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3-Alkenyl-2-silyloxyindoles in Vinylogous Mannich Reactions: Synthesis of Aminated Indole-Based Scaffolds and Products

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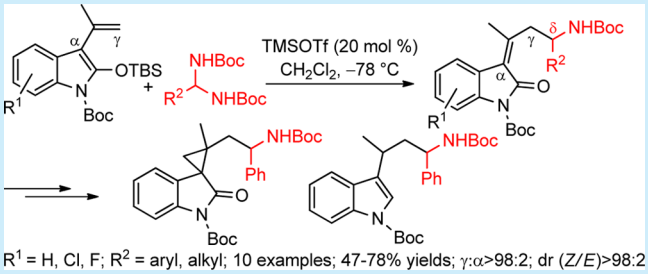
Supporting Information

ABSTRACT: The first Lewis acid catalyzed vinylogous Mukaiyama-type Mannich addition of 3-alkenyl-2-silyloxyindoles to in situ generated *N*-Boc imines has been established, which affords chiral α-alkylidene-δ-amino-2-oxindole products with good efficiency and complete γ-site- and *Z*-selectivity. The reaction is wide in scope, as it can be applied with equal convenience to different silyloxyindole donors and aromatic or aliphatic aminal-derived aldimine acceptors. The utility of these scaffolds is demonstrated by their easy transformation into either spirocyclopropane oxindole or homotryptamine-like products, featuring nontraditional indole-based skeleton connections.



The construction of small molecules equipped with heteroatom-containing functional groups and a spatially defined arrangement is an ongoing issue in organic synthesis. Synthetic chemistry is indeed dedicated in flanking medchem research looking for new molecular probes which may interrogate clinically relevant biological targets.[1] Accordingly, efficient and stereoselective synthetic routes to access arrays of such molecules are highly desirable and amenable to further functional group adjustment, skeletal manipulation, and physicochemical refinement. Exploitation of the indole and 2-oxindole nuclei in synthesis represents a formidable opportunity to prove this concept, given the overwhelming presence of these matrices in bioactive natural products and nature-inspired synthetic drugs.[2] (Poly)cyclic indole architectures are found, for example, in spirotryprostatin B **I** (Figure 1), a natural 3,3′-pyrrolinyl spirooxindole exhibiting antitumor activity,[3] and sunitinib **II**, an artificial 3-pyrroloalkylidene oxindole currently used as a multitargeted receptor tyrosine kinase inhibitor.[4] In most cases, a 2-aminoethyl appendage at the C3 indole core is found, which is reminiscent of the tryptamine-derived biogenesis of the naturally occurring compounds. In recent years, the faithful reproduction of natural indole products and their structural modification by synthesis have been the focus of extensive efforts, resulting in the invention and execution of new powerful stereocontrolled methods.[5] An even more challenging task would include the construction of rare or undisclosed skeletal connections, thus further broadening the horizon of structural diversity.

A couple of such examples include communesin B **III** (Figure 1), a cytotoxic and insecticidal natural compound featuring a nonconventional perhydro α-carboline nucleus,[6] and

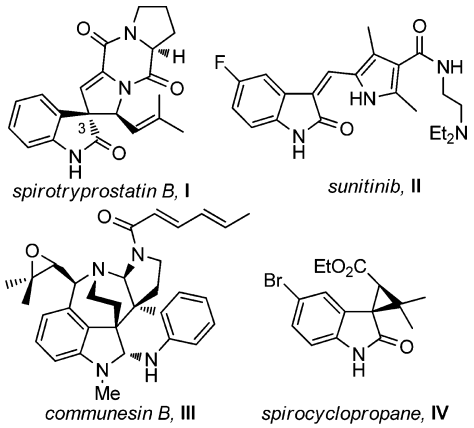


Figure 1. Biologically relevant natural and unnatural indole-based compounds.

oxindole **IV**, an NNRT HIV-1 inhibitor containing an unusual spirocyclopropane oxindole frame.[7]

Inspired by these considerations, an indole-related synthon was recently launched by our group, namely γ-enolizable alkylidene oxindole **A** (Scheme 1), whose unprecedented pronucleophilic character at its exocyclic vinylogous γ-carbon site was discovered and usefully exploited in asymmetric vinylogous aldol and Michael-type addition reactions.[8] As a further step, we were wondering whether this inherently

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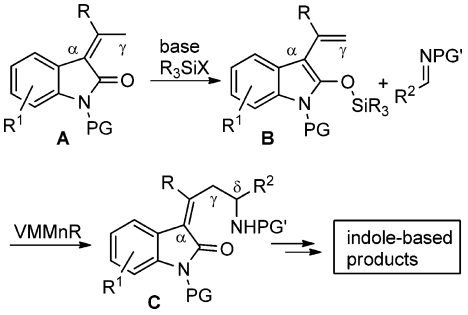
Scheme 1. Application of the Vinylogous Mukaiyama-Type Mannich Reaction (VMMnR) on γ-Enolizable 3-Alkylidene-2-oxindoles



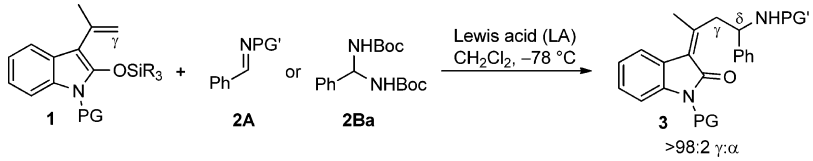
bidentate α,γ-pronucleophile could serve with equal ease as a vinylogous donor component in a Mannich addition reaction to aldimine acceptors;[9,10] it may then be feasible to obtain unusual α-alkylidene-δ-amino-oxindoles **C**, heralding possible further elaboration into diverse indole products.[11]

Here, it is reported for the first time that the vinyl *N*,*O*-ketene acetal **B**, derived from oxindole **A** by γ-enolization/*O*-silylation, can undergo smooth Lewis acid catalyzed Mukaiyama−Mannich addition to diverse aldimines in a strictly vinylogous sense, giving rise to a series of variously substituted α-alkylidene-δ-amino oxindoles **C** in good yield and with excellent diastereoselectivity. We also disclose that the Mannich base adducts are readily converted to indole-based products which incorporate nontraditional skeleton connections.

Initially, *N*-Boc-protected 3-(2-propenyl)-2-trimethylsilyloxyindole (**1a**), prepared from the corresponding 3-isopropylidene-2-oxindole precursor (see Supporting Information), and *N*-Ts phenylmethanimine (**2Aa**) were selected as the starting substrates. Using an excess of $BF_3{\cdot}OEt_2$ as the Lewis acid promoter in CH_2Cl_2 at −78 °C, the reaction furnished the desired Mannich base product **3a** in a 58% yield and with a 95:5 *Z*/*E* diastereomeric ratio (Table 1, entry 1). Encouraged by this result, the evaluation of differently protected substrates and screening of reaction conditions were carried out. Replacing the Boc group with methoxycarbonyl within oxindole **1** resulted in diminished reaction efficiency (entry 2), while decreasing the amount of $BF_3{\cdot}OEt_2$ (from 2.0 to 1.0 mol equiv) turned out to be fruitful, consigning the Mannich product **3a** in a good 70% isolated yield (entry 3). Choosing *N*-Boc phenylmethanimine (**2Ab**) and using the silyloxyindole as the limiting reagent further improved the reaction efficiency. In this instance, *Z*-diastereoselectivity proved excellent, since no *E*-configured isomers were detected under NMR analysis of the crude reaction mixture (entry 4). Lowering the Lewis acid loading further to 20 mol % led to a slight increase in product yield, while maintaining optimal *Z*/*E* diastereoselectivity (entry 5). The use of alternative Lewis acid catalysts such as TMSOTf or AgOTf (*inter alia*) disclosed that the coupling reactions could be equally viable (entries 6 and 7). Control reactions carried out in the absence of any Lewis acid or in the presence of potentially activating protic solvents (*i*PrOH/H_2O)[12] gave no appreciable results, thus emphasizing the crucial role of the Lewis acid catalyst in triggering the vinylogous Mannich reaction (not shown). Among the reaction temperatures and solvents examined,[13] it turned out that those initially screened (−78 °C, CH_2Cl_2) corresponded to the most suitable conditions. Noticeably, all the reactions proceeded with exclusive formation of the vinylogous products **3**, with no detection of adducts arising from attack at the oxindole α-position.

Although results could be considered satisfying in terms of both efficiency and selectivity, we still remained concerned about the operational practicality and reproducibility. The preparation of *N*-Ts and *N*-Boc imines **2A** from the corresponding sulfonamine (and hence aldehyde) precursors is common practice, but a real limitation was found during the purification procedure of such substrates, whose contamination with the respective aldehyde precursors sometimes put at risk the good performance of the VMMnR itself.[14] To overcome these drawbacks, and following a recent brilliant report by Maruoka et al.,[15] we opted for the use of easily made, bench-stable, and purified aminals of type **2B**, which may generate the

Table 1. Optimization of the VMMnR of Propenyl Silyloxyindoles 1 with Phenylmethanimines 2A or Aminal 2Ba[a]



entry	**1** (SiR_3, PG)	**2A** (PG′)	**2B**	LA (mol %)	**3** (yield %)[b]	dr (*Z*/*E*)[c]
1[d]	**1a** (TMS, Boc)	**2Aa** (Ts)	–	$BF_3{\cdot}OEt_2$ (200)	**3a** (58)	95:5
2[d]	**1b** (TMS, Moc)	**2Aa** (Ts)	–	$BF_3{\cdot}OEt_2$ (200)	**3b** (45)	94:6
3[d]	**1a** (TMS, Boc)	**2Aa** (Ts)	–	$BF_3{\cdot}OEt_2$ (100)	**3a** (70)	95:5
4	**1a** (TMS, Boc)	**2Ab** (Boc)	–	$BF_3{\cdot}OEt_2$ (100)	**3c** (73)	>98:2
5	**1a** (TMS, Boc)	**2Ab** (Boc)	–	$BF_3{\cdot}OEt_2$ (20)	**3c** (75)	>98:2
6	**1a** (TMS, Boc)	**2Ab** (Boc)	–	TMSOTf (20)	**3c** (76)	>98:2
7	**1a** (TMS, Boc)	**2Ab** (Boc)	–	AgOTf (20)	**3c** (79)	>98:2
8	**1a** (TMS, Boc)	–	**2Ba**	$BF_3{\cdot}OEt_2$ (20)	**3c** (73)	>98:2
9	**1a** (TMS, Boc)	–	**2Ba**	TMSOTf (20)	**3c** (78)	>98:2
10	**1c** (TBS, Boc)	–	**2Ba**	TMSOTf (20)	**3c** (78)	>98:2
11	**1c** (TBS, Boc)	–	**2Ba**	$BF_3{\cdot}OEt_2$ (20)	**3c** (23)	>98:2

[a]Unless otherwise noted, reactions were carried out on a 0.2 mmol scale of siloxyindole **1** (1.0 equiv) using **2A** or **2B** (1.5 equiv) in dry CH_2Cl_2 (0.1 M) at −78 °C for 20 h. [b]Isolated yield after flash column chromatography. [c]Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d]The reaction was carried out using **1** (1.5 equiv) and **2A** (1.0 equiv).

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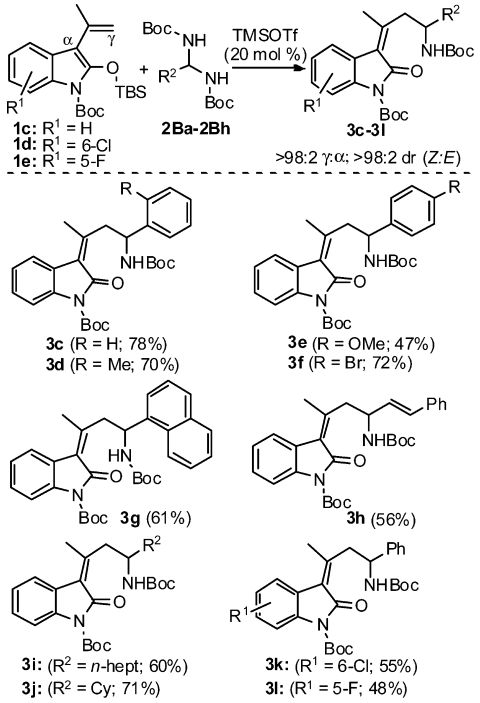
corresponding *N*-Boc imines in situ upon Lewis acid treatment. Thus, after a brief adjustment of the reaction procedure and using aminal **2Ba** (entries 8−11), we found that reacting TBS-protected oxindole **1c** with aminal **2Ba** in the presence of trimethylsiloxy triflate (TMSOTf, 20 mol %) in CH_2Cl_2 at −78 °C easily produced the expected product **3c** in a good 78% yield with complete *Z*-diastereoselectivity (entry 10).[16] To provide convincing evidence of its scalability, the reaction between **1c** and **2Ba** was carried out on a 5× scale (1.0 mmol); in this instance, the TMSOTf catalyst could be minimized to as little as a 5 mol % loading, providing product **3c** with equal convenience (78% yield, >98:2 *Z*/*E* dr).

With optimal conditions found, we next explored the general applicability of the reaction (Scheme 2). A series of aryl-

Scheme 2. Generality of the VMMnR Varying the Silyloxyindole and Aminal Substrates[a]



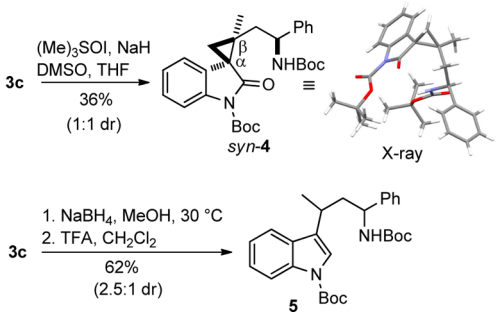
[a]Conditions detailed in Table 1 (entry 10) and in the Supporting Information.

substituted *N*-Boc aminals **2Ba−2Be** reacted smoothly with **1c** under identical conditions, affording the corresponding Mannich bases **3c−3g** in moderate to good yields (47−78%) and optimal levels of *Z*-diastereoselectivity demonstrating, in some cases (e.g., **3e**, **3g**), a slight impact of the electronic or steric nature of the aminal aryl substituents on the reaction performances. The reaction could be applied to aliphatic aminals derived from octanal and cyclohexanecarboxyaldehyde; in these instances, the expected Mannich products **3i** and **3j** were isolated in good 60% and 71% yields, respectively. Also, the reaction with the cinnamaldehyde-derived aminal gave product **3h** in a 56% yield, with exclusive γ-1,2-attack. Interestingly, even in these cases, the reaction maintained excellent levels of diastereoselection, affording the *Z*-configured product exclusively. Subsequently, oxindole substrates **1d** and **1e** bearing different halogen substituents in the aryl portion were examined. Again, reaction conditions revealed to be suitable, providing the corresponding 6-chlorooxindole **3k** and 5-fluorooxindole **3l** in reasonable yields and optimal geometrical selectivity.

The *Z*-configuration of the carbon−carbon double bond within products **3** was unequivocally ascertained by analysis of the $^1H-^1H$ NOESY NMR spectra of representative compounds **3c** and **3j**. In particular, crucial NOE contacts between the exocyclic methyl group and the indole H-4 proton were observed, thus defining the olefin *Z*-geometry. The stereochemistry of the remaining products **3** was assigned by analogy. The complete *Z*-selectivity of compounds **3** may be rationalized by assuming a preferred *s*-cis conformation of silyloxyindoles **1** in the transition state. As suggested by internal energy calculations (data not shown), the *s*-trans conformers, leading to *E*-configured isomers, are slightly less stable, probably due to unfavorable energy-raising allylic strain.

The synthetic potential of the α-alkenyl-δ-amino-2-oxindole scaffolds in our hands was demonstrated by transformation into varied indole products (Scheme 3). Thus, treatment of

Scheme 3. Exploiting the VMMnR Products in Synthesis



compound **3c** with trimethylsulfoxonium iodide in NaH under the Corey−Chaykovsky conditions[17] resulted in the synthesis of compound **4**, a rare spirocyclopropane oxindole structure featuring two contiguous quaternary stereocenters at the α and β positions.[18] Compound **4** was obtained in an unoptimized 36% yield as a separable 1:1 diastereomeric mixture; the relative configuration of crystalline *syn*-**4** was firmly established by single crystal X-ray analysis,[19] as portrayed in Scheme 3 (eq 1). Also, subjecting oxindole **3c** to $NaBH_4$ in methanol afforded the corresponding saturated *N*,*O*-acetal (not shown), which rapidly underwent dehydration upon acidic conditions to give the homotryptamine analogue **5** (eq 2).

Summarizing, we herein demonstrated for the first time that the *tert*-butyldimethylsilyloxydienes derived from γ-enolizable 3-alkylidene-2-oxindoles could nicely serve as extended carbon nucleophiles in Lewis acid catalyzed vinylogous Mukaiyama-type Mannich coupling with both aromatic and aliphatic *N*-Boc aminals. The reactions performed well in most circumstances, providing α-alkylidene-δ-amino-2-oxindoles in good yields and complete γ-site and *Z*-selectivities. Starting from these functional scaffolds, a couple of indole-based architectures, including spirocyclopropaneoxindole **4** and homotryptamine **5** could be obtained in 1−2 steps, which embedded nonconventional molecular frameworks. The results obtained in the present VMMnR hold promise for application of the procedure in an enantioselective format; work is presently ongoing in this direction.

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■ ASSOCIATED CONTENT

Supporting Information

Data for new compounds, experimental procedures, X-ray analysis of *syn*-**4**, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) CCDC 977131 (racemic *syn*-**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.