

# Pt(II)- or Au(III)-Catalyzed [3+2] Cycloaddition of Metal-Containing Azomethine Ylides: Highly Efficient Synthesis of the Mitosene Skeleton

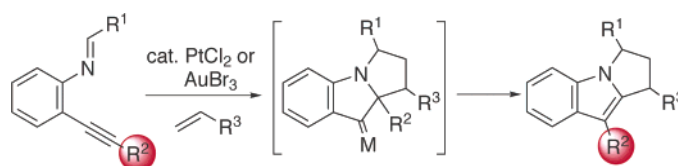
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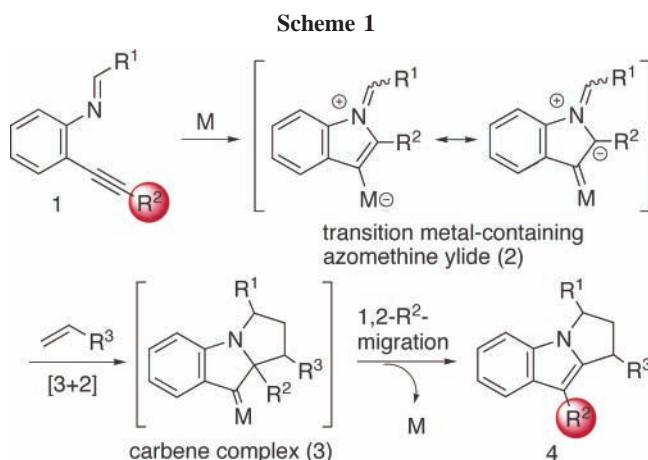
## ABSTRACT



Only 1–3 mol % of PtCl<sub>2</sub> or AuBr<sub>3</sub> was sufficient to promote generation and [3+2] cycloaddition of transition-metal-containing azomethine ylides derived from *N*-(*o*-alkynylphenyl)imines bearing an *internal* alkyne moiety. A highly efficient method for the preparation of synthetically useful tricyclic indole derivatives having a substituent at the 3-position of the indole nucleus was established by this method.

In connection with our continuing research for the development of new catalytic reactions on the basis of electrophilic activation of alkynes by group 6 metal carbonyls,<sup>1</sup> we recently reported that a novel reactive species, the tungsten-containing azomethine ylides **2** (M = W(CO)<sub>5</sub>), could be generated by treatment of *N*-(*o*-ethynylphenyl)imine derivatives **1** (R<sup>1</sup> = Ph, OR; R<sup>2</sup> = H) with a catalytic amount of tungsten hexacarbonyl under photoirradiation conditions.<sup>2</sup> [3+2] Cycloaddition reactions of thus-generated ylides **2** with electron-rich alkenes readily proceeded to give the non-heteroatom-stabilized tungsten carbene complex intermediates **3** (M = W(CO)<sub>5</sub>),<sup>2b</sup> which underwent facile 1,2-

hydrogen migration to afford the corresponding polycyclic indole derivatives **4** in good yield (Scheme 1). More interestingly, when *N*-(*o*-alkynylphenyl)imine derivatives having an *internal* alkyne moiety **1** (R<sup>1</sup> = Ph; R<sup>2</sup> = alkyl, aryl) were employed as substrate, a novel 1,2-migration<sup>2a,b,f,3</sup> of alkyl or aryl groups was observed to give tricyclic indole



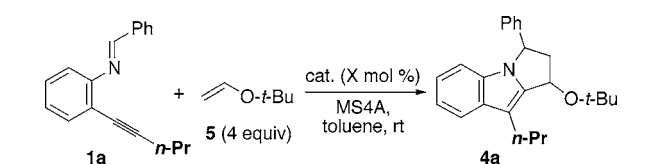
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derivatives having a substituent at the 3-position of the indole nucleus in good yield. Although this internal alkyne protocol affords a highly efficient method for the preparation of 3-substituted tricyclic indole skeletons<sup>4</sup> such as mitomycins,<sup>5,6</sup> the efficiency of the tungsten catalyst was moderate and a stoichiometric amount of W(CO)<sub>6</sub> was necessary to bring the reaction to completion. Thus, it is strongly desired to develop highly efficient catalytic reactions employable for the substrates containing an *internal* alkyne moiety. In this paper, the excellent catalytic activity of third-row transition-metal complexes such as Pt(II) and Au(III) for the generation and reaction of metal-containing azomethine ylides derived from *N*-(*o*-alkynylphenyl)imine derivatives containing an *internal* alkyne moiety is described.

Since a number of high-valent, late transition-metal complexes were found to be efficient catalysts for electrophilic activation of alkynes in the past decade,<sup>7</sup> we initially investigated the reaction of an imine derivative **1a** having an *n*-propyl group on the alkyne terminus with *tert*-butyl vinyl ether **5** in toluene by the use of such metal complexes instead of tungsten carbonyl, and the results are summarized in Table 1. Interestingly, various metal complexes such as

**Table 1.** Screening of Metal Complexes



entry	catalyst	X/mol %	time/h	yield/%	(cis:trans)
1	Mo(CO) <sub>6</sub> /hν	100	16	15	(21:79)
2	Re(CO) <sub>5</sub> Cl/hν	10	5.5	70	(64:36)
3	[IrCl(cod)] <sub>2</sub>	5	26	73	(19:81)
4	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	11	2	71	(54:46)
5 <sup>a</sup>	PtCl <sub>2</sub>	10	9.5	90	(58:42)
6	PtCl <sub>4</sub>	10	25	57	(49:51)
7	AuCl	10	29	49	(55:45)
8	AuCl <sub>3</sub>	10	1.2	82	(57:43)
9	AuBr <sub>3</sub>	10	0.5	70	(53:47)
10 <sup>a</sup>	W(CO) <sub>6</sub> /hν	100	13	76	(22:78)
11 <sup>a</sup>		10	22	33	(17:83)

<sup>a</sup> 10 equiv of vinyl ether was used.

Re(I),<sup>8</sup> Ir(I),<sup>9</sup> Pd(II),<sup>10</sup> Pt(II),<sup>7,11,12</sup> and Au(III)<sup>13,14</sup> are found to catalyze this reaction efficiently, giving the same product **4a** as that obtained by the tungsten-promoted reaction<sup>2a</sup> in good to excellent yield. These metal complexes exhibit much

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higher catalytic activity than the tungsten carbonyl complex, and in particular, PtCl<sub>2</sub> and AuBr<sub>3</sub> were found to be the best catalysts in terms of product yield and reaction time, respectively. The same mechanism as that for W(CO)<sub>6</sub>, as depicted in Scheme 1, is proposed for these reactions. Electrophilic activation of the *internal* alkyne moiety by these metals induces the nucleophilic, 5-endo mode of cyclization of the imino nitrogen onto the alkyne moiety to generate the corresponding metal-containing azomethine ylides **2**. Successive [3+2] cycloaddition and 1,2-alkyl migration give tricyclic indole with regeneration of the catalyst. On the contrary, molybdenum carbonyl gave the desired product **4a** in low yield and, except for Pd(II), the reactions with some other second-row transition-metal complexes such as RuCl<sub>3</sub>, Ru<sub>3</sub>(CO)<sub>12</sub>/hν, and RhCl<sub>3</sub> were rather sluggish. In addition, catalytic activities of Pt(IV) chloride<sup>15</sup> and Au(I)<sup>7,13,16</sup> chloride were lower than those of Pt(II) and Au(III), respectively.

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These results indicate that soft-metal complexes, such as third-row transition-metal complexes, with moderate Lewis acidity are the catalysts of choice for the present reaction.

Further optimization of the reaction conditions for the Pt(II)- and Au(III)-catalyzed reactions revealed that both catalysts have equally excellent catalytic activity. For example, the reaction of **1a** with *tert*-butyl vinyl ether was completed within 2.5 h at room temperature by using only 3 mol % of AuBr<sub>3</sub>, giving the desired product **4a** in 80% yield (Table 2, entry 1). Even when the amount of the catalyst

**Table 2.** Generality of the [3+2] Cycloaddition Reaction Catalyzed by PtCl<sub>2</sub> or AuBr<sub>3</sub>

entry	R <sup>1</sup>	R <sup>2</sup>	1	5 (4 equiv)	cat. (X mol %)	MS5A, toluene, rt	4	yield/% <sup>a</sup>
1	Ph	<i>n</i> -Pr	<b>1a</b>	AuBr <sub>3</sub>	3	2.5	<b>4a</b>	80
2 <sup>b</sup>		<i>n</i> -Pr	<b>1a</b>		1	42	<b>4a</b>	81
3		Me	<b>1b</b>		3	22	<b>4b</b>	81
4		<i>c</i> -Hex	<b>1c</b>		3	2	<b>4c</b>	89
5		Ph	<b>1d</b>		3	0.5	<b>4d</b>	62
6 <sup>b,c</sup>	<i>O</i> - <i>i</i> -Pr	<i>n</i> -Pr	<b>1e</b>		10	1	<b>4e</b>	60
7	Ph	<i>n</i> -Pr	<b>1a</b>	PtCl <sub>2</sub>	3	72	<b>4a</b>	81
8 <sup>d</sup>		<i>n</i> -Pr	<b>1a</b>		3	6	<b>4a</b>	89
9 <sup>d,e</sup>		<i>n</i> -Pr	<b>1a</b>		1	16.5	<b>4a</b>	74
10 <sup>d</sup>		Me	<b>1b</b>		3	3.5	<b>4b</b>	88
11 <sup>c,d</sup>		<i>c</i> -Hex	<b>1c</b>		3	35	<b>4c</b>	84
12 <sup>d</sup>		Ph	<b>1d</b>		3	7	<b>4d</b>	84
13 <sup>c,f</sup>	<i>O</i> - <i>i</i> -Pr	<i>n</i> -Pr	<b>1e</b>		3	2	<b>4e</b>	95

<sup>a</sup> The diastereomer ratio of the product **4** is described in the Supporting Information. <sup>b</sup> Concentration of **1** was 0.03 M. <sup>c</sup> 10 equiv of vinyl ether was used. <sup>d</sup> The reactions were carried out at 50 °C. <sup>e</sup> Concentration of **1** was 0.3 M. <sup>f</sup> The reaction was carried out at 50 °C in the presence of MS5A.

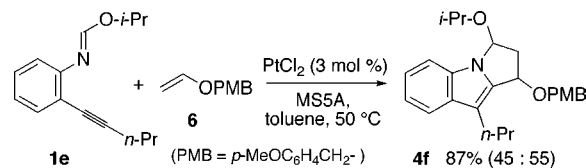
was further reduced to 1 mol %, the reaction still proceeded at room temperature without decreasing the yield of **4a**, although much more time (42 h) was required to complete the reaction (entry 2). In the case of PtCl<sub>2</sub> (3 mol %), the reaction proceeded very slowly at room temperature and a small amount of the starting material **1a** was recovered even after 72 h (entry 7). However, the starting material was consumed by carrying out the reaction at 50 °C with 3 or 1

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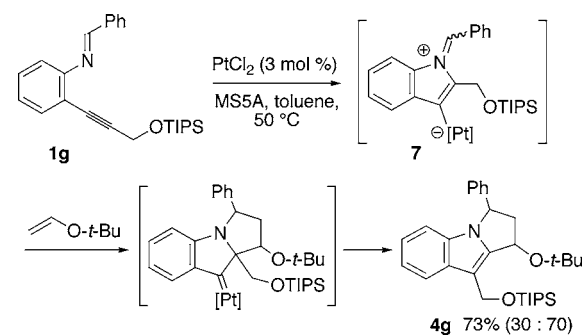
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mol % of PtCl<sub>2</sub>, and the corresponding product **4a** was obtained in 89 or 74% yield, respectively (entries 8 and 9). Both Au(III) and Pt(II) catalysts showed a wide generality of substrates, as summarized in Table 2. The reactions of methyl-substituted derivative **1b** (entries 3 and 10) and bulky cyclohexyl derivative **1c** (entries 4 and 11) proceeded smoothly with either catalyst to give the desired tricyclic indoles possessing the corresponding alkyl group at the 3-position of the indole nucleus in high yield. The phenyl substituent was also employable as a migrating group (entries 5 and 12). Furthermore, not only aldimine derivatives but also an imidate **1e** could be a precursor of the metal-containing azomethine ylide (entries 6 and 13). In this case, the Pt(II)-catalyzed reaction (3 mol %) gave a much superior result (95% yield) as compared with the Au(III)-catalyzed one (10 mol % of AuBr<sub>3</sub>, 60% yield). The obtained indole **4e** has a synthetically useful *N,O*-acetal moiety, and further functionalization of the product would be possible.

The reaction of **1e** with *para*-methoxybenzyl vinyl ether **6** also proceeded without any problems by the catalytic use of PtCl<sub>2</sub> to give the desired tricyclic indole **4f**, having a benzyloxy group on the pyrrolidine ring, in high yield.



As already mentioned, the present results strongly suggested that platinum(II) and gold(III) carbene complexes, plausible reaction intermediates, readily underwent 1,2-migration of an adjacent substituent to the carbene carbon, giving the corresponding tricyclic indoles. Because primary and secondary alkyl groups as well as the phenyl group appeared to be applicable as a migrating group, we further investigated the 1,2-migration of a functionalized substituent to expand the scope of this reaction, and a siloxymethyl group was chosen considering the application to the synthesis of the mitosene family.<sup>5,6</sup> Gratifyingly, the desired [3+2] cycloaddition of platinum-containing azomethine ylide **7** and the 1,2-migration of the siloxymethyl group occurred smoothly to give the corresponding tricyclic indole **4g** in good yield. This product contains a hydroxymethyl equivalent, a commonly observed functionality in mitosenes, at the desired position of the indole nucleus and would be a highly useful synthetic precursor for mitomycins and their analogues.<sup>5,6</sup>



In conclusion, we have successfully established the generality and efficiency of the reaction of transition-metal-containing azomethine ylides. Third-row transition-metal complexes, especially PtCl<sub>2</sub> and AuBr<sub>3</sub>, turned out to be highly efficient catalysts for the reaction of *internal* alkyne substrates.<sup>17</sup> The present results demonstrate novel aspects of transition-metal-containing dipoles and their high utility as a synthetic method for the construction of various synthetically valuable indole derivatives.

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(17) The reactions of a *terminal* alkyne substrate with a catalytic amount of PtCl<sub>2</sub> or AuBr<sub>3</sub> were rather sluggish, and the corresponding tungsten-catalyzed reaction gave the desired tricyclic indole in high yield as previously reported.<sup>2a</sup>

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**Supporting Information Available:** Preparative methods and spectral and analytical data of compounds **1** and **4** and X-ray data for *trans-4c* (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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