DOI: 10.1002/ejoc.201101446

3-Alkenyl-2-silyloxyindoles: An Enabling, Yet Understated Progeny of Vinylogous Carbon Nucleophiles

Gloria Rassu,*[a] Vincenzo Zambrano,[a] Rossella Tanca,[a] Andrea Sartori,[b] Lucia Battistini,[b] Franca Zanardi,[b] Claudio Curti,*[b] and Giovanni Casiraghi*[b]

Keywords: Aldol reactions / Asymmetric catalysis / Nitrogen heterocycles / Silicon / Nucleophiles

We introduce novel 3-alkenyl-2-silyloxyindole nucleophiles and demonstrate their utility by developing an unprecedented vinylogous Mukaiyama-type aldol reaction with aromatic aldehydes. This reaction displays excellent levels of γ-site selectivity and diastereoselectivity and delivers valuable hydroxylated oxindoles bearing a substituted exocyclic double bond at the C-3 position. A preliminary trial of an asymmetric, catalytic version was conducted, and it showed promising enantioselectivity for the desired vinylogous aldol products.

Introduction

The oxindole moiety is central in a number of natural and man-made alkaloid products, many of which display attractive profiles for biological and pharmaceutical applications.[1] A common feature of this complex compound progeny is the substitution of the indole C-3 position, a pattern present in several 3,3-spirofused and 3,4-bridged oxindoles, such as marcfortine B,[2] welwitindolinone C,[3] and gelsemine[4] core structures (Figure 1). These motives can be realized in diverse synthetic ways, among which the direct or indirect aldol-, Mannich-, and Michael-type C-3 functionalization of simple oxindole matrices is one of the most suited protocols.[5] In spite of the efficiency of this approach and the amount of literature data available, there is no information on the use of 3-alkylidene oxindoles and 3-alkenyl-2-silyloxyindoles arising from them as the nucleophilic components in vinylogous aldolizations and related processes,[6] a maneuver that would render a number of structurally diverse hydroxylated oxoindolinylidene frameworks expediently accessible.

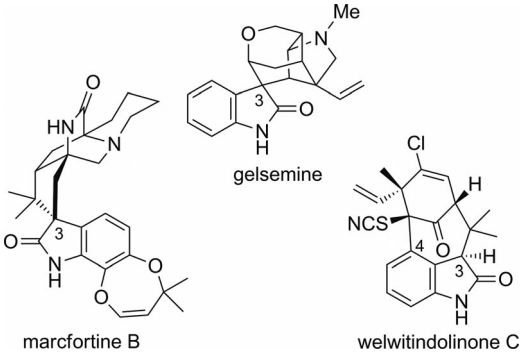
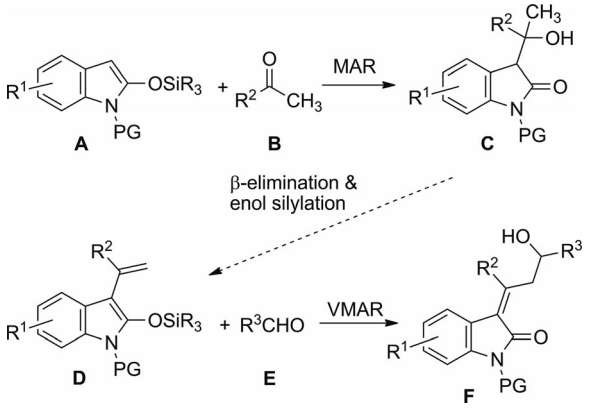


Figure 1. Relevant naturally occurring members of the oxindole alkaloid family.

Scheme 1 depicts a scenario where a "normal" Mukaiyama-type aldol reaction (MAR) and a related vinylogous variant (VMAR)[7] are confronted. Focusing on oxindole products **C** and **F**, one can realize that extended 3-alkylidene indolinones **F**, arising from vinyl-silyl ketene N,O-acetals **D** bearing an exocyclic double bond with two prochiral carbon atoms, are structurally more adorned as compared to carbinols **C**. This elects indolinones **F** as privileged structures that can be subjected to various synthetic manipula-



Scheme 1. Mukaiyama aldol reaction (MAR) and vinylogous Mukaiyama aldol reaction (VMAR) involving 2-silyloxyindoles **A** and **D**.

[a] Istituto di Chimica Biomolecolare del CNR,
Traversa La Crucca 3, 07100 Li Punti, Sassari, Italy
Fax: +39-079-2841299
E-mail: gloria.rassu@icb.cnr.it
[b] Dipartimento Farmaceutico, Università degli Studi di Parma,
Parco Area delle Scienze 27A, 43124 Parma, Italy
Fax: +39-0521-905006
E-mail: claudio.curti@unipr.it
giovanni.casiraghi@unipr.it

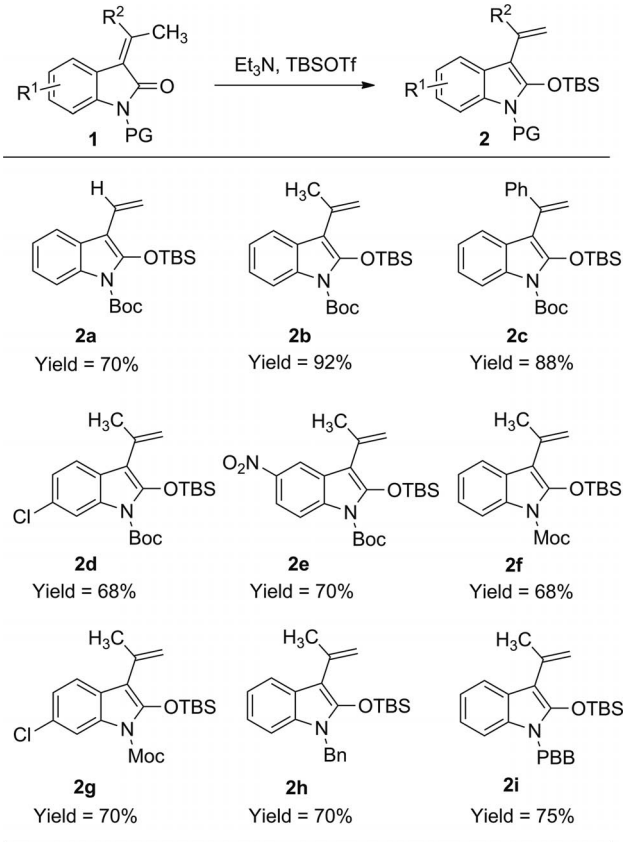
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101446.

tions en route to relevant indole and oxindole targets of varied origin and function.

As part of our ongoing studies on vinylogous aldol and related reactions of heterocyclic 2-silyloxydienes,[7a–7c,8] herein we describe, for the first time, the preparation of variously shaped 3-alkenyl-2-silyloxyindoles and their validation as the nucleophilic components of a remarkably selective, vinylogous Mukaiyama aldol reaction with aromatic aldehyde acceptors. This unprecedented method enables the preparation of diverse hydroxylated indolinones bearing an exocyclic double bond at the indole C-3 position.

Results and Discussion

Our initial investigation focused on the assembly of several methyl-substituted methylene indolinones **1**, which were quickly obtained from readily available oxindole or isatin matrices by known standard procedures.[9,10] The subsequent enol silylation stage was carried out by exposing the corresponding 3-alkylidene oxindoles **1** to a 1:1.5 mixture of the TBS-triflate/Et_3N couple at room temperature (Scheme 2). This simple protocol smoothly afforded the expected products, which were obtained in a pure state and good isolated yield after chromatography. Noteworthy, all indole nucleophiles, be they solid or oily materials, showed remarkable stability in air, which allowed storage in a refrigerator for months under a nonprotected atmosphere, with no protodesilylation or decomposition.[11]



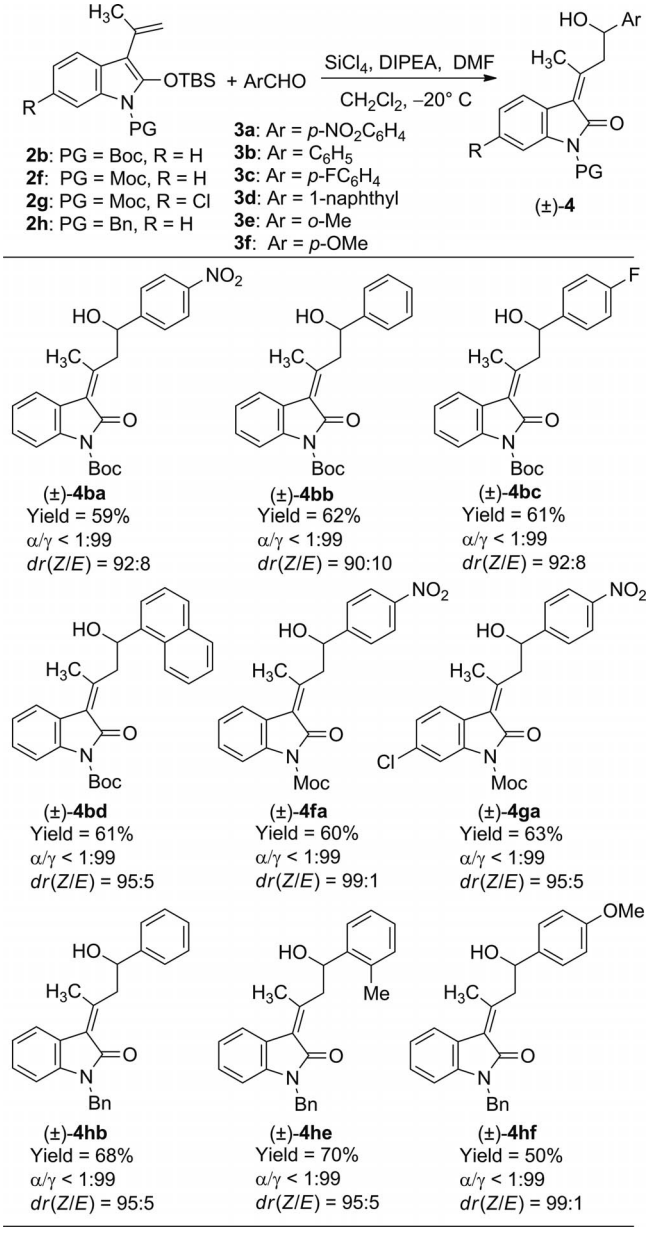
Scheme 2. Preparation of 3-alkenyl-2-silyloxyindoles **2** from indolinones **1**. Reactions were carried out by using alkylidene oxindoles **1** (0.33 mmol), Et_3N (2.0 equiv.), and TBSOTf (1.5 equiv.) in anhydrous CH_2Cl_2 (0.1 M) at room temperature for 2 h. Yields refer to pure, isolated products; see the Supporting Information for details. TBS = *t*BuMe$_2$Si; Boc = *t*BuOCO; Moc = MeOCO; Bn = benzyl; PBB = *p*-bromobenzyl.

Of the compound repertoire in Scheme 2, acetone-derived indole nucleophiles **2b**, **2f**, **2g**, and **2h** were selected as test candidates in VMARs to aromatic aldehydes. As the opening move, we explored diverse Lewis acid catalysts in the VMAR between **2b** and *p*-nitrobenzaldehyde (**3a**) in different solvents, with varied reaction temperatures. This short trial delineated our best reaction conditions as 1:1 donor/acceptor molar ratio, 1.2 equiv. $SiCl_4$, 40 mol-% DMF, and 2.0 equiv. DIPEA in anhydrous CH_2Cl_2 at –20 °C for 12 h. Under these conditions, a smooth addition was observed and, upon aqueous $NaHCO_3$ quenching, desired adduct **4ba** was obtained in a fair 59% isolated yield after chromatography, with virtually complete γ-site selectivity and 92:8 *Z*/*E* diastereoselectivity (Scheme 3).[12]

With these conditions elaborated, we next explored other aldehyde acceptors, including benzaldehyde (**3b**), *p*-fluorobenzaldehyde (**3c**), and 1-naphthaldehyde (**3d**). Comparing the results revealed that the ring substituents had only a marginal impact on the VMAR performance, with all reactions occurring with similar efficiency and selectivity, giving the respective vinylogous aldols **4bb**, **4bc**, and **4bd** in reasonable isolated yields. Moc-substituted indoles **2f** and **2g** were explored with *p*-nitrobenzaldehyde (**3a**). Equally, the additions were productive and, regardless of the nature of the nucleophile, *Z* adducts **4fa** and **4ga** were formed almost exclusively with complete γ-site selectivity. *N*-Benzyl-protected indole **2h** was also a pertinent substrate and reacted with proper aldehydes to afford the expected aldol adducts **4hb**, **4he**, and **4hf** in good yields and diastereoselectivities. Of note, not only benzaldehyde (**3b**) was tolerated, but also aldehydes with electron-donating groups in the aromatic ring such as *o*-tolualdehyde (**3e**) and *p*-methoxybenzaldehyde (**3f**). Rather unexpectedly, substituted candidate **2e**, carrying a strong electron-withdrawing group at the indole ring, proved recalcitrant to react with **3a**, and only a minute amount of the expected aldol product formed after 12 h at room temperature.[13]

A final exploratory trial in an asymmetric, catalytic environment was conducted by choosing Denmark's highly performing (*R*,*R*)-bisphosphoramide **5** in combination with $SiCl_4$ as the chiral catalyst, reasoning that this system could here effect an efficient enantioface discrimination in the nucleophilic attack at the aldehyde carbonyl, as was the case for related asymmetric coupling reactions employing other enoxysilane matrices.[8c,8h,8i]

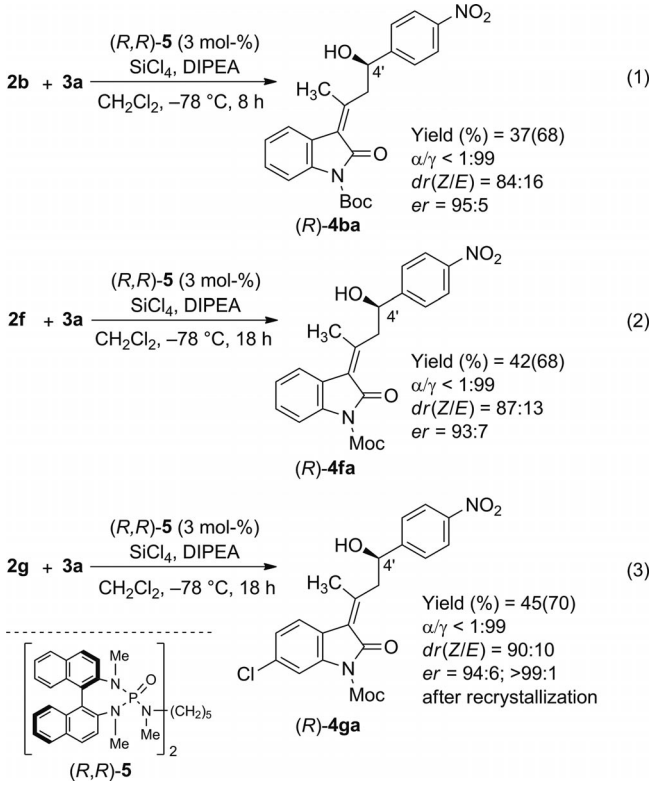
As probes we evaluated *N*-Boc- and *N*-Moc indole nucleophiles **2b**, **2f**, and **2g** in reactions with *p*-nitrobenzaldehyde (**3a**). With the use of ligand **5** (3.0 mol-%), $SiCl_4$ (1.1 equiv.), and DIPEA (10 mol-%) in CH_2Cl_2 at –78 °C, we were delighted to see that the corresponding enantioenriched products (*R*)-**4ba**, (*R*)-**4fa**, and (*R*)-**4ga** were obtained in acceptable yields of 37–45%, with 100% γ-site



Scheme 3. $SiCl_4$-assisted vinylogous Mukaiyama aldol addition of olefinic indole silyldienolates **2b**, **2f**, **2g**, and **2h** to aromatic aldehydes **3a**–**f**. All reactions were carried out with silyloxyindoles **2** (0.26 mmol), aldehydes **3** (1.0 equiv.), $SiCl_4$ (1.2 equiv.), DMF (40 mol-%), diisopropylethylamine (2.0 equiv.) in anhydrous CH_2Cl_2 (0.1 M) at –20 °C for 12 h. Yields refer to pure, isolated products; α/γ ratio and *dr* were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures; see the Supporting Information for details.

selectivity, and >84:16 *dr* in favor of the Z-configured isomers,[14] with promising *er* values ranging from 93:7 to 95:5 (Scheme 4).

On the basis of several precedents on the use of catalyst **5**·$SiCl_4$ to assist vinylogous enantioselective Mukaiyama aldol-type additions of enolsilanes to aromatic aldehydes, we assume that the present aldolization involving indole nucleophiles also proceeds through the same catalytic path-



Scheme 4. Preliminary asymmetric VMAR trials of indole silyldienolates **2b**, **2f**, and **2g** catalyzed by the $SiCl_4$·(*R*,*R*)-**5** system. Yields refer to isolated yields after chromatography (conversions in parentheses); *dr* determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures; *er* determined by HPLC on chiral stationary phases.

way, with the nucleophile entering the *Re* face of the aldehyde carbonyl preferentially.[8c,8h,8i] This is expected to produce major 4′*R*-configured adducts, as shown in Scheme 4.

Conclusions

In summary, we present a series of novel 3-alkenyl-2-silyloxyindole nucleophiles and validate their utility in the unprecedented vinylogous Mukaiyama aldol addition to aromatic aldehydes. This route furnishes valuable hydroxylated 3-alkylidene oxindoles with virtually complete γ-site selectivity and excellent levels of diastereoselectivity in favor of the *Z*-configured adducts. A trial of an asymmetric, catalytic variant showed promising enantioselectivity for the expected enantioenriched aldol products. Further investigations to exploit these novel indole silicon dienolates in vinylogous aldol and related vinylogous reactions, including asymmetric catalysis, are currently underway in our laboratory.

Experimental Section

Preparation of Oxindole (±)-(*Z*)-4ba as a Representative Procedure for the Diastereoselective $SiCl_4$-Assisted VMAR: To a flame-dried,

10-mL round-bottomed flask containing a portion of diisopropylethylamine (90 μL, 0.52 mmol, 2.0 equiv.) cooled to –20 °C was sequentially added $SiCl_4$ (1 M in CH_2Cl_2, 310 μL, 0.31 mmol, 1.2 equiv.), DMF (8 μL, 0.10 mmol, 0.4 equiv.), a solution of 4-nitrobenzaldehyde (**3a**; 39 mg, 0.26 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (1.0 mL), and a solution of silyloxyindole **2b** (100 mg, 0.26 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at –20 °C for 12 h, whereupon a saturated aqueous solution of $NaHCO_3$ (3.0 mL) was added allowing the temperature of the mixture to reach room temperature. The two phases were separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 3 mL) and EtOAc (1 × 3 mL). The organic layers were collected, dried with $MgSO_4$, and filtered, and the filtrate was concentrated in vacuo. The diastereomeric ratio (*Z*/*E*) of the addition products was determined to be 92:8 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc, 75:25) to give (±)-(*Z*)-**4ba** (65 mg, 59%) as white crystals (CH_2Cl_2/hexane). M.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H, Ar), 7.80 (d, *J* = 7.8 Hz, 1 H, H7), 7.69 (d, *J* = 8.6 Hz, 2 H, Ar), 7.59 (d, *J* = 7.6 Hz, 1 H, H4), 7.32 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1 H, H6), 7.19 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1 H, H5), 5.20 (ddd, *J* = 9.2, 5.3, 3.8 Hz, 1 H, H4′), 3.57 (d, *J* = 5.3 Hz, 1 H, OH), 3.45 (dd, *J* = 12.4, 9.1 Hz, 1 H, H3′a), 3.32 (dd, *J* = 12.4, 3.8 Hz, 1 H, H3′b), 2.37 (s, 3 H, H1′), 1.68 (s, 9 H, *t*Bu, Boc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4 (Cq), 155.8 (Cq), 152.0 (Cq), 148.9 (Cq), 147.2 (Cq), 138.1 (Cq), 128.5 (CH), 126.4 (2 C, CH), 124.5 (Cq), 124.1 (CH), 123.8 (CH), 123.7 (2 C, CH), 123.5 (Cq), 114.7 (CH), 84.7 (Cq), 73.6 (CH), 46.9 (CH_2), 28.1 (3 C, CH_3), 25.8 (CH_3) ppm. MS (ESI, 50 eV): *m*/*z* = 447.1 [M + Na]$^+$. $C_{23}H_{24}N_2O_6$ (424.45): calcd. C 65.08, H 5.70, N 6.60; found C 65.01, H 5.78, N 6.52.

Preparation of Oxindole (*R*,*Z*)-4ba as a Representative Procedure for the Catalytic, Asymmetric $SiCl_4$-Assisted VMAR: Diisopropylethylamine (4.5 μL, 0.025 mmol, 0.1 equiv.) was added by syringe to a flame-dried, 20-mL, two-necked round-bottomed flask containing a solution of bisphosphoramide (*R*,*R*)-**5** (6.5 mg, 0.007 mmol, 0.03 equiv.) in anhydrous CH_2Cl_2 (1.2 mL) under an argon atmosphere. The resulting solution was cooled to –78 °C (bath temperature) over 15 min, then $SiCl_4$ (1 M in CH_2Cl_2, 284 μL, 0.28 mmol, 1.1 equiv.) was added in one portion. After 10 min, 4-nitrobenzaldehyde (**3a**; 43 mg, 0.28 mmol, 1.1 equiv.) was added in one portion followed by the slow dropwise addition (over 5 min) of a solution of silyloxyindole **2b** (100 mg, 0.26 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at –78 °C for 8 h, whereupon a solution $NaHCO_3$ (43 mg, 0.50 mmol, 2.0 equiv.) in H_2O (1.5 mL) was added, and the temperature was allowed to reach room temperature. This biphasic mixture was promptly separated, and the aqueous phase was washed with EtOAc (3 × 5 mL). The organic layers were collected, dried with $MgSO_4$, and filtered, and the filtrate was concentrated. The diastereomeric ratio of the addition products was determined to be 84:16 (68% conversion) by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The crude residue, dissolved in EtOAc, was purified by silica gel flash chromatography (petroleum ether/EtOAc, 85:15) to yield (*R*,*Z*)-**4ba** (41 mg, 37%) as colorless crystals. M.p. 143–144 °C (CH_2Cl_2/hexane). $[\alpha]_D^{20}$ = –28.8 (*c* = 0.6, $CHCl_3$). ^{1}H and ^{13}C NMR spectroscopic data as for the corresponding racemic compound (vide supra). HPLC [Regis (*S*,*S*)-Whelk-O 1, 20 °C, hexane/EtOH = 70:30, 0.6 mL/min, 254 nm): t_R = 12.63 (minor), 13.42 min (major); *er* = 95:5. Bisphosphoramide (*R*,*R*)-**5** was almost quantitatively recovered by washing the silica chromatography pad with a EtOAc/NH_3-saturated MeOH (90:10).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, copies of the ^{1}H NMR and ^{13}C NMR spectra, and chiral HPLC traces.

Acknowledgments

We gratefully acknowledge the Regione Autonoma della Sardegna (L.R. 07.08.2007, n.7) and Università degli Studi di Parma for financial support. R.T. thanks the Regione Autonoma della Sardegna for a M&B fellowship. We thank the Centro Interdipartimentale Misure "G. Casnati" (Università degli Studi di Parma) for instrumental facilities. We also thank Eugenia Accorsi Buttini (Università degli Studi di Parma) for preliminary experiments.

[1] a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209–2219; b) G. Cerchiaro, A. M. da Costa Ferreira, *J. Braz. Chem. Soc.* **2006**, *17*, 1473–1485; c) E. Fattorusso, O. Taglialatela-Scafati in *Modern Alkaloids. Structure, Isolation, Synthesis and Biology*, Wiley-VHC, Weinheim, **2008**; d) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758; e) S. Peddibhotla, *Curr. Bioact. Compd.* **2009**, *5*, 20–38; f) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2964; g) A. U. Rahman, A. Basha in *Indole Alkaloids*, Hartwood Academic Publishers, Amsterdam, **1997**; h) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003–3025.

[2] a) J. Polonsky, M.-A. Merrien, T. Prangé, C. Pascard, S. Moreau, *J. Chem. Soc., Chem. Commun.* **1980**, 601–602; b) T. Prangé, M.-A. Buillion, M. Vuilhorgne, C. Pascard, J. Polonsky, *Tetrahedron Lett.* **1981**, *22*, 1977–1980; c) M. Yamazaki, E. Okuyama, M. Kobayashi, H. Inoue, *Tetrahedron Lett.* **1981**, *22*, 135–136.

[3] a) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942; b) J. I. Jimenez, U. Huber, R. E. Moore, G. M. L. Patterson, *J. Nat. Prod.* **1999**, *62*, 569–572.

[4] a) T. G. Wormley, *Am. J. Pharm.* **1870**, *42*, 1–16; b) F. M. Lovell, R. Pepinsky, A. J. C. Wilson, *Tetrahedron Lett.* **1959**, *1*, 1–5; c) H. Conroy, J. K. Chakrabarti, *Tetrahedron Lett.* **1959**, *1*, 6–13.

[5] For representative reviews concerning the C-3 functionalization of oxindoles, see: a) W. C. Sumpter, *Chem. Rev.* **1945**, *37*, 443–479; b) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407; c) A. Millemaggi, R. J. K. Taylor, *Eur. J. Org. Chem.* **2010**, 4527–4547; for selected examples, see: d) S. Adhikari, S. Caille, M. Hanbauer, V. X. Ngo, L. E. Overman, *Org. Lett.* **2005**, *7*, 2795–2797; e) J. M. Ellis, L. E. Overman, H. R. Tanner, J. Wang, *J. Org. Chem.* **2008**, *73*, 9151–9154; f) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203; g) K. Shen, X. H. Liu, K. Zheng, W. Li, X. L. Hu, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 3736–3742; h) X.-L. Liu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron Lett.* **2011**, *52*, 903–906; i) X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem.* **2011**, *76*, 4008–4017.

[6] For an early example of a base-assisted Claisen-type vinylogous condensation of 3-ethylidene oxindole with ethyl oxalate, see: L. Horner, *Justus Liebigs Ann. Chem.* **1941**, *548*, 117–146.

[7] For representative reviews on this subject, see: a) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929–1972; b) G. Casiraghi, F. Zanardi, L. Battistini, G. Rassu, *Synlett* **2009**, 1525–1542; c) G. Casiraghi, L. Battisitni, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076–3154; d) S. E. Denmark, J. R. Heemstra Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760–4777; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698; e) T. Brodmann, M. Lorenz, R. Schackel, S. Sim-

sek, M. Kalesse, *Synlett* **2009**, 174–192; f) S. V. Pansare, E. K. Paul, *Chem. Eur. J.* **2011**, *17*, 9770–8779.

[8] a) C. Curti, A. Sartori, L. Battistini, G. Rassu, F. Zanardi, G. Casiraghi, *Tetrahedron Lett.* **2009**, *50*, 3428–3431; b) V. Zambrano, G. Rassu, A. Roggio, L. Pinna, F. Zanardi, C. Curti, G. Casiraghi, L. Battistini, *Org. Biomol. Chem.* **2010**, *8*, 1725–1730; c) C. Curti, B. Ranieri, L. Battistini, G. Rassu, V. Zambrano, G. Pelosi, G. Casiraghi, F. Zanardi, *Adv. Synth. Catal.* **2010**, *352*, 2011–2022; d) C. Curti, L. Battistini, F. Zanardi, G. Rassu, V. Zambrano, L. Pinna, G. Casiraghi, *J. Org. Chem.* **2010**, *75*, 8681–8684; e) C. Curti, L. Battistini, B. Ranieri, G. Pelosi, G. Rassu, G. Casiraghi, F. Zanardi, *J. Org. Chem.* **2011**, *76*, 2248–2252; f) L. Battistini, L. Dell′Amico, A. Sartori, C. Curti, G. Pelosi, G. Casiraghi, O. A. Attanasi, G. Favi, F. Zanardi, *Adv. Synth. Catal.* **2011**, *353*, 1966–1972; g) C. Curti, L. Battistini, A. Sartori, A. Lodola, M. Mor, G. Rassu, G. Pelosi, F. Zanardi, G. Casiraghi, *Org. Lett.* **2011**, *13*, 4738–4741; for recent achievements on this subject from other laboratories, see: h) S. E. Denmark, J. R. Heemstra Jr., *J. Org. Chem.* **2007**, *72*, 5668–5688; i) S. E. Denmark, B. M. Eklov, P. J. Yao, M. D. Eastgate, *J. Am. Chem. Soc.* **2009**, *131*, 11770–11787; j) E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2006**, *118*, 7388–7391; *Angew. Chem. Int. Ed.* **2006**, *45*, 7230–7233; k) O. Tamura, K. Takeda, N. Mita, M. Sakamoto, I. Okamoto, N. Morita, H. Ishibashi, *Org. Biomol. Chem.* **2011**, *9*, 7411–7419; l) N. Zhu, B.-C. Ma, Y. Zhang, W. Wang, *Adv. Synth. Catal.* **2010**, *352*, 1291–1295; m) Q.-Y. Zhao, M. Shi, *Tetrahedron* **2011**, *67*, 3724–3732; n) Q.-Y. Zhao, Z.-L. Yuan, M. Shi, *Adv. Synth. Catal.* **2011**, *353*, 637–643; o) T. Qin, R. P. Johnson, J. A. Porco Jr., *J. Am. Chem. Soc.* **2011**, *133*, 1714–1717; p) R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558–9560; q) Q. Chabaud, T. Jousseaume, P. Retailleau, C. Guillou, *Eur. J. Org. Chem.* **2010**, 5471–5481; r) A. Takahashi, H. Yanai, M. Zhang, T. Sonoda, M. Mishima, T. Taguchi, *J. Org. Chem.* **2010**, *75*, 1259–1265.

[9] B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397. See the Supporting Information for details.

[10] a) J. M. Ellis, L. E. Overman, H. R. Tanner, J. Wang, *J. Org. Chem.* **2008**, *73*, 9151–9154; b) A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053. See the Supporting Information for details.

[11] Two additional TMS-substituted 2-silyloxyindoles were also synthesized. However, their intrinsic lability and sensitivity to moisture discouraged synthetic application. See the Supporting Information for preparation and characterization.

[12] The origin of the adducts can be derived from the formula abbreviation **4xy**. The first letter identifies the indole donor, whereas the second letter identifies the aldehyde acceptor.

[13] The adduct was isolated in 12% yield as a 64:36 *Z*/*E* isomeric mixture. See the Supporting Information for preparation and characterization.

[14] For all unsaturated candidates **4**, the *Z* double bond geometry was certified by ^{1}H–^{1}H NOESY NMR correlation analyses. See the Supporting Information for details.

Received: October 3, 2011
Published Online: December 16, 2011

