Synthetic Methods

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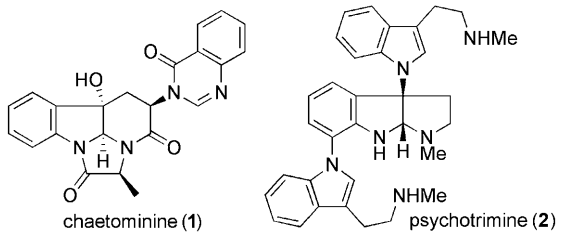
Catalytic Oxyamidation of Indoles**

*Stéphane Beaumont, Valérie Pons, Pascal Retailleau, Robert H. Dodd, and Philippe Dauban**

In memory of Keith Fagnou

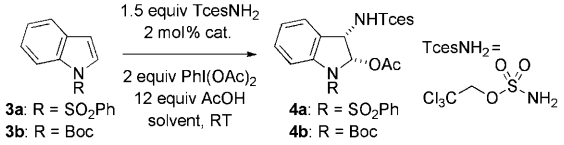
Since the first preparation of indole by Baeyer in 1866,[1] its chemistry has been extensively investigated as a consequence of its prevalence in the structures of many biologically active natural products, including some useful drugs.[1,2] Indole chemistry still remains an area of great interest as demonstrated by several recent reviews dedicated to this field.[3] In particular, much attention has been focused towards the development of methodologies for oxidative functionalization at the C2 and C3 positions,[4] a field pioneered by Witkop,[1c] since these oxidations can provide rapid routes to new natural products that contain an indole framework, such as chaetominine (**1**)[5] and psychotrimine (**2**).[6]



The catalytic oxidative difunctionalization of alkenes offers a direct route to various important scaffolds, such as vicinal diamines and aminoalcohols. Although efficient procedures have been described using palladium(II) chemistry,[7] catalytic nitrene transfers offer a possible alternative. The latter generally afford C–H-aminated or olefin aziridination products,[8] but recent studies have demonstrated that formal alkene oxyamidation can be achieved in the case of glucals[9] and indoles.[10] These nitrene transfers have been successfully developed by tethering an acylnitrene or a sulfamoylnitrene onto the substrate, thereby ensuring efficiency and complete regioselectivity for the intramolecular nitrene delivery. In order to enhance the scope of this catalytic oxidative alkene functionalization reaction, the development of the analogous intermolecular process would be highly appealing although it is more challenging as it would likely afford a mixture of isomers. In this context, we report our studies toward such catalytic intermolecular indole oxyamidation reactions.

During the course of experiments investigating the application of catalytic nitrene transfers involving iodine(III) oxidants to indolic derivatives, we were intrigued by the formation of a major product that arises from a formal oxyamidation process at the indole C2 and C3 positions, as clearly observed by NMR spectroscopy. A short initial screening of the reaction parameters allowed us to determine that good conversions were achieved using reagents and conditions previously developed by Du Bois et al. for the catalytic C–H amination and olefin aziridination reactions.[11,12] Importantly, in the presence of trichloroethylsulfamate ($TcesNH_2$),[11a] 2 mol% of $[Rh_2(esp)_2]$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid),[11b] and PhI$(OAc)_2$, the crystalline product **4a** was formed from *N*-(phenylsulfonyl)indole **3a** (Table 1, entry 1). X-ray crystallography confirmed that *cis*-oxyamidation had taken place exclusively;[13] the trichloroethanesulfamoyl moiety was installed at the C3 position (see the Supporting Information), thereby matching the regio- and stereoselectivities previously reported for the related intramolecular process by Padwa and co-workers.[10a,b]

Table 1: Catalytic acetyloxyamidation of indoles **3**.



Entry	Substrate	Solvent	Catalyst	Yield [%][a]
1	**3a**	C_6H_6	$[Rh_2(esp)_2]$	50[b]
2	**3a**	C_6H_6	$[Rh_2(esp)_2]$	76
3	**3a**	toluene	$[Rh_2(esp)_2]$	72
4	**3a**	CH_3CN	$[Rh_2(esp)_2]$	74
5	**3a**	CH_2Cl_2	$[Rh_2(esp)_2]$	67
6	**3a**	C_6H_6	$[Rh_2(OAc)_4]$	45
7	**3a**	C_6H_6	$[Rh_2(NHCOCF_3)_4]$	73[c]
8	**3a**	C_6H_6	$CuPF_6$	0
9	**3a**	C_6H_6	$[Rh_2(esp)_2]$	55[d]
10	**3b**	C_6H_6	$[Rh_2(esp)_2]$	79

[a] Yield of isolated product. [b] Reaction was performed in the absence of AcOH. [c] Compound **4a** was isolated as a mixture of *cis*/*trans* isomers in a 19:81 ratio. [d] Reaction was performed in the presence of MgO.

[*] Dr. S. Beaumont, V. Pons, Dr. P. Retailleau, Dr. R. H. Dodd, Dr. P. Dauban
Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, UPR 2301 CNRS
Avenue de la Terrasse, 91198 Gif-sur-Yvette (France)
Fax: (+33) 1-6907-7247
E-mail: philippe.dauban@icsn.cnrs-gif.fr

[**] S.B. and V.P. contributed equally to this work. We wish to thank the Institut de Chimie des Substances Naturelles for financial support and fellowships. We also kindly acknowledge the support and sponsorship from COST Action D40 "Innovative Catalysis: New Processes and Selectivities".

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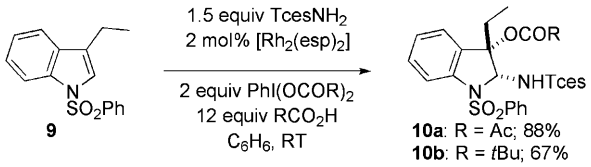
Optimization of the reaction conditions by the addition of excess acetic acid (12 equiv) to the reaction mixture afforded an improved yield of 76% (Table 1, entry 2). The highest yield was obtained with benzene, but the use of toluene or acetonitrile gave comparable yields (Table 1, entries 3–5). The highest conversions were observed using rhodium(II) complexes, particularly $[Rh_2(esp)_2]$ and $[Rh_2(NHCOCF_3)_4]$ (Table 1, entries 2 and 7), whereas no reaction occurred in the presence of a copper salt (Table 1, entry 8). Surprisingly, whilst the *cis* isomer is usually isolated exclusively, the *trans* isomer is predominantly formed in the presence of $[Rh_2(NHCOCF_3)_4]$ (Table 1, entry 7). Finally, the addition of MgO induced a decrease in reactivity (55% yield; Table 1, entry 9). The reaction also tolerated a Boc group at the N1 position (entry 10).

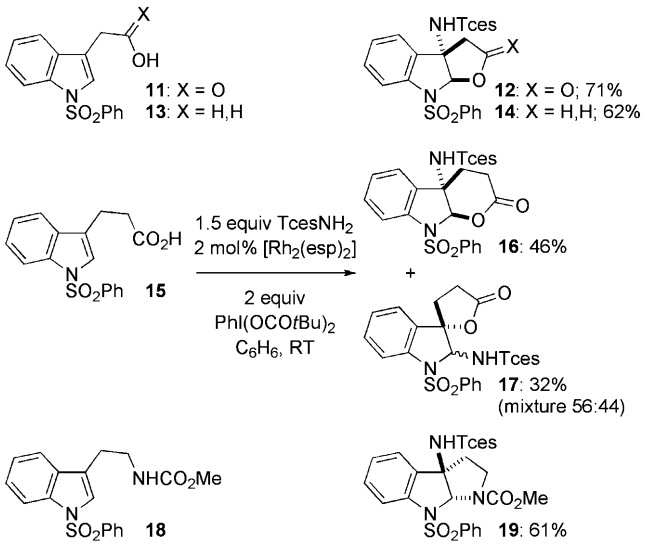
We then decided to screen a series of nucleophiles for compatibility with the oxidizing conditions. Changing the ligands on the hypervalent iodine reagent by replacing $PhI(OAc)_2$ with $PhI(OCOtBu)_2$ and addition of excess pivalic acid allowed us to isolate the corresponding *cis*-pivalate derivative **5** in 51% yield (Table 2, entry 1). Whilst all of our attempts to introduce a trifluoroacetyl group failed, it was possible to introduce other carboxylic acids for which the corresponding iodine(III) reagents are not available. Conducting the reaction in the presence of $PhI(OAc)_2$ and benzoic acid led to a nearly equimolar mixture of the expected product **6** and the previously isolated compound **4a** (Table 2, entry 2). A higher selectivity was observed with $PhI(OCOtBu)_2$, with the concomitant formation of the undesired pivaloyloxy derivative **5** in lower yields (7% and 9% in the presence of benzoic and phenylacetic acid, respectively; Table 2, entries 3 and 4). Pleasingly, these side reactions could be avoided by using iodosylbenzene, allowing compound **7** to be isolated as the sole product in 52% yield (entry 5). Furthermore, *cis*-oxyaminated products were always obtained regardless of the carboxylic acid introduced. However, a different result was observed when an alcohol was used as the nucleophile. Thus, the reaction in the presence of methanol affords *trans*-oxyaminated compound **8** (Table 2, entry 6) as the major product; the stereochemistry was confirmed by X-ray crystallography (see the Supporting Information).[13] This derivative was exclusively formed even in the presence of $[Rh_2(NHCOCF_3)_4]$ (Table 2, entry 7). Therefore, this result suggests that the stereochemistry of the oxyamidation reaction can be controlled by careful choice of the O-nucleophile.

Surprisingly, the reaction of acetic or pivalic acid with 3-ethylindole **9** led to the formation of **10a** and **10b** in 88% and 67% yield, respectively (Scheme 1). Whilst the oxidative addition once again took place in a *cis* manner, a reversal of the regioselectivity was observed with the nitrogen-containing moiety introduced at the C2 position, as confirmed by X-ray crystallographic analysis of **10a** (see the Supporting Information).[13] Notably, this oxyamidation is highly chemoselective: no benzylic C–H amination products were isolated.[11,12c,d]



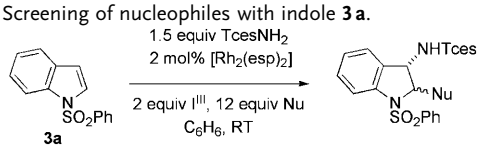
Scheme 1. Catalytic oxyamidation of 3-ethylindole **9**.

We also envisaged experiments in which the nucleophile is linked to the indolic substrate. Therefore, carboxylic acid **11** and alcohol **13** afforded the corresponding fused lactone **12** and tetrahydrofuran **14** in 71% and 62% yield, respectively (Scheme 2). The same relative stereochemistry was also observed in the transformation of the homologous carboxylic



Scheme 2. Catalytic intramolecular oxyamidation of indole derivatives.

Table 2: Screening of nucleophiles with indole **3a**.

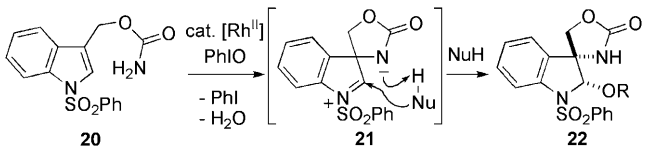


Entry	I^{III} oxidant	Nucl.	Product	Yield [%][a]
1	$PhI(OCOtBu)_2$	$tBuCO_2H$	**5**	51
2	$PhI(OAc)_2$	$PhCO_2H$		23[b]
3	$PhI(OCOtBu)_2$	$PhCO_2H$	**6**	37[c]
4	$PhI(OCOtBu)_2$	$BnCO_2H$		40[d]
5	PhIO	$BnCO_2H$	**7**	52
6	$PhI(OCOtBu)_2$	MeOH		97[e]
7	$PhI(OCOtBu)_2$	MeOH	**8**	81[f]

[a] Yield of isolated product. [b] Accompanied by 22% of the acetyloxy analogue **4a**. [c] Accompanied by 7% of **5**. [d] Accompanied by 9% of **5**. [e] Isolated as a mixture of *cis*/*trans* isomers in a 16:81 ratio. [f] Reaction using $[Rh_2(NHCOCF_3)_4]$ as the catalyst. *trans*-**8** was formed exclusively.

acid **15** into the six-membered lactone **16**. However, the formation of the latter was accompanied by that of the spiro lactone **17**, isolated as a mixture of isomers. Finally, we were pleased to observe that a nitrogen nucleophile was compatible with the reaction conditions. Thus, the use of carbamate **18** allowed the isolation of tetrahydropyrrolo[2,3-b]indoline **19** in 61% yield, which can be considered as a synthetic precursor to psychotrimine **2**.

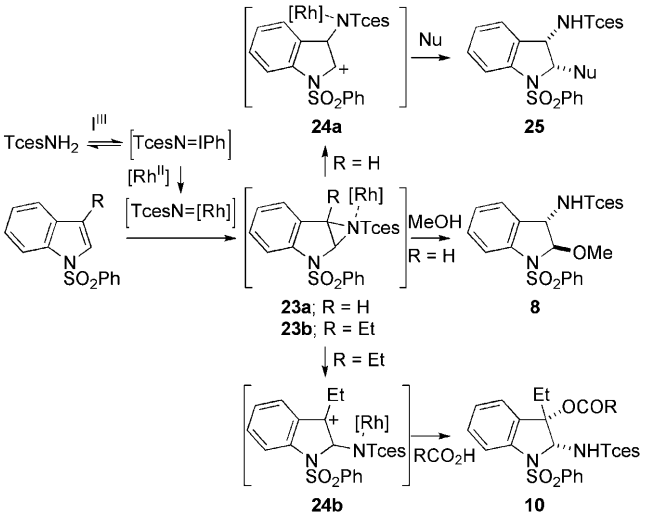
These results raised questions about the exact mechanism of this transformation. In the paper by Padwa et al. that described the intramolecular addition of a nitrene that was generated from 3-indolyl carbamate **20**, the formation of an aziridine intermediate was excluded based on the observation that only *cis* products were isolated using alcohols or carboxylic acids as nucleophiles.[10a,b] Instead, the authors proposed a stepwise mechanism involving the initial formation of a metallanitrene that is subsequently attacked by the indole π bond to afford the zwitterionic species **21** (Scheme 3). Deprotonation of the nucleophile and attack at the iminium carbon would then occur simultaneously, thus leading to the *cis*-oxyaminated product **22**.



Scheme 3. Hypothetical mechanism for the intramolecular indole oxyamidation reaction.[10]

The mechanism proposed by Padwa is consistent with an intermolecular *cis* aminohydroxylation reaction using carboxylic acids. However, the *trans* stereochemistry observed with methanol or in the case of an intramolecular nucleophilic attack led us to envisage another scenario.[14] Therefore, we postulate that the intermolecular nitrene delivery might lead to an aziridine intermediate. The course of the reaction would then depend on the indole substitution as well as on the nature of the nucleophile (Scheme 4). Thus, the metallanitrene generated from the reaction between the $TcesNH_2$-derived iminoiodane and the rhodium(II) catalyst could add onto the indole π-bond to afford aziridine **23**. The latter would undergo fast ring opening to give rise to a carbocation, the nature of which depends on the substitution pattern at the C3 position. In the case of **23a** (R = H), formation of iminium **24a** would be favored whereas aziridine **23b** (R = Et) would preferentially afford the more stable tertiary benzylic cation **24b**. Both intermediates would then be attacked in a *cis* manner by nucleophiles, presumably owing to conformational effects.[15] In contrast, methanol would be nucleophilic enough to trap the postulated aziridine in a classical S_N2-type substitution, thereby leading to the expected *trans* product **8**.[16]

Noteworthy is the influence of the rhodium complex on the ratio of *cis* and *trans* products. As assumed in previously published studies,[9a,d,e,10c] the rhodium(II) catalyst may remain bound to the nitrogen of the aziridine while the ring-opening is taking place. Coordination is likely to accelerate or decelerate the formation of the cationic species depending on the nature of the ligand bound to the catalyst; this could account for the relatively larger amounts of isolated *trans*-products **4a** and **8** obtained using the $[Rh_2(NHCOCF_3)_4]$ catalyst.[17]



Scheme 4. Proposed mechanism for the intermolecular oxyamidation reaction.

In conclusion, the application of rhodium-catalyzed nitrene transfers to indolic derivatives has allowed the development of an efficient intermolecular oxyamidation reaction that gives access to 2,3-substituted indolines. A key feature of this transformation is the ability to control either its stereoselectivity by changing the nucleophile or its regioselectivity by the introduction of a substituent at C3. Moreover, the scope of the reaction has been extended to include nitrogen nucleophiles, thereby paving the way for the development of the catalytic diamination of indoles. Work is now in progress to study the reaction scope as well as to apply this methodology to the total synthesis of natural indole derivatives.

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[12] Sulfonamide-derived nitrenes afforded poor conversions (29% in the case of $NsNH_2$) and the use of sulfonimidamides proved unsuccessful. For some of our earlier studies of nitrenes that were generated from sulfonimidamides, see: a) P. Di Chenna, F. Robert-Peillard, P. Dauban, R. H. Dodd, *Org. Lett.* **2004**, *6*, 4503–4505; b) C. Fruit, F. Robert-Peillard, G. Bernardinelli, P. Müller, R. H. Dodd, P. Dauban, *Tetrahedron: Asymmetry* **2005**, *16*, 3484–3487; c) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343–350; d) F. Collet, R. H. Dodd, P. Dauban, *Org. Lett.* **2008**, *10*, 5473–5476.

[13] CCDC 756161 (**4a**), 756162 (**8**), 756163 (**10a**), and 756164 (**12**) 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.

[14] The formation of *cis* and *trans* compounds may have been a consequence of epimerization of the initially formed *cis* product that arises from nucleophilic attack of the iminium group. Therefore, we envisaged a regeneration of the iminium group from **4a** or **8** under the reaction conditions, followed by the introduction of a different O-nucleophile. However, despite many attempts, only the starting materials were recovered.

[15] Should the nucleophilic attack involve deprotonation of the nucleophile and simultaneous substitution, the use of a deuterated reagent would allow the incorporation of deuterium into the final product. However, reaction of indole **3a** under the standard conditions in the presence of CH_3CO_2D or CD_3OD led to only **4a** and **8**, respectively, without traces of the expected deuterated analogues.

[16] The higher nucleophilicity of MeOH is suggested by the absence of products that arise from the attack of the acid released from $PhI(OCO_tBu)_2$.

[17] A different scenario, which has been suggested by one of the referees, would involve competing reactions between ylide intermediates and aziridines that are influenced by the nature of the catalyst.

