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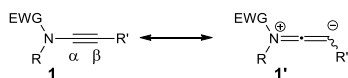
Transition Metal-Free Tunable Chemoselective *N*-Functionalization of Indoles with Ynamides

Alexandre Hentz, Pascal Retailleau, Vincent Gandon, Kevin Cariou, and Robert H. Dodd*

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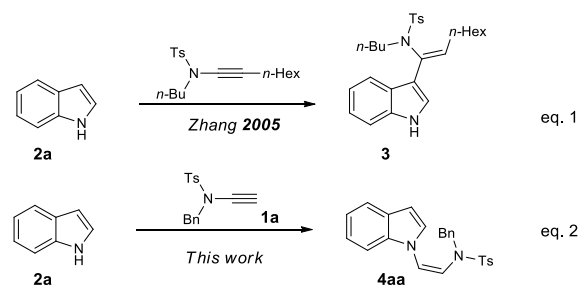
Abstract: Two unprecedented *N*-functionalizations of indoles with ynamides are described. By varying the electron-withdrawing group borne by the ynamide nitrogen, *Z*-indolo-etheneamides or indolo-amidines can be selectively obtained under the same metal-free reaction conditions. The scope and synthetic potential of these reactions as well as some mechanistic insights provided by DFT calculations are reported.

Ynamides are characterized as nitrogen-substituted alkynes with an electron-withdrawing group at the nitrogen (providing increased stability) and constitute highly versatile synthetic building blocks.^[1] The nitrogen-substituted triple bond can react like other alkynes but can also exhibit specific reactivity due to the possible delocalization of the lone pair, rendering the α position electrophilic and the β position nucleophilic (Scheme 1).^[1]



Scheme 1. Resonance structures of ynamides

Because of the strong polarization of the triple bond, examples of addition at the β position are rare and usually involve metallic species.^[2-7] On the other hand, nucleophilic attack on the α position is much more common.^[1,8] For instance, Zhang reported that using a catalytic amount of triflimide, a variety of vinyl-heterocycles could be obtained through a highly regioselective hydroarylation process.^[9] In the case of indole **2a**, the reaction exclusively took place at the 3 position of the indole and the α position of the ynamide to give 3-vinylindole **3** (Scheme 2, eq. 1). During the course of studies involving the reaction of ynamides with indolic derivatives, our curiosity was aroused by a by-product that seemed to arise from the direct addition of the indole nitrogen on the ynamide (eq. 2).



Scheme 2. 3-Vinylation vs *N*-vinylation of Indole

Indeed, when reacting indole **2a** with ynamide **1a** in DMF at 80 °C in the presence of an excess of sodium *tert*-butoxide, compound **4aa** was isolated with a 7% yield (Table 1, entry 1). To the best of our knowledge, such an intermolecular addition of a nitrogen nucleophile to an ynamide is unprecedented and only two intramolecular examples, first by Urabe^[10] (in which case a copper assisted process is proposed) and more recently by Cossy,^[11] have been reported. A handful of reports describe the addition of indoles and related heterocycles to non-activated alkynes leading to *N*-vinyl derivatives.^[12] In these cases, the *Z*-isomer is usually obtained as the major product, however these reactions only take place at high temperature (80 °C-120 °C) and are limited to arylacetylenes. We thus sought to further investigate the formation of compound **4aa** and initiated optimization of the reaction conditions.

Table 1. Optimization of the reaction conditions

Entry	X	Base (n equiv)	Temp.	Time (h)	Yield (%) ^[a]
1	1	<i>t</i> -BuONa (1.5)	80 °C	22	7
2	1	<i>t</i> -BuONa (1.5)	R.T.	22	20
3	1	<i>t</i> -BuONa (2)	R.T.	72	40
4 ^[c]	1	<i>t</i> -BuONa (1)	R.T.	30	50 ^b
5 ^[c]	2	<i>t</i> -BuONa (2)	R.T.	30	quant.
6 ^[c]	2	NaOH (2)	R.T.	30	87 ^[b]
7 ^[c]	2	KOH (2)	R.T.	30	42 ^[b]
8 ^[c]	2	LiOH (2)	R.T.	30	14 ^[b]
9 ^[c]	2	<i>t</i> -BuONa (2)	R.T.	4.5 ^[d]	100 ^[b]

[a] Isolated yields, unless indicated otherwise. [b] Conversion determined by ¹H NMR analysis of the crude product mixture. [c] 3 Å molecular sieves were added. [d] 18-Crown-6 was added.

First, lowering the reaction temperature to R.T. (entry 2) and increasing the amount of base to 2.0 equiv. (entry 3) did not allow complete conversion but the yield was increased to 40%. As side-

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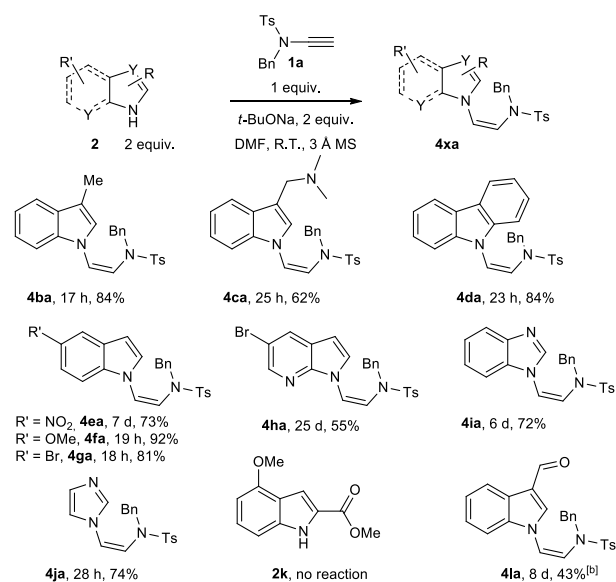
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products coming from the hydrolysis of the ynamide were detected,^[13] molecular sieves were added to the reaction mixture and a 50% conversion was now achieved (entry 4). We then decided to use a two-fold amount of indole and full conversion of the ynamide as well as a quantitative yield of product **4aa** were thus attained (entry 5). Alkali hydroxides were also tested and whereas they did promote the reaction, yields were lower, presumably because these salts are less soluble in DMF (entries 6-8). Finally, the role of the cation did not seem to be decisive since addition of 18-crown-6 to the reaction mixture did not change the outcome of the reaction, although it did proceed faster (entry 9).

With these optimal conditions in hand (Table 1, entry 5) we began to explore the scope of the reaction by first varying the indolic partner (Scheme 3). 3-Substituted derivatives such as skatole and gramine as well as carbazole reacted equally well, giving excellent yields of the corresponding adducts **4ba-4da**. From a mechanistic point of view, these results tend to rule out a process initiated by reaction at the 3-position followed by a rearrangement but rather point towards a direct reaction with the indolyl nitrogen (*vide infra* for more details). Electronic effects were then probed by studying the influence of a substituent at the 5-position of the indole nucleus. An electron-withdrawing group (nitro) greatly lowered the reactivity and compound **4ea** could only be obtained in good yield after an extended reaction time of 7 days. On the other hand, electron-donating 5-OMe and 5-Br substituents were well tolerated and the reaction was also slightly accelerated. In the latter case an X-ray crystallographic analysis of **4ga** was performed to further ascertain the structure of this new family of indolic derivatives.^[14] 7-Azaindole, benzimidazole as well as imidazole derivatives **4ha-4ja** could also be formed, while an ester group at the 2 position (**2k**) shut down the reactivity. Nevertheless, an EWG such as an aldehyde was tolerated at the 3 position and compound **4la** could be obtained with a moderate 43% yield after prolonged reaction time in the presence of 18-crown-6.

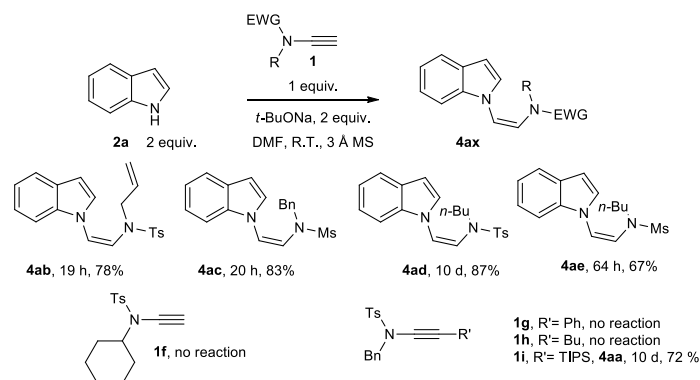


Scheme 3. Heterocycles scope^[a]

[a] Isolated yields. [b] 18-Crown-6 was added.

We then turned our attention to the ynamide partner (Scheme 4). Both *N*-tosyl and *N*-mesyl groups were tolerated as long as the nitrogen atom bore a primary alkyl substituent such as allyl (**4ab**),

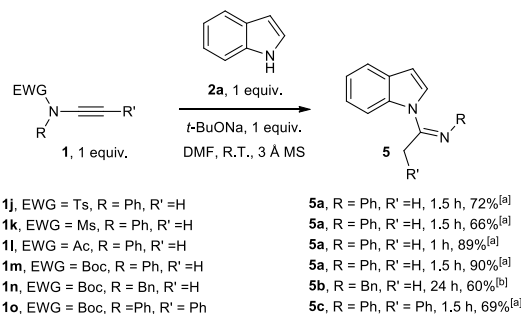
benzyl (**4ac**) or *n*-butyl (**4ad**, **4ae**). Nevertheless, the reaction proved quite sensitive to steric hindrance as the reaction time was extended for the *n*-butyl substrates and no reactivity was observed for the bulkier cyclohexyl derivative **1f**. Substituted ynamides such as **1g** and **1h** also did not react and only led to complex mixtures after prolonged reaction times and/or at higher temperatures. The case of the TIPS-substituted ynamide **1i** is noteworthy, as after 10 days of reaction unsilylated adduct **4aa** was obtained. Our assumption is that this substituted ynamide does not react either, but the basic reaction conditions allow the slow desilylation of **1i** to give **1a**, which in turn reacts with the indole to finally yield **4aa**.



Scheme 4. Ynamide scope^[a]

[a] Isolated yields.

A drastic change in the reactivity pattern was witnessed when aniline-derived ynamide **1j** was reacted with indole **2a**, giving rise to amidine **5a**, which formally results from the addition of the indole nitrogen to the α position of **1**^[15] followed by tautomerization and loss of the tosyl group (Scheme 5, in this case only one equivalent of both the indole and the base were sufficient to reach complete conversion). Methanesulfonamide, acetamide and *tert*-butoxycarbamate derivatives (**1k-1m**, respectively) led to the same product **5a**, the structure of which was further confirmed by crystallographic analysis.^[14] Moreover, benzylamine-derived ynamide **1n** also yielded an amidine derivative (**5b**), indicating that this change in reactivity can be tuned not only by changing the R group but also by changing the nature of the EWG (compare **1a** with **1n**). Finally, Ph-substituted ynamide **1o** was submitted to the same reaction conditions to give amidine **5c** with 69% yield.

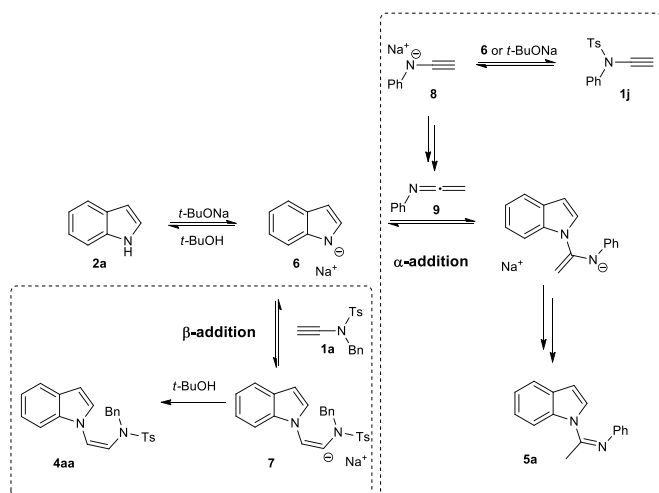


Scheme 5. Reactivity switch

[a] Isolated yields. [b] NMR yield using 1,3,5-trimethoxybenzene as internal standard: **5b** 60%, **1m** 15% and *N*-Boc-Indole 15%.

This reactivity switch prompted us to devise a mechanistic scenario for these unusual transformations (Scheme 6). First, it can be assumed that the indole is deprotonated by the base to give **6**. For *N,N*-sulfonyl-alkyl ynamides such as **1a**, direct addition at the β

position would generate anion **7** and compound **4aa** after protonation. For *N*-sulfonyl-*N*-aryl-, *N*-Ac- and *N*-Boc-ynamides (**1j-n**), either the indole anion or the base could cleave the protecting group to give amide **8**^[16] which after protonation and tautomerization would generate the highly reactive **ketenimine** **9**.^[17] Addition of the indole anion on the **ketenimine** would then lead to amidine **5a** after protonation and tautomerization. It can be hypothesized that the stabilization of anion **8** facilitates the cleavage of the protecting group under basic conditions in a similar fashion as for pyrroles or indoles.^[18] Alternatively, the ynamide could also act as group donor, transferring the protecting group onto the indole that could be deprotected thereafter.^[19]



Scheme 6. Mechanism proposal

As the addition process of **6** to **1a** to give **7** seems counterintuitive in view of the polarization of the ynamide triple bond, DFT calculations were carried out at the M05-2X^[20]/6-31+G(d,p)^[21] level to provide insights on its feasibility. We first looked at the natural charges of ynamide **1a** and the deprotonated indole (Figure **1**). As expected, C_β of **1a** bears a negative charge (-0.270), and as does the nitrogen atom **6** (-0.602). In spite of this unfavorable charge repulsion, a transition state corresponding to the addition of **6** to C_β could be located (**TS_{A-7}**). The corresponding free energy of activation is quite low (9.6 kcal/mol) and the addition is appreciably exothermic by 12.5 kcal/mol. It should be noted that in agreement with the experimental data, **TS_{A-7}** leads to the *Z*-carbanion **7**. The *E* diastereomer did not converge and collapsed to the *Z* form. It is likely that electron-electron repulsion strongly favors a *trans* relationship between the *sp*² orbital holding the electron pair at C_α of the carbanion and the electron-rich indole moiety. In **TS_{A-7}**, a charge of -0.231 is transferred from the indolate to the ynamide. A great part of this excess negative charge is managed by C_α (-0.183) and by the electron-withdrawing Ts group (-0.079).

The approach of the indolate to the ynamide proceeds in a very peculiar way, as revealed by the structure of **TS_{A-7}** (Figure **2**). There is no alignment of C_β, the nitrogen atom of the indolate, and the center of the C3-C4 bond marked in purple (148° instead of 180°). Thus, there is no overlap of the in-plane nitrogen *sp*² orbital of the indolate (corresponding to its HOMO-2, see Supporting Information) with the π* orbitals of the alkyne moiety of the ynamide (corresponding to its LUMO).^[22] Instead, the indolate presents its HOMO π system, inducing the repulsion of the C_β electrons towards C_α, forming a nascent carbanion at C_α and reducing the negative charge at C_β. Thus,

the approach of the nucleophile reduces the dipole moment of the alkyne moiety.

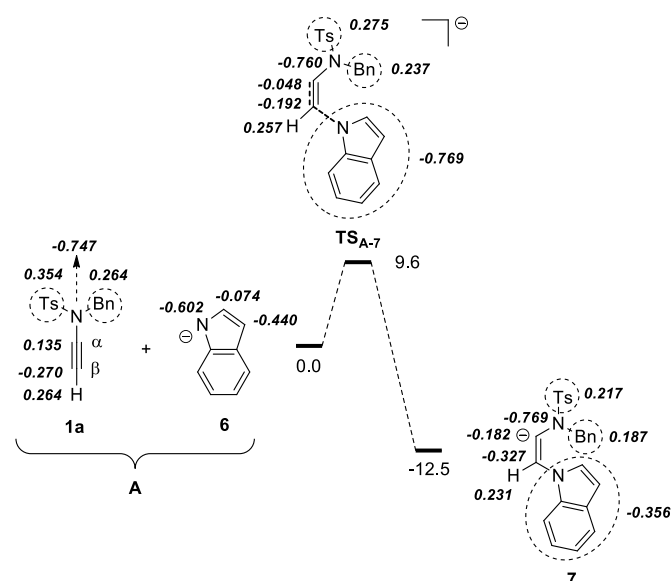


Figure 1. Computed free energy profile (ΔG , kcal/mol) for the addition of the indolate **6** to the β position of ynamide **1a** (NBO charges of atoms and circled fragments are indicated in bold)

This situation could be compared to the addition of Br₂ to an alkene giving rise to a charge transfer complex, yet in this case the polarization of Br₂ induces a positive charge on the bridging bromine in the approach transition state.^[23] More relevant is the addition of singlet oxygen to an enecarbamate.^[24] In the computed transition state corresponding to the first step of a [2+2] cycloaddition, the approach of the enecarbamate induces the polarization of the O–O double bond, the rupture of its π component and the formation of a sigma bond between carbon and the least yet still negatively charged oxygen. In our case, this is the stabilization of the resulting carbanion by the electron-withdrawing group that rationalizes the reaction between the two nucleophilic partners.^[25]

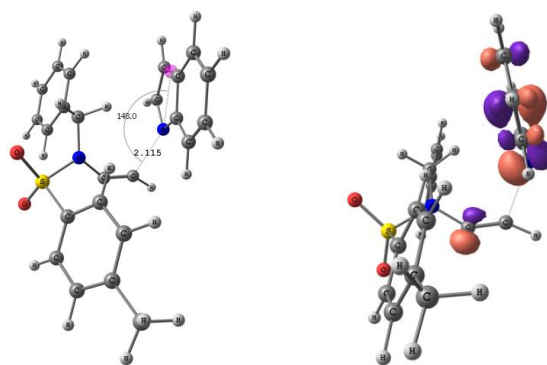
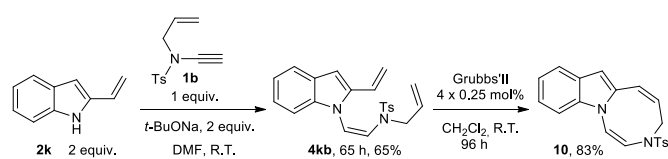


Figure 2. Computed structure of **TS_{A-7}** and orbital contour plot of the HOMO

Having opened an access to hitherto unknown and novel compounds, we then investigated if further functionalizations were possible to obtain new polycyclic frameworks that might possess interesting biological activities.^[26] To this purpose, 2-vinylindole **2k** was reacted with *N*-tosyl-*N*-allylynamide **1b** to give **4kb** which could then be cyclized using Grubbs' second generation catalyst to afford

1,4-diazocinoindole **10** (Scheme 7). Crystallization of **10** allowed structure determination by X-ray analysis.^[14]



Scheme 7. Access to polycyclic drug-like scaffolds

In conclusion we have discovered two new reaction pathways involving ynamides under basic reaction conditions. First, indole derivatives add to the β position of unsubstituted *N*-tosyl-*N*-alkyl ynamides to yield (*Z*)-2-indolo-etheneamides with complete regioselectivity. At first counterintuitive, this process could be rationalized by DFT calculations. Moreover these unprecedented molecular scaffolds give access to potentially biologically relevant structures as exemplified by the preparation of 1,4-diazocinoindole **10**. On the other hand, under the same reaction conditions, *N*-phenyl and/or *N*-carboxyl ynamides react with indole through the more classical addition to the α position, albeit with the concomitant loss of the EWG. This process not only grants access to indolylamidines but also suggests a mild *in situ* generation of ketenimines,^[27] which could be of considerable synthetic interest. Studies in these directions are currently underway in our laboratory and will be reported in due course.

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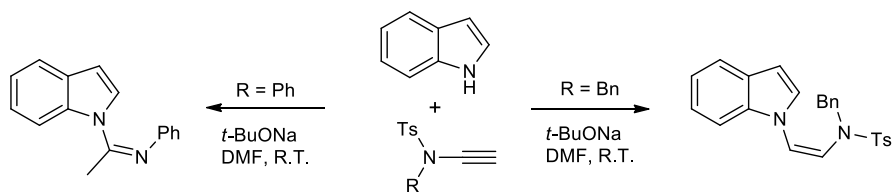
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Synthetic Methods

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Metal-Free Tunable Chemoselective *N*-
Functionalization of Indoles with
Ynamides



Two birds with one stone: Under basic reaction conditions, two distinct manners of *N*-functionalizing indoles with ynamides are reported. On the one hand, unsubstituted *N*-tosyl-*N*-alkyl ynamides undergo addition on the β position to yield (*Z*)-2-indoloetheneamide with complete regioselectivity. On the other hand, *N*-phenyl and/or *N*-carboxyl ynamides undergo addition on the α position, albeit with the concomitant loss of the EWG.