SHORT COMMUNICATION

DOI: 10.1002/ejoc.201101446

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


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 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 oxoindolinylidenes frameworks expediently accessible.

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 indolines 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 indolines F as privileged structures that can be subjected to various synthetic manipula-
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/Et₃N 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]

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. SiCl₄, 40 mol-% DMF, and 2.0 equiv. DIPEA in anhydrous CH₂Cl₂ at –20 °C for 12 h. Under these conditions, a smooth addition was observed and, upon aqueous NaHCO₃ 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, 4be, 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, 4hc, 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)-bisphosphoramidate 5 in combination with SiCl₄ 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-%), SiCl₄ (1.1 equiv.), and DIPEA (10 mol-%) in CH₂Cl₂ 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 selectivity and 92:8 Z/E diastereoselectivity.

Scheme 2. Preparation of 3-alkenyl-2-silyloxyindoles 2 from indolinones 1. Reactions were carried out by using alkylidene oxindoles 1 (0.33 mmol), Et₃N (2.0 equiv.), and TBSOTf (1.5 equiv.) in anhydrous CH₂Cl₂ (0.1 m) at room temperature for 2 h. Yields refer to pure, isolated products; see the Supporting Information for details. TBS = tBuMe₂Si; Boc = tBuOCO; Moc = MeOCO; Bn = benzyl; PBB = p-bromobenzyl.
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Scheme 3. SiCl₄-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.), SiCl₄ (1.2 equiv.), DMF (40 mol-%), diisopropylethylamine (2.0 equiv.) in anhydrous CH₂Cl₂ (0.1 mol) at –20 °C for 12 h. Yields refer to pure, isolated products; α/γ ratio and dr were determined by ¹H 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·SiCl₄ 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 pathway, 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 (±)-4ba as a Representative Procedure for the Diastereoselective SiCl₄-Assisted VMAR: To a flame-dried,
3-Alkenyl-2-silyloxyindoles

10-mL round-bottomed flask containing a portion of disopropylmethyamine (90 μL, 0.52 mmol, 2.0 equiv.) cooled to −20 °C was sequentially added SiCl₄ (1 m in CH₂Cl₂, 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 CH₂Cl₂ (1.0 mL), and a solution of silyloxyindole 2b (100 mg, 0.26 mmol, 1.0 equiv.) in anhydrous CH₂Cl₂ (1.0 mL). The resulting mixture was stirred at −20 °C for 12 h, whereupon a saturated aqueous solution of NaHCO₃ (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 CH₂Cl₂ (3×3 mL) and EtOAc (1×3 mL). The organic layers were collected, dried with MgSO₄, and filtered, and the filtrate was concentrated in vacuo. The diastereomeric ratio (Z/E) of the addition products was determined to be 92.8:1 by ¹H 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% yield) as white crystals (CH₂Cl₂/hexane). M.p. 130–132 °C. ¹H NMR (400 MHz, CDCl₃): 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 (dd, J = 7.6, 7.6, 1.1 Hz, 1 H, H6), 7.19 (dd, J = 7.7, 7.7, 1.0 Hz, 1 H, H5), 5.20 (dd, J = 9.2, 5.3, 3.8 Hz, 1 H, H4'), 3.75 (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, 1Bu, Boc) ppm. ¹³C NMR (100 MHz, CDCl₃): 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, CH₂), 124.5 (Cq), 124.1 (CH₂), 123.8 (CH), 123.7 (2 C, CH₃), 114.7 (CH), 84.7 (Cq), 73.6 (CH₆), 46.9 (CH₂), 28.1 (3 C, CH₃), 25.8 (CH₃) ppm. MS (ESI, 50 eV); m/z = 447.1 [M + Na]+. C₂₃H₂₅N₂O₆ (424.45) calculd: C 65.08, H 5.70, N 6.60; found C 65.01, H 5.78, N 6.52.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, copies of the ¹H NMR and ¹³C 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.


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[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, the Z double bond geometry was certified by 1H–1H NOESY NMR correlation analyses. See the Supporting Information for details.

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