

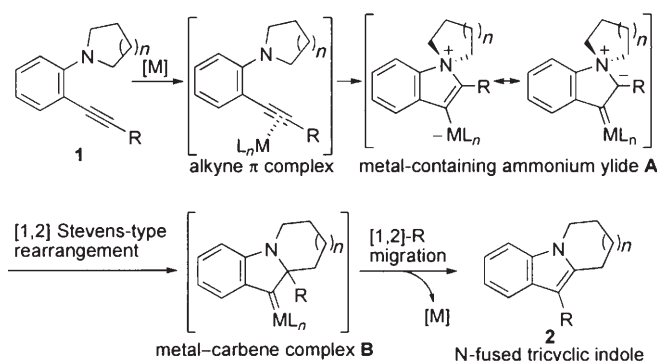
Synthesis of N-Fused Tricyclic Indoles by a Tandem [1,2] Stevens-Type Rearrangement/1,2-Alkyl Migration of Metal-Containing Ammonium Ylides**

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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.^[1] To expand the concept of metal-containing ylides, we have examined the generation and reaction of a newly designed metal-containing ammonium ylide,^[2] 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^[3] 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 $[\text{W}(\text{CO})_6]$ or $[\text{ReBr}(\text{CO})_5]$ 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, metal-containing 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^[4] 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 $[\text{W}(\text{CO})_6]$ (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



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 °C) resulted in lower conversion even with 300 mol % of $[\text{W}(\text{CO})_6]$ (Table 1, entry 2).

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

Entry	Catalyst (mol %)	Conditions ^[a]	Yield of 2a [%] ^[b]
1	$[\text{W}(\text{CO})_6]$ (10)	A	65
2	$[\text{W}(\text{CO})_6]$ (300)	B	14
3	$[\text{ReBr}(\text{CO})_5]$ (10)	A	9
4	PtCl_2 (10)	A or B	n.d.
5	$[\text{AuPPh}_3](\text{SbF}_6)$ (10)	A or B	n.d.
6	AuBr_3 (10)	B	n.d.
7	$[\{\text{IrCl}(\text{cod})\}_2]$ (5)	B	n.d.
8	PtCl_4 (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: $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux under O_2 , 10 h. [b] n.d. = not detected. cod = 1,5-cyclooctadiene, M.S. = molecular sieves.

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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.^[5,6] Other metal catalysts, such as PtCl_2 , PtCl_4 , $[\text{AuPPh}_3]\text{SbF}_6$, AuBr_3 , and $[\{\text{IrCl}(\text{cod})\}_2]$, 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

nitrogen atom to the metal center.^[7] In contrast, $[\text{W}(\text{CO})_6]$, which has a lower affinity for harder bases, such as an amine nitrogen atom, activates the alkyne preferentially and effectively. $[\text{ReBr}(\text{CO})_5]$ also showed some activity under photoirradiation 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** ($n = 1$, $\text{R} = \text{Ph}$), in which an aromatic sp^2 -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.^[8,9,10]

Table 2: Variation of the alkyne substituent ($n = 1$).^[a]

Entry	R	Yield [%]
1	<i>n</i> Pr (2b)	62
2	$\text{CH}_2\text{CH}_2\text{OTIPS}$ (2c)	74
3	$\text{CH}_2\text{CH}_2\text{OBn}$ (2d)	65
4 ^[b]	Ph (2e)	65

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

Table 3 shows the generality of this tandem [1,2] Stevens-type 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^3 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 $[\text{W}(\text{CO})_6]$.^[11] Reexamination of the metal catalyst revealed that $[\text{ReBr}(\text{CO})_5]$ 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).^[12] The $[\text{ReBr}(\text{CO})_5]$ -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 ($n = 1$).^[a]

Entry	Substrate	Product	<i>t</i> [h]	Yield [%]
1			10	45
2			5	80 ^[b]
3			4	70
4			4	68
5			10	52 (63 ^[b])

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

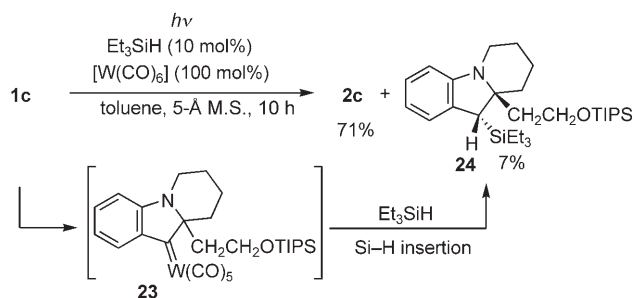
Table 4: Generality of the reaction ($n = 2$).^[a]

Entry	Substrate	Product	<i>t</i> [h]	Yield [%]
1			10	73
2			4	63
3			10	74
4			10	75
5			8	54

[a] Reaction conditions: $[\text{ReBr}(\text{CO})_5]$ (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).

Finally, the intermediacy of carbene complex **B** was confirmed by the following trapping experiment: The treatment of **1c** with a stoichiometric amount of $[\text{W}(\text{CO})_6]$ in the presence of triethylsilane (10 equiv) under photoirradiation gave the Et_3Si -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.^[13,14]



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 $[\text{W}(\text{CO})_6]$ or $[\text{ReBr}(\text{CO})_5]$ 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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