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Cycloadducts

Dearomatization of 3-Nitroindoles with Highly γ-Functionalized Allenoates in Formal (3+2) Cycloadditions

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Abstract: 3-Nitroindoles are easily reacted with highly substituted γ-allenoates in the presence of a commercially available phosphine catalyst. For instance, allenoates derived from biomolecules such as amino and deoxycholic acids are combined for the first time with 3-nitroindole. The corresponding dearomatized (3+2) tricyclic cycloadducts are obtained as α-regioisomers exclusively. DFT computations shed light on this multi-step reaction mechanism and on the selectivities observed in the sequence.

In organic synthesis, electron-poor alkenes are essential building blocks, used as electrophiles in many chemical transformations. When the same alkene moiety is embedded in an aromatic ring, the resonance stabilization energy renders this compound almost inert towards most neutral nucleophiles. The possible interaction of an aromatic double bond bearing an electron-withdrawing group with different nucleophilic species is, however, of great synthetic interest, since this approach leads to complex tridimensional structures from easily available raw materials. Nucleophilic dearomatization reactions have been developed for some time, mainly with polar organometallic nucleophiles.[1] Regarding the electrophilic aromatic compounds, nitro(hetero)arenes have been regularly used with different types of nucleophiles because of the highly electron-withdrawing character of the nitro group.[2] In most cases, the addition is reversible and trapping the intermediate Meisenheimer nitronate is a key to push the reaction forward. An intramolecular catching is likely to be particularly useful, since it could facilitate the reaction of the transient species to generate a dearomatized polycyclic compound, following a formal cycloaddition process. Actually, concerted cycloadditions involving electron-poor aromatics can be considered as the upper limit of this type of reactivity.[3] Normal electron demand (4+2) cycloadditions involving nitroarenes and electron-rich dienes have been described by us and others.[4] Nitroarenes can also react in tandem (4+2)/(3+2) processes and in this case the intermediate nitronate is trapped in a subsequent (3+2) cycloaddition.[5] Concerted or formal (3+2) reactions on nitro aromatic compounds have also been reported lately, mainly on 3-nitroindoles. Those involve azomethine ylides,[6] azomethine imines,[7] trimethylenemethanes,[8] vinyl-cyclopropanes,[9] -aziridines[10] or -epoxides[11] under palladium catalysis, or isothiocyanato oxindoles and thiol derivatives[12] (Figure 1).

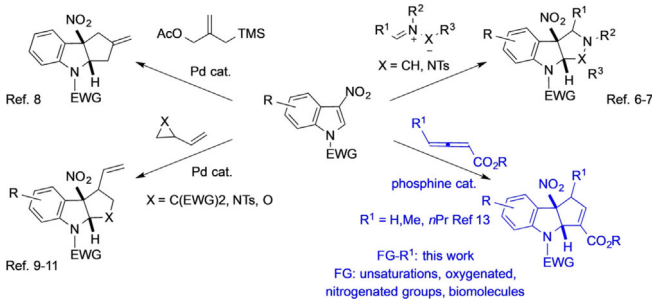

Figure 1. (3+2) Cycloadditions and annulations involving 3-nitroindole derivatives.

Very recently, Zhang, Lu, Shi, Bandini, and Ye independently described the reactivity of 3-nitroindoles with buta-2,3-dienoates in (3+2) dearomatizing annulation processes.[13] The expected cyclopentaindolines were elegantly obtained resorting to chiral (or not) phosphine catalysis. Bandini reported these reactions in the presence of γ-alkyl allenoates (Figure 1).[13d]

These very recent publications prompted us to report our own results directed toward the dearomatization of 3-nitroindoles in (3+2) annulations using allenoates bearing functional groups in the γ position.[14,15] Allenoates bearing alkene, alkyne, silylether, and amine moieties were thus employed to attain elaborated indolines or dihydrobenzofurans. Our own investigations started before these reactions were reported on 3-nitroindoles. Thus, ignoring if the nitrated aromatic double

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bond would behave as the electron-poor 2π component, we reacted nitroindole **1a** and ethyl 2,3-butadienoate (**2a**) (2 equiv) in the presence of 20 mol% of the cheap and easily accessible triphenylphosphine. This first test, run in toluene at room temperature, led to a promising result since the expected indoline **3aa** was formed within 48 h. The process regioselectivity proved to be complete, and the α-isomer is the only cycloadduct observed (62% conversion, 42% isolated yield). Increasing the reaction time did not lead to any improvement. Optimization of the reaction conditions included adjustment of the solvents and of the loading and nature of the catalyst (see the Supporting Information (SI) for details). This did not lead to better results. Only the use of a solvent mixture (toluene : CH_2Cl_2, 1:1), which better solubilizes both substrates and intermediates, leads to slightly improved results. In 2007, Yu showed that the addition of water to the reaction medium has a positive impact on the reaction course, facilitating the [1,2]-proton shift required after cyclization to release the cyclopentenic adduct and the catalyst.[16] We thus added water to the solvent mixture and were pleased to observe that it indeed leads to a significant improvement, as the reaction is faster and indoline **3aa** is isolated in a 72% yield after 17 h (Figure 2).[17]

The reactivity of 3-nitroindoles **1b–d** was then explored, beginning with a modulation of the nitrogen protecting/activating group (Figure 2). Interestingly the carbamate (*N*-Boc) indole **1c** is converted into indoline **3ca** in 78% yield while the other indoles are less efficient.[18] The N-Ts indole **1a**, which displays a similar reactivity, was preferred for the rest of the study since its preparation is straightforward. Likewise, changing the ester substitution on the allenoate has little effect: using benzyl allenoate **2b** affords the corresponding indoline **3ab** in a similar yield.

We then turned our attention to allenoates bearing a γ-substitution. Allenoate **2c**, with a methyl group, is assembled with nitroindole **1a** into **3ac**, obtained in a 60% overall yield (d.r. = 1:1). The methylated dipole is less reactive than its unsubstituted counterpart and a higher 45 °C reaction temperature is required in this case, in the presence of a more nucleophilic tri-*n*-butylphosphine.

So far, this type of cycloaddition has never been described with more hindered allenoates. Pleasingly, involving the γ-*i*Pr or γ-Cy allenoates **2d** and **2e** at 45 °C leads to the formation of the expected indolines **3ad** and **3ae**, isolated in 64 and 63% yields (3:2 and 3:1 d.r.), respectively. The major adducts feature a *trans* relationship between the nitro and alkyl groups as shown by NOESY experiments (see SI). A gram scale reaction can be performed with the isopropyl substituted allenoate **2d** and furnishes **3ad** in a 56% isolated yield, with only a slight erosion on this scale. The unreacted starting indole (20%) can be recovered (yield brsm : 70%).

The reaction was then extended to functionalized allenoates, bearing alkynyl or alkenyl groups appendages ready for further transformations.[19] At 60 °C, these cycloadditions led to indolines **3af** and **3ag** isolated in 44[20] and 62% yield (3:2 and 3:1 d.r.), respectively. Hitherto unreported, the γ-substituent of the allenoate can also bear a chain possessing a heteroatom such

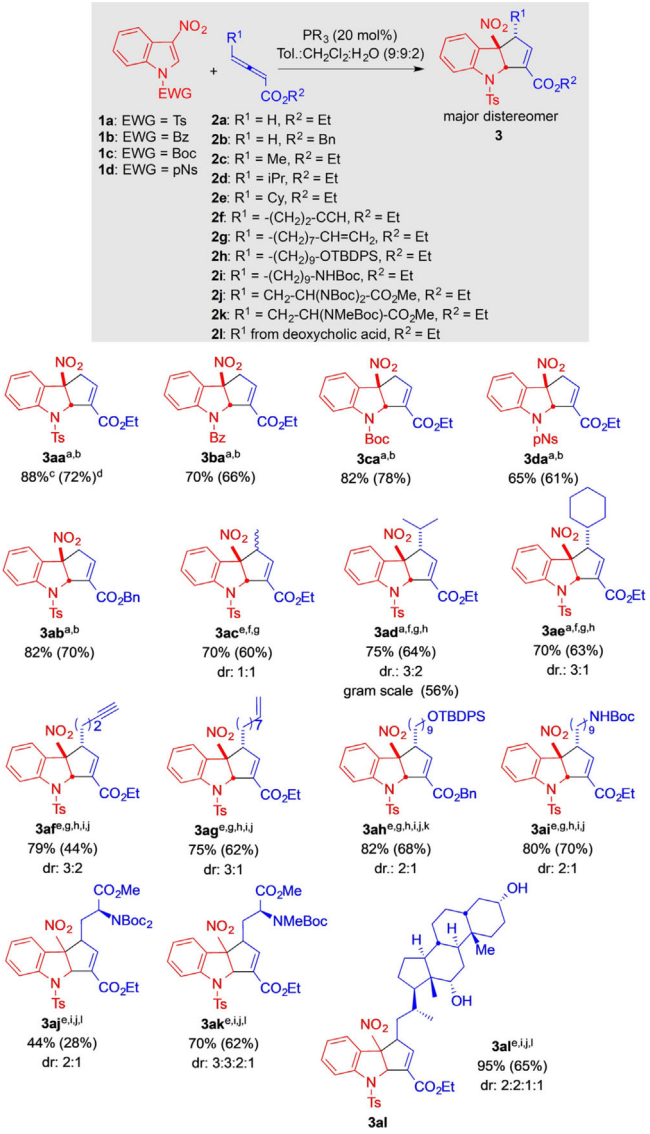


Figure 2. (3 + 2) Annulations involving 3-nitroindole derivatives. [a] Using PPh_3. [b]: Reaction performed at r.t. [c]: Conversion rate determined by ^1H NMR on the crude reaction mixture. [d]: Overall isolated yield. [e]: Using P*n*Bu_3. [f]: Reaction performed at 45 °C. [g]: Isolated as a diastereomeric mixture. [h]: Only the *trans* major diastereomer is depicted in the figure. [i]: Reaction performed at 60 °C. [j]: Reaction performed in the presence of an allenoate synthesized from a Mukaiyama salt intermediate (see SI), containing an inert isomer. [k]: Reaction performed in non-degassed conditions. [l]: Diastereomers were separated by reversed phase chromatography (HPLC).

as a silyloxy ether or NBoc protected amine. The dearomatization occurs in good yields and similar diastereoselectivities, **3ah** and **3ai** being isolated in 68 and 70% yields, respectively (2:1 d.r.). To a lesser extent, amino acid substituted allenoate derived from glutamic acid **2j** proves also reactive and furnishes **3aj** in a 28% yield. Interestingly, NOESY experiments show that only the cycloadducts featuring a *trans* relationship between the ring junction and the substituent brought by the allenoate were formed (2:1 d.r.), and the *cis* isomers are not observed here. The yield drop observed in this case was assigned to the lower stability of the diBoc protected allenoate. To address this issue, the NMeBoc protected allenoate **2k** was

considered and better conversion and yield are noted (respectively 70 and 62%, 3:3 (*trans*):2:1 (*cis*) d.r.).[20] With this chiral dipole, the facial selectivity leads to the formation of the stereomers resulting from the attack of the dipole on both faces of the nitroindole (see SI for assignment of the *cis*/*trans* stereoselectivity).

The allenoate derived from the deoxycholic acid **2l**, combining a sterically hindered and unprotected biomolecule remains reactive toward nitroindole **1a** in the usual conditions, (95% conversion, 2:2 (*trans*):1:1 (*cis*) d.r.) (see SI). All diastereomers could be separated by HPLC in an overall 65% yield.

The reaction was next tried on a 3-nitrobenzofurannic derivative **4** and we were pleased to observe an efficient dearomative (3+2) annulation in the presence of **2a** and PPh_3 (Figure 3). Cycloadduct **5** was isolated in 67% yield.[21]

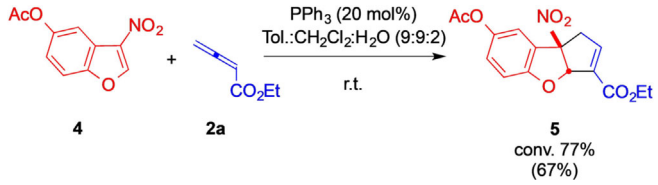


Figure 3. Formal (3+2) cycloaddition of 3-nitrobenzofuran **4** with allenoate **2a**.

In these dearomative processes, all substituted allenoates lead to the exclusive formation of the corresponding α-regioisomers. This suggests that the potential pathways generating the α and γ-regiosisomers are clearly differentiated. In contrast, the *cis*/*trans* diastereoselectivity of the formal cycloaddition is modestly controlled and competitive mechanisms for the corresponding diastereomeric routes are expected (vide infra for DFT calculations). At any rate, all these examples show the great potential of this methodology, that remain efficient with highly functionalized and hindered allenoates.

To get an insight into the reaction mechanism, DFT calculations were undertaken on a realistic model,[22] considering nitropyrrole **A** in the presence of PMe_3 (**B**), taken as phosphine model, and the unsubstituted allenoate $\mathbf{C_1}$ (Figure 4, see SI for details).

Addition of the phosphine catalyst on $\mathbf{C_1}$ leads to the reactive 1,3-dipole $\mathbf{D_1}$, whose most stable conformation expectedly shows a favorable P–O ester interaction (P–O = 2.97 Å).[16b] This associative step is highly activated ($\Delta G^{\neq} = 20.33$ kcal mol^{-1}), and thermodynamically favored ($\Delta G_r = -2.7$ kcal mol^{-1}). $\mathbf{D_1}$ features a high energy HOMO, with largest coefficient and charge

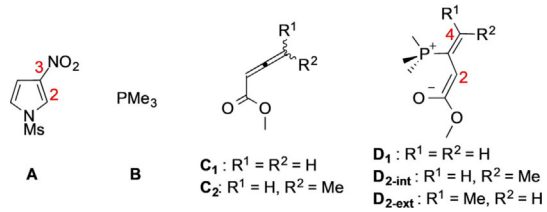
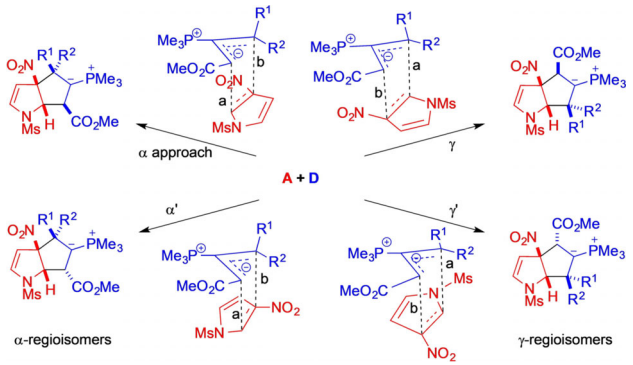


Figure 4. Model substrates used in DFT calculations.

on the C2 atom (0.39/−0.58 vs. 0.31/−0.55 on C4). Since the nitropyrrole largest LUMO coefficient is located on the C2 carbon atom, the α-regioisomer formation is rationalized by simple FMO analysis (see SI).

The reaction pathways between nitropyrrole **A** and dipole $\mathbf{D_1}$ were then examined computationally, considering four approaches for this cycloaddition step, namely the two leading to the α- and γ-regioisomer and two stereoarrangements in both cases (equivalent to *endo*/*exo* approaches in a (4+2) cycloaddition) (Table 1).

Table 1. DFT calculations on the formal (3+2) cycloaddition steps.



Entry	Approach	D	$\Delta G^{\neq}$ TSa[a,b,d]	ΔG_r E[a,b]	$\Delta G^{\neq}$ TSb[a,c,d]	ΔG_r F[a,c]
1	α	$\mathbf{D_1}$	11.6	−5.4	**13.2**	2.2
2	α′	$\mathbf{D_1}$	12.4	−5.1	**10.9**	1.1
3	γ	$\mathbf{D_1}$	**13.9**	−5.7	9.6	3.3
4	γ′	$\mathbf{D_1}$	**14.0**	−5.4	8.5	1.0
5	α	$\mathbf{D_{2\text{-int}}}$	12.6	−4.3	**17.0**	7.4
6	α	$\mathbf{D_{2\text{-ext}}}$	17.0	−2.4	**16.8**	10.7
7	α′	$\mathbf{D_{2\text{-int}}}$	15.7	−4.9	**16.6**	5.1
8	α′	$\mathbf{D_{2\text{-ext}}}$	**20.1**	−1.5	14.2	7.9
9	γ	$\mathbf{D_{2\text{-int}}}$	**18.1**	−2.0	14.3	7.5
10	γ	$\mathbf{D_{2\text{-ext}}}$	**23.3**	−0.3	17.1	9.4
11	γ′	$\mathbf{D_{2\text{-int}}}$	**19.8**	0.3	11.9	4.9
12	γ′	$\mathbf{D_{2\text{-ext}}}$	**22.6**	3.9	16.3	9.2

[a] Gibbs Free Energy differences relative to **A** and **D** ($\mathbf{D_1}$ or $\mathbf{D_{2\text{-int}}}$), in kcal mol^{-1}. [b] TSa, adduct: transition state and zwitterionic adduct for the first step (formation of C–C bond a). [c] TSb, cycloadduct: transition state and cycloadduct for the second step (formation of C–C bond b). [d] Rate-determining TS in bold.

Two-step mechanisms are computed in all cases, with the formation of bonds a and b in two subsequent steps. The first step leads to the formation of a zwitterionic Michael adduct, which then cyclizes intramolecularly in a second step.

The first transition states appear to be relatively lower in energy than expected for a dearomatizing process (between 11.6 and 14.0 kcal mol^{-1}, Table 1, entries 1–4), and should thus be representative of a relatively easy step, in accordance with a dearomatization occurring at room temperature. In line with the FMO and charge analyses, formation of the bond between the two C2 carbon atoms of both the dipole and nitropyrrole, associated to the α arrangement, is favored for this first step. More surprising is the stability of the dearomatized Michael adduct (between −5.1 and −5.7 kcal mol^{-1}) and the relatively

high barriers for the second step ($\Delta G^{\neq}$(TSb) between 8.5 and 13.2 kcal mol^{-1}, with respect to separated substrates, between 13.9 and 18.6 kcal mol^{-1} with respect to the Michael adduct, see SI), which are unexpectedly high values for an intramolecular cyclization step. These figures suggest that, for the α approaches, the determining step is not the dearomatizing one but rather the intramolecular cyclization.[23] Formation of the α-cycloadduct appears to be favored over the γ-one by only a small energy difference (0.6 kcal mol^{-1}, see SI). This is not in line with the experimental data, which show that the α-regioisomers are exclusively formed in all cases. In contrast, the small difference between the α and α′ approaches reflects the diastereoselectivity observed experimentally.

The prototropy step was next considered starting from the unsubstituted cycloadduct **Fα** (Table 1). A direct proton transfer appears to be energy demanding ($\Delta G^{\neq}$ = 41.9 kcal mol^{-1}, Figure 5).[24] This high value suggests that this intramolecular

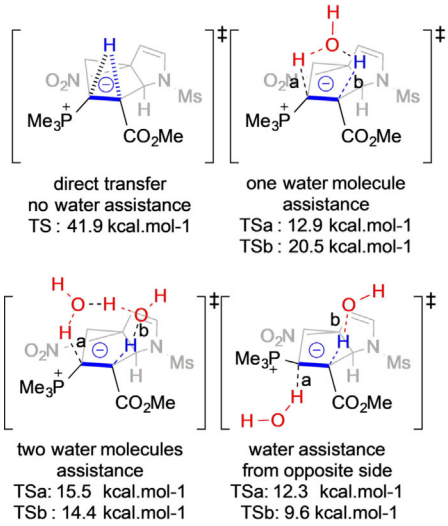


Figure 5. Different propotropy paths considered.

process is highly unlikely and that the presence of water molecules (intentionally added or from the reaction mixture) favors the process. Performing the prototropy in the presence of one or two water molecules is much easier and favors the protonation/deprotonation (see SI). The most favored computed path involves a protonation from the side opposite to the one bearing the proton to be abstracted, followed by a deprotonation step involving an hydroxide anion ($\Delta G^{\neq}$ = 12.3 kcal mol^{-1}, $\Delta G^{\neq}$ = 9.6 kcal mol^{-1}, respectively). Even if other combinations of cycloadduct/water molecules can be considered, these results show unambiguously that the prototropy sequence is favored when water molecules are present in the reaction medium. Here again, this is in line with the experimental data that show that introduction of water to the medium accelerates the whole process (Figure 6).[25]

The final step of the sequence involves the regeneration of the phosphine catalyst and appears to be highly favorable both from the kinetic and thermodynamic points of view ($\Delta G^{\neq}$ = +2.8 kcal mol^{-1}, ΔG_r = −18.5 kcal mol^{-1}). The stability of

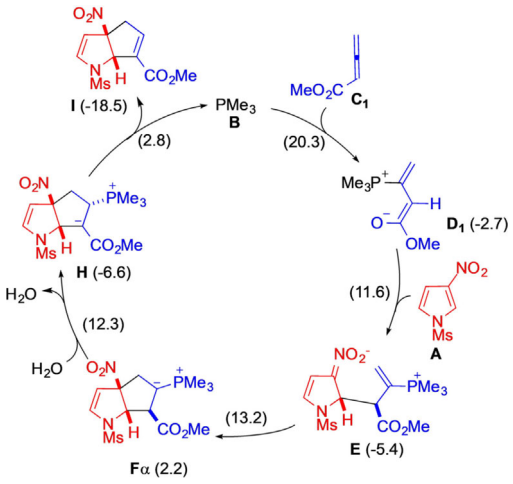


Figure 6. Proposed mechanism with calculated ΔG values ($\Delta G^{\neq}$ and ΔG_r in kcal mol^{-1} respective to separated (A + B + C + $H_2$0).

the final cycloadduct probably drives the reaction to completion, by shifting all the possible equilibria, and explains the whole sequence.

We then considered the same process in the presence of a γ-methyl substituted allenoate **C_2**. The dipole generated by interaction of **C_2** with phosphine **B** can lead to two isomeric dipoles, depending on the position of the methyl group, namely **$D_{2\text{-int}}$** and **$D_{2\text{-ext}}$**. **$D_{2\text{-int}}$** is computationally more stable than **$D_{2\text{-ext}}$**, by 7.7 kcal mol^{-1}, probably due to unfavorable steric interactions between the hydrogen atoms of PMe_3 and Me in the latter.

Since these interactions can vary a lot during the cycloaddition process, both dipole configurations were considered in the calculations. Thus, combining the α/γ approaches with the diastereomeric arrangements α/α′ and γ/γ′ leads to the computations of eight different pathways (Table 1, entries 5–12).[26] In this case, the *cis*/*trans* diastereomers for both the α and γ isomers are possibly formed depending on the approach. The same trends as before are observed and the following conclusions can be drawn: i) the presence of the Me group significantly increases the activation barriers, in line with the experience which shows that a higher reaction temperature is required with substituted allenoates ii) depending on the approach, the highest energy TS can either be the first or the second one, iii) the computed values for a given TS or intermediate are very sensitive to the approach (α/γ/α′/γ′/dipole configuration) as Gibbs free energies span on a range of about 10.7 kcal mol^{-1} in each case; iv) despite these differences, no clear-cut preference for one pathway can be drawn, as the rate determining activation Gibbs Free Energies (first or the second step depending on the arrangements) are all between 19.2 and 24.6 kcal mol^{-1}.[22] In particular, the differences between the approaches leading to the *trans* vs. *cis* diastereomers are relatively small and this can explain the modest diastereomeric ratios observed experimentally. Considering the regioselectivity, the α-isomers are controlled by the second step, whereas the γ ones are controlled by the first one, probably because this step involves a more sterically demanding organization as-

sociated to an energetically disfavored dearomatizing step. As these two steps have very different entropic and electronic components (associative (or not) step, charge separation, dearomatization, steric hindrance), the precision associated with DFT in these conditions does not make it possible to draw any conclusion, considering the small energy differences observed here (0.9 kcal mol^{-1}).[27] These values suggest that the formation of the γ isomers could be possible by modifying the reaction conditions.

In conclusion, we have shown that dearomatizing (3 + 2) formal cycloadditions involving 3-nitroindoles are possible with highly and diversely substituted γ-allenoates. The functionalized α-cycloadducts are exclusively obtained, with *cis/trans* diastereoselectivities up to 3:1. This latter result can be understood on the basis of DFT calculations, which suggest that the energy barriers of the diastereomeric approaches are not significantly different. In contrast, DFT calculations do not explain the exclusive formation of the α-regioisomers, but rather suggest that both the α and γ-pathways are not highly different and, thus, small variations in the reaction conditions could modify the preferred pathway toward the formation of the complementary γ-regioisomer. Expectedly, the dearomatizing step is the determining one during the formation of the γ-cycloadducts, for steric and electronic reasons. Astonishingly, however, this is not true for the formation of the α-regioisomers, for which the determining step appears to be the subsequent intramolecular cyclization. Efforts directed toward the development of γ-regioselective pathways by modifying the experimental conditions and substrates substitutions are currently under way.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulation · allenoate · dearomatization · density functional calculation · nitrondole

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[17] Even a smaller amount of water in the medium is sufficient (3.2 equiv representing a drop).

[18] This surprising result, in which the Boc-protected indole appears to be more reactive than the Ts-protected one is reminiscent of the work published recently, see ref. [13], as well as some results we had reported before, see: a) I. Chataigner, C. Panel, H. Gérard, S. R. Piettre, *Chem. Commun.* **2007**, 3288.

[19] The allenoates are accessible from the corresponding carboxylic acids, via the in situ generation of ketenes, using Mukaiyama salt. See: R. L. Funk, P. M. Novak, M. M. Abelman, *Tetrahedron Lett.* **1988**, *29*, 1493 – 1496. They were obtained as mixture with isomeric alkyne esters, which proved inert in the reaction conditions. See the Supporting Information.

[20] For this compound, several HPLC purifications were required to get the pure separated diastereomers, leading to a decrease of the overall isolated yield.
[21] This result contrasts with those reported by Zhang (ref. [13a]) in the presence of the differently substituted 2-nitrobenzofuran, which proved inert in the presence of an allenoate dipole precursor and required the involvement of MBH carbonates. In contrast, the possible dearomative (3 + 2) annulation on 2-nitrobenzofurans with allenoates has been reported recently, see: a) J.-Q. Zhao, L. Yang, Y. You, Z.-H. Wang, K.-X. Xie, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan, *Org. Biomol. Chem.* **2019**, *17*, 5294 – 5304; b) X.-H. Yang, J.-P. Li, D.-C. Wang, M.-S. Xie, G.-R. Qu, H.-M. Guo, *Chem. Commun.* **2019**, *55*, 9144 – 9147.
[22] For calculation cost reasons, PMe_3 was considered as a model phosphine (see for instance refs. [16] and [13d]), and 3-nitropyrrole was considered as a model of 3-nitroindole (see for instance ref. [18]). No noticeable difference in the calculation conclusion was observed between these two heterocycles.
[23] Rate-determining TSs are determined relative to the starting adducts in each case (**A** + **D** for the first step, Michael adduct **E** for the second). See the Supporting Information.
[24] The direct proton transfer was already reported to be high in energy. See refs. [13d] and [16b], for instance.
[25] In the recently published papers, some reactions were performed in the absence of water. In these cases, the more acidic dipeptidic catalysts used can probably act as a proton transfer agent.
[26] These arrangements can explain the formation of *trans/cis* diastereomers. Alternatively, rotation of the allylic chain on the zwitterion can justify the formation of the two diastereomers. See ref. [13d], SI. These rotations require a protonation/rotation/deprotonation sequence on the zwitterion and the computed values (evaluated using the nudged elastic band method) are in the same range as ours. They were not computed in our case.
[27] Studies are underway to assess the impact of the calculation method and of the selected models on the competition between the two stages of these formal cycloaddition.

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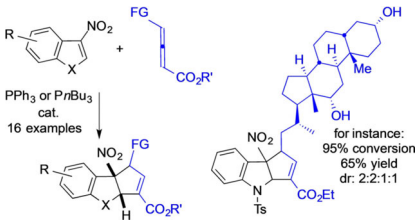
3-Nitroindoles and benzofurans are easily reacted with substituted γ-allenoates in the presence of a commercially available phosphine catalyst. For instance highly functionalized allenoates derived from biomolecules such as amino or deoxycholic acids are combined with 3-nitroindole to yield the corresponding cyclopentaindolines.



Cycloadducts

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Dearomatization of 3-Nitroindoles with Highly γ-Functionalized Allenoates in Formal (3 + 2) Cycloadditions