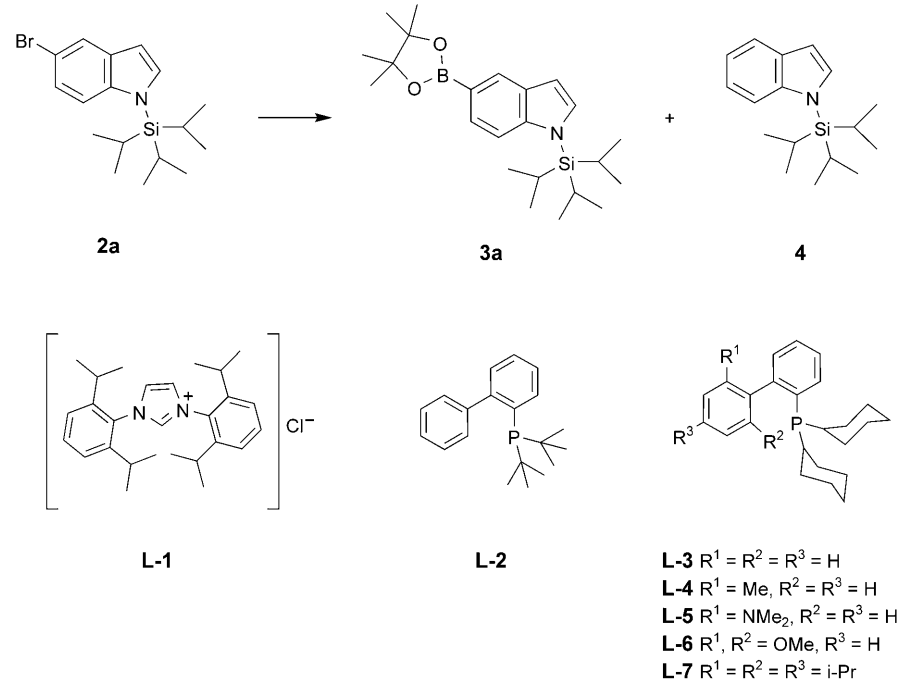


Table. *Reaction of* **2a** *with Pinacolborane (*pinBH*) and Different Catalysts* (see *Scheme 3*). Conditions: **2a** (2.0 mmol); pinBH (2.4 mmol), Pd (2.0 mol-%), Pd/ligand 1:2, Et_3N (6.0 mmol), 1,4-dioxane, $T = 80°$.

Entry	Catalyst	Time [h]	Product distribution [%][a])		
			2a	**3a**	**4**
1	$[Pd(dppf)Cl_2]$[3])	22	75	21	4
2	$[Pd(PPh_3)_4]$	22	68	28	4
3	$[Pd(OAc)_2]$	22	55	0	45
4	$[Pd\{P(C_6H_{11})_3\}_2Cl_2]$	22	98	2	0
5	$[Pd(OAc)_2]$/**L-1**	22	66	8	26
6	$[Pd(OAc)_2]$/**L-2**	22	35	17	48
7	$[Pd(OAc)_2]$/**L-3**	2	0	92	8
8	$[Pd(OAc)_2]$/**L-4**	2	0	89	11
9	$[Pd(OAc)_2]$/**L-5**	2	0	83	17
10	$[Pd(OAc)_2]$/**L-6**	22	25	34	41
11	$[Pd(OAc)_2]$/**L-7**	22	3	55	42

[a]) Based on a calibrated UV experiment (trace at 230 nm).

ligand **L-3** was used, fast transformation of **2a** into **3a** was observed, with only a small amount of **4** being formed after complete consumption of **2a** (*Entry 7*). Catalysts prepared from $[Pd(OAc)_2]$ and the 2-substituted ligands **L-4** and **L-5** also induced a fast transformation of **2a**, but compared to the catalyst ligated by **L-3**, the amount of **4**

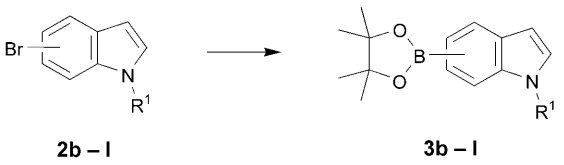
increased (*Entries 8* and *9*). The 2,6-disubstituted ligands **L-6** and **L-7** proved to be less efficient and led to substantial debromination, as reflected by the dominant formation of **4** (*Entries 10* and *11*).

2.3. *Preparative-Scale Synthesis.* Based on the screening results outlined above, we decided to use the inexpensive catalyst prepared from $[Pd(OAc)_2]$ and **L-3** for the preparative-scale (25 mmol) synthesis of various substituted indole-based 'pinacolboronates'. A catalyst load of 1.0 mol-% of $[Pd(OAc)_2]$ and 2.2 mol-% of **L-3** was sufficient to provide **3a** in 82% isolated yield from the reaction of **2a** with 1.2 equiv. of pinBH and 3.0 equiv. of Et_3N in 1,4-dioxane at 80°; the side product **4** was isolated in 6% yield after chromatographic separation.

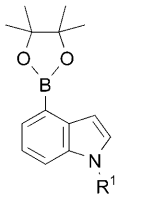
Under these conditions, the 4-bromoindoles **2b**–**d**, the 5-bromoindoles **2e**–**g**, the 6-bromoindoles **2i**–**k**, and 7-bromo-1-methylindole (**2l**) were all transformed into the corresponding pinacolboronates in isolated yields of 69–84% (*Scheme 4*). The compounds resulting from debromination of the starting materials, although detected by LC/MS in the crude reaction mixtures, could be readily removed by chromatography.

Noteworthy, the transformation of the amide-bearing substrate **2h** into **3h** required 1.5 equiv of pinBH and a prolonged reaction time to achieve complete transformation (77% yield). Two minor side products were detected by LC/MS, but not isolated.

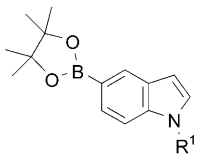
Scheme 4



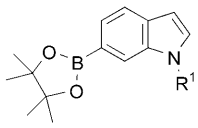
2b – l **3b – l**



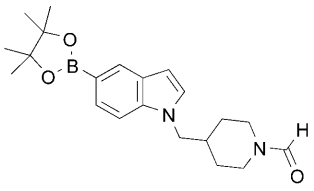
3b R^1 = Me
3c R^1 = $(CH_2)_2OMe$
3d R^1 = $CH_2C(O)OMe$



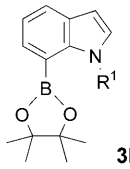
3e R^1 = Me
3f R^1 = $(CH_2)_2NMe_2$
3g R^1 = $(CH_2)_2N[(CH_2)_2]_2NMe$



3i R^1 = Me
3j R^1 = $(CH_2)_2OMe$
3k R^1 = $CH_2C(O)OMe$



3h



3l R^1 = Me

Conclusion. – We have established a procedure to synthesize pinacol-type indolylboronates from substituted 4-, 5-, 6-, or 7-bromoindoles. The inexpensive pinBH was demonstrated to be an efficient borylating agent. The reaction is readily catalyzed by the complex formed from $[Pd(OAc)_2]$ (1 mol-%) and the biphenylphospine ligand **L-3** (2.2 mol-%).

We gratefully acknowledge the help of our colleagues, Dr. *H.-C. Holst* and Mrs. *A. Rösler* (NMR); Dr. *J. Volz* and Mrs. *C. Schaub* (HR-MS); Mrs. *M. Beschle* and Mrs. *K.-M. Nagy* (LC/MS), and Mrs. *J. Bald* (excellent technical assistance). We also thank Dr. *B. Bartels* for helpful discussions during manuscript preparation.

Experimental Part

General. All Pd-catalyzed reactions were performed under Ar atmosphere using *Schlenk* techniques. 1,4-Dioxane and Et_3N for Pd-catalyzed reactions were distilled from CaH_2 under Ar. $[Pd(OAc)_2]$ (99.98%) was from *Aldrich*, $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ was from *Alfa Aesar*, $[Pd\{P(C_6H_{11})_3\}_2Cl_2]$ was from *ABCR*, $[Pd(PPh_3)_4]$ was from *Lancaster*, **L-1** was from *Fluka*, and **L-2** to **L-7** were purchased from *Strem*. Neutral alumina (*MP Alumina N – Super I*) contained 5% H_2O. Microwave-assisted reactions: *Biotage Initiator Sixty.* Column chromatography (CC): silica gel *60* (230–400 mesh ASTM, *Merck*). Bulb-to-bulb distillation: *Büchi 585* apparatus. M.p.: *Büchi 540* melting-point apparatus; uncorrected. Anal. HPLC and LC/MS: *Agilent 1100* system equipped with a binary pump, a well-plate autosampler, a column thermostat, a diode-array detector, and an API-ESI-MS detector; gradient elution with solvent *A* (H_2O/MeCN/1M aq. HCO_2H/1M aq. NH_4HCO_2 975:15:5:5) and solvent *B* (H_2O/MeCN/1M aq. HCO_2H/1M aq. NH_4HCO_2 15:975:5:5). *Condition 1*: *Agilent Zorbax SB-Aq* column (3.5 μm, 2.1×50 mm; 1.0 ml/min), with the following gradient: 10% *B* for 0.5 min, 10–90% *B* in 2.5 min, 90% *B* for 2 min. *Condition 2*: *Waters XTerra MS C_{18}* column (3.5 μm, 4.6×30 mm, 1.5 ml/min), with the following gradient: 50% *B* for 0.5 min, 50–80% *B* in 2.5 min, 80% *B* for 3 min. ^{1}H-NMR: *Bruker-DPX-200* (200 MHz) and *Bruker AV-400* (400 MHz); δ in ppm rel. to Me_4Si as internal standard, coupling constants *J* in Hz. HR-ESI-MS: *Bruker Daltronic Microtof*; in *m*/*z*.

(1-Formylpiperidin-4-yl)methyl Methanesulfonate (**8**). Methyl formate (18.02 g, 0.30 mol) was added dropwise to a stirred soln. of **7** (23.04 g, 0.20 mol) in anh. CH_2Cl_2 (100 ml). After complete addition, stirring was continued at r.t. for 16 h. The solvent was removed *in vacuo*, and the residue was dried azeotropically with toluene (3×100 ml). The resulting pale-yellow oil was dissolved in anh. CH_2Cl_2 (250 ml), and Et_3N (30.36 g, 0.30 mol) was added. To this stirred mixture cooled to 0° (ice/NaCl), a soln. of methanesulfonyl chloride (MsCl; 27.44 g, 0.24 mol) in anh. CH_2Cl_2 (100 ml) was added dropwise, keeping the temp. below 15°. After complete addition, stirring was continued for 2 h at r.t. The mixture was washed with 1N aq. HCl (200 ml) and H_2O (100 ml), dried ($MgSO_4$), and filtered through a short pad of neutral alumina (rinsing with several portions of CH_2Cl_2). The crude product was crystallized from AcOEt/hexane to yield 38.82 g (88%) of pure **8**. Colorless solid. M.p. 98° (AcOEt/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.03 (*s*, 1 H); 4.47 (*m*, 1 H); 4.09 (*m*, 2 H); 3.68 (*m*, 1 H); 3.10 (*m*, 1 H); 3.02 (*s*, 3 H); 2.64 (*m*, 1 H); 2.05 (*m*, 1 H); 1.86 (*m*, 2 H); 1.22 (*m*, 2 H). HR-ESI-MS: 222.0794 ($[M+H]^+$, $C_8H_{16}NO_4S^+$; calc. 222.0795).

General Procedure (*GP 1*) for the N-*Alkylation of Bromoindoles.* NaH (60% dispersion in mineral oil; 5.00 g, *ca.* 125.0 mmol) was washed oil-free with hexane (25 ml), and then suspended in anh. DME (225 ml) and DMSO (25 ml). The bromoindole **1** (100.0 mmol) was cautiously added to the well-stirred suspension in small portions. The mixture was stirred at r.t. for 30 min, before the appropriate electrophile (120.0 mmol) was added slowly. Stirring was continued at r.t. until the starting material was consumed (LC/MS, *Condition 1*). Ice-cold H_2O (50 ml) was added dropwise, followed by brine (50 ml). The mixture was stirred for another 15 min, the org. layer was separated, and concentrated *in vacuo*. The aq. layer was extracted with AcOEt (3×100 ml), the org. phases were combined, washed with

brine (50 ml), dried ($MgSO_4$), filtered through a short pad of neutral alumina, and concentrated *in vacuo*. The crude products were further purified by CC, followed by bulb-to-bulb distillation or crystallization.

*4-Bromo-1-methyl-1*H-*indole* (**2b**). Prepared according to *GP 1* from 4-bromoindole (**1a**) and MeI, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 20.00 g (95%). Pale-yellow oil after bulb-to-bulb distillation (95°/3×10^{-3} mbar). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.27 (*d*, *J* = 7.6, 1 H); 7.26 (*d*, *J* = 7.8, 1 H); 7.09 (*d*, *J* = 3.2, 1 H); 7.07 (*d*, *J* = 7.8, 1 H); 6.53 (*d*, *J* = 3.2, 1 H); 3.79 (*s*, 3 H). HR-ESI-MS: 209.9916 ($[M+H]^+$, $C_9H_9BrN^+$; calc. 209.9913).

*4-Bromo-1-(2-methoxyethyl)-1*H-*indole* (**2c**). Prepared according to *GP 1* from **1a** and 1-bromo-2-methoxyethane, and purified by CC (SiO_2; cyclohexane/AcOEt 4:1). Yield: 24.13 g (95%). Pale-yellow oil after bulb-to-bulb distillation (180°/8×10^{-3} mbar), solidifying upon standing at r.t. M.p. 38°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (*d*, *J* = 7.9, 1 H); 7.27 (*d*, *J* = 7.9, 1 H); 7.21 (*d*, *J* = 3.2, 1 H); 7.06 (*dd*, *J* = 7.9, 1 H); 6.55 (*dd*, *J* = 3.2, 0.6, 1 H); 4.27 (*t*, *J* = 5.5, 2 H); 3.69 (*t*, *J* = 5.5, 2 H); 3.30 (*s*, 3 H). HR-ESI-MS: 254.0170 ($[M+H]^+$, $C_{21}H_{33}BrN_3O_2^+$; calc. 254.0175).

*Methyl (4-Bromo-1*H-*indol-1-yl)acetate* (**2d**). Prepared according to *GP 1* from **1a** and methyl bromoacetate, and purified by CC (SiO_2; cyclohexane/AcOEt 4:1). Yield: 18.72 g (70%). Pale-yellow oil after bulb-to-bulb distillation (180°/8×10^{-3} mbar). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (*d*, *J* = 7.3, 1 H); 7.19 (*d*, *J* = 7.8, 1 H); 7.13 (*d*, *J* = 3.2, 1 H); 7.07 (*dd*, *J* = 7.8, 7.3, 1 H); 6.62 (*d*, *J* = 3.2, 1 H); 4.84 (*s*, 2 H); 3.74 (*s*, 3 H). HR-ESI-MS: 267.9974 ($[M+H]^+$, $C_{11}H_{11}BrNO_2^+$; calc. 267.9968).

*5-Bromo-1-methyl-1*H-*indole* (**2e**). Prepared according to *GP 1* from **1b** and MeI, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 15.81 g (75%). Colorless solid. M.p. 41° (hexane) (lit. m.p. 42–43° [17]). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.73 (*d*, *J* = 1.8, 1 H); 7.29 (*dd*, *J* = 8.7, 1.8, 1 H); 7.17 (*d*, *J* = 8.7, 1 H); 7.03 (*d*, *J* = 3.1, 1 H); 6.41 (*d*, *J* = 3.1, 1 H); 3.76 (*s*, 3 H). HR-ESI-MS: 209.9918 ($[M+H]^+$, $C_9H_9BrN^+$; calc. 209.9913).

*4-[(5-Bromo-1*H-*indol-1-yl)methyl]piperidine-1-carbaldehyde* (**2h**). Prepared according to *GP 1* from **1b** and **8**, and purified by CC (SiO_2; AcOEt). Yield: 26.58 g (83%). Colorless solid. M.p. 88–89° (AcOEt/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.99 (*s*, 1 H); 7.75 (*d*, *J* = 2.0, 1 H); 7.29 (*dd*, *J* = 8.8, 2.0, 1 H); 7.16 (*d*, *J* = 8.8, 1 H); 7.03 (*d*, *J* = 3.2, 1 H); 6.44 (*d*, *J* = 3.2, 1 H); 4.44 (*m*, 1 H); 3.99 (*m*, 2 H); 3.60 (*m*, 1 H); 2.98 (*m*, 1 H); 2.54 (*m*, 1 H); 2.11 (*m*, 1 H); 1.60 (*m*, 2 H); 1.20 (*m*, 2 H). HR-ESI-MS: 343.0417 ($[M+Na]^+$, $C_{15}H_{17}BrN_2NaO^+$; calc. 343.0416).

*6-Bromo-1-methyl-1*H-*indole* (**2i**). Prepared according to *GP 1* from **1c** and MeI, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 19.88 g (95%). Pale-yellow oil after bulb-to-bulb distillation (90°/3×10^{-3} mbar). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.47 (*d*, *J* = 8.3, 1 H); 7.46 (br. *s*, 1 H); 7.19 (*dd*, *J* = 8.3, 1.6, 1 H); 7.01 (*d*, *J* = 3.1, 1 H); 6.44 (*d*, *J* = 3.1, 1 H); 3.75 (*s*, 3 H). HR-ESI-MS: 209.9920 ($[M+H]^+$, $C_9H_9BrN^+$; calc. 209.9913).

*6-Bromo-1-(2-methoxyethyl)-1*H-*indole* (**2j**). Prepared according to *GP 1* from **1c** and 1-bromo-2-methoxyethane, and purified by CC (SiO_2; cyclohexane/AcOEt 4:1). Yield: 25.10 g (99%). Pale-yellow oil after bulb-to-bulb distillation (180°/7×10^{-3} mbar), solidifying upon standing at r.t. M.p. 46°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.50 (*s*, 1 H); 7.47 (*d*, *J* = 8.4, 1 H); 7.19 (*d*, *J* = 8.4, 1 H); 7.13 (*d*, *J* = 3.2, 1 H); 6.46 (*d*, *J* = 3.2, 1 H); 4.23 (*t*, *J* = 5.5, 2 H); 3.68 (*t*, *J* = 5.5, 2 H); 3.31 (*s*, 3 H). HR-ESI-MS: 254.0180 ($[M+H]^+$, $C_{11}H_{13}BrNO^+$; calc. 254.0175).

*Methyl (6-Bromo-1*H-*indol-1-yl)acetate* (**2k**). Prepared according to *GP 1* from **1c** and methyl bromoacetate, and purified by CC (SiO_2; cyclohexane/AcOEt 4:1). Yield: 19.05 g (71%). Pale-yellow oil after bulb-to-bulb distillation (180°/4×10^{-2} mbar), solidifying upon standing at r.t. M.p. 75°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.48 (*d*, *J* = 8.3, 1 H); 7.40 (*s*, 1 H); 7.24 (*dd*, *J* = 8.3, 1.7, 1 H); 7.05 (*d*, *J* = 3.2, 1 H); 6.53 (*d*, *J* = 3.2, 1 H); 4.81 (*s*, 2 H); 3.76 (*s*, 3 H). HR-ESI-MS: 267.9958 ($[M+H]^+$, $C_{11}H_{11}BrNO_2^+$; calc. 267.9968).

*7-Bromo-1-methyl-1*H-*indole* (**2l**). Prepared according to *GP 1* from **1d** and MeI, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 16.65 g (79%). Colorless solid. M.p. 52° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.52 (*dd*, *J* = 7.7, 0.9, 1 H); 7.33 (*dd*, *J* = 7.7, 0.9, 1 H); 6.97 (*d*, *J* = 3.1, 1 H); 6.89 (*dd*, *J* = 7.7, 1 H); 6.44 (*d*, *J* = 3.1, 1 H); 4.14 (*s*, 3 H). HR-ESI-MS: 209.9915 ($[M+H]^+$, $C_9H_9BrN^+$; calc. 209.9913).

*2-(5-Bromo-1*H-*indol-1-yl)ethyl Methanesulfonate* (**6**). Et(i-Pr)$_2$N (14.31 g, 110.70 mmol) and 4-(dimethylamino)pyridine (DMAP; 0.90 g, 7.38 mmol) was added to a soln. of **5** [23] (17.72 g, 73.81 mmol) in anh. CH_2Cl_2 (270 ml). The stirred mixture was cooled to 0°, and a soln. of MsCl (10.14 g,

88.56 mmol) in anh. CH_2Cl_2 (100 ml) was added dropwise at a rate to keep the temp. below 15°. After complete addition, stirring was continued for 1 h at r.t. The mixture was washed with H_2O (100 ml), dried ($MgSO_4$), and filtered through a short pad of neutral alumina (rinsing with several portions of CH_2C_2). The crude product was purified by CC (SiO_2; cyclohexane/AcOEt 1:1), and crystallized from AcOEt/hexane to yield 22.48 g (96%) of **6**. Colorless solid. M.p. 64°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.76 (*d*, *J* = 1.7, 1 H); 7.33 (*dd*, *J* = 8.8, 1.7, 1 H); 7.22 (*d*, *J* = 8.8, 1 H); 7.14 (*d*, *J* = 3.2, 1 H); 6.48 (*d*, *J* = 3.2, 1 H); 4.47 (*m*, 4 H); 2.66 (*s*, 3 H). HR-ESI-MS: 317.9795 ($[M+H]^+$, $C_{11}H_{13}BrNO_3S^+$; calc. 317.9794).

General Procedure (*GP 2*) *for the Reaction of* **6** *with Secondary Amines.* Six pressure vials, each equipped with a stirring bar, were charged with equal parts of a soln. of **6** (15.91 g; 50.0 mmol) and the appropriate amine (250.0 mmol) in THF (50 ml). The vials were capped, and heated in a single-mode microwave oven at 140° for 30 min. The mixtures were pooled, and concentrated *in vacuo*. The residue was partitioned between AcOEt (250 ml) and H_2O (100 ml). The org. layer was washed with brine (100 ml), dried ($MgSO_4$), and filtered through a short pad of neutral alumina (rinsing with several portions of AcOEt). The crude products were further purified by bulb-to-bulb distillation.

*2-(5-Bromo-1*H*-indol-1-yl)-*N,N*-dimethylethanamine* (**2f**). Prepared according to *GP 2* from **6** and an 11M aq. Me_2NH soln. Yield: 12.25 g (92%). Colorless oil after bulb-to-bulb distillation (160°/3×10^{-2} mbar). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.74 (*d*, *J* = 1.7, 1 H); 7.28 (*dd*, *J* = 8.8, 1.7, 1 H); 7.20 (*d*, *J* = 8.8, 1 H); 7.14 (*d*, *J* = 3.2, 1 H); 6.42 (*d*, *J* = 3.2, 1 H); 4.20 (*t*, *J* = 7.1, 2 H); 2.68 (*t*, *J* = 7.1, 2 H); 2.28 (*s*, 6 H). HR-ESI-MS: 267.0496 ($[M+H]^+$, $C_{12}H_{16}BrN_2^+$; calc. 267.0491).

*5-Bromo-1-[2-(4-methylpiperazin-1-yl)ethyl]-1*H*-indole* (**2g**). Prepared according to *GP 2* from **6** and 1-methylpiperazine. Yield: 15.05 g (93%). Pale-yellow oil after bulb-to-bulb distillation (195°/3×10^{-2} mbar), solidifying upon standing at r.t. M.p. 62°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.73 (*d*, *J* = 2.0, 1 H); 7.28 (*dd*, *J* = 8.8, 2.0, 1 H); 7.21 (*d*, *J* = 8.8, 1 H); 7.14 (*d*, *J* = 3.2, 1 H); 6.41 (*d*, *J* = 3.2, 1 H); 4.20 (*t*, *J* = 6.9, 2 H); 2.73 (*t*, *J* = 6.9, 2 H); 2.48 (*m*, 8 H); 2.28 (*s*, 3 H). HR-ESI-MS: 322.0911 ($[M+H]^+$, $C_{15}H_{21}BrN_3^+$; calc. 322.0913).

Catalyst Screening. A *Schlenk* tube equipped with a magnetic stirring bar was charged with $[Pd(OAc)_2]$ (9 mg, 0.040 mmol) and an the appropriate ligand (0.088 mmol) under Ar atmosphere. (Alternatively, the tube was charged with 0.04 mmol of a Pd^0 catalyst.) The tube was evaporated, back-filled with Ar, and treated with 1,4-dioxane (5.0 ml) *via* syringe. After stirring for 30 min at r.t., Et_3N (6.0 mmol) was added *via* syringe, followed by a soln. of **2a** (705 mg, 2.0 mmol) in anh. 1,4-dioxane (5.0 ml). Then, neat pinBH (307 mg, 2.4 mmol) was added, and the mixture was stirred at 80° (HPLC, *Condition 2*). The rel. amounts of **2a**, **3a**, and **4** were determined from UV traces at 230 nm (see *Table*). The rel. response rates were calculated from repeated injections of samples containing equimolar amounts of **2a**, **3a**, and **4**.

General Procedure (*GP 3*) *for the Borylation of Bromoindoles.* An Ar-filled *Schlenk* flask equipped with a magnetic stirring bar was charged with $[Pd(OAc)_2]$ (0.056 g, 0.25 mmol) and ligand **L-3** (0.193 g, 0.55 mmol). The flask was evaporated, back-filled with Ar, and anh. 1,4-dioxane (50 ml) was added. After stirring for 30 min at r.t., Et_3N (7.59 g, 75.0 mmol) was added *via* syringe, followed by a soln. of the appropriate bromoindole (25.0 mmol) in anh. 1,4-dioxane (50 ml). Neat pinBH (3.83 g, 30.0 mmol, 1.2 equiv)[4]) was added, and the mixture was stirred at 80° (LC/MS; *Condition 1*). After complete consumption of the starting material (2–8 h), the mixture was allowed to cool to r.t. *Celite* (1 g) and activated charcoal (1 g) were added, and stirring was continued for 15 min. After suction filtration, the solvent was removed *in vacuo*. The residue was diluted with cyclohexane (or AcOEt in the case of **3f**–**h**), and filtered through a short pad of neutral alumina (rinsing with several portions of cyclohexane (or AcOEt)). The crude product was purified by CC, followed by bulb-to-bulb distillation or crystallization.

*5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[tris(1-methylethyl)silyl]-1*H*-indole* (**3a**) *and 1-[Tris(1-methylethyl)silyl]-1*H*-indole* (**4**). Prepared according to *GP 3* from **2a**, and purified by CC (SiO_2; hexane).

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[4]) For **2h**, 4.80 g (37.5 mmol, 1.5 equiv.) of pinBH were used.

Data of **3a** (slower eluting). Yield: 8.20 g (82%). Colorless oil after bulb-to-bulb distillation (195°/8×10^{-3} mbar), solidifying upon standing at r.t. M.p. 107°. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.15 (*s*, 1 H); 7.59 (*d*, *J* = 8.4, 1 H); 7.49 (*d*, *J* = 8.4, 1 H); 7.23 (*d*, *J* = 3.3, 1 H); 6.63 (*d*, *J* = 3.3, 1 H); 1.70 (*sept.*, *J* = 7.5, 3 H); 1.35 (*s*, 12 H); 1.13 (*d*, *J* = 7.5, 18 H). HR-ESI-MS: 400.2841 ($[M+H]^+$, $C_{23}H_{39}BNO_2Si^+$; calc. 400.2838).

Data of **4** (faster eluting). See [19]. Yield: 0.40 g (6%). Colorless oil.

*1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3b**). Prepared according to *GP 3* from **2b**, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 5.10 g (79%). Colorless solid. M.p. 93° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.62 (*d*, *J* = 6.9, 1 H); 7.42 (*d*, *J* = 8.2, 1 H); 7.22 (*dd*, *J* = 8.2, 6.9, 1 H); 7.09 (*d*, *J* = 3.1, 1 H); 6.97 (*d*, *J* = 3.1, 1 H); 3.79 (*s*, 3 H); 1.38 (*s*, 12 H). HR-ESI-MS: 280.1477 ($[M+Na]^+$, $C_{15}H_{20}BNNaO_2^+$; calc. 280.1479).

*1-(2-Methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3c**). Prepared according to *GP 3* from **2c**, and purified by CC (SiO_2; cyclohexane/AcOEt 3:1). Yield: 5.19 g (69%). Colorless solid. M.p. 100° (^{t}BuOMe/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.61 (*d*, *J* = 7.1, 1 H); 7.45 (*d*, *J* = 8.3, 1 H); 7.21 (*m*, 2 H); 6.99 (*d*, *J* = 3.2, 1 H); 4.29 (*t*, *J* = 5.6, 2 H); 3.68 (*t*, *J* = 5.6, 2 H); 3.28 (*s*, 3 H); 1.38 (*s*, 12 H). HR-ESI-MS: 302.1920 ($[M+H]^+$, $C_{17}H_{25}BNO_3^+$; calc. 302.1922).

*Methyl [4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indol-1-yl]acetate* (**3d**). Prepared according to *GP 3* from **2d**, and purified by CC (SiO_2; cyclohexane/AcOEt 3:1). Yield: 6.22 g (79%). Colorless solid. M.p. 81° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.64 (*d*, *J* = 6.9, 1 H); 7.35 (*d*, *J* = 8.1, 1 H); 7.22 (*dd*, *J* = 8.1, 6.9, 1 H); 7.13 (*d*, *J* = 3.2, 1 H); 7.06 (*d*, *J* = 3.2, 1 H); 4.86 (*s*, 2 H); 3.71 (*s*, 3 H), 1.38 (*s*, 12 H). HR-ESI-MS: 316.1709 ($[M+H]^+$, $C_{17}H_{23}BNO_4^+$; calc. 316.1715).

*1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3e**). Prepared according to *GP 3* from **2e**, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 5.05 g (78%). Colorless solid. M.p. 112° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.15 (*s*, 1 H); 7.66 (*d*, *J* = 8.3, 1 H); 7.31 (*d*, *J* = 8.3, 1 H); 7.03 (*d*, *J* = 3.1, 1 H); 6.49 (*d*, *J* = 3.1, 1 H); 3.78 (*s*, 3 H); 1.36 (*s*, 12 H). HR-ESI-MS: 258.1656 ($[M+H]^+$, $C_{15}H_{21}BNO_2^+$; calc. 258.1660).

N,N-*Dimethyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indol-1-yl]ethanamine* (**3f**). Prepared according to *GP 3* from **2f**, and purified by bulb-to-bulb distillation (185°/8×10^{-3} mbar). Colorless oil. Yield: 6.62 g (84%). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.15 (*s*, 1 H); 7.65 (*d*, *J* = 8.3, 1 H); 7.34 (*d*, *J* = 8.3, 1 H); 7.12 (*d*, *J* = 3.2, 1 H); 6.50 (*d*, *J* = 3.2, 1 H); 4.23 (*t*, *J* = 7.1, 2 H); 2.68 (*t*, *J* = 7.1, 2 H); 2.28 (*s*, 6 H); 1.36 (*s*, 12 H). HR-ESI-MS: 315.2248 ($[M+H]^+$, $C_{18}H_{28}BN_2O_2^+$; calc. 315.2238).

*1-[2-(4-Methylpiperazin-1-yl)ethyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3g**). Prepared according to *GP 3* from **2g**. Yield: 6.97 g (75%). Colorless solid. M.p. 115° (SiO_2; ^{t}BuOMe/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.15 (*s*, 1 H); 7.65 (*d*, *J* = 8.3, 1 H); 7.34 (*d*, *J* = 8.3, 1 H); 7.13 (*d*, *J* = 3.2, 1 H); 6.50 (*d*, *J* = 3.2, 1 H); 4.24 (*t*, *J* = 7.1, 2 H); 2.75 (*t*, *J* = 7.1, 2 H); 2.49 (*m*, 8 H); 2.29 (*s*, 3 H); 1.36 (*s*, 12 H). HR-ESI-MS: 370.2642 ($[M+H]^+$, $C_{21}H_{33}BN_3O_2^+$; calc. 370.2660).

*4-{[5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indol-1-yl]methyl}piperidine-1-carbaldehyde* (**3h**). Prepared according to *GP 3* from **2h**, and purified by CC (SiO_2; AcOEt). Yield: 7.16 g (78%). Colorless solid. M.p. 151–152° (AcOEt/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.17 (*s*, 1 H); 7.99 (*s*, 1 H); 7.66 (*dd*, *J* = 8.3, 1.0, 1 H); 7.30 (*d*, *J* = 8.3, 1 H); 7.02 (*d*, *J* = 3.2, 1 H); 6.52 (*d*, *J* = 3.2, 1 H); 4.42 (*m*, 1 H); 4.02 (*m*, 2 H); 3.58 (*m*, 1 H); 2.96 (*m*, 1 H); 2.53 (*m*, 1 H); 2.13 (*m*, 1 H); 1.60 (*m*, 2 H); 1.36 (*s*, 12 H); 1.19 (*m*, 2 H). HR-ESI-MS: 369.2352 ($[M+H]^+$, $C_{21}H_{30}BN_2O_3^+$; calc. 369.2344).

*1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3i**). Prepared according to *GP 3* from **2i**, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 4.64 g (72%). Colorless solid. M.p. 98° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.83 (*s*, 1 H); 7.62 (*d*, *J* = 8.0, 1 H); 7.54 (*d*, *J* = 8.0, 1 H); 7.10 (*d*, *J* = 3.1, 1 H); 6.47 (*d*, *J* = 3.1, 1 H); 3.83 (*s*, 3 H); 1.38 (*s*, 12 H). HR-ESI-MS: 258.1664 ($[M+H]^+$, $C_{15}H_{21}BNO_2^+$; calc. 258.1660).

*1-(2-Methoxyethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H-*indole* (**3j**). Prepared according to *GP 3* from **2j**, and purified by CC (SiO_2; cyclohexane/AcOEt 3:1). Yield: 5.95 g (79%). Colorless solid. M.p. 71° (^{t}BuOMe/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.83 (*s*, 1 H); 7.63 (*d*, *J* = 7.9, 1 H); 7.54 (*d*, *J* = 7.9, 1 H); 7.23 (*d*, *J* = 3.1, 1 H); 6.48 (*d*, *J* = 3.1, 1 H); 4.33 (*t*, *J* = 5.6, 2 H); 3.70 (*t*, *J* = 5.6, 2 H); 3.30 (*s*, 3 H); 1.37 (*s*, 12 H). HR-ESI-MS: 302.1894 ($[M+H]^+$, $C_{17}H_{25}BNO_3^+$; calc. 302.1898).

*Methyl [6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl]acetate* (**3k**). Prepared according to *GP 3* from **2k**, and purified by CC (SiO_2; cyclohexane/AcOEt 3:1). Yield: 6.13 g (77%). Colorless solid. M.p. 98° (^{t}BuOMe/hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.74 (*s*, 1 H); 7.64 (*d*, *J* = 7.9, 1 H); 7.57 (*d*, *J* = 7.9, 1 H); 7.14 (*d*, *J* = 3.2, 1 H); 6.57 (*dd*, *J* = 3.2, 0.8, 1 H); 4.92 (*s*, 2 H); 3.74 (*s*, 3 H); 1.37 (*s*, 12 H). HR-ESI-MS: 316.1703 ($[M+H]^+$, $C_{17}H_{23}BNO_4^+$; calc. 316.1715).

*1-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole* (**3l**). Prepared according to *GP 3* from **2l**, and purified by CC (SiO_2; cyclohexane/AcOEt 9:1). Yield: 4.79 g (74 %). Colorless solid. M.p. 95° (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.71 (*dd*, *J* = 7.5, 1.1, 1 H); 7.66 (*dd*, *J* = 7.5, 1.1, 1 H); 7.09 (*dd*, *J* = 7.5, 1 H); 7.01 (*d*, *J* = 3.2, 1 H); 6.48 (*d*, *J* = 3.2, 1 H); 3.97 (*s*, 3 H); 1.39 (*s*, 12 H). HR-ESI-MS: 258.1652 ($[M+H]^+$, $C_{15}H_{21}BNO_2^+$; calc. 258.1660).

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Received January 20, 2006