## Heterocycle Synthesis

## Synthesis of N-Fused Tricyclic Indoles by a Tandem [1,2] Stevens-Type Rearrangement/1,2-Alkyl Migration of Metal-Containing Ammonium Ylides\*\*

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We reported previously that novel metal-containing carbonyl or azomethine ylides could be generated by the nucleophilic attack of a carbonyl oxygen atom or imino nitrogen atom onto alkynes activated by electrophilic transition-metal complexes. The resulting species, which behave as both ylides ([3+2])cycloaddition) and carbene complexes (e.g. C-H insertion, 1,2-H or 1,2-alkyl shift), can be used as intermediates for the efficient preparation of synthetically useful, polycyclic compounds.<sup>[1]</sup> To expand the concept of metal-containing ylides, we have examined the generation and reaction of a newly designed metal-containing ammonium ylide,<sup>[2]</sup> which would enable concise access to a variety of polycyclic indoles with an N-fused ring. A recent report by Zhang and co-workers on a Pt-catalyzed reaction of N-(2-alkynylphenyl)lactams<sup>[3]</sup> prompted us to report our own approach, in which the main difference is the use of N-(2-alkynylphenyl)amines instead of lactams as the nucleophilic component. This transformation requires the use of  $[W(CO)_6]$  or  $[ReBr(CO)_5]$  as the alkynophilic reagent.

The underlying strategy for the catalytic process described herein is depicted in Scheme 1: Upon the treatment of *o*-alkynylphenyl pyrrolidine or piperidine derivatives **1** with an appropriate electrophilic transition-metal complex, metalcontaining ammonium ylides **A** would be generated by the nucleophilic attack of the nitrogen atom onto the electrophilically activated alkyne moiety. Ylides **A** would then undergo ring expansion through a [1,2] Stevens-type rearrangement<sup>[4]</sup> to give carbene complexes **B**, which would undergo subsequent 1,2-alkyl migration to form N-fused tricyclic indole derivatives **2** with regeneration of the catalyst.

After extensive screening of transition-metal catalysts and reaction conditions with N-(2-(prop-1-ynyl)phenyl)pyrrolidine (**1a**) as the substrate, we found that the photoirradiation of a solution of **1a** and [W(CO)<sub>6</sub>] (10 mol%) in toluene in the presence of 5-Å molecular sieves at room temperature gave the desired tricyclic indole derivative **2a** in 65% yield



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**Scheme 1.** Strategy for the generation of a metal-containing ammonium ylide and its tandem [1,2] Stevens-type rearrangement/1,2-alkyl migration.

(Table 1, entry 1). Photoirradiation was crucial for the efficient generation of the unsaturated tungsten species; the reaction under thermal conditions (toluene,  $80 \,^{\circ}$ C) resulted in lower conversion even with 300 mol % of [W(CO)<sub>6</sub>] (Table 1, entry 2).

**Table 1:** Examination of various electrophilic transition-metal complexes as catalysts (**1** a: *n* = 1, R = Me).

Entry	Catalyst (mol%)	Conditions <sup>[a]</sup>	Yield of <b>2a</b> [%] <sup>[b]</sup>
1	[W(CO) <sub>6</sub> ] (10)	А	65
2	[W(CO) <sub>6</sub> ] (300)	В	14
3	[ReBr(CO) <sub>5</sub> ] (10)	А	9
4	PtCl <sub>2</sub> (10)	A or B	n.d.
5	$[AuPPh_3](SbF_6)$ (10)	A or B	n.d.
6	AuBr <sub>3</sub> (10)	В	n.d.
7	$[{\rm IrCl(cod)}_2]$ (5)	В	n.d.
8	PtCl <sub>4</sub> (10)	B or C	n.d.

[a] A: 5-Å M.S.,  $h\nu$ , toluene, room temperature, 10 h; B: 5-Å M.S., toluene, 80 °C, 10 h; C: ClCH<sub>2</sub>CH<sub>2</sub>Cl, reflux under O<sub>2</sub>, 10 h. [b] n.d. = not detected. cod = 1,5-cyclooctadiene, M.S. = molecular sieves.

Careful analysis of the product by 2D NMR spectroscopy confirmed the formation of a tricyclic indole system with an N-fused six-membered ring and a methyl substituent at the 3 position of the indole nucleus. This result supported the validity of our original strategy.<sup>[5,6]</sup> Other metal catalysts, such as PtCl<sub>2</sub>, PtCl<sub>4</sub>, [AuPPh<sub>3</sub>]SbF<sub>6</sub>, AuBr<sub>3</sub>, and [{IrCl(cod)}<sub>2</sub>], were found to be inactive for this transformation under thermal or photoirradiation conditions, probably as a result of deactivation of the catalyst through strong coordination of the amine



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nitrogen atom to the metal center.<sup>[7]</sup> In contrast,  $[W(CO)_6]$ , which has a lower affinity for harder bases, such as an amine nitrogen atom, activates the alkyne preferentially and effectively.  $[ReBr(CO)_5]$  also showed some activity under photo-irradiation conditions to give a small amount of the product **2a** (Table 1, entry 3).

The facile introduction of substituents of various types at the 3-position of the indole nucleus by incorporating these substituents into the substrate at the alkyne terminus is a valuable feature of this reaction. Tricyclic indole derivatives functionalized with silyl or benzyl ethers were prepared successfully in good yield (Table 2, entries 2 and 3). Furthermore, the reaction of **1e** (n = 1,  $\mathbf{R} = \mathbf{Ph}$ ), in which an aromatic sp<sup>2</sup>-hybridized carbon atom is bonded to the alkyne terminus, also proceeded smoothly to give the product **2e** of 1,2-phenyl migration in good yield. As the substrates can be prepared readily by coupling reactions, and as the reaction proceeds catalytically under mild reaction conditions, the present protocol provides a useful method for the construction of variously functionalized N-fused tricyclic indole skeletons.<sup>[8,9,10]</sup>

Table 2: Variation of the alkyne substituent (n = 1).<sup>[a]</sup>

Entry	R	Yield [%]
1	<i>n</i> Pr ( <b>2b</b> )	62
2	CH <sub>2</sub> CH <sub>2</sub> OTIPS ( <b>2</b> c)	74
3	$CH_2CH_2OBn$ (2d)	65
4 <sup>[b]</sup>	Ph ( <b>2e</b> )	65

[a] Reaction conditions:  $[W(CO)_6]$  (10 mol%), 5-Å M.S., toluene,  $h\nu$ , room temperature, 10 h. [b] 30 mol%  $[W(CO)_6]$ . Bn = benzyl; TIPS = triisopropylsilyl.

Table 3 shows the generality of this tandem [1,2] Stevenstype rearrangement/1,2-alkyl migration reaction of pyrrolidine derivatives. Other 5-membered azacycles, such as indoline and isoindoline derivatives, are suitable for this transformation; thus, substrates **3** and **5** were converted into the tetracyclic indole derivatives **4** and **6**, respectively, in good yield (Table 3, entries 1 and 2). The ring expansion of the tungsten-containing ammonium ylide generated from **3** proceeded regioselectively at the sp<sup>3</sup> carbon atom adjacent to the N atom. The presence of an electron-donating or electron-withdrawing group on the benzene ring did not affect the reaction significantly (Table 3, entries 3–5).

In contrast to the reaction of pyrrolidine derivatives, the reaction of the piperidine derivative **13** did not proceed smoothly even with an increased loading of  $[W(CO)_6]$ .<sup>[11]</sup> Reexamination of the metal catalyst revealed that  $[ReBr(CO)_5]$  was highly effective for the reaction of **13**, in remarkable contrast to that of the pyrrolidine derivative **1a**, and afforded the desired ring-expansion product **14** in good yield (Table 4, entry 1).<sup>[12]</sup> The  $[ReBr(CO)_5]$ -catalyzed reaction of the silyl ether derivative **15** was also successful. Furthermore, the Re catalyst system was effective for a variety of 6-membered azacycles, such as the 4-phenylpiperidine and morpholine derivatives **17** and **19**, which were converted into the corresponding tricyclic indoles fused with a 7-membered ring in good yield (Table 4, entries 3 and 4). The

**Table 3:** Generality of the reaction (n = 1).<sup>[a]</sup>



[a] Reaction conditions:  $[W(CO)_6]$  (10 mol%), 5-Å M.S., toluene,  $h\nu$ , room temperature. [b] 1 equivalent  $[W(CO)_6]$ .

**Table 4:** Generality of the reaction (n=2).<sup>[a]</sup>



[a] Reaction conditions: [ReBr(CO)<sub>5</sub>] (10 mol%), 5-Å M.S., toluene,  $h\nu$ , room temperature.

high regioselectivity of the [1,2] Stevens-type rearrangement was again observed in the reaction of the tetrahydroisoquinoline derivative **21** (Table 4, entry 5).

## Communications

Finally, the intermediacy of carbene complex **B** was confirmed by the following trapping experiment: The treatment of **1c** with a stoichiometric amount of  $[W(CO)_6]$  in the presence of triethylsilane (10 equiv) under photoirradiation gave the Et<sub>3</sub>Si-substituted tricyclic indoline derivative **24** in 7% yield along with the usual tricyclic indole product in 71% yield (Scheme 2). The formation of **24** indicates unambiguously the existence of the carbene complex **23** as an intermediate. Such species are the key intermediates of the [1,2] Stevens-type rearrangement of metal-containing ammonium ylides, and the intermediacy of **23** strongly supports the proposed mechanism of this reaction.<sup>[13,14]</sup>



Scheme 2. Trapping of the intermediate carbene complex.

In conclusion, we have developed an efficient method for the preparation of N-fused tricyclic indole derivatives through a tandem [1,2] Stevens-type rearrangement/1,2-alkyl migration reaction of newly designed metal-containing ammonium ylides. By using  $[W(CO)_6]$  or  $[ReBr(CO)_5]$  as the catalyst, the alkyne moiety was activated efficiently even in the presence of the amine functionality.

## **Experimental Section**

General procedure: An *N*-(*o*-alkynylphenyl)amine (0.150 mmol) was added as a solution in toluene (1.0 mL) to a suspension of tungsten hexacarbonyl or bromopentacarbonylrhenium (0.015 mmol) and 5-Å molecular sieves in toluene (1.0 mL) at room temperature. The resulting mixture was irradiated with a high-pressure Hg lamp at room temperature until the complete disappearance of the starting material was confirmed by TLC. The mixture was then filtered through a short pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC to afford the corresponding polycyclic indole derivative.

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- [10] Classical methods for the generation of ammonium ylides require the use of a strong base or a fluoride source to form the anion; see Ref. [2e,f].
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