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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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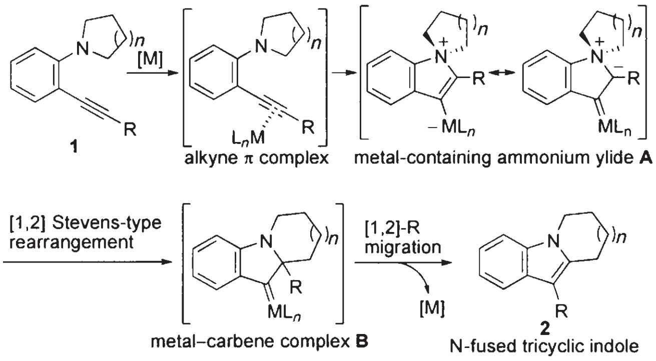
We reported previously that novel metal-containing carbonyl or azomethine ylides could be generated by the nucleophilic attack of a carbonyl oxygen atom or imino nitrogen atom onto alkynes activated by electrophilic transition-metal complexes. The resulting species, which behave as both ylides ([3+2] 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.[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 [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, 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.



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

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)$_6$] (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 (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 [W(CO)$_6$] (Table 1, entry 2).

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

Entry	Catalyst (mol%)	Conditions[a]	Yield of **2a** [%][b]
1	[W(CO)$_6$] (10)	A	65
2	[W(CO)$_6$] (300)	B	14
3	[ReBr(CO)$_5$] (10)	A	9
4	PtCl$_2$ (10)	A or B	n.d.
5	[AuPPh$_3$](SbF$_6$) (10)	A or B	n.d.
6	AuBr$_3$ (10)	B	n.d.
7	[{IrCl(cod)}$_2$] (5)	B	n.d.
8	PtCl$_4$ (10)	B or C	n.d.

[a] A: 5-Å M.S., *hν*, toluene, room temperature, 10 h; B: 5-Å M.S., toluene, 80 °C, 10 h; C: ClCH$_2$CH$_2$Cl, reflux under O$_2$, 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.[5,6] Other metal catalysts, such as PtCl$_2$, PtCl$_4$, [AuPPh$_3$]SbF$_6$, AuBr$_3$, and [{IrCl(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

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nitrogen atom to the metal center.[7] 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 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** ($n=1$, R = 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]

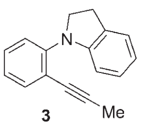
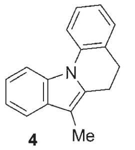
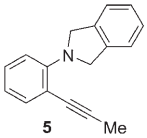
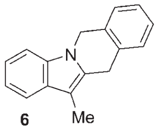
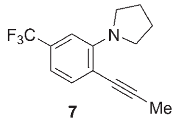
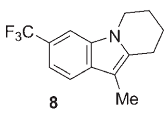
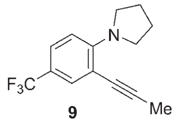
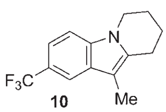
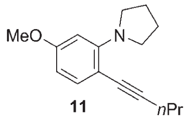
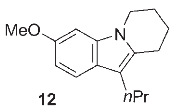
Entry	R	Yield [%]
1	*n*Pr (**2b**)	62
2	CH_2CH_2OTIPS (**2c**)	74
3	CH_2CH_2OBn (**2d**)	65
4[b]	Ph (**2e**)	65

[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] 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).

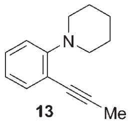
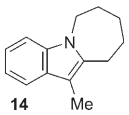
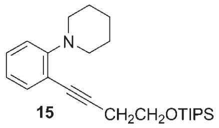
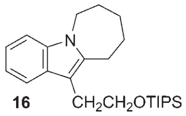
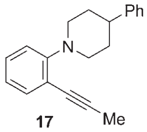
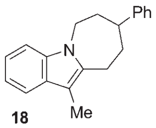
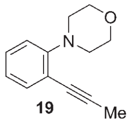
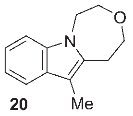
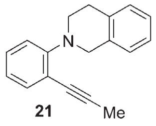
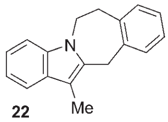
In contrast to the reaction of pyrrolidine derivatives, the reaction of the piperidine derivative **13** did not proceed smoothly even with an increased loading of $[W(CO)_6]$.[11] Reexamination of the metal catalyst revealed that $[ReBr(CO)_5]$ was highly effective for the reaction of **13**, in remarkable contrast to that of the pyrrolidine derivative **1a**, and afforded the desired ring-expansion product **14** in good yield (Table 4, entry 1).[12] 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 high regioselectivity of the [1,2] Stevens-type rearrangement was again observed in the reaction of the tetrahydroisoquinoline derivative **21** (Table 4, entry 5).

Table 3: Generality of the reaction ($n=1$).[a]

Entry	Substrate	Product	*t* [h]	Yield [%]
1	 **3**	 **4**	10	45
2	 **5**	 **6**	5	80[b]
3	 **7**	 **8**	4	70
4	 **9**	 **10**	4	68
5	 **11**	 **12**	10	52 (63[b])

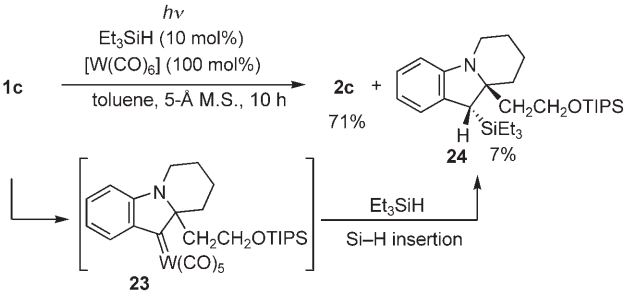
[a] Reaction conditions: $[W(CO)_6]$ (10 mol%), 5-Å M.S., toluene, $h\nu$, room temperature. [b] 1 equivalent $[W(CO)_6]$.

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

Entry	Substrate	Product	*t* [h]	Yield [%]
1	 **13**	 **14**	10	73
2	 **15**	 **16**	4	63
3	 **17**	 **18**	10	74
4	 **19**	 **20**	10	75
5	 **21**	 **22**	8	54

[a] Reaction conditions: $[ReBr(CO)_5]$ (10 mol%), 5-Å M.S., toluene, $h\nu$, room temperature.

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$_3$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.[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 [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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[1] For the synthesis of azacycles, see: a) H. Kusama, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2002**, *124*, 11592; b) J. Takaya, H. Kusama, N. Iwasawa, *Chem. Lett.* **2004**, *33*, 16; c) H. Kusama, Y. Miyashita, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 289; d) H. Kusama, Y. Suzuki, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 895; for the synthesis of oxacycles, see: e) H. Kusama, H. Funami, M. Shido, Y. Hara, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2005**, *127*, 2709; f) N. Iwasawa, M. Shido, H. Kusama, *J. Am. Chem. Soc.* **2001**, *123*, 5814; g) H. Kusama, H. Funami, N. Iwasawa, *Synthesis* **2007**, 2014; h) H. Kusama, H. Funami, J. Takaya, N. Iwasawa, *Org. Lett.* **2004**, *6*, 605; see also: i) H. Kusama, N. Iwasawa, *Chem. Lett.* **2006**, *35*, 1082.

[2] a) F. G. West, J. S. Clark in *Nitrogen, Oxygen and Sulfur Ylide Chemistry* (Ed.: J. S. Clark), Oxford University Press, Oxford, **2002**, p. 115; b) Y. Sato in *Nitrogen, Oxygen and Sulfur Ylide Chemistry* (Ed.: J. S. Clark), Oxford University Press, Oxford, **2002**, p. 134; c) M. P. Doyle, D. C. Forbes in *Nitrogen, Oxygen and Sulfur Ylide Chemistry* (Ed.: J. S. Clark), Oxford University Press, Oxford, **2002**, p. 141; d) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263; e) E. Vedejs, F. G. West, *Chem. Rev.* **1986**, *86*, 941; f) S. H. Pine, *Org. React.* **1970**, *18*, 403.

[3] G. Li, X. Huang, L. Zhang, *Angew. Chem.* **2008**, *120*, 352; *Angew. Chem. Int. Ed.* **2008**, *47*, 346.

[4] a) T. S. Stevens, E. M. Creighton, A. B. Gordon, M. MacNicol, *J. Chem. Soc.* **1928**, 3193; b) J. A. Vanecko, H. Wan, F. G. West, *Tetrahedron* **2006**, *62*, 1043, and references therein.

[5] This type of [1,2] Stevens-type rearrangement of ylide species **A** is unprecedented, except for the recent example reported by Zhang and co-workers of a 1,2-migration reaction of lactam derivatives. In the latter reaction, an acylium intermediate generated from the alkenyl metal intermediate is proposed as a key intermediate; see Ref. [3]

[6] For 1,3-migration reactions of allyl, methoxymethyl, acyl, and sulfonyl groups from alkenyl palladium or gold zwitterionic intermediates related to **A**, see: a) I. Nakamura, Y. Mizushima, U. Yamagishi, Y. Yamamoto, *Tetrahedron* **2007**, *63*, 8670; b) I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, *Angew. Chem.* **2007**, *119*, 2334; *Angew. Chem. Int. Ed.* **2007**, *46*, 2284; c) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024; d) T. Shimada, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 10546; see also: e) F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181; f) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.* **2007**, *119*, 1913; *Angew. Chem. Int. Ed.* **2007**, *46*, 1881; g) S. Cacchi, G. Fabrizi, P. Pace, *J. Org. Chem.* **1998**, *63*, 1001; for the synthesis of 3-substituted benzofurans and benzothiophenes via related intermediates, see: h) I. Nakamura, T. Sato, M. Terada, Y. Yamamoto, *Org. Lett.* **2007**, *9*, 4081; i) A. Fürstner, E. K. Heilmann, P. W. Davies, *Angew. Chem.* **2007**, *119*, 4844; *Angew. Chem. Int. Ed.* **2007**, *46*, 4760; j) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem.* **2006**, *118*, 4585; *Angew. Chem. Int. Ed.* **2006**, *45*, 4473; k) I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022; l) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863; m) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785.

[7] In entries 5 and 7 of Table 1, *N*-(4-X-butyl)-2-methylindole (X = Br or Cl), which probably resulted from a ring-opening reaction of the ylide **A** upon attack by a halide anion, was obtained in low yield (< 20 %) along with recovered starting material.

[8] A vast number of alkaloids have polycyclic indole skeletons; see: a) W. Gul, M. T. Hamann, *Life Sci.* **2005**, *78*, 442; b) G. A. Cordell, *The Alkaloids: Chemistry and Biology*, *Vol. 60*, Elsevier Science, San Diego, **2003**.

[9] These substrates can be prepared readily through a Pd-catalyzed amination and Sonogashira coupling reaction of 1-bromo-2-iodobenzene.

[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].

[11] With 1 equivalent of [W(CO)$_6$], the product **14** was obtained in only 16 % yield, and 51 % of the starting material was recovered.

[12] For examples of $[ReX(CO)_5]$-catalyzed reactions (X = Cl, Br) through the electrophilic activation of alkynes, see: a) H. Kusama, H. Yamabe, Y. Onizawa, T. Hoshino, N. Iwasawa, *Angew. Chem.* **2005**, *117*, 472; *Angew. Chem. Int. Ed.* **2005**, *44*, 468; b) L. L. Ouh, T. E. Müller, Y. K. Yan, *J. Organomet. Chem.* **2005**, *690*, 3774; c) R. Hua, X. Tian, *J. Org. Chem.* **2004**, *69*, 5782; see also: d) Y. Kuninobu, A. Kawata, K. Takai, *Org. Lett.* **2005**, *7*, 4823 and Ref. [1c].

[13] Metal carbenoids are well known to insert readily into the Si–H bond of silanes, even intermolecularly; see: a) J. A. Connor, P. D. Rose, R. M. Turner, *J. Organomet. Chem.* **1973**, *55*, 111; b) J. A. Connor, J. P. Day, R. M. Turner, *J. Chem. Soc. Dalton Trans.* **1976**, 108; see also Ref. [1e].

[14] Although the exact mechanism of the present [1,2] Stevens-type rearrangement is not yet clear, the ring expansion with cationic intermediates proposed by Zhang and co-workers[3] seems less likely in our case, as primary alkyl cations, which are not usually generated in a nonpolar solvent, such as toluene, must be involved. Furthermore, the formation of Friedel–Crafts-type products, which are side products in the reaction described by Zhang and co-workers, was not observed in our reaction.