Synthetic Methods

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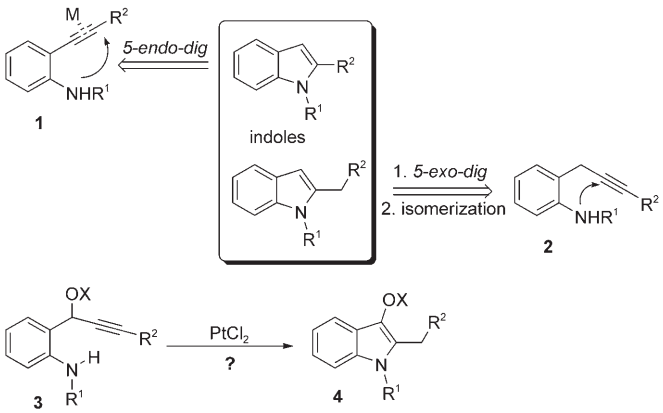
From $PtCl_2$- and Acid-Catalyzed to Uncatalyzed Cycloisomerization of 2-Propargyl Anilines: Access to Functionalized Indoles**

Kevin Cariou, Baptiste Ronan, Serge Mignani, Louis Fensterbank, and Max Malacria**

Indoles are ubiquitous motifs in pharmaceuticals as well as in important natural products. New and straightforward methods to access these substrates are thus always highly desirable.[1] In this context, the metal-catalyzed cycloisomerization of polyunsaturated precursors is an ideal process to be explored. One of the main strategies has consisted of a 5-*endo-dig* metal-catalyzed[2,3] cyclization of acetylenic derivatives (Scheme 1). *Ortho*-Halogenoanilines constitute valuable

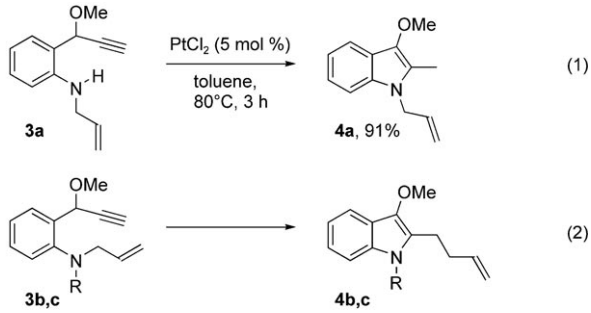


Scheme 1. Transition-metal-catalyzed formation of indoles from *o*-alkynylanilines and *o*-propargylanilines. M = metal.

starting materials for the synthesis of substrates **1** and can even be used to generate in situ the akynylaryl species by a Sonogashira-type coupling reaction prior to cyclization.[2d] A recent variant based on imines has also been reported.[4] To the best of our knowledge, the alternative 5-*exo-dig* isomerization approach from precursors **2** has received much less attention,[5] and we decided to examine this potentially new route.

Platinum(II)-based catalysis has recently witnessed a tremendous development which has led to new synthetic methods[6] as well as versatile applications in the total synthesis[7] of natural products and asymmetric catalysis.[8] Recently, we reported on the use of allenyne and enynamide partners,[9] and showed that the substituent at the propargylic position had a dramatic influence on the course of the $PtCl_2$-catalyzed cycloisomerization of various enyne systems.[10] To examine the scope of the reaction and to generate diverse platforms we have thus investigated flexible propargylic precursors of type **3**[11,12] (Scheme 1) on which we can easily vary the oxygen, nitrogen, and alkyne substituents (X, R^1, and R^2).

Our initial studies involving substrate **3a** (Scheme 2, Eq. (1) were highly encouraging, and enabled indole **4a** to be isolated in 91 % yield. We next examined more challenging



Entry	R	Catalyst	Solvent	*T*	*t* [h]	**4** [%]
1	**3b**, allyl	$PtCl_2$ (5 mol%)	toluene	80°C	1	92
2	**3b**, allyl	SiO_2 (5 equiv)	CH_2Cl_2	RT	6	87
3	**3c**, Me	$PtCl_2$ (5 mol%)	toluene	RT	12	60
4	**3c**, Me	SiO_2 (5 equiv)	CH_2Cl_2	RT	1	90

Scheme 2. Indole formation and allyl transfer.

precursors. Gratifyingly, *N*,*N*-diallyl precursor **3b** also underwent the transformation [Scheme 2, Eq. (2)]. In this case, an additional transfer of an allyl group from the nitrogen to the terminal alkyne carbon atom occurred (Scheme 2, entry 1). This formally constitutes an aminoallylation of the triple bond followed by an isomerization of the unsaturated bond. An analogous allyl transfer has been previously described by Fürstner et al. in the synthesis of furan derivatives. However, in this case, stabilization of the vinyl–metal intermediate via an enolate species seems necessary since only acetylenic

[*] K. Cariou, Prof. Dr. L. Fensterbank, Prof. Dr. M. Malacria
Laboratoire de Chimie Organique, UMR CNRS 7611
Institut de Chimie Moléculaire, FR 2769
Université Pierre et Marie Curie, Paris 6, case 229
4, place Jussieu, 75005 Paris (France)
Fax: (+33) 1-4427-7360
E-mail: fensterb@ccr.jussieu.fr
malacria@ccr.jussieu.fr
Dr. B. Ronan, Dr. S. Mignani
Oncology Dept., Medicinal Chemistry
Centre de Recherche de Paris, Bât. Grignard
Sanofi-Aventis
13, Quai Jules Guesde, 94400 Vitry-sur-Seine (France)

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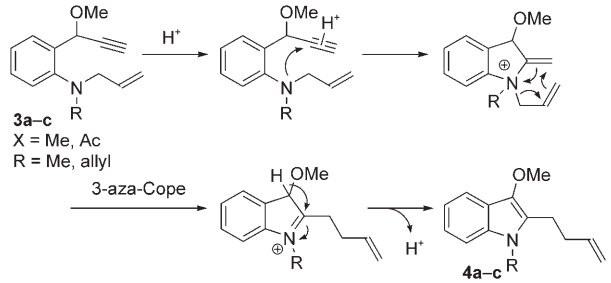
esters and nitriles were reported to undergo the transfer reaction.[6b]

In our case, such activation is not required. More interestingly, this transformation can take place under metal-free conditions: simple stirring of the reaction mixture in the presence of silica (500 wt%) provided a similar yield of **4b** (entry 2).[13] When the *N*-methyl,*N*-allyl substrate **3c** was submitted to both reaction conditions, only the allyl moiety was transferred (entries 3 and 4). The presence of silica provided a smooth and better-yielding reaction.

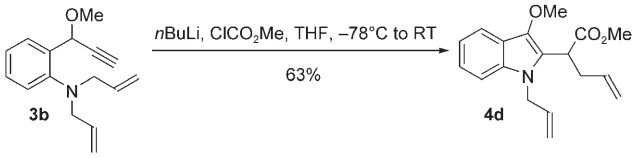
There are several mechanistic issues associated with this new reaction which depend on the reaction conditions. The preliminary step in the case of the proton-catalyzed reaction would correspond to an activation of the triple bond via a putative vinylic carbocation that is immediately trapped by the internal nitrogen-based nucleophile (Scheme 3). The



Scheme 3. Proposed mechanism for Brønsted acid catalysis.

resulting ammonium intermediate is then ready to undergo a charge-accelerated 3-aza-Cope rearrangement.[14] A final generation of the aromatic indole nucleus would then steer the evolution of the reaction. In the case of the metal-catalyzed process, a similar mechanism based on an initial π complexation of the alkyne partner would be involved.

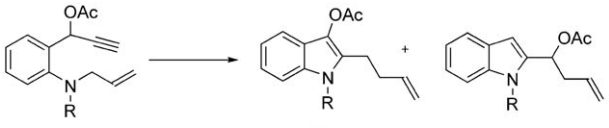
These findings led us to explore catalyst-free conditions, and we carried out the following sequence from **3b**. After deprotonation, methylchloroformate was added to activate the alkyne function towards the 5-*exo* attack of the nitrogen atom, which enabled indole **4d** to be obtained in 63% yield (Scheme 4). Presumably, intramolecular Michael addition to



Scheme 4. Cyclization by activation of the triple bond.

the triple bond generates an allenolate system that can undergo [3,3] sigmatropic rearrangement.[14c] Final proton exchange yields **4d**. This new cascade, which includes five elementary steps, opens up new perspectives for the straightforward preparation of functionalized indole scaffolds.

We then examined precursor **3e**, which presented an additional challenge since a propargylic acetate group with potential migrating ability was present.[10,15] This reaction showed a dramatic temperature effect (Scheme 5, entries 1–4). The precursor underwent a clean transformation to the



Entry	R	Catalyst	Solvent	*T*	*t* [h]	**4** [%]	**4'** [%]
1	**3e**, allyl	$PtCl_2$ (5 mol%)	toluene	RT	1	94	-
2	"	$PtCl_2$ (5 mol%)	toluene	40°C	1	92	-
3	"	$PtCl_2$ (5 mol%)	toluene	80°C	1	22	57
4	"	$PtCl_2$ (5 mol%)	toluene	110°C	1	-	60[a]
5	"	$AuCl_3$ (5 mol%)	CH_2Cl_2	RT	0.3	58	15
6	"	$NaAuCl_4$ (5 mol%)	CH_2Cl_2	RT	0.3	63	-
7	"	SiO_2		RT		71[b]	-
8	"	PTSA (1 equiv)	toluene	RT	1	54	-
9	"	BF_3•Et_2O (1 equiv)	CH_2Cl_2	–78°C to RT	6	degradation	
10	**3f**, Me	$PtCl_2$ (5 mol%)	toluene	110°C	0.5	19	19
11	"	$PtCl_2$ (5 mol%)	toluene	RT	12	23	13
12	"	SiO_2 (5 equiv)	CH_2Cl_2	RT	0.5	67	-
13	**3g**, Bn	$PtCl_2$ (5 mol%)	toluene	RT	24	-	45
14	"	SiO_2 (5 equiv)	CH_2Cl_2	RT	2	70	-

Scheme 5. Reactivity of *O*-acyl substrates **3e–g**. [a] A diene derivative resulting from a loss of AcOH was also isolated (13%). [b] Complete conversion was observed during flash chromatography. PTSA = *para*-toluenesulfonic acid, Bn = benzyl.

expected indole **4e** at RT, while performing the reaction above 80°C gave a new indole adduct (**4′e**) in which an additional migration of the acetate group had occurred. Thus, this cycloisomerization process involves the migration of two groups.

The use of a gold(III) catalyst gave **4e** as the major product, along with **4′e** as a minor fraction (Scheme 5, entries 5 and 6). We also examined the scope of the acid-catalyzed cycloisomerization of precursor **3e** (entries 7–9). Once again, silica proved to be a better reagent for catalyzing the **3e** to **4e** transformation than PTSA, while $BF_3{\cdot}Et_2O$ led only to degradation. It should be noted that no trace of **4′e** was observed in these acid-catalyzed reactions. Thus, this new route for achieving a heterocyclic ring closure with concomitant reorganization of an enyne system under metal-free conditions is highly attractive in terms of simplicity and versatility.

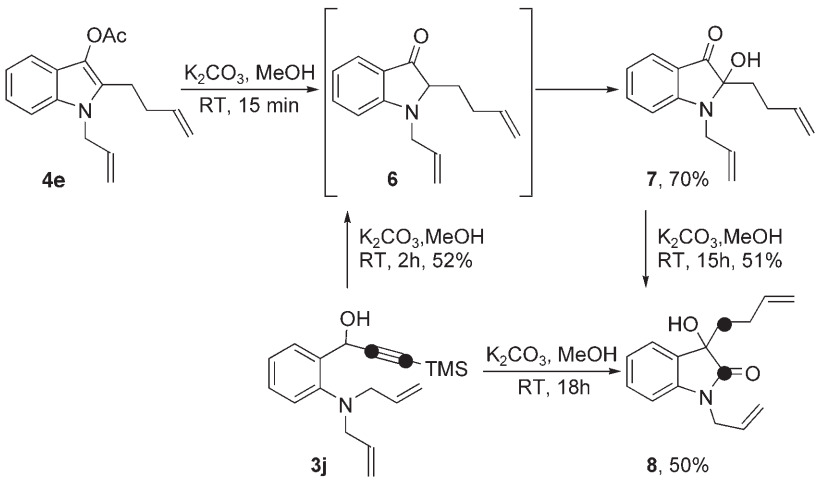
The *N*-methyl,*N*-allyl substrate **3f** reacted in a similar fashion, with the transfer of the allyl group only. No real selectivity in the formation of product **4′f** could be obtained when $PtCl_2$ was used as the catalyst (Scheme 5, entries 10–12). In contrast, the *N*-benzyl,*N*-allyl precursor **3g** showed total selectivity, and gave exclusively indole **4′g** when exposed to $PtCl_2$. Regioisomer **4g** was smoothly obtained when silica was used as the catalyst (Scheme 5, entries 13 and 14).

The formation of **4e–g** likely occurs through the same mechanistic pathways as discussed before (Scheme 3). Interestingly, **4e** could not be isomerized into **4′e** upon prolonged heating (refluxing toluene) or in the presence of $PtCl_2$. This finding implies that migration of the acetate moiety takes place during the cycloisomerization process. Studies on this

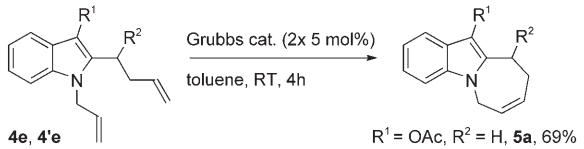
particular issue are currently underway. It has to be noted that intractable mixtures were obtained with internal alkynes (phenyl, cyclopropyl, and *n*-butyl groups were tested).

The structures of **4e** and **4′e** prompted us to attempt a ring-closing metathesis reaction between the two pendant unsaturated groups to access an azepinoindole skeleton.[16] Indeed, these substrates reacted cleanly to afford tricyclic indoles **5a** and **5b** in the presence of the Grubbs first-generation catalyst (Scheme 6).[17]

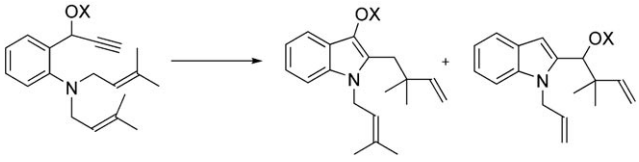
The behavior of diprenyl substrates **3h** and **3i** followed the same fate (Scheme 7) and provided additional mechanistic insight, since no scrambling occurred in the transfer of the prenyl group. This finding would argue against the intervention of a dissociative pathway in this step[6b] and is consistent with a concerted process, possibly catalyzed by platinum.



Scheme 8. Formation of hydroxyindolones. TMS = trimethylsilyl.



Scheme 6. Ring-closing metathesis to provide azepinoindoles.



Entry	X	Catalyst	Solvent	*T*	*t* [h]	**4** [%]	**4'** [%]
1	**3h**, Me	$PtCl_2$ (5 mol%)	toluene	40°C	1	50	-
2	**3h**, Me	SiO_2 (5 equiv)	CH_2Cl_2	RT	6	81	-
3	**3i**, Ac	$PtCl_2$ (5 mol%)	toluene	RT	72	14	38
4	**3i**, Ac	$PtCl_2$ (5 mol%)	toluene	110°C	2	-	50
5	**3i**, Ac	SiO_2 (5 equiv)	CH_2Cl_2	RT	6	67	-

Scheme 7. Behavior of *N*,*N*-diprenyl substrates **3h** and **3i**.

Having several valuable protected 3-hydroxyindoles in our hands, we turned our attention to 3-indolones. Methanolysis of **4e** readily led to 2-hydroxyindol-3-one **7**, presumably by rapid oxidation of indolone **6** (Scheme 8).[18] By taking advantage of the structure of **7**, we were able to promote an α-ketol rearrangement under the same reaction conditions,[19] thus obtaining the 3-hydroxyindol-2-one **8**.[20] This interesting finding prompted us to improve the efficiency by using a less complex precursor. Desilylation of compound **3j** with K_2CO_3 furnished 2-hydroxyindol-3-one **7** directly in 2 h (Scheme 8). We postulate that compound **3j** is first desilylated and then cycloisomerizes to give indolone **6** through the previously discussed 3-aza-Cope rearrangement. Subsequent oxidation gives rise to the 2-hydroxyindol-3-one **7**, which can be considered as the kinetic product. Indeed, increasing the reaction time (to 18 h) allowed the selective formation of **8** (Scheme 8). These simple reaction conditions allow the formation of a fairly complex structure in a single step that involves a desilylation/cycloisomerization/oxidation/rearrangement sequence and features the formal breaking of the triple bond (highlighted by the black dots).

In conclusion, we have devised an expedient route to 2,3-functionalized indoles and notably 3-alkoxyindoles, which relies on the use of $PtCl_2$ or proton catalysis. The most intriguing aspect of this process is that the tuning of substituents on the nitrogen atom, as well as reaction conditions, notably temperature, allows an easy and versatile access to a myriad of indole substrates. Complementary to this approach is the unprecedented skeletal rearrangement described in the transformation of **3j** into 3-hydroxyindolone **8**, which can serve as a versatile scaffold for further elaborations, including natural product synthesis.[21]

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