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γ-Regioselective Functionalization of 3-Alkenylindoles *via* 1,6-Addition to Extended Alkylideneindolenine Intermediates

Giulio Bertuzzi,[a] Lucia Lenti,[a,b] Denisa Giorgiana Bisag,[a] Mariafrancesca Fochi,[a] Marino Petrini[b]* and Luca Bernardi[a]*

[a] Department of Industrial Chemistry "Toso Montanari" & INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, V. Risorgimento 4, 40136 Bologna (Italy)
E-mail: luca.bernardi2@unibo.it

[b] School of Science and Technology, Chemistry Division, Università di Camerino, V. S. Agostino 1, 62032 Camerino (Italy)
E-mail: marino.petrini@unicam.it

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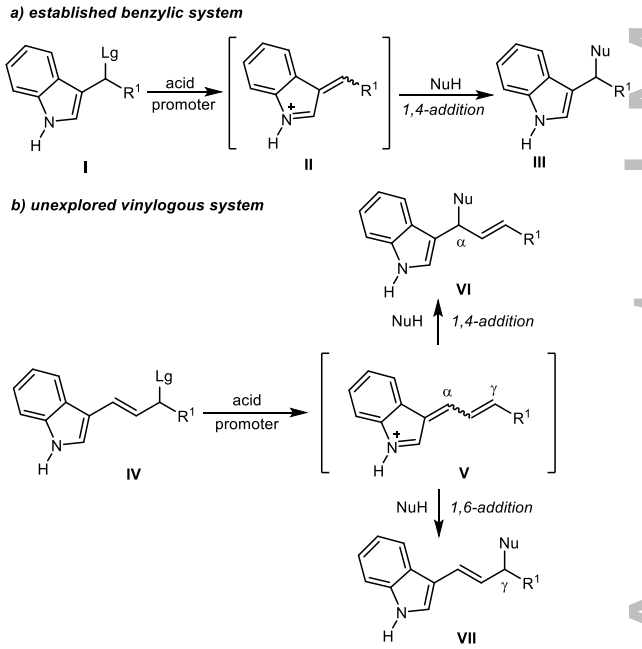
Abstract. Alkylideneindolenines are widely employed key electrophilic intermediates for the α-functionalization of the C-3 side chain of indoles. However, the reactivity of their extended (vinylogous) counterparts has not been carefully explored so far. These intermediates can undergo 1,4- or 1,6-addition with functionalization at α- or γ-position of the side chain, resulting in regioisomeric mixtures of products. This work demonstrates that a complete γ-regioselectivity can be achieved in the reaction of 3-indol-3-yl allylic alcohols with various nucleophiles. This process is catalysed by just 1 mol% zinc(II) triflate at room temperature and entails the 1,6-selective addition of the nucleophile to an extended protonated alkylideneindolenine generated *in situ*. Indoles, pyrroles, anilines and thiols can be efficiently used as nucleophilic partners for this reaction, delivering the corresponding 3-vinyl substituted, γ-functionalised indole products in moderate to good yields.

Keywords: alcohols; iminium ions; indoles; Lewis acids; thiols; vinylogy.

The functionalization of C-3 side chain of indoles exploiting the reactivity of alkylideneindolenine intermediates is a well-known strategy in the synthesis of indole containing compounds.[1] In this context, one of the most common approaches is based on the reactivity of a suitable precursor **I** which under acidic conditions suffers the elimination of a leaving group (Lg) generating an iminium ion intermediate **II** (Scheme 1a). The subsequent 1,4-addition of a nucleophile results in the functionalized product **III**. This procedure enables the introduction in the side chain of a notable number of functional groups including heteroatom based nucleophiles, even in an enantioselective fashion. A step forward in the development of this strategy is to employ a vinylogous[2] derivative **IV** for a related purpose, allowing the formation of an extensively conjugated iminium ion **V** (Scheme 1b).[3] Reaction of this intermediate **V** with a nucleophile may in principle occur at the α or γ reactive positions of the side chain thus generating a couple of regioisomeric adducts **VI** and **VII** *via* 1,4 or 1,6-addition respectively. Concerning the nature of the leaving group that could be involved in these processes, the hydroxyl function undoubtedly plays a central role since it can be readily installed and then efficiently removed under Brønsted or Lewis acidic conditions.[1,4]



Scheme 1. General strategies for the functionalization of indole C3-side chain *via* alkylideneindolenine intermediates **II** and **V**.

A literature survey shows that reaction of related 3-phenyl allylic alcohols with typical heteroaromatic nucleophiles has been investigated in some detail, often leading to regioisomeric mixtures of products.[5] The utilization of 3-indol-3-yl allylic alcohols (*i.e.* **IV**,

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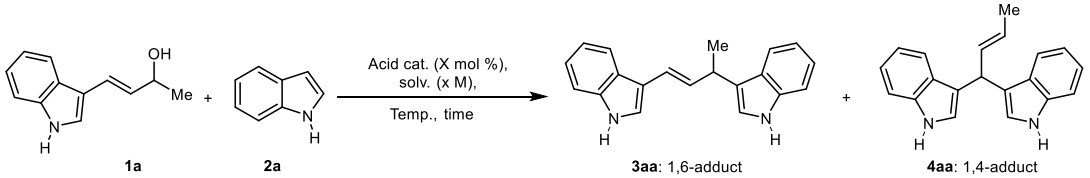
with Lg = OH) in the same reaction has been rather neglected and, to the best of our knowledge, there are no systematic studies on the achievement of γ-regiochemical control using these substrates.[6] It should be observed that functionalized derivatives of type **VII** retaining the conjugated alkenyl moiety would be of some practical interest since they are pivotal intermediates in the synthesis of polycyclic derivatives through Diels-Alder-type reactions.[7]

This communication reports our preliminary studies on the generation of extended alkylideneindolenine intermediates **V** from 3-indol-3-yl allylic alcohols **1** and their γ-regioselective functionalization exploiting a 1,6-addition reaction. This new vinylogous reactivity is demonstrated with different nucleophilic species.

At the outset of this work, we explored different substrates and catalytic strategies for the generation of extended alkylideneindolenine intermediates of type **V** *in situ* and their ensuing reaction with nucleophiles. After several unsuccessful attempts, many of which were hampered by the poor stability of the precursors and/or the intermediates, we observed promising reactivity by treating allylic alcohol **1a** and indole **2a** with diphenyl phosphoric acid as Brønsted acid catalyst,[8] in dichloromethane at low temperature (Table 1, entry 1). Due to its modest stability, we decided to work with a slight excess of substrate **1a**. Indeed, **1a** proved to be very reactive under these conditions, since in only 1 h it was completely consumed, furnishing, along with a certain amount of unidentified by-products, a 2:1 regioisomeric mixture of bis-indoles **3aa** (1,6-adduct) and **4aa** (1,4-adduct) in low overall yield. Different organic acids, such as acetic acid and trifluoroacetic acid, were then tested but led to unsatisfactory results in terms of reactivity (see the Supporting Information). We thus moved to Lewis acid catalysts.[9] Preliminary tests with $BF_3{\cdot}Et_2O$ showed a complete regioselectivity in favour of the γ-isomer **3aa**. This was considered a relevant result since demonstrated that the regioselectivity was not due to an intrinsic substrates bias but was (at least partially) controlled by the catalytic species (*vide infra*). Even if the conversion of indole **2a** was far from satisfactory (entry 2), this result led us to speculate that Lewis acids could give better results compared to Brønsted acids. However, the regioisomeric ratio dropped considerably when $ZrCl_4$ was used (entry 3). It was hypothesized that this was due to the hydrolysis of the catalyst, generating HCl and promoting the α-functionalization. We thus moved to more water compatible Lewis acids, such as metal triflates. It was contextually found that only 5 mol% of catalyst was generally enough for the complete consumption of **1a** and that a dilution of the reaction mixture led to more clean reaction crudes. Among others (entry 4 and Supporting Information), we were pleased to find that non-toxic and cheap $Zn(OTf)_2$ furnished the most promising results (high regioselectivity and moderate conversion, entry 5). Interestingly, a solvent switch from dichloromethane to THF led to improved conversion and yield values accompanied by a significant drop in the **3aa**/**4aa** ratio (entry 6), while the use of CH_3CN, besides rendering a higher conversion, displayed an excellent regioselectivity (entry 7).[10] To overcome the rapid decomposition of **1a**, we decided to add it portion-wise over a period of 4 hours and to increase its excess from 1.5 to 2.0 equivalents. These modifications had a very positive effect on the conversion value and improved also the yield slightly (entry 8). Pleasingly, a decrease in the catalytic loading to 1 mol% furnished comparable results, whereas a further decrease up to 0.1 mol% led to a much slower reaction (entries 9 and 10).[11] Finally, when the $Zn(OTf)_2$ catalyzed reaction was performed in the presence of 5 mol% $(PhO)_2PO_2Na$, a dramatically different regiochemical outcome was observed: a 1:1 **3aa**/**4aa** mixture was obtained, a result similar to the one obtained with the catalytic phosphoric acid (compare entry 1 with entry 11). These results suggest that the presence of a nucleophilic anion, such as diphenyl phosphate, gives a non-regioselective addition (*vide infra*).

Table 1. Optimization of the reaction conditions. Representative results.[a]



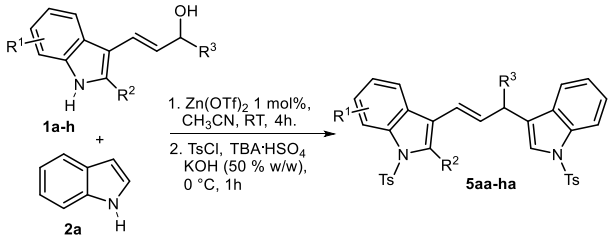
1a **2a** **3aa**: 1,6-adduct **4aa**: 1,4-adduct

Entry	Catalyst [mol %]	Solvent [Conc. (M)]	Temp (°C)	Time (h)	Conv. (%)[b] [Yield (%)][c]	**3aa**/**4aa**[b]
1	$(PhO)_2PO_2H$ [10]	DCM [0.2]	-30	1	41 [28]	2:1
2	$BF_3{\cdot}Et_2O$ [10]	DCM [0.2]	-30	4	30 [nd]	>20:1
3	$ZrCl_4$ [10]	DCM [0.2]	-30	4	50 [nd]	1.4:1
4	$Yb(OTf)_3$[5]	DCM [0.05]	rt	6	45 [nd]	10:1
5	$Zn(OTf)_2$ [5]	DCM [0.05]	rt	6	50 [43]	10:1
6	$Zn(OTf)_2$ [5]	THF [0.05]	rt	3	77 [72]	2.5:1
7	$Zn(OTf)_2$ [5]	CH_3CN [0.05]	rt	3	67 [54]	>20:1
8[d]	$Zn(OTf)_2$ [5]	CH_3CN [0.05]	rt	4	84 [64]	>20:1

9[d]	$Zn(OTf)_2$ [1]	CH_3CN [0.05]	rt	4	85 [65]	>20:1
10[d]	$Zn(OTf)_2$ [0.1]	CH_3CN [0.05]	rt	4	50 [30]	>20:1
11	$Zn(OTf)_2$ [1]/$(PhO)_2PO_2Na$[5]	CH_3CN [0.05]	rt	4	50 [30]	1:1

[a] Conditions: alcohol **1a** (0.15 mmol), indole **2a** (0.10 mmol), catalyst (x mol%), solvent (x M based on **2a**) [b] Determined by ^1H NMR spectroscopy on the crude mixture (with respect to indole **2a**). [c] Determined by ^1H NMR spectroscopy on the crude mixture using bibenzyl as internal standard. [d] Conditions: indole **2a** (0.1 mmol), alcohol **1a** (0.05 mmol every hour until 0.20 mmol (2.0 equiv.) were reached), $Zn(OTf)_2$ (x mol%), CH_3CN (2.0 mL, 0.05 M based on **2a**), rt, 4h.

Table 2. Scope of the reaction between 3-indol-3-yl allylic alcohols **1** and indoles **2**: variation of the allylic alcohol partner **1**. [a]

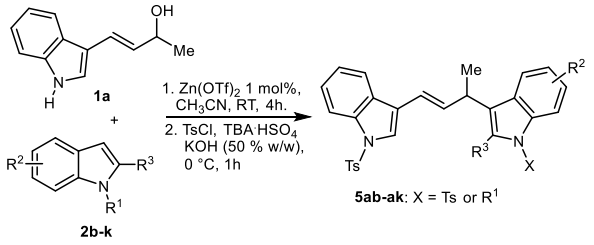


Entry	**1**	R^1	R^2	R^3	**5**	Yield[b] (%)
1	**1a**	H	H	Me	**5aa**	79
2	**1b**	H	Me	Me	**5ba**	50
3	**1c**	4-Br	H	Me	**5ca**	40
4	**1d**	5-Br	H	Me	**5da**	51
5	**1e**	5-MeO	H	Me	**5ea**	75
6	**1f**	6-Cl	H	Me	**5fa**	65
7	**1g**	H	H	Et	**5ga**	65
8	**1h**	H	H	*n*-Bu	**5ha**	51

[a] Conditions: indole **2a** (0.1 mmol), alcohol **1** (0.05 mmol every hour until 0.20 mmol (2.0 equiv.) were reached), $Zn(OTf)_2$ (1 mol%), CH_3CN (2.0 mL, 0.05 M based on **2a**), rt, 4h. ^1H NMR sampling showed the exclusive presence of the single γ-regioisomer in all cases. Then, TsCl (0.24 mmol), $KOH_{(aq.)}$ 50% w/w (100 μL), $TBA{\cdot}HSO_4$ (0.01 mmol), 0 °C, 1 h. [b] Isolated yield after chromatography on silica gel.

With optimal conditions in hand (Table 1, entry 9), we tested the generality of the process by varying the substitution pattern on the allylic alcohol partner **1** (Table 2). Relatively unstable bis-indoles **3** were more conveniently isolated as di-tosylated products **5**, obtained by direct treatment of the reaction mixtures with tosyl chloride, aqueous potassium hydroxide and a phase-transfer catalyst (tetra-*n*-butylammonium hydrogen sulfate). The first results collected showed that the presence of a substituent at the C-2 position of the indole was tolerated (substrate **1b**), although displaying a slightly detrimental effect on the yield compared to the unsubstituted substrate **1a** (Table 2, entries 1 and 2). On the other hand, products **5ca**-**5fa** were achieved in moderate to good yields, regardless of the presence of electron-withdrawing or electron-donating groups at positions C-4, C-5 and C-6 of the indole framework in alcohols **1c**-**1f** (entries 3-6). Interestingly, the presence of more sterically demanding groups, such as ethyl or *n*-butyl at the terminal reactive position of substrates **1g** and **1h**, did not affect the regioselectivity of the reaction. The expected products **5ga** (entry 7) and **5ha** (entry 8) were obtained in 65% and 51% yield respectively and in regioisomerically pure form, in line with the results obtained with the methyl substituted substrates **1a-f**.[12]

Table 3. Scope of the reaction between 3-indol-3-yl allylic alcohols **1** and indoles **2**: variation of the indole partner **2**.[a]



Entry	**2**	R^1	R^2	R^3	**5**	X	Yield[b] (%)
1	**2b**	Me	H	H	**5ab**	Me	56
2	**2c**	H	H	Me	**5ac**	H	66
3	**2d**	H	H	vinyl	**5ad**	H	52
4	**2e**	H	H	Ph	**5ae**	H	83
5	**2f**	H	5-Me	H	**5af**	Ts	60
6	**2g**	H	5-MeO	H	**5ag**	Ts	72
7	**2h**	H	5-Cl	H	**5ah**	Ts	35
8	**2i**	H	6-Cl	H	**5ai**	Ts	45
9	**2j**	H	7-Me	H	**5aj**	H	66
10	**2k**	H	7-MeO	H	**5ak**	H	55

[a] Conditions: indole **2** (0.1 mmol), alcohol **1a** (0.05 mmol every hour until 0.20 mmol (2.0 equiv.) were reached), $Zn(OTf)_2$ (1 mol%), CH_3CN (2.0 mL, 0.05 M based on **2**), rt, 4h. ^1H NMR sampling showed the exclusive presence of the γ-regioisomer in all cases. Then, TsCl (0.24 mmol), $KOH_{(aq.)}$ 50% w/w (100 μL), $TBA{\cdot}HSO_4$ (0.01 mmol), 0 °C, 1 h. [b] Isolated yield after chromatography on silica gel.

We moved then to explore the possible variations of the nucleophilic partner. First of all, we successfully employed ten different indoles **2** (Table 3) under the optimized reaction conditions previously used for the parent indole **2a**. It is worth of note that compounds **5**, bearing substituents at positions C-2 (**5ac-5ae**, Table 3, entries 2-4) and C-7 (**5aj**,**5ak**, entries 9-10) on the indole ring deriving from **2**, did not afford di-tosylated products, but adducts bearing a single tosyl group on the unsubstituted indole derived from allylic alcohol **1**. Presumably, steric hindrance hampered the introduction of the second tosyl group. The results obtained showed that the full regioselectivity of the reaction was maintained even

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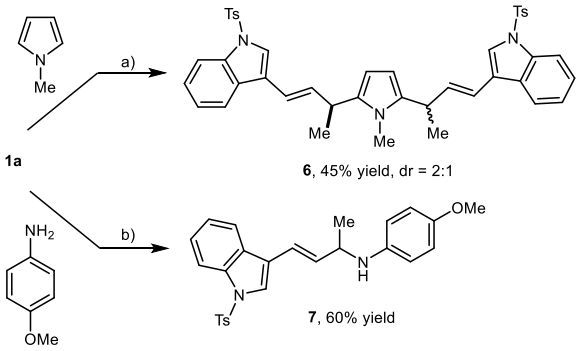
with *N*-methylindole **2b** (entry 1), although the yield was slightly lower compared to **2a**. Substituents at position C-2 in indoles **2b-e** (entries 2-4) were well tolerated, irrespectively of their steric bulkiness. Indoles **2f-k** bearing both electron-withdrawing and electron-donating substituents at positions C-5, C-6 and C-7 afforded in regioisomerically pure form the corresponding products **5af-ak** (entries 5-10). Diminished yields in the case of electron-poor substrates **2h** and **2i** were obtained.

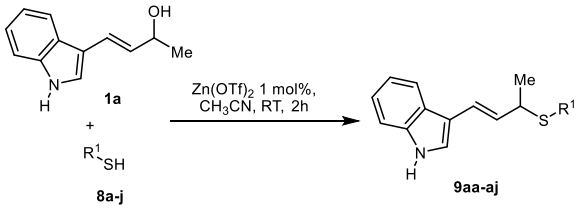
In order to broaden the scope of this newly disclosed reactivity of extended alkylideneindolenines, we searched for additional nucleophiles, able to react with allylic alcohol **1a**. As shown in Scheme 2, we found that *N*-methylpyrrole reacted with **1a** under the same reaction conditions used for indoles **2**, affording the doubly functionalized pyrrole product **6** in 45% (un-optimized) yield. While the γ-regioselectivity of the reaction was again complete, a 2:1 mixture of diastereoisomers was obtained. Also *p*-methoxyaniline was found to be reactive towards the alkylideneindolenine derived from **1a** in a vinylogous fashion, delivering the corresponding allyl aniline **7** in 60% yield. In this case, an increased catalyst loading (10 mol%) was required to achieve satisfactory results.



Scheme 2. Reaction of **1a** with *N*-methylpyrrole and *p*-methoxyaniline. [a] Reaction conditions: nucleophile (0.1 mmol), alcohol **1a** (0.05 mmol every hour until 0.20 mmol (2.0 equiv.) were reached), $Zn(OTf)_2$ (1 mol%), CH_3CN (2.0 mL, 0.05 M based on **2**), rt, 4h. Then, TsCl (0.24 mmol), $KOH_{(aq.)}$ 50% w/w (100 μL), $TBA{\cdot}HSO_4$ (0.01 mmol). [b] As in [a] but with 10 mol% $Zn(OTf)_2$.

Moreover, as we moved to test sulphur nucleophiles in the reaction with **1a**, we pleasingly found that both aromatic and aliphatic thiols **8** were very efficient reaction partners (Table 4).[13] It is interesting to note that a smaller excess of **1a** (1.2 equivalents instead of 2.0) and a reduced reaction time (2 h instead of 4 h) were sufficient for the complete and smooth conversion of the starting thiols **8**. In addition, the tosylation step could be avoided, as products **9** were found to be stable enough to allow isolation by chromatography on silica gel. In more detail, products **9aa-ae**, derived from thiophenols **8a-e** bearing electron-withdrawing or electron-donating substituents at different positions of their aromatic rings, were obtained with fully satisfactory yields (entries 1-5). Similarly, good results were achieved using both secondary and primary aliphatic thiols **8f-j**, which gave the corresponding products **9af-aj** in 50-90% yields (entries 6-10).

Table 4. Scope of the reaction between 3-indol-3-yl allylic alcohol **1a** and thiols **8a-j**. [a]

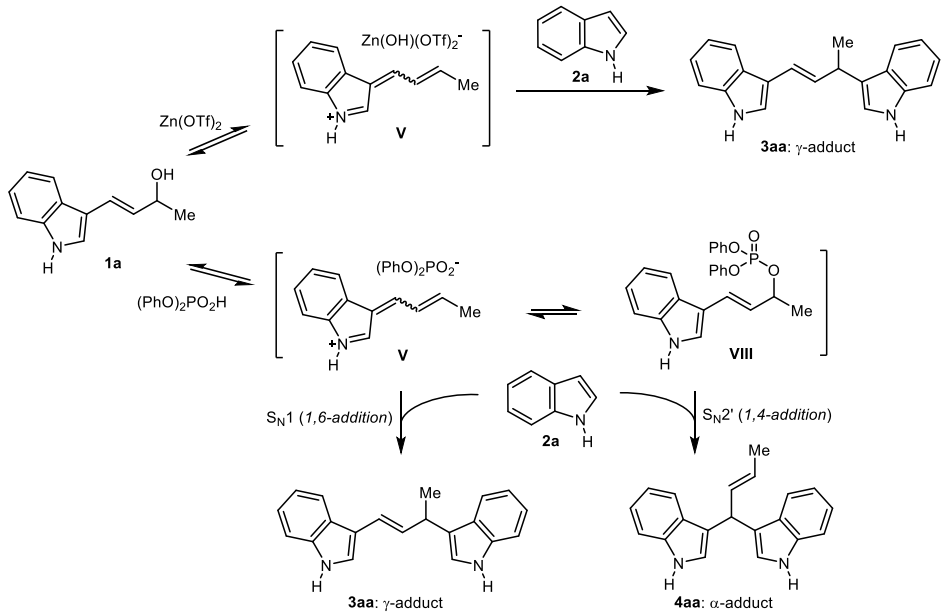


Entry	**8**	R^1	**9**	Yield[b] (%)
1	**8a**	Ph	**9aa**	90
2	**8b**	4-ClC_6H_4	**9ab**	76
3	**8c**	4-$MeOC_6H_4$	**9ac**	95
4	**8d**	2-MeC_6H_4	**9ad**	76
5	**8e**	2-Naphthyl	**9ae**	71
6	**8f**	$PhCH_2$	**9af**	60
7	**8g**	Et	**9ag**	50
8	**8h**	*i*-Pr	**9ah**	80
9	**8i**	*c*-C_5H_9	**9ai**	86
10	**8j**	2-furfuryl	**9aj**	90

[a] Conditions: thiol **8** (0.1 mmol), alcohol **1a** (0.06 mmol every hour until 0.12 mmol (1.2 equiv.) were reached), $Zn(OTf)_2$ (1 mol%), CH_3CN (2.0 mL, 0.05 M based on **8**), rt, 2 h. ^1H NMR sampling showed the exclusive presence of the γ-regioisomer in all cases. [b] Isolated yield after chromatography on silica gel.

On the basis of the obtained results it is possible to propose two plausible reaction pathways for the Brønsted acid and the Lewis acid catalysed processes, exemplified in Scheme 3 for the reaction between substrate **1a** and indole **2a**.[14] The lack of reactivity of (*E*)-3-(1*H*-Indol-3-yl)prop-2-en-1-ol (a primary alcohol related to **1a**)[12] confirms the formation of an alkylideneindolenine intermediate in the reaction and rules out a direct S_N2-type pathway, which would have been favourable for this unsubstituted substrate. When the Lewis acid used bears a non-nucleophilic anion such as triflate, the indoleninium cation **V**[15] formed react with nucleophiles in a fully 1,6-regioselective fashion leading to γ-functionalized derivatives (Scheme 3, top). Conversely, when the reaction is run in the presence of phosphoric acid catalyst, the alkylideneindoleninium intermediate may be partially and reversibly captured by the weakly nucleophilic phosphate counterion (Scheme 3, bottom). This trapping is likely to occur in a γ-regioselective fashion, in line with the 1,6-addition of the other nucleophiles. While the "free" alkylideneindoleninium cation reacts with γ-regioselectivity by 1,6-nucleophilic addition, the trapped intermediate **VIII** may undergo an S_N2'-type substitution with nucleophiles, ultimately rendering

the α-regioisomer. In this context, the lack of regioselectivity observed introducing sodium diphenylphosphate together with zinc(II) triflate (Table 1, entry 11) corroborates the proposed reaction course. An additional hint to this hypothesis derives from the proven feasibility of S_N2' reaction pathways in the frame of chiral phosphoric acid catalysis.[16]



Scheme 3. Proposed rationalisation of the regiochemical outcomes observed using zinc triflate *vs* diphenylphosphoric acid as catalysts.

In conclusion, we set up a new regioselective protocol for remote functionalization of vinylogous alkylideneindolenine systems, employing a mild Lewis acid catalysed dehydration of 3-indol-3-yl allylic alcohols **1** for the *in situ* generation of the extended intermediate. The developed procedure was found to tolerate a variety of nucleophiles, such as indoles, pyrroles, anilines and thiols, representing a general platform for the formation of new C-C, C-N and C-S bonds at the terminal position of the extended conjugated system. Thirty differently γ-functionalized 3-vinylindoles have been thus successfully synthesized in moderate to good yields and regioisomerically pure form under mild reaction conditions, and with a catalyst loading as low as 1 mol%.

Experimental Section

General procedure for the synthesis of products 5-7
In a test tube equipped with a magnetic stirring bar, indole **2** (0.1 mmol), for products **5**, *N*-methylpyrrole (0.1 mmol), for product **6**, 4-methoxyaniline (0.1 mmol) for product **7**, is added to a solution of $Zn(OTf)_2$ in CH_3CN (2 mL: 0.5 mM corresponding to 0.36 mg of $Zn(OTf)_2$, 0.001 mmol, 1 mol% for products **5** and **6**; 5 mM corresponding to 3.6 mg of $Zn(OTf)_2$, 0.01 mmol, 10 mol% for product **7**). Alcohol **1** (0.05 mmol) is added and the reaction is stirred at room temperature for 1 h. Then, 0.05 mmol of **1** are added every hour, until, after 3 h, 0.2 mmol (2 equiv.) were reached. After an additional hour, a small fraction of this mixture is analyzed by ^{1}H NMR to determine the regiosiomeric ratio of the addition products, which was always found to be >20:1. The reaction mixture is then cooled to 0 °C and TsCl (45.7 mg, 0.24 mmol), tetrabutylammonium hydrogensulfate (3.4 mg, 0.01 mmol) and a 50% w/w aqueous solution of KOH (100 μL) are added and the stirring is continued at 0 °C for 1 h. Hereafter, the reaction mixture is filtered through a short Celite® plug, the plug washed with DCM (5 mL) and the solvents evaporated *in vacuo*. The crude residue is then purified by column chromatography on silica gel to obtain products **5-7** as solids. Adducts **5-7** were formed as single *E*-isomers in all cases.

(*E*)-3,3'-(But-1-ene-1,3-diyl)bis(1-tosyl-1*H*-indole) 5aa
Following the general procedure, from (*E*)-4-(1*H*-indol-3-yl)but-3-en-2-ol **1a** and indole **2a**, product **5aa** was obtained as an off-white solid (m.p. = 112-115 °C) in 79% yield after column chromatography on silica gel (*n*-hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (*pseudo*tt, *J* = 8.1, 0.9 Hz, 2H), 7.79 – 7.73 (m, 4H), 7.58 (*pseudo*dddd, *J* = 23.5, 7.9, 1.3, 0.8 Hz, 2H), 7.49 (s, 1H), 7.40 (d, *J* = 1.1 Hz, 1H), 7.31 (*pseudo*ddt, *J* = 8.5, 7.2, 1.5 Hz, 2H), 7.25 – 7.17 (m, 6H), 6.47 – 6.36 (m, 2H), 3.83 (tt, *J* = 7.1, 6.1 Hz, 1H), 2.33 (s, 6H), 1.55 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.9, 144.8, 135.5, 135.4, 135.3, 135.1, 134.9, 130.3, 129.88, 129.86, 129.82, 129.1, 126.82, 126.77, 126.4, 124.8, 124.6, 123.3, 123.2, 123.0, 122.3, 120.3, 120.1, 119.8, 113.8, 113.7, 34.4, 21.5 (2 overlapped signals), 20.2 ppm; ESI-MS: 617 [M + Na^+].

General procedure for the synthesis of products 9
In a test tube equipped with a magnetic stirring bar, thiol **8** (0.1 mmol) is added to a 0.5 mM solution of $Zn(OTf)_2$ in CH_3CN (2 mL: 0.5 mM, corresponding to 0.36 mg of $Zn(OTf)_2$, 0.001 mmol, 1 mol%). Alcohol **1a** (11.3 mg, 0.06 mmol) is added and the reaction is stirred at room temperature for 1 h. Then, another portion of **1a** is added (11.3 mg, 0.06 mmol) and the mixture stirred for an additional hour. A small fraction of this crude mixture is analyzed by means of ^{1}H NMR and the regioisomeric ratio was found to be >20:1 in all cases. The solvent is then evaporated *in vacuo* without heating and the crude residue

is purified by short column chromatography on silica gel to obtain pure products **9** as oils. Adducts **9** were formed as single *E*-isomers in all cases. Products **9** are not sufficiently stable for the mass spectrometry analysis: the major detected fragment at 170 m/z can be attributed to the protonated alkylideneindolenine resulting from thiol elimination. On the other hand, products **9** show fully consistent ^{1}H and ^{13}C NMR spectra.

(*E*)-3-(3-(Phenylthio)but-1-en-1-yl)-1*H*-indole 9aa

Following the general procedure, from (*E*)-4-(1*H*-indol-3-yl)but-3-en-2-ol **1a** and thiophenol **8a**, product **9aa** was obtained as a colourless oil in 90% yield after column chromatography on silica gel (*n*-hexane/EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 (bs, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.35 (ddd, J = 8.0, 1.4, 0.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.25 – 7.12 (m, 5H), 6.44 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9, 8.2 Hz, 1H), 3.96 (dqd, J = 7.8, 6.8, 0.9 Hz, 1H), 1.52 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.6, 135.0, 133.3, 128.7, 128.5, 127.2, 125.6, 123.1, 122.7, 122.5, 120.2, 120.1, 114.7, 111.3, 47.3, 21.0 ppm.

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[10] A reaction performed in the presence of 2,6-di-(*tert*-butyl)pyridine gave a similar result (see the Supporting Information). Thus, the active catalyst is the Lewis acidic species ($Zn(OTf)_2$), and not a Brønsted acid (TfOH) generated by hydrolysis. For a discussion on "hidden" proton catalysis, see: T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484-493.

[11] For comparison, (*E*)-4-phenylbut-3-en-2-ol was reacted with indole **2a** under the conditions described in Table 1, entry 9. The reaction gave 35% conversion and a 55:45 mixture of regioisomeric products. The poor regioselectivity is in line with the results obtained with other Lewis acids in this reaction,[5] while the low conversion highlights the importance of the indole group in this reaction.

[12] (*E*)-3-(1*H*-Indol-3-yl)prop-2-en-1-ol (a primary alcohol related to **1a**) did not react with indole **2a** even when 10 mol% of the Lewis acid was employed as catalyst. In contrast, a 3-indol-3-yl allylic alcohol substrate bearing a phenyl group at the 1-position gave a nearly 1:1 regioisomeric mixture of products. We speculate that the high γ-regioselectivity in the reactions with the alkyl substrates **1a-h** can be partially ascribed to the higher stability of the conjugated products **3** compared to the deconjugated adducts **4**. In the case of the phenyl-substituted substrate, this bias towards the vinylogous product **3** is not present. Besides, steric effects might additionally hinder γ-reactivity. As a result, the reaction affords both regioisomers also under the optimized conditions.

[13] The reaction of **1a** with aliphatic and aromatic thiols promoted by the Brønsted acid ($(PhO)_2P(O)OH$) under various reaction conditions afforded only traces of

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desired products, resulting mostly in degradation. For the addition of thiols to alkylideneindolenines generated from indol-3-yl α-acyloins under acid catalysis, see: A. Suárez, F. Martínez, R. Sanz, *Org. Biomol. Chem.* **2016**, *14*, 11212-11219.

[14] For a full discussion including additional control experiments, see the Supporting Information.

[15] Experiments with an *N*-methyl substrate related to **1a** gave very similar results, suggesting indoleninium ion, rather than indolenine, as the electrophilic species of the reaction.

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γ-Regioselective Functionalization of 3-Alkenylindoles *via* 1,6-Addition to Extended Alkylideneindolenine Intermediates

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Giulio Bertuzzi, Lucia Lenti, Denisa Giorgiana Bisag, Mariafrancesca Fochi, Marino Petrini* and Luca Bernardi*