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

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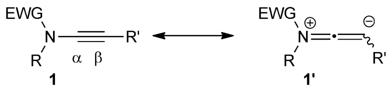
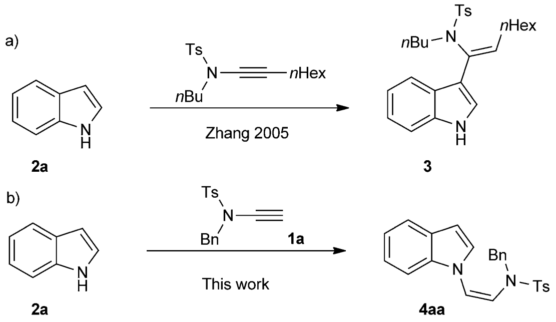
Abstract: *Two unprecedented N functionalizations of indoles with ynamides are described. By varying the electron-withdrawing group on the ynamide nitrogen atom, either Z-indolo-etheneamides or indolo-amidines can be selectively obtained under the same metal-free reaction conditions. The scope and synthetic 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 atom (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 because of the possible delocalization of the lone pair, thus 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] In contrast, nucleophilic attack on the α-position is much more common.[1,8] For instance, Zhang reported that by 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 the indole **2a**, the reaction exclusively took place at the 3-position of the indole and the α-position of the ynamide to give the 3-vinylindole **3** (Scheme 2a). 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 atom to the ynamide (Scheme 2b).

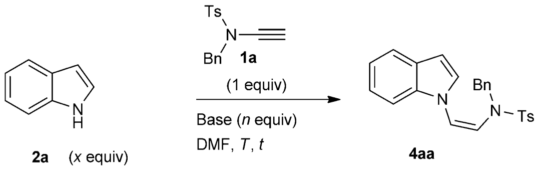


Scheme 2. 3-Vinylation versus N vinylation of indole. Ts = 4-toluenesulfonyl.

Indeed, when reacting **2a** with the ynamide **1a** in DMF at 80 °C in the presence of an excess of sodium *tert*-butoxide, **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 and co-workers[10] (in which case a copper assisted process is proposed) and more recently by Aubineau and Cossy,[11] have been reported. A handful of reports describe the addition of indoles and related heterocycles to non-

Table 1: Optimization of the reaction conditions.



Entry	x	Base (n equiv)	T [°C]	t [h]	Yield [%][a]
1	1	*t*BuONa (1.5)	80	22	7
2	1	*t*BuONa (1.5)	RT	22	20
3	1	*t*BuONa (2)	RT	72	40
4[c]	1	*t*BuONa (1)	RT	30	50[b]
5[c]	2	*t*BuONa (2)	RT	30	quant.
6[c]	2	NaOH (2)	RT	30	87[b]
7[c]	2	KOH (2)	RT	30	42[b]
8[c]	2	LiOH (2)	RT	30	14[b]
9[c]	2	*t*BuONa (2)	RT	4.5[d]	100[b]

[a] Yields are those of isolated products, unless indicated otherwise. [b] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [c] 3 Å molecular sieves (M.S.) were added. [d] Added 18-crown-6. DMF = *N*,*N*-dimethylformamide.

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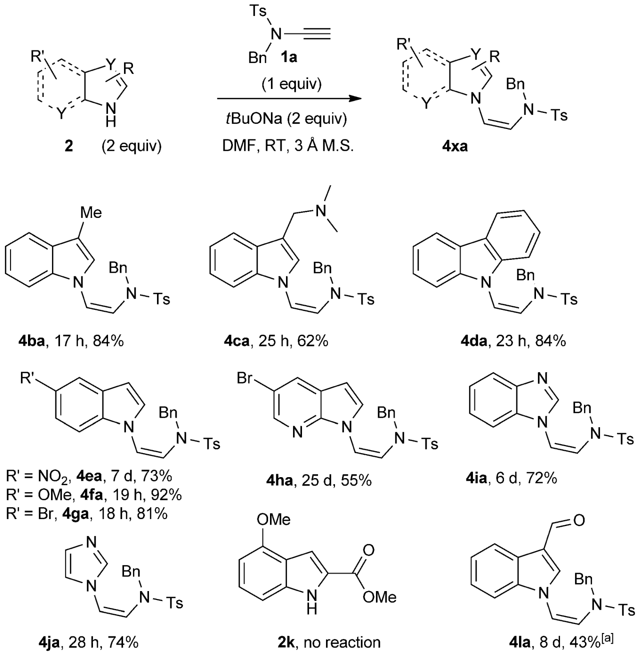
activated alkynes leading to N-vinyl derivatives.[12] In these cases, the *Z* isomer is usually obtained as the major product, however, these reactions only take place at high temperature (80–120 °C) and are limited to arylacetylenes. We thus sought to further investigate the formation of **4aa** and initiated optimization of the reaction conditions.

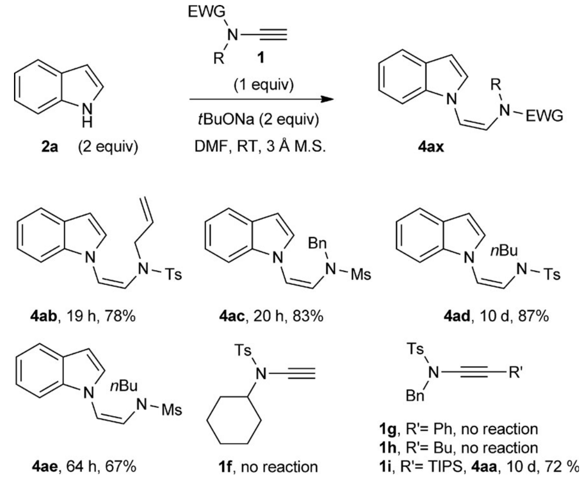
First, lowering the reaction temperature to room temperature (Table 1, entry 2) and increasing the amount of base to 2.0 equivalents (entry 3) did not allow complete conversion but the yield was increased to 40 %. As side-products coming from the hydrolysis of the ynamide were detected,[13] molecular sieves were added to the reaction mixture and a 50 % conversion was thus achieved (entry 4). We then decided to use a twofold amount of indole and full conversion of the ynamide as well as a quantitative yield of **4aa** were attained (entry 5). Alkali hydroxides were also tested and although 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 the optimal reaction 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, thus giving excellent yields of the corresponding adducts **4ba–da**. From a mechanistic point of view, these results tend to rule out a process initiated by reaction at the 3-position with a subsequent rearrangement, but rather point towards a direct reaction with the indolyl nitrogen atom (see below 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 **4ea** could only be obtained in good yield after an extended reaction time of 7 days. In contrast, 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 the imidazole derivatives **4ha–ja** could also be formed, while an ester group at the 2-position (**2k**) shut down the reactivity. Nevertheless, an electron-withdrawing group (EWG) such as an aldehyde was tolerated on the 3-position and the compound **4la** was obtained with a moderate 43 % yield after prolonged reaction time in the presence of 18-crown-6.



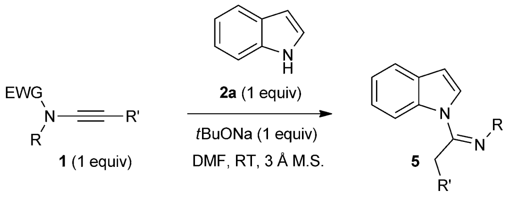
Scheme 3. Heterocycles scope. Yields are those of the isolated products. [a] 18-crown-6 was added.

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, because after 10 days of reaction the unsilylated adduct **4aa** was obtained. Our assumption is that this substituted ynamide does not react either, but the basic reaction conditions allow slow desilylation of **1i** to give **1a**, which in turn reacts with the indole to finally yield **4aa**.



Scheme 4. Ynamide scope. Yields are those of isolated product. Ms = methanesulfonyl, TIPS = triisopropylsilyl.

A drastic change in the reactivity pattern was witnessed when the aniline-derived ynamide **1j** was reacted with the indole **2a**, thus giving rise to the amidine **5a**, which formally results from the addition of the indole nitrogen atom to the α-position of **1**[15] with subsequent 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



1j, EWG = Ts, R = Ph, R' =H	**5a**, R = Ph, R' =H, 1.5 h, 72%[a]
1k, EWG = Ms, R = Ph, R' =H	**5a**, R = Ph, R' =H, 1.5 h, 66%[a]
1l, EWG = Ac, R = Ph, R' =H	**5a**, R = Ph, R' =H, 1 h, 89%[a]
1m, EWG = Boc, R = Ph, R' =H	**5a**, R = Ph, R' =H, 1.5 h, 90%[a]
1n, EWG = Boc, R = Bn, R' =H	**5b**, R = Bn, R' =H, 24 h, 60%[b]
1o, EWG = Boc, R =Ph, R' = Ph	**5c**, R = Ph, R' = Ph, 1.5 h, 69%[a]

Scheme 5. Reactivity switch. [a] Yields are those of isolated product. [b] Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard: **5b** 60%, **1m** 15% and *N*-Boc-indole 15%. Boc = *tert*-butoxycarbonyl.

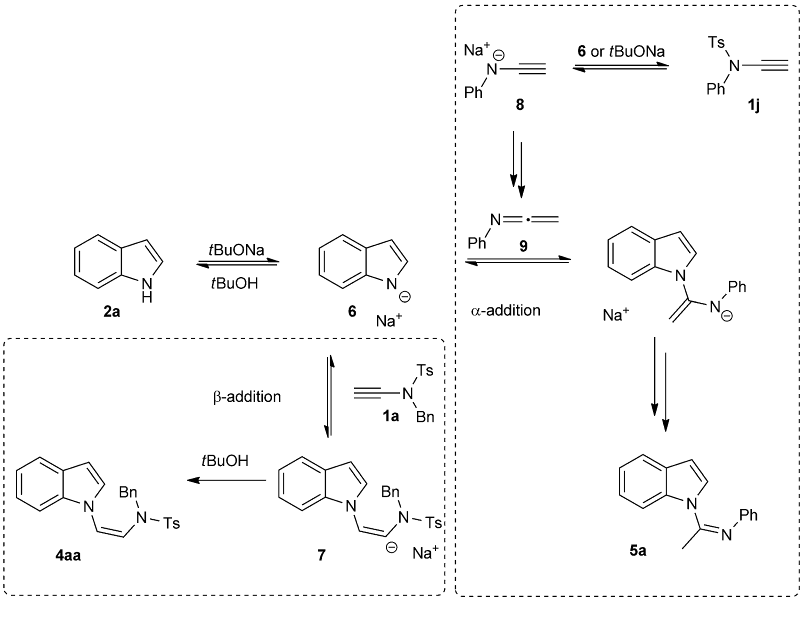
conversion). Methanesulfonamide, acetamide, and *tert*-butoxycarbamate derivatives (**1k–m**) led to the same product, **5a**, the structure of which was further confirmed by crystallographic analysis.[14] Moreover, the benzylamine-derived ynamide **1n** also yielded an amidine derivative (**5b**), thus 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, the phenyl-substituted ynamide **1o** was submitted to the same reaction conditions to give the amidine **5c** with 69% yield.

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 the anion **7** and **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 the 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 the amidine **5a** after protonation and tautomerization. It can be hypothesized that the stabilization of **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, thus transferring the protecting group onto the indole which could be deprotected thereafter.[19]

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) as does the nitrogen atom of **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$_{A\text{-}7}$**). The corresponding free energy of activation is quite low (9.6 kcal mol^{-1}) and the addition is appreciably exothermic by 12.5 kcal mol^{-1}. It should be noted that in agreement with the experimental data, **TS$_{A\text{-}7}$** 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$_{A\text{-}7}$**, a charge of −0.231 is transferred from the indolate to the ynamide. A significant part of this excess negative charge is carried 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$_{A\text{-}7}$** (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 the 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, thus inducing the repulsion of the C_β electrons towards C_α and 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.

This situation could be compared to the addition of Br_2 to an alkene giving rise to a charge-transfer complex, yet in this case the polarization of Br_2 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 bond, the rupture of its π component, and the formation of a σ bond between the carbon atom and the least negatively charged oxygen atom. In



Scheme 6. Mechanism proposal.

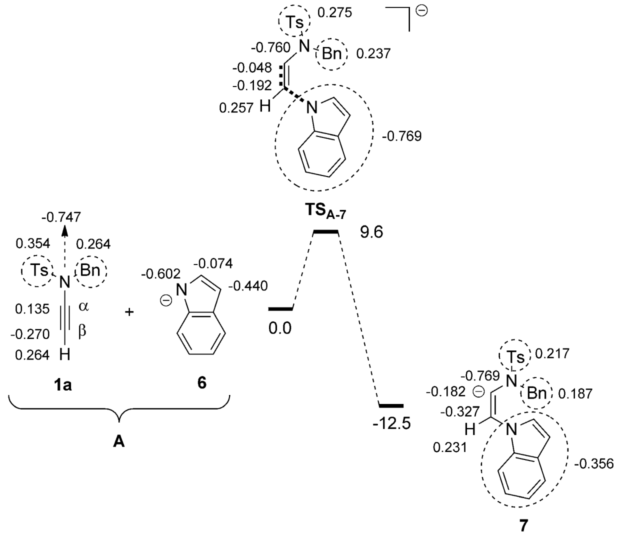


Figure 1. Computed free-energy profile (ΔG, kcal mol^{-1}) for the addition of the indolate **6** to the β-position of the ynamide **1a** (NBO charges of atoms and circled fragments are indicated in bold).

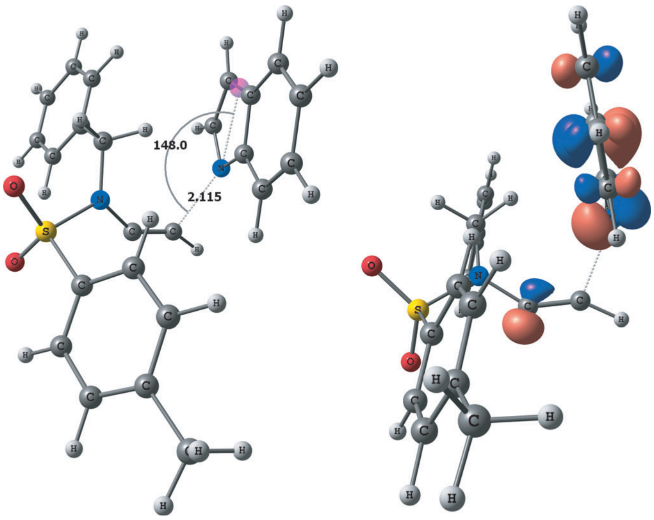
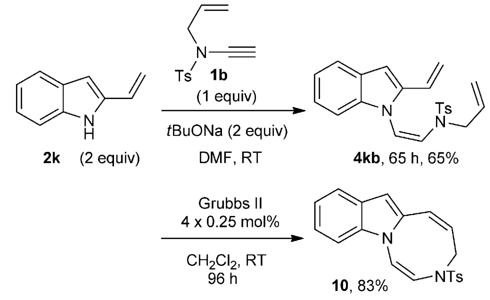


Figure 2. Computed structure of **TS$_{A-7}$** and orbital contour plot of the HOMO.

our case, it is the stabilization of the resulting carbanion by the electron-withdrawing group which rationalizes the reaction between the two nucleophilic partners.[25]

Having opened an access to hitherto unknown and novel compounds, we then investigated if further functionalizations were possible to obtain new polycyclic frameworks which 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]

In conclusion we have discovered two new reaction pathways involving ynamides under basic reaction conditions.



Scheme 7. Access to polycyclic druglike scaffolds.

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 **10**. In contrast, 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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Keywords: alkynes · density functional calculations · heterocycles · reaction mechanisms · synthetic methods

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[1] For reviews on the chemistry of ynamines, see: a) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560–578; b) G. Evano, A. Coste, K. Jouvin, *Angew. Chem.* **2010**, *122*, 2902–2921; *Angew. Chem. Int. Ed.* **2010**, *49*, 2840–2859; c) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Shi, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064–5106; d) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar, L.-L. Wei, *Tetrahedron* **2001**, *57*, 7575–7606; e) G. Himbert in *Methoden Der Organischen Chemie (Houben-Weyl)* (Eds.: H. Kropf, E. Schaumann), Georg Thieme, Stuttgart, **1993**, pp. 3267–3443; f) J. Ficini, *Tetrahedron* **1976**, *32*, 1449–1486.

[2] For nickel-catalyzed phosphonylation, see: A. Fadel, F. Legrand, G. Evano, N. Rabasso, *Adv. Synth. Catal.* **2011**, *353*, 263–267.

[3] For gold-catalyzed intramolecular addition, see: a) C. Laroche, S. M. Kerwin, *J. Org. Chem.* **2009**, *74*, 9229–9232; b) A. S. K. Hashmi, R. Salathé, W. Frey, *Synlett* **2007**, 1763–1766.

[4] For iron-catalyzed carbonylation, see: M. Pizzetti, A. Russo, E. Petricci, *Chem. Eur. J.* **2011**, *17*, 4523–4528.

[5] Hydroboration has been shown to take place at the β-position, see: a) B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473–8480; b) P. Valenta, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2010**, *132*, 14179–14190; c) R. W. Hoffmann, D. Brückner, *New J. Chem.* **2001**, *25*, 369–373.

[6] For titanium-mediated coupling at the β position, see: R. Tanaka, S. Hirano, H. Urabe, F. Sato, *Org. Lett.* **2003**, *5*, 67 – 70.

[7] Thiyl radicals also add to the β-position. See: a) C. Laroche, J. Li, S. M. Kerwin, *J. Med. Chem.* **2011**, *54*, 5059 – 5069; b) B. Banerjee, D. N. Litvinov, J. Kang, J. D. Bettale, S. L. Castle, *Org. Lett.* **2010**, *12*, 2650 – 2652.

[8] For recent examples, see: a) A. H. Sato, K. Ohashi, K. Ito, T. Iwasawa, *Tetrahedron Lett.* **2013**, *54*, 2878 – 2881; b) A. H. Sato, K. Ohashi, T. Iwasawa, *Tetrahedron Lett.* **2013**, *54*, 1309 – 1311; c) G. Compain, K. Jouvin, A. Martin-Mingot, G. Evano, J. Marrot, S. Thibaudeau, *Chem. Commun.* **2012**, *48*, 5196 – 5198; d) D. L. Smith, W. R. F. Goundry, H. W. Lam, *Chem. Commun.* **2012**, *48*, 1505 – 1507; e) N. Shindoh, Y. Takemoto, K. Takasu, *Heterocycles* **2011**, *82*, 1133 – 1136; f) S. Kanemura, A. Kondoh, H. Yasui, H. Yorimitsu, K. Oshima, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 506 – 514; g) H. Yasui, H. Yorimitsu, K. Oshima, *Chem. Lett.* **2008**, *37*, 40 – 41.

[9] a) Y. Zhang, *Tetrahedron* **2006**, *62*, 3917 – 3927; b) Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 6483 – 6486.

[10] Y. Fukudome, H. Naito, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2008**, *130*, 1820 – 1821.

[11] T. Aubineau, J. Cossy, *Chem. Commun.* **2013**, *49*, 3303 – 3305.

[12] a) A. K. Verma, M. Patel, M. Joshi, P. R. Likhar, R. Tiwari, K. Parang, *J. Org. Chem.* **2014**, *79*, 172 – 186; b) M. Joshi, M. Patel, R. Tiwari, A. K. Verma, *J. Org. Chem.* **2012**, *77*, 5633 – 5645; c) A. K. Verma, M. Joshi, P. Singh, *Org. Lett.* **2011**, *13*, 1630 – 1633; d) A. V. Ivachtchenko, E. B. Frolov, O. D. Mitkin, S. E. Tkachenko, I. M. Okun, A. V. Khvat, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 78 – 82; e) D. Tzalis, C. Koradin, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 6193 – 6195.

[13] Namely, the acetamide arising from the hydration of the triple bond as well as the corresponding primary sulfonamide were identified in the crude reaction mixture.

[14] See the Supporting Information. CCDC 979017 (**4ga**), 979018 (**5a**) and 979019 (**10**) contain 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.

[15] Only two examples of base-mediated nitrogen addition on the α-position have been reported. For pyrrolidin-2-one, see: a) A. Coste, F. Couty, G. Evano, *Org. Lett.* **2009**, *11*, 4454 – 4457; for oxazolidin-2-one, see: b) K. Dooleweerdt, H. Birkedal, T. Ruhland, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 9447 – 9450; for gold-catalyzed nitrogen addition to the α-position, see: c) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2009**, *11*, 4208 – 4211.

[16] a) During finalization of this manuscript a related process involving the cleavage of one tosyl group of highly activated *N*,*N*-ditosylynamides has been reported: Y. Kong, L. Yu, Y. Cui, J. Cao, *Synthesis* **2014**, 183 – 188; b) for palladium-catalyzed generation of ketenimines through N-to-C allyl transfer followed by trapping with an amine, see: Y. Zhang, K. A. DeKorver, A. G. Lohse, Y.-S. Zhang, J. Huang, R. P. Hsung, *Org. Lett.* **2009**, *11*, 899 – 902.

[17] a) H.-W. Winter, C. Wentrup, *Angew. Chem.* **1980**, *92*, 743 – 744; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 720 – 721; b) R. Huisgen, J. Wulff, *Tetrahedron Lett.* **1967**, *10*, 917 – 920.

[18] Boc cleavage on indoles under basic conditions has precedent with Cs_2CO_3: a) D. K. Mohapatra, K. A. Durugkar, *ARKIVOC* **2005**, *xiv*, 20 – 28; with MeONa: b) I. Hasan, E. R. Marinelli, L.-C. Chang Lin, F. W. Fowler, A. B. Levy, *J. Org. Chem.* **1981**, *46*, 157 – 164. Although a thorough base screening has not been carried out, sodium methoxide was also found to be suitable for this reaction when starting with the ynamide **1m**.

[19] Indeed, minor amounts of *N*-Ts-indole and *N*-Boc-indole could be detected in the crude reaction mixture starting from the ynamides **1j** and **1m–o**, respectively.

[20] Y. Zhao, N. E. Schultz, D. G. Truhlar, *J. Chem. Theory Comput.* **2006**, *2*, 364 – 382.

[21] Gaussian 09, Revision D.01, M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2009**.

[22] This π* orbital is found in the LUMO of the ynamide (see the Supporting Information).

[23] X. Assfeld, J. Garapon, D. Rinaldi, M. F. Ruiz-López, J. L. Rivail, *J. Mol. Struct.* **1996**, *371*, 107 – 116.

[24] R. Rajeev, R. B. Sunoj, *J. Org. Chem.* **2012**, *77*, 2474 – 2485.

[25] For a theoretical study aimed at rationalizing the reaction of two electrophiles together, see: H. Gérard, I. Chataigner, *J. Org. Chem.* **2013**, *78*, 9233 – 9242.

[26] I. Stansfield, C. Ercolani, A. Mackay, I. Conte, M. Pompei, U. Koch, N. Gennari, C. Giuliano, M. Rowley, F. Narjes, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 627 – 632.

[27] M. Alajarin, M. Marin-Luna, A. Vidal, *Eur. J. Org. Chem.* **2012**, 5637 – 5653.