Dearomative (3+2) Cycloadditions of Unprotected Indoles.

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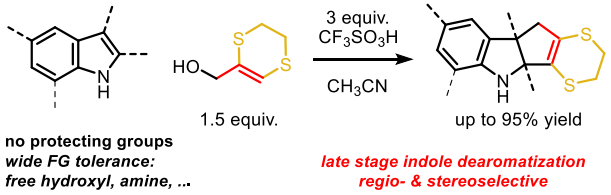
Supporting Information Placeholder

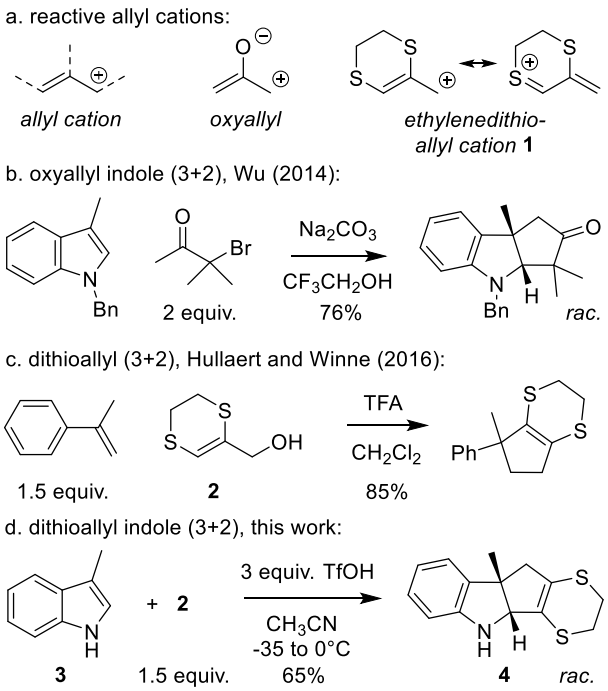


ABSTRACT: The (3+2) cycloaddition of various indoles with a dithioallyl cation affords dearomatized cyclopentannulated adducts, with complete control of regioselectivity and excellent chemo- and diastereoselectivity. The success of the reaction critically relies on the use of an excess of very strong Brønsted acid, which paradoxically prevents carbocationic side reactions. The reaction tolerates sensitive functionalities such as basic amines or free hydroxyls, and we demonstrate its use in late stage derivatisation of highly functionalized, unprotected indoles.

Allyl cations and oxyallyl cations are versatile synthetic intermediates that can be generated and used as reactive electrophiles in alkylations (Scheme 1a).[1] Due to their amphiphilic character, oxyallyl-type cations can also be used in cycloaddition reactions. In particular, their cycloaddition reactivity has been studied for the development of stereoselective cycloheptannulation and cyclopentannulation methods, through their respective (4+3) and (3+2) cycloadditions.[2] Of those two options, oxyallyl cyclopentannulation methodology has so far been the least developed,[3] although cyclopentanoid scaffolds are widespread and medicinally relevant motifs, for which only few general approaches exist.[4] The development of generic methods that allow the parallel synthesis of variously substituted cyclopentanoids is thus of high interest, and allyl cation (3+2) cycloadditions are placed among a select few synthetic organic transformations that are well-suited for this purpose,[3a] together with the better-known Pauson-Khand reaction,[5] and trimethylenemethane (TMM) cycloaddition.[6] More recently, donor-acceptor cyclopropanes have emerged as a potent class of amphiphilic reagents for (3+2) cycloadditions.[7]

In previous studies, we investigated the (3+2) cycloaddition reactivity of the sulfur-heterocyclic allyl cation **1** (Scheme 1 a and c).[8] This reactive intermediate can be regarded as a thio-analog of more classical oxyallyls, with additional stabilization of the allyl cation ground state via thionium resonance. Thio-substituted oxyallyl cations have been studied extensively in seminal work by Harmata in (4+3) cycloadditions,[9] and also to some degree in (3+2)

SCHEME 1. Previous reports and new transformation.



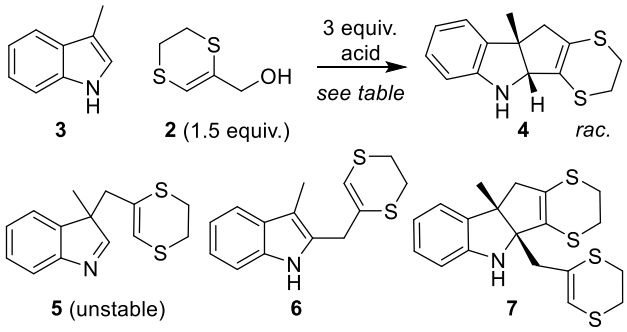
cycloadditions by Kuwajima.[10] Reactions of olefins with unsubstituted or alkyl-substituted allyl cations have been studied in classical works by Mayr and others, but mostly afford unpredictable results and complex reaction mixtures.[11] In stark contrast to generic thioallyl cations, the cyclic ethylenedithio-bridged cation **1** was found to undergo smooth and stereoselective cyclopentannulations with a wide range of styrene and other conjugated alkene substrates (Scheme 1c),[8] in line with the more controlled reactivity observed for oxyallyl cations. The overall transformation also amounts to a method that constitutes a formal (3+2) cycloaddition of a "naked" allyl cation species onto olefins, as the ethylenedithio-bridge can be removed via chemoselective hydrodesulfurisation of the cyclopentannulated substrate.[8d]

Inspired by the elegant work of Wu and coworkers into the applications of oxyallyls and azaoxyallyls in dearomative cycloadditions of indoles (Scheme 1c),[12,13] we became intrigued by the potential of ethylenedithio-bridged allyl cations of the type **1** for such potent dearomative transformations (cf. Scheme 1d). Cyclopentane-fused indoles are indeed common motifs found in bioactive natural products.[4,5,7a] The derivatisation of indoles via a cyclopentannulation also offers an attractive perspective for 'late stage' derivatisation of typical scaffolds that are found in compound screening libraries, although existing methods do require protecting groups and/or specific substitution patterns of indoles and dearomatizing reaction partners.[7,14]

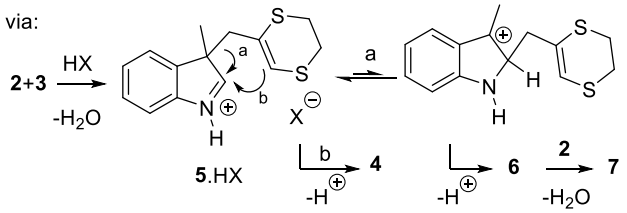
In our previous studies of the cycloaddition chemistry of the ethylene dithiobridged allyl cation **1**,[8d] we observed only a single example of an indole substrate with a very specific substitution pattern and no other functionalites, that underwent the desired dearomative cycloaddition. We separated an adduct in very low yield through fortuitous crystallization from an unseperable mixture of side products (see SI for XRD), showing the challenging nature of such transformations. For generic indole substrates, we initially only found very complex reaction mixtures, indicative of many competing Friedel-Crafts type and other rearomatisation pathways. However, intrigued by the potential of the method, and its similarity and possible good complimentary to successful oxyallyl approaches developed by Wu (Scheme 2b),[12] we started our current investigation with the aim to better understand and control the observed reactivity for these striking dearomative processes.[14,15] In this letter, we can now report the ultimate successful outcome of these investigations.

As a suitable generic indole substrate, we chose simple unprotected skatole **3** (3-methylindole) (Scheme 2), as its benzyl protected version had been shown to be an excellent substrate in base-promoted dearomative oxyallyl (3+2) cycloadditions developed by Wu (Scheme 1b).[13] As our thioallyl methodology requires acidic, and not basic reaction conditions, we reasoned protection of the indole NH might not be required, which would further open up the utility of the methodology. However, submitting skatole **3** and the allylic alcohol **2** (as a precursor of cation **1**) to our previously developed standard conditions for thioallyl cation (3+2) cycloadditions (excess CF_3CO_2H in CH_2Cl_2), gave a very complex, but not intractable reaction mixture (see table in Scheme 2). Careful analysis revealed the formation of three distinct major addition products, isolated in low mass balance: the expected cyclopentannulated product **4**, the Friedel-Crafts C2-allylated indole **6**, and its cyclopentannulated derivative **7**. This initial result is very disappointing in terms of synthetic utility, and is also quite representative for most generic indoles we assayed under these and other reaction conditions. However, the desired cyclopentannulated product **4** was isolated in small amount as a single regio- and diastereomer. The low mass balance in these experiments could later be attributed to the formation of the allylated indoline product **5**, a putative labile intermediate that resisted isolation, but is suspected to be the major reaction product based on our mechanistic rationale and later observations with other indole substrates (*vide infra*).

SCHEME 2. Optimization of the Reaction conditions.



solvent	acid	temp.	% conv. **2**	**4**:**6**:**7**	**4** (isol.)
CH_2Cl_2	TFA	-78°C - rt	85%	1:1:1	<10%
CH_3NO_2	TFA	-35°C - rt	69%	3:4:0	-
CF_3CH_2OH	TFA	0°C - rt	79%	3:5:0	-
CH_3CN	TFA	0°C - rt	74%	1:1:0	-
CH_3CN	*p*TsOH	-35°C - rt	90%	7:3:0	62%
CH_3CN	TfOH	-35°C - 0°C	100%	7:3:0	65%

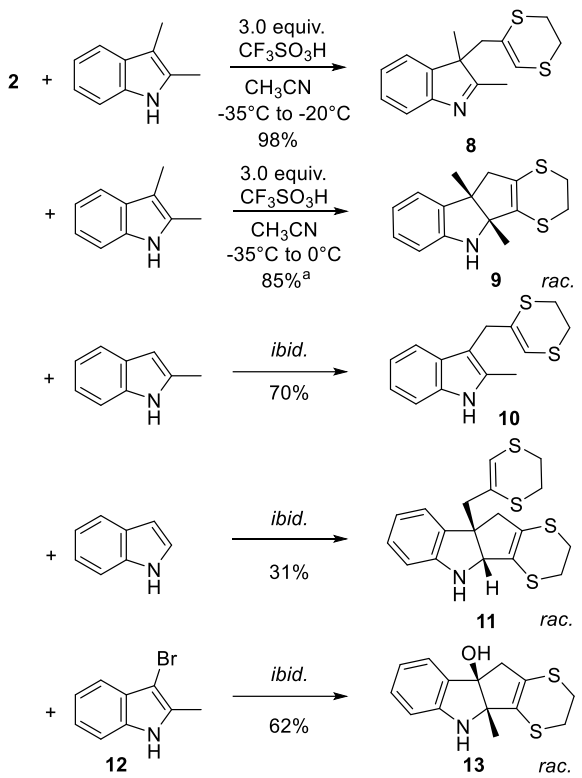


Based on our mechanistic analysis shown in Scheme 2, it seemed reasonable that a change in reaction conditions could sufficiently change the thermodynamic landscape in favor of the desired cyclisation pathway. A first major improvement of the reaction outcome was found by switching solvents. In dichloromethane, mass balances of the reactions were found to be low and the double adduct **7** was always formed as a major product at high conversions. In contrast, in more polar, but crucially non-nucleophilic and low-basicity solvents, somewhat more sluggish reactions resulted, but much higher mass balances were obtained. More importantly, only two major products were observed in these more polar solvents, being the desired cyclopentannulated indoline product **4** and the C2-allylated indole **6**. We believe both of these products predominantly reside in their ionic, protonated forms in these polar solvents with excess acid, and this irreversible protonation step prevents

rearomatisation to the nucleophilic indole **6**, effectively blocking formation of the cyclopentannulation product **7**. The best selectivity between pathway a and b (~1:1) was obtained in acetonitrile. Then, logically switching to even stronger Brønsted acids to prevent the rearomatisation pathway, gave swifter reactions at lower temperatures, and actually also further improved the selectivity in favor of the desired tetracyclic indoline **4** (final entry of table in Scheme 2). As the only side product **6** does not contain a basic amine function, it can be quite readily separated via chromatography, and thus synthetically useful isolated yields can be achieved for this cyclopentannulation of a very challenging unprotected C3-alkyl indole. This result encouraged us to further probe the utility of the transformation, eventhough the general applicability of the required very harsh reaction conditions seemed unpromising.

With the improved reactions conditions in hand, we turned our attention to alternatively substituted indole substrates (Scheme 3). Simple 2,3-dimethylindole reacted swiftly with allyl alcohol **2**, but at low temperatures the C3-allylated product **8** (*cf.* **5**) was cleanly formed, and could be isolated as the sole reaction product. However, letting the reaction run to higher temperatures gave complete

Scheme 3. Primary substituent Effects on Reactivity.



a. Under further improved conditions, 95% isolated yield could be obtained for this substrate, see SI for details.

formation of the expected cyclopentannulated product **9**, isolated in high yield, confirming a highly efficient stepwise (3+2) cycloaddition pathway. As expected, C2-alkylated indoles primarily give electrophilic aromatic substitution (Friedel-Crafts allylation) at the free C3-H position (*viz* **10**). Conversely, indole itself showed more complex behavior, giving bis-adduct **11** as the major reaction product. This points to an unavoidable *in situ* rearomatisation of the initial iminium intermediate. Finally, we could find a practical solution for C3-unalkylated indoles, by first brominating this position. The expected adduct derived from bromo-indole **12** did undergo hydrolysis to the 3-hydroxy indoline adduct **13**, presumably during aqueous work-up.

Although excess amounts of triflic acid are generally not regarded as 'mild' reaction conditions, and may be deemed incompatible with a large degree of functionality, we have actually found the inverse effect. In fact, as can be seen in Figure 1, a much wider functional group tolerance is observed, compared to our original method on styrene type substrates using milder acids.[8] We believe a key factor herein is the high reactivity of indoles and the persistent protonation of all relevant reaction intermediates including the indoline reaction product, which prevents acidic degradation or overalkylation pathways. Electron withdrawing groups on the aromatic ring are tolerated (**16**-**18**), which is a remarkable improvement in substrate scope compared to our previous findings with styrene substrates (see SI).[8d] Peripheral nitriles, carboxylic acids and even basic amines are tolerated (**19-23**). Tryptamine only gave a low yield of the expected adduct **21**, and specific limitations in functional group tolerance were encountered in substrates where a nucleophilic functionality can intercept the intermediate C2-cation. The aberrant reaction of **2** with tryptol is an example here, as a tertrahydrofuroindole is formed (see **24**). Similarly, N-tosyl tryptamine actually fared worse than its free amine version, as the C3-allylated pyrroloindoline **25** was isolated as main product here. Conformationally locked substrates do not pose this problem (cf. **22** and **23**).

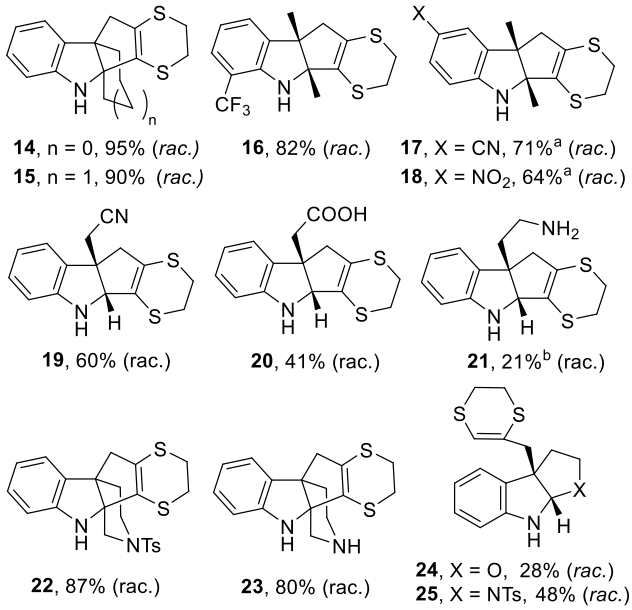


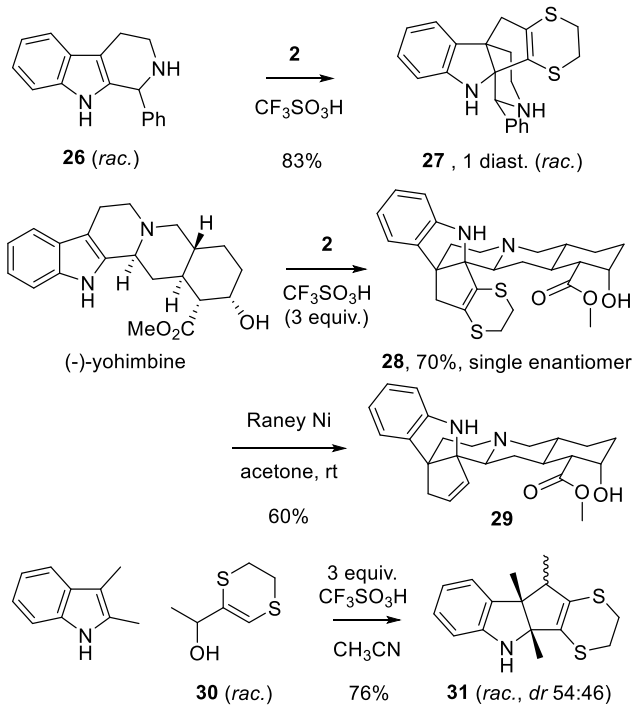
Figure 1. Substrate scope and functional group tolerance. a. 2 equiv. of the indole substrate was reacted with 1 equiv. of **2** b. This adduct was isolated as its N-acyl amide, see SI for details.

The success of unprotected indoles in this dearomative cycloaddition is remarkable. In fact, N-alkylated indoles actually performed much worse, as low conversions and com-

plex reaction mixtures cannot be avoided with these. Interestingly, N-benzoylated indoles did smoothly undergo the dearomative cycloaddition, although this resulted in a loss or even a switch of regioselectivity (see SI for details).

Spurred by the wide substrate scope and functional group tolerance, we also investigated the reactions of the simple Pictet-Spengler product **26** (derived from tryptamine and benzaldehyde), to probe the induction of a nearby stereogenic center (Scheme 4). Indeed, this indole underwent a very smooth reaction with allyl alcohol **2** to afford the pentacyclic indoline **27**, isolated in high yield as a single diastereomer. Likewise, in a remarkable display of chemo-, regio and stereoselectivity, the cyclopentannulation of the well-known indole alkaloid yohimbine with allyl alcohol **2** proceeded exceedingly smoothly, taking into account the delicate functionality of this natural alkaloid drug compound. A subsequent chemoselective hydrodesulfurisation of the cycloadduct **28** with Raney nickel, afforded the cyclopentannulated analogue of yohimbine **29** as a single enantiomer. These desulfurisations proceed smoothly, but care must be taken to avoid overreduction to the cyclopentane (see SI).[16] Finally, we also explored the more substituted allyl alcohol **30**, to probe the effect on overall efficiency and stereo- and regioselectivity. This methyl-substituted allyl alcohol smoothly afforded the expected indoline **31** from 2,3-dimethylindole, in good isolated yield and with the same high regioselectivity, but the process lacked stereoselectivity with respect to the introduced methyl.[17] This result stands in contrast with our previous findings with substituted allyl alcohols in intramolecular (4+3) and (3+2) dihydrodithiin cycloaddition with simple diene or alkene substrates, which did show high levels of stereoinduction.[8a,8b]

Scheme 4. Applications in stereoselective late-stage indole Derivatization.



In summary, we have developed a novel generally applicable dearomative cyclopentannulation method for unprotected indole substrates. The substrate scope of the method compares favorably to the limited existing methods that can achieve similar transformations.[15] The functional group tolerance is surprisingly wide, and reaction outcomes can be related to the stepwise cationic mechanism involving a stepwise (3+2) cycloaddition allyl cation cycloaddition, which is supported by experimental observations of intermediates and divergent reaction pathways. In spite of the stepwise mechanism, high degrees of stereoselectivity can be achieved. The synthetic utility of the novel process is clearly encouraging, in particular for the late stage modification of functional indole substrates, as well as for the rapid *de novo* assembly of polycyclic scaffolds from readily available, robust heterocyclic building blocks. Future research along these lines will focus on applications in synthesis of this method, and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Electronic Supplementary Information (ESI) contains experimental procedures, and characterization data for all new compounds (available as PDF)

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Author Contributions

The draft manuscript was written by JW together with BR, which was then reviewed by the coauthors. All authors have given approval to the final version of the manuscript. JW and JH designed the overall research approach and together formulated the main research ideas. BR completed all of the synthetic experiments and was also involved in the design of the project. KVH acquired funding for and fully performed the key structural analysis based on single crystal XRD.

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(17) In related ongoing studies aimed at synthetic applications of the (3+2) methodology for non-indole substrates, we have found good to excellent levels of stereo-induction with the alcohol **30**. These results will be reported in due course.