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Asymmetric Synthesis

Catalytic Asymmetric Reactions of 4-Substituted Indoles with Nitroethene: A Direct Entry to Ergot Alkaloid Structures

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Abstract: A domino Friedel–Crafts/nitro-Michael reaction between 4-substituted indoles and nitroethene is presented. The reaction is catalyzed by BINOL-derived phosphoric acid catalysts, and delivers the corresponding 3,4-ring-fused indoles with very good results in terms of yields and diastereo- and enantioselectivities. The tricyclic benzo[*cd*]indole products bear a nitro group at the right position to serve as precursors of ergot alkaloids, as demonstrated by the formal synthesis of 6,7-secoagroclavine from one of the adducts. DFT calculations suggest that the outcome of the reaction stems from the preferential evolution of a key nitronic acid intermediate through a nucleophilic addition pathway, rather than to the expected "quenching" through protonation.

Ergot alkaloids have been the subject of longstanding interest.[1] Besides being the causative agents of the serious disease ergotism and used as hallucinogenic drugs, ergot alkaloids and derivatives have seen their powerful biological activities subdued for medical purposes. Pharmaceutical usefulness arises from subtle modifications of their naturally occurring structures, which feature a distinctive tricyclic 4-amino-1,3,4,5-tetrahydrobenzo[*cd*]indole framework with a modified methallyl residue at the 5-position, often fused within an additional ring (Figure 1 a). Biosynthetically derived from tryptophan through intriguing enzymatic pathways,[2] total syntheses of several members of this class of natural compounds have been reported, with the archetype lysergic acid having been the most pursued.[3] Concurrently, the construction of the synthetically challenging 1,3,4,5-tetrahydrobenzo[*cd*]indole scaffold has recently received considerable attention, even in its unadorned and racemic/achiral forms.[4] In this context, we have reported an enantioselective approach to this scaffold, based on the organocatalytic domino reaction of indoles **1** bearing a Michael acceptor at the 4-position with α,β-unsaturated aldehydes.[5]

The domino reaction of these substrates **1** with nitroethene[6] **2** leads to benzo[*cd*]indoles **3** having the nitro group at a strategic position to serve as precursors of ergot alkaloids (Figure 1 b). This reaction has been attempted with a view to ergot synthesis. However, results were disappointing and the reaction was thus discarded in favor of less direct routes for compounds related to **3**.[4d,7,8] We hypothesized that recent advances in the activation of nitro compounds by weak H-bond donor catalysts[9] could offer a solution for this transformation, giving also an unprecedented stereocontrolled access to compounds **3**. However, initial experiments (Figure 1 c) showed that thiourea catalysts that were useful in simpler Friedel–Crafts (FC) reactions[10] were not able to promote any reaction between substrates **1 a**–**c** and nitroethene **2**, possibly due to the known[5a] poor nucleophilicity of indoles **1**. A more acidic BINOL-derived phosphoric acid[11] catalyst, such as **PA1**, proved instead to be useful. Substrate **1 a** furnished with promising enantioselectivity and as a single *trans*-diastereoisomer the desired product **3 a** with moderate (70%) conversion. This result was somewhat unexpected. The reaction should proceed through a nitronate/nitronic acid, formed upon the FC addition. In principle, the **PA** catalyst should be able to easily "quench" this species through protonation, due to its acidity.[12] Indeed, the presence of a competition between nitro-Michael and "quenching" pathways was revealed by the exclusive formation of the side product **3′** not only in the reaction with indole **1 b** featuring a weak ester Michael acceptor, but also with **1 c** bearing an *N*-acyl pyrrole, an efficient moiety for nitro-Michael reactions (Figure 1 c).[13] It is worth stressing that only few examples of organocatalytic domino reactions[14] have dealt with this type of sequential process (H-bond-promoted addition of a neutral nucleophile triggering a subsequent transformation),[15] none of which has involved a phosphoric acid as catalyst.

Prior to embarking on the study and optimization of the reaction, we decided to resort to a computational approach to shed some light on the reaction pathway of this unusual phos-

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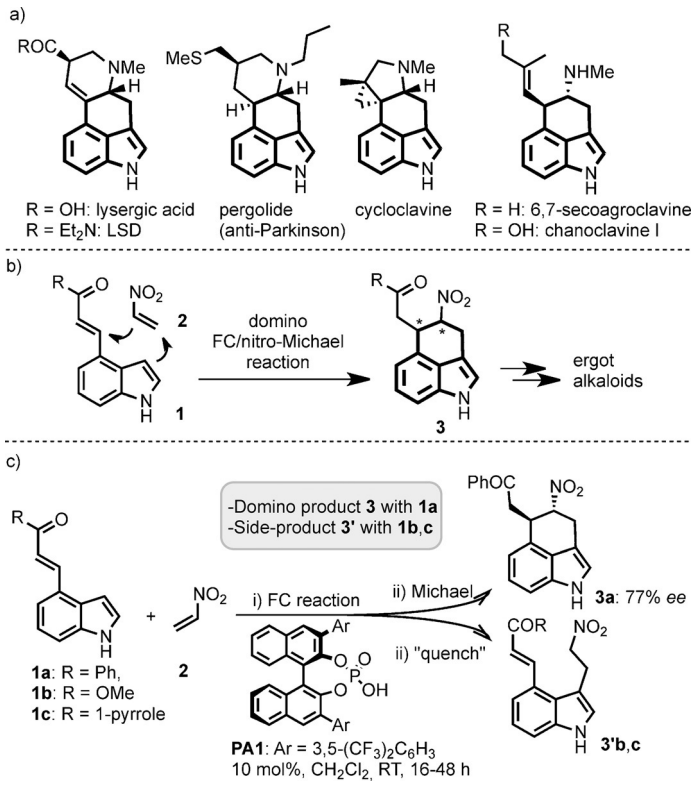


Figure 1. Ergot alkaloid structures and domino reaction of indoles **1** with nitroethene **2**. a) Some naturally occurring and semisynthetic ergot alkaloid derivatives (the 1,3,4,5-tetrahydrobenzo[*cd*]indole framework is highlighted); b) Friedel–Crafts (FC)-triggered nitro-Michael reaction en route to ergot alkaloids; c) preliminary results: thioureas do not promote the reaction. Phosphoric acids can catalyze the reaction, by two competing pathways (nitro-Michael vs. intermediate "quench").

phoric acid-catalyzed transformation. Previous computational studies of the phosphoric acid-catalyzed FC addition of indoles to nitroalkenes[16] focused on the C–C bond-forming step, neglecting subsequent H-transfer events (i.e., rearomatization and nitronate protonation) that are crucial in this cascade process, dictating its evolution. Here, several pathways following the first C–C bond formation can, in principle, be envisaged. The FC reaction might evolve through a H-relay process releasing the catalyst and a chiral indolenine. Alternatively, catalyst-coordinated nitronic acid intermediates could form upon indole rearomatization or N–H abstraction. Besides, indole rearomatization might occur prior to or after the Michael addition step. These hypotheses were evaluated by DFT calculations using the B3LYP-D functional (see the Supporting Information for details), studying the full catalytic cycle for the reaction between nitroethene **2** and the methyl ketone derivative **1 d**, chosen as a model of substrates bearing a ketone Michael acceptor. We used the phosphoric acid derived from [1,1′-biphenyl]-2,2′-diol as a model of BINOL-derived chiral phosphoric acids (Figure 2).

First, two possibilities were found for the initial nucleophilic attack of the indole on electrophile **2**. In the first case (**TS1**) the catalyst coordinates to both the nitro group and the indole N–H, whereas in the second (**TS1′**), it coordinates to the nitro group and the C3–H of the indole. In both cases, protonation of the nitro group occurs concertedly with the expected C–C bond formation.[17] The reaction occurring through **TS1** is favored by 6.4 kcal mol^{-1} over **TS1′**, in line with the previously determined pathway followed in related FC processes.[16a] While N–H abstraction was not productive, a TS for the indole rearomatization through C3-deprotonation (**TS2**) was located, associated with

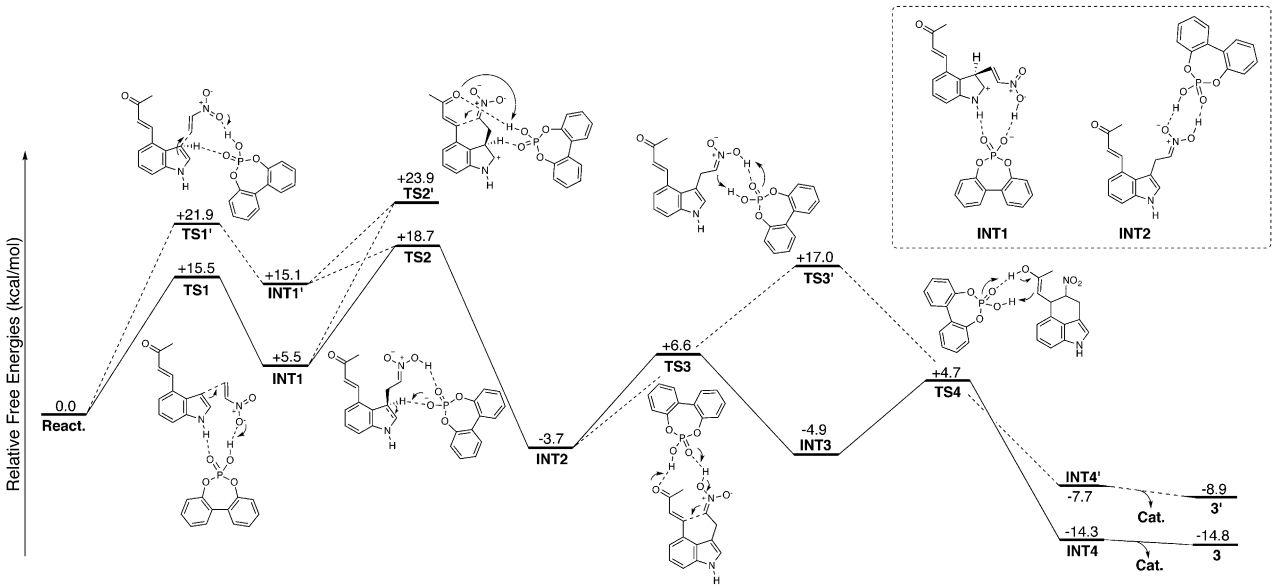


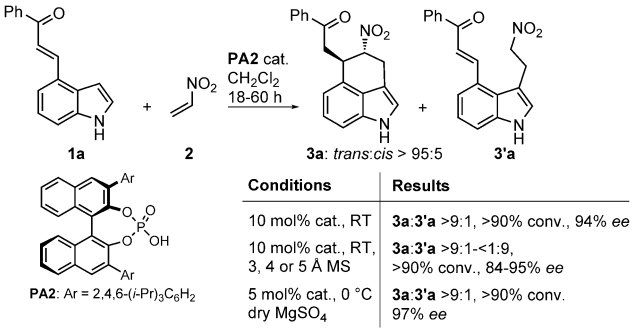
Figure 2. Free energy profile for the formation of products **3 d** and **3′ d** from the reaction between (*E*)-4-(1*H*-indol-4-yl)but-3-en-2-one (**1 d**) and nitroethene **2**. See the Supporting Information for optimized ball-and-stick structures.

an energy barrier of 18.7 kcal mol^{-1} relative to the reactants. This step does not occur through a proton-relay process releasing the catalyst, but leads instead to intermediate **INT2**. Alternatively, we have found that a direct cyclization could occur before rearomatization through **TS2′**. However, the energy barrier for this possibility is higher than that for the rearomatization (23.9 vs. 18.7 kcal mol^{-1}), which makes this option less likely.[18] After the rearomatization, a nitro-Michael addition can occur with the catalyst coordinating to both the nitro group and the carbonyl moiety (**TS3**). In this step, associated with a low energy barrier (10.3 kcal mol^{-1}), the deprotonation of the nitro group and the protonation of the carbonyl occur concertedly with the *trans*-selective C–C bond formation.[19] After cyclization through **TS3**, a keto–enol tautomerization is required to generate final product **3 d**. We found that the catalyst can also promote this process through **TS4**, with a low barrier.

As discussed above, the formation of cyclized product **3** is in competition with the formation of side-product **3′**. This can be formed if **INT2** evolves through a nitronic acid–nitro tautomerization, instead of the cyclization. A transition state (**TS3′**) with an energy barrier of 20.7 kcal mol^{-1} relative to **INT2**, and involving the catalyst, was identified for this tautomerization. The energy required for this step is likely overestimated by our calculations,[20] with **TS3′** being the best approximation we have found. Nevertheless, given the exclusive formation of cyclized product **3 d**, it can be concluded that the energy required for this tautomerization should be higher than about 13 kcal mol^{-1} relative to **INT2**.[20]

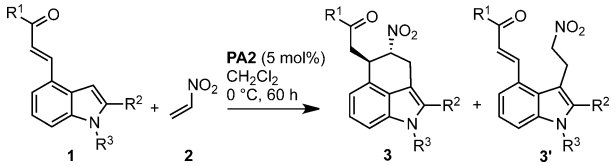
To summarize, the reaction occurs through a nucleophilic attack of the indole **1** on nitroethene **2**, followed by a rearomatization occurring before the cyclization and ensuing keto–enol tautomerization. The catalyst is involved in all steps, including the stereodetermining cyclization event, accounting for the enantioenrichment of product **3 a** when an enantiopure catalyst was used (Figure 1 c). A rather high energy barrier associated with the nitronic acid–nitro tautomerization step (nitronate "quench") makes the cyclization to the desired products **3** possible and prevailing even with an acidic catalyst, provided that a highly reactive Michael acceptor is employed (i.e., **TS3** energy is sufficiently low).

To optimize the catalytic asymmetric version of the reaction, we screened various chiral phosphoric acid catalysts[11] and reaction conditions, using **1 a** as substrate in the reaction with nitroethene **2** (see the Supporting Information and Scheme 1). This screening initially identified catalyst **PA2** [(*R*)-TRIP, 10 mol %], a solvent that is non-coordinating but able to solubilize indole **1 a** (CH_2Cl_2), and ambient temperature as suitable conditions to afford **3 a** with very good results. We then tested dehydrating agents as additives, in order to increase the catalyst activity. Activated molecular sieves (3, 4, or 5 Å) gave scarcely reproducible results, and surprisingly shifted occasionally the reaction pathway towards the open-chain adduct **3′a**.[21] The obtainment of **3′a** allowed us to perform a control experiment (see the Supporting Information) confirming the expected[12] and computed (Figure 2) incapability of the catalyst to resume **3′a** to **3 a**. Instead, we found that $MgSO_4$ as drying agent had a beneficial effect, allowing a reduced catalyst loading and a lower reaction temperature, leading to increased enantioselectivity.



Scheme 1. Representative screening results.

Table 1. Scope of the catalytic enantioselective domino reaction.[a]



Entry	1	R^1	R^2	R^3	Yield[b] [%]	*ee*[c] [%]
1	**1 a**	Ph	H	H	**3 a**: 95	97
2[d]	**1 b**	OMe	H	H	**3′b**: 62	–
3[d]	**1 c**	pyrrol-1-yl	H	H	**3′c**: 94	–
4	**1 d**	Me	H	H	**3 d**: 96	54
5	**1 e**	4-$MeOC_6H_4$	H	H	**3 e**: 91	97
6	**1 f**	4-BrC_6H_4	H	H	**3 f**: 95	97
7	**1 g**	4-MeC_6H_4	H	H	**3 g**: 98	98
8	**1 h**	2-naphthyl	H	H	**3 h**: 98	>99
9	**1 i**	*t*Bu	H	H	**3 i**: 90	93
10[e]	**1 j**	$CH(OMe)_2$	H	H	**3 j**: 82	96
11	**1 k**	Ph	Me	H	**3 k**: 90	94
12[f]	**1 l**	Ph	H	Me	**3 l**: 75	95
13[g]	**1 m**	Ph	H	allyl	**3 m**: 70	93

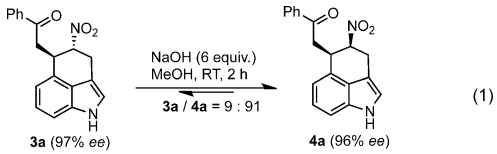
[a] Conditions: indole **1** (0.10 mmol), **PA2** (0.005 mmol, 5 mol %), nitroethene **2** (1.5 M toluene solution, 0.15 mmol), dry $MgSO_4$ (30 mg), CH_2Cl_2 (300 μL), 0 °C, 60 h, then filtering through a plug of silica gel, solvent evaporation, and analysis by ^{1}H NMR spectroscopy; d.r. of products **3** was found to be >95:5 in all cases. [b] After chromatography on silica gel. [c] Determined by chiral stationary phase HPLC. [d] In the presence of 4 Å MS instead of $MgSO_4$, RT, 24 h. [e] RT, 24 h. [f] 0.225 mmol **2**. [g] **PA2** (0.0075 mmol, 7.5 mol %), RT.

We then applied these conditions to substrates **1 a**–**m** bearing different Michael acceptor groups and indole cores. The results (Table 1) show that, besides the simple phenyl derivative **1 a** (entry 1), other electronically/sterically different aryl acceptors in **1 e**–**h** provided the corresponding products **3 e**–**h** with excellent results (entries 5–8). The ester and *N*-acyl pyrrole derivatives **1 b** and **1 c** gave exclusively the open-chain adducts **3′b** and **c**, even under the optimized conditions. Molecular sieves provided better yields than $MgSO_4$ in these simple FC reactions (Table 1, entries 2 and 3).[21] The methyl ketone substrate **1 d** unfortunately gave a reduced enantioselectivity in the product **3 d** (Table 1, entry 4). However, the reaction scope is not restricted to Michael acceptors bearing aryl groups. Sub-

strates **1i** and **1j**, bearing a *tert*-butyl and a dimethoxymethyl substituent at the ketone, respectively, afforded the products **3i** and **j** with excellent results (Table 1, entries 9 and 10), suggesting that it is the bulkiness of the acceptor that is essential to achieving excellent enantiocontrol in this reaction. As expected, the 2-methylindole derivative **1k** performed very well in the reaction (Table 1, entry 11). In contrast with simpler FC reactions, wherein catalyst coordination to the indole N–H is generally required for enantioselectivity,[16] the computed pathway of this transformation predicts this interaction to be absent in the stereodetermining step (Figure 2, **TS3**), while being useful for reactivity, as it is related to the RDS (**TS1** vs. **TS1′**). Indeed, the products **3l** and **m**, derived from the *N*-alkyl substrates **1l** and **m**, were obtained with excellent enantioselectivities, although slightly modified conditions were required to achieve good yields (Table 1, entries 12 and 13).

Treatment of **3a** with NaOH in MeOH caused equilibration favoring the *cis* stereoisomer **4a** [Eq. (1)]. DFT calculations indicated that this *cis* isomer (**4a**) is more polar than the *trans* (**3a**), and thus accounted for **4a** being favored in a polar medium such as MeOH. Equilibration occurred through a selective epimerization at the α-nitro stereogenic center and not through a retro-nitro-Michael pathway that would have led to racemization. We determined the relative configuration of compounds **3a** and **4a** as *trans* and *cis*, respectively, by a thorough computational (DFT) and NMR analysis (see the Supporting Information). Their absolute configuration was inferred as shown by comparing the calculated (TD-DFT) with the experimental Electronic Circular Dichroism (ECD) spectra.[22]

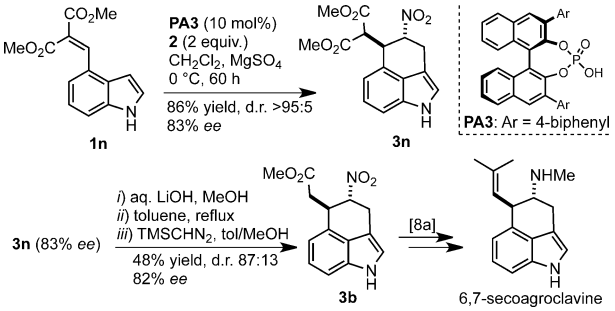
To increase the synthetic utility of this methodology, we thought to convert one of the ketone groups of compounds **3** into a more versatile ester group. However, all attempts to effect a Baeyer–Villiger oxidation on **3e** failed, presumably due



(1)

to the sensitivity of the benzo[*cd*]indole structure to oxidative conditions. Thus, we investigated other indole substrates featuring masked unsaturated esters/amides[23] as Michael acceptors at the 4-position. After considerable experimentation (see the Supporting Information), we found that an alkylidene malonate could serve as suitable acceptor moiety for the reaction. Using a different catalyst **PA3**, substrate **1n** bearing this group provided the corresponding product **3n** with synthetically useful results (Scheme 2). The malonate ester could be converted in three steps and with a small loss of diastereoenrichment into the previously inaccessible ester-substituted adduct **3b**. This compound, in racemic form, is the key intermediate in a reported synthesis of 6,7-secoagroclavine.[8a]

In summary, indoles **1** bearing a Michael acceptor at the 4-position react well with nitroethene **2** in the presence of chiral phosphoric acid catalysts, delivering the corresponding tricyclic



Scheme 2. Reaction with substrate **1n** and elaboration of product **3n**.

trans products **3** with very good results. As revealed by DFT calculations, the reaction is a unique example of evolution of a nitronate/nitronic acid intermediate towards a nucleophilic pathway, in favor of the ordinary "quench" of this intermediate through protonation. The benzo[*cd*]indole products **3** feature a nitro group at a strategic position to serve as ergot alkaloid precursors. Since diastereoisomer equilibration in MeOH favors the *cis* isomers (**4**), all four stereoisomers of the tricyclic system can be potentially accessed with this methodology.

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Keywords: asymmetric synthesis · Brønsted acids · indoles · nitroalkenes · organocatalysis

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[12] For the same reason, as verified in a control experiment (see the Supporting Information), a phosphoric acid should be unable to resume undesired **3**′ to tricyclic **3**. Thus, the nitronate "quench" is an irreversible process. Phosphoric acid-catalyzed direct additions proceeding through enol/nitronic acid intermediates have been reported, but only in the presence of a base (e.g., imine), at high temperature, or with enol-rich substrates (e.g., cyclohexanone): a) Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790; b) M. Rueping, A. P. Antonchick, *Org. Lett.* **2008**, *10*, 1731; c) G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden, J. Blanchet, *Org. Lett.* **2010**, *12*, 3582; d) I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960; *Angew. Chem.* **2015**, *127*, 1983; e) X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205; f) M. Yamanaka, M. Hoshino, T. Katoh, K. Mori, T. Akiyama, *Eur. J. Org. Chem.* **2012**, 4508; g) A. R. Burns, A. G. E. Madec, D. W. Low, I. D. Roy, H. W. Lam, *Chem. Sci.* **2015**, *6*, 3550.

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[17] **TS1**′ evolves to intermediate **INT1**′, in which the anionic catalyst coordinates the nitronic acid and the C3–H of the indole (see the Supporting Information). However, this intermediate should be in rapid equilibrium with the more stable **INT1**, provided that the indole is unsubstituted at nitrogen. For *N*-substituted indoles, the first part of the process could occur through **TS1**′-**INT1**′-**TS2**.

[18] To locate **TS2**′, one proton had to be shifted from the protonated nitro group to the catalyst, to allow the protonation of the electrophilic ketone during the cyclization.

[19] The lowest energy pathway represented in Figure 2 leads to the formation of product *trans*-**3**. We also computed the pathway leading to the *cis* isomer, and we found it to be associated with higher energy barriers (see the Supporting Information), in agreement with the experimental results.

[20] We have also optimized the corresponding transition states for the reaction occurring on the ester-substituted indole **1b** that, when subjected to reaction conditions, only afforded product **3**′**b**. In this case, the barriers for the formation of the two products are closer in energy, mainly due to an increase in the energy required for the cyclization. The calculations, however, still predict the preferential formation of the cyclization product **3b**, in disagreement with the experiments. This could be an indirect proof that the barriers that we found for the tautomerizations giving the open-chain products **3**′**a** or **3**′**b** are slightly overestimated. Based on the experimental outcome of the reactions and on the calculated barriers for the cyclizations affording **3a** or **3b**, a more realistic value for the energy barriers of the tautomerization step lies between 13 and 18 kcal mol^{-1}. For additional discussion, see the Supporting Information.

[21] FC of indoles with nitroalkenes catalyzed by phosphoric acids are performed with MS: a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed.* **2008**, *47*, 4016; *Angew. Chem.* **2008**, *120*, 4080; b) K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799; c) Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang, S.-L. You, *Chem. Eur. J.* **2009**, *15*, 3351. It can be speculated that molecular sieves (MS) have a role that goes beyond simple dehydration in these reactions. We hypothesize that MS serve as external proton sources providing an alternative pathway for the nitronic acid – nitro tautomerization. In some Lewis acid-catalyzed reactions, MS have been assumed to facilitate the reverse tautomerization (nitro – nitronic acid): d) C. Palomo, R. Pazos, M. Oiarbide, J. M. García, *Adv. Synth. Catal.* **2006**, *348*, 1161; e) M. Hasegawa, F. Ono, S. Kanemasa, *Tetrahedron Lett.* **2008**, *49*, 5220.

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