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A Bimetallic Catalyst and Dual Role Catalyst: Synthesis of *N*-(Alkoxycarbonyl)indoles from 2-(Alkynyl)phenylisocyanates

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3-Allyl-*N*-(alkoxycarbonyl)indoles are synthesized via the reaction of 2-(alkynyl)phenylisocyanates and allyl carbonates in the presence of $Pd(PPh_3)_4$ (1 mol %) and CuCl (4 mol %) bimetallic catalyst. It is most probable that Pd^0 acts as a catalyst for the formation of a π-allylpalladium alkoxide intermediate and Cu^I behaves as a Lewis acid to activate the isocyanate, and the cyclization step proceeds with a cooperative catalytic activity of Pd and Cu. On the other hand, *N*-(alkoxycarbonyl)-indoles are produced via the reaction of 2-(alkynyl)phenylisocyanates and alcohols under a catalytic amount of Na_2PdCl_4 (5 mol %) or $PtCl_2$ (5 mol %). Pd^{II} or Pt^{II} catalyst exhibits dual roles; it acts as a Lewis acid to accelerate the addition of alcohols to isocyanates and as a typical transition-metal catalyst to activate the alkyne for the subsequent cyclization.

Introduction

Indoles are one of the most widely distributed heterocyclic compounds in nature.[1] The indole ring appears in tryptophan, an essential amino acid, and metabolites of tryptophan are important in the biological chemistry of both plants and animals. In plants, the structural variety of indole alkaloids including indole-3-acetic acid and its secondary metabolites are known as a plant growth hormone. In animals, serotonin (5-hydroxytryptamine) is known as a crucial neurotransmitter in the central nervous system.[2] The potent physiological properties of these indole derivatives led to vast research of their use as medicines in the field of pharmaceutical chemistry. Among the successful examples as drugs are indomethacin,[3] one of the first nonsteroidal anti-inflammatory agents, sumatriptan, which is used in the treatment of migraine headaches, and pindolol,[4] one of the β-adrenergic blockers. Several naturally occurring indoles also have clinical importance. Vincristine,[5] a dimeric indole alkaloid, and closely related compounds were the first of the anti-mitotic class of chemotherapeutic agents for cancer. The mitomycins[6] and derivatives of ellipticine[7] are other examples of compounds having antitumor activity. That is why intensive investigations on the indoles for both the reactivity and the development of the synthetic way have been done. There is still sustained interest for the development of new strategies for the construction of indole skeletons.

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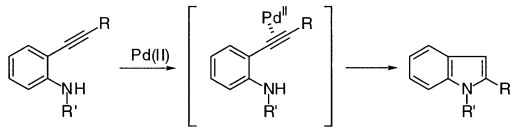
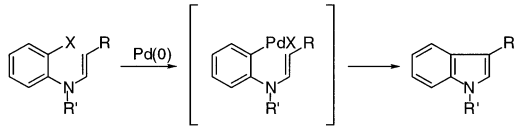
Various methodologies for the preparation of indoles have developed.[1] For example, the Fischer synthesis,[8] the Reissert synthesis,[9] and the Madelung synthesis[10] are known as classical methods. They are often utilized for the preparations of a variety of indoles in many cases; however, there are disadvantages for each procedure. In the Fischer protocol, the reaction is usually conducted under acidic conditions with high temperatures. In the Reissert and Madelung protocols, the reactions generally need more than 1 equiv of strong base. Because of their reaction conditions, these methodologies are highly limited in terms of the compatibility with a wide variety of functional groups.[11] Recent advances of transition-metal chemistry in organic synthesis have provided new catalytic methodologies for the synthesis of indoles.[12] Among the transition metals, palladium is the most well studied and employed metal for the construction of indole skeletons. The representative procedures in the past are categorized as follows: (1) the intramolecular cyclization of *o*-alkynylanilines through the formation of Pd^{II}−alkyne complexes (eq 1),[13−16] (2) the cyclization via the intramolecular Heck reaction of *N*-allylanilines or *N*-arylenamines (eq 2),[17,18] and (3) the cyclization via the intermolecular Heck-type reaction between *o*-haloanilines and alkynes (eq 3).[19] These methodologies usually have high

(1) Pd(II)-alkyne complex



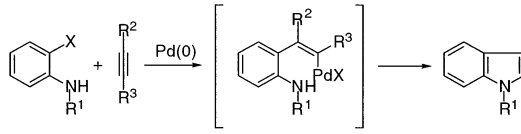
(1)

(2) Intramolecular Heck reaction



(2)

(3) Heck-type reaction and cyclization



(3)

compatibilities with a wide variety of functional groups and meet the requirements for green chemistry to a certain extent because only a catalytic amount of palladium is needed to complete the reaction. Recently, we found a new palladium-catalyzed indole synthesis from 2-alkynyl-*N*-arylideneanilines in which the hydropalladation of the alkyne followed by the formal nucleophilic attack of vinylpalladium species to imine becomes a driving force of the cyclization (eq 4).[20] More recently, we have discovered an efficient method for the construction of indole skeletons from isocyanides under a palladium catalyst (eq 5).[21−25] The reaction proceeds through a π-allylpalladium mimic of the Curtius rearrangement to

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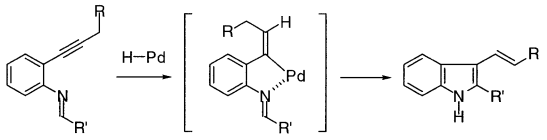
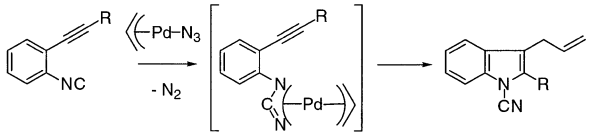
form a heteroatom-containing bis-π-allylpalladium intermediate.

(4) Hydropalladation and cyclization



(4)

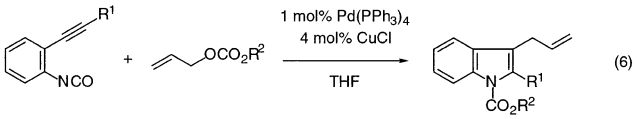
(5) Palladium mimic of the Curtius rearrangement and cyclization



(5)

Now, we report new and efficient methods for the synthesis of *N*-(alkoxycarbonyl)indoles starting from 2-(alkynyl)phenylisocyanates (eqs 6 and 7). To accomplish

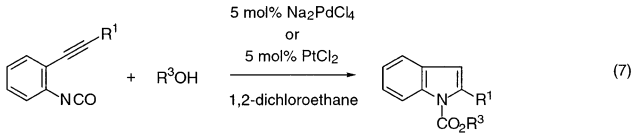
(6) 3-Allyl-*N*-(alkoxycarbonyl)indole synthesis under a bimetallic catalyst



(6)

1 2 3

(7) *N*-(Alkoxycarbonyl)indole synthesis under a dual role catalyst



(7)

1 5 6

the new transformations shown in eqs 6 and 7, two different types of catalyst systems were developed: (i) *bimetallic catalyst* and (ii) *dual role catalyst*. The bimetallic catalyst Pd^0–Cu^I is effective for the synthesis of the 3-allyl-*N*-(alkoxycarbonyl)indoles **3** from the 2-(alkynyl)phenylisocyanates **1** and allyl carbonates **2**, in which the synergistic effect of the two different transition metals makes the whole catalytic cycle operative (Scheme 1, vide post).[26] On the other hand, the dual role catalyst, Pd^{II} or Pt^{II}, is effective for the synthesis of the *N*-(alkoxycarbonyl)indoles **6** from the 2-(alkynyl)phenylisocyanates **1** and alcohols **5**, in which Pd^{II} or Pt^{II} exhibits simultaneously both a Lewis acidic and a typical transition metallic property to make the transformation feasible (Scheme 2, vide post).

Results and Discussion

A Pd^0–Cu^I Bimetallic Catalyst for the Synthesis of 3-Allyl-*N*-(alkoxycarbonyl)indoles from 2-(Alkynyl)phenylisocyanates and Allyl Carbonates.[26]

In the research field of transition-metal-catalyzed organic synthesis, one of the modern trends is to use a bimetallic catalyst system in order to explore not only more efficient but also entirely new transformations. Representative examples of such bimetallic catalysis in palladium-catalyzed reactions[27] are shown in Figure 1: (1) cat. Pd^0–cat. Cu^I in the Sonogashira coupling reaction, in which a catalytic amount of Cu^I activates terminal acetylenes to form copper–acetylide species;[28] (2) cat. Pd^0–cat. Cu^I in the Stille coupling reaction, in which organostannanes are transmetalated into organocoppers to effect acceleration of the coupling;[29] (3) cat. Pd^0–excess Ag^I in the Heck reaction, in which Ag salts abstract a halide ion of PdLn complex to produce a reactive cationic Pd intermediate;[30] (4) cat. Pd^0–cat. Rh^I in the asymmetric Tsuji–Trost-type reaction, in which Rh activates pronucleophiles by coordinating to a cyano group.[31] Accordingly, the above examples (1) and (2) are categorized into the Pd^0–M system, while the examples (3) and (4) belong to the Pd^0–LA (Lewis acid) family.

We first investigated several catalytic systems for the reaction of **1a** with **2a** (eq 8). The results are summarized in Table 1. After a number of trials to search for an effective bimetallic catalyst system, we found that the combination of $Pd(PPh_3)_4$ and CuCl exhibited a high catalytic activity for the cyclization to form the desired allylindole **3a**[32] (Table 1, entry 1). The other copper additives, such as CuBr, CuI, CuOTf, and CuOAc, were less effective (Table 1, entries 2–5). $CuCl_2$ catalyst inhibited the formation of both **3a** and **4a** (Table 1, entry 6). Among metals other than copper, $ZnCl_2$ was usable as a partner for the bimetallic catalyst, Pd^0–M (Table 1, entries 7–9). The other additives such as LiCl, *n*-Bu_4NCl, and K_2CO_3 did not give the desired allylindole **3a** (Table 1, entries 10–12). Without the addition of CuCl, the reaction gave only the *N*-allylaniline derivative **4a** as the sole product and the allylindole **3a** was not obtained at all (Table 1, entry 13). The molar ratio of $Pd(PPh_3)_4$ to CuCl was crucial to realize the best catalytic activity for the formation of allylindoles; the ratio of Pd^0 to CuCl should be 1:4 (Table 1, entry 14). Further, the reaction proceeded efficiently even under 1 mol % $Pd(PPh_3)_4$ and 4 mol % CuCl as catalysts (Table 1, entry 15). As for the palladium catalyst, $Pd(PPh_3)_4$ showed the best catalytic activity when combined with CuCl. Other palladium catalysts such as $Pd(OAc)_2/PPh_3$, $Pd_2(dba)_3$·

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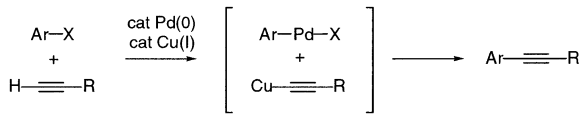
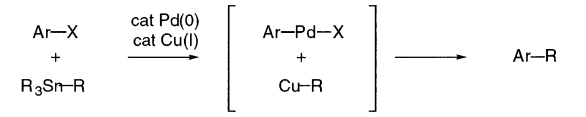
Pd(0)-M: A starting substrate is converted into a more reactive organometallic reagent

(1) Sonogashira coupling reaction

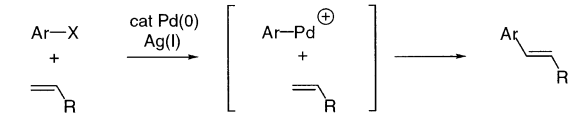


(2) Stille coupling reaction



Pd(0)-LA: Lewis acid activates a starting material or intermediate

(3) Heck reaction



(4) Asymmetric Tsuji-Trost reaction

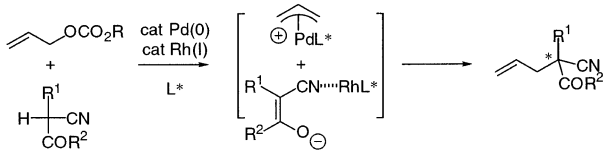
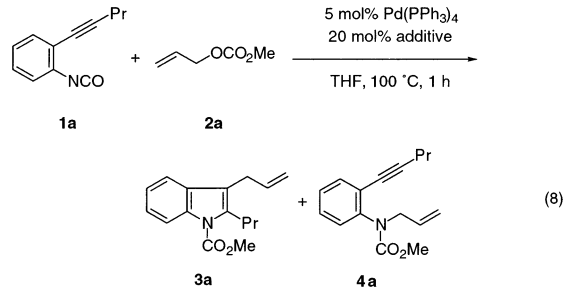


FIGURE 1. Bimetallic catalyst system in the palladium-catalyzed reactions.

$CHCl_3$/dppe, and $Pd_2(dba)_3$·$CHCl_3$/(2-furyl)$_3$P were less effective. THF was solvent of choice; other solvents such as toluene, CH_3CN, and DMF gave the desired allylindole **3a** in lower yields.



(8)

A wide applicability of the Pd^0−Cu^I bimetallic catalyst system in the synthesis of the 3-allyl-*N*-(alkoxycarbonyl)-indoles **3** is shown in Table 2. Longer reaction times were required when the substituents R^1 at the alkyne terminal of **1** became sterically bulky (Table 2, entries 1 and 2). When R^1 was a *tert*-butyl group, the corresponding allylindole **3c** was not obtained at all and the allylaniline derivative **4c** was formed as the sole product (Table 2, entry 3). The aryl-substituted isocyanates **1d**−**f** gave the corresponding allylindoles **3d**−**f** in good yields (Table 2, entries 4−6). The above results indicate that the electronic nature of the *para* substitutents on aromatic ring does not exert a significant influence on the yield of indole products. As for the allyl carbonates, the reaction proceeded irrespective of the bulkiness of the substituents R^2 (Table 2, entries 1, 7, and 8). Even allyl phenyl carbonate **2d** and allyl benzyl carbonate **2e** gave the corresponding allylindoles **3i** and **3j** in good yields (Table 2, entries 9 and 10). The reaction of **1a** with cinnamyl methyl carbonate **2f** took place to give *N*-(methoxycarbonyl)-3-(3-phenyl-2-propenyl)-2-propylindole **3k** in 65% yield.

TABLE 1. Investigation for Effective Bimetallic Catalysts, Pd^0−M[a]

		yield,[b] %	
entry	additive, M	**3a**	**4a**
1	CuCl	78 (73)	0
2	CuBr	70	trace
3	CuI	27	20
4	$[CuOTf]_2$·benzene[c]	37	0
5	CuOAc	26	37
6[d]	$CuCl_2$	0	0
7	$ZnCl_2$	62	0
8	$PdCl_2$	0	74
9	AgCl	0	70
10	LiCl[e]	0	0
11	*n*-Bu_4NCl	0	80
12	K_2CO_3	0	87
13	none	0	89 (83)
14	CuCl[f]	0	78 (82)
15	CuCl[g]	78 (81)	0

[a] Unless otherwise noted, the reaction of **1a** with **2a** (2 equiv) was carried out in the presence of $Pd(PPh_3)_4$ (5 mol %) and an additional catalyst M (20 mol %) in THF (0.5 M) at 100 °C for 1 h under Ar atmosphere. [b] Yields were determined by ^1H NMR with *p*-xylene as an internal standard. Isolated yields are shown in parentheses. [c] $[CuOTf]_2$·benzene (10 mol %) was used. [d] The starting material **1a** was recovered in 29% NMR yield. [e] The starting material **1a** was recovered in 69% NMR yield. [f] CuCl (5 mol %) was used. [g] $Pd(PPh_3)_4$ (1 mol %) and CuCl (4 mol %) were used.

A proposed mechanism for the formation of the 3-allyl-*N*-(alkoxycarbonyl)indoles **3** under Pd^0−Cu^I bimetallic catalyst is shown in Scheme 1. Initially, Pd^0 reacts with the allyl carbonates **2** to give the π-allylpalladium alkoxide complex **A** with extrusion of CO_2. The π-allylpalladium alkoxide complex **A** reacts selectively with the isocyanate group activated by the coordination of CuCl,[33] as shown in the complex **B**, to form the π-allylpalladium intermediate **C**.[34] The palladium intermediate **C**, in

(33) The activations of alkyl isocyanates and carbodiimides by CuCl were reported, see: (a) Schmidt, V. E.; Moosmüller, F. *Liebigs Ann. Chem.* **1955**, *597*, 235−240. (b) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245−3247. (c) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131−132.

(34) For the palladium-catalyzed reaction of isocyanates, see: (a) Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157−1158. (b) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792−3794. (c) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933−7935. (d) Trost, B. M.; Hurnaus, R. *Tetrahedron Lett.* **1989**, *30*, 3893−3896. (e) Xu, D.; Sharpless, B. *Tetrahedron Lett.* **1993**, *34*, 951−952. (f) Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 1173−1177. (g) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709−3715. (h) Larksarp, C.; Alper, H. *J. Org. Chem.* **1999**, *64*, 4152−4158.

SCHEME 1. Proposed Mechanism for the Formation of 3-Allyl-*N*-(alkoxycarbonyl)indoles under a Bimetallic Catalyst

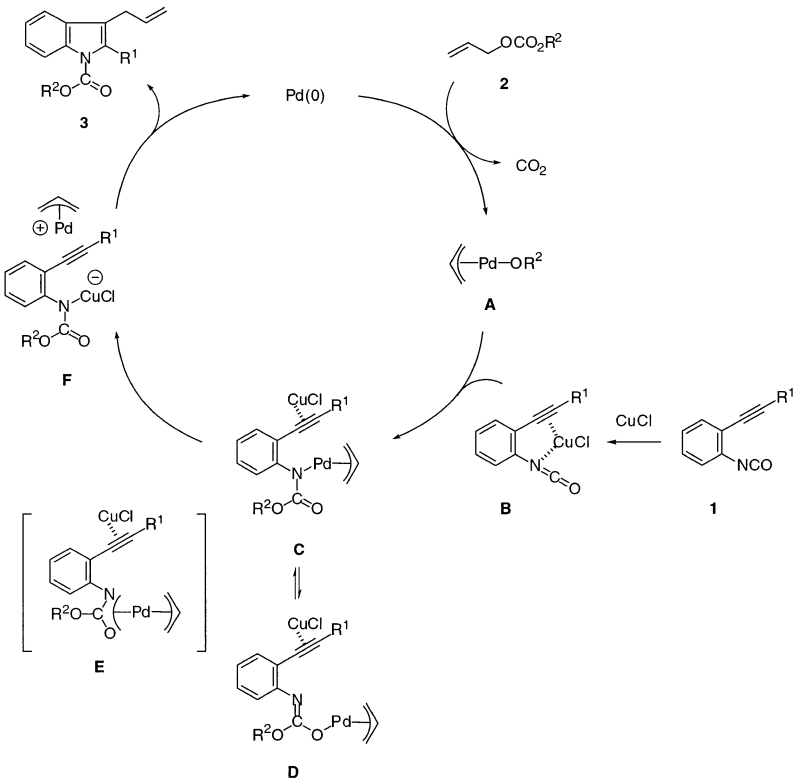
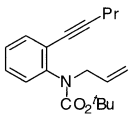


TABLE 2. 3-Allyl-*N*-(alkoxycarbonyl)indoles 3 from 2-(Alkynyl)phenylisocyanates 1 and Allyl Carbonates 2[a]

entry	1	R^1	2	R^2	reaction time, h	3	yield, %[b]
1	**1a**	Pr	**2a**	Me	1	**3a**	81
2[c]	**1b**	cyclopentyl	**2a**	Me	3	**3b**	71
3	**1c**	*t*-Bu	**2a**	Me	5	**3c**	0[d]
4[c]	**1d**	Ph	**2a**	Me	2	**3d**	62
5[e]	**1e**	*p*-$MeOC_6H_4$	**2a**	Me	6	**3e**	62
6[e]	**1f**	*p*-$CF_3C_6H_4$	**2a**	Me	7	**3f**	65
7	**1a**	Pr	**2b**	*i*-Pr	1	**3g**	69
8	**1a**	Pr	**2c**	*t*-Bu	1	**3h**	72
9	**1a**	Pr	**2d**	Ph	1	**3i**	86
10	**1a**	Pr	**2e**	Bn	1	**3j**	83

[a] Unless otherwise noted, the reaction of **1** with **2** (1.2 equiv) was conducted in the presence of $Pd(PPh_3)_4$ (1 mol %) and CuCl (4 mol %) in THF (1 M) under Ar atmosphere at 100 °C for the time shown in Table 2. [b] Isolated yield. [c] The reaction was conducted in 0.5 M THF solution. [d] The aniline derivative **4c** was obtained in 42% isolated yield. [e] Two equivalents of **2a** were used.



4c

which palladium is bonded to a nitrogen atom, could be in equilibrium with the palladium intermediate **D** bonded to an oxygen atom, or more probably could be represented as a heteroatom containing bis-π-allylpalladium analogue **E**.[35] To reach the final products **3** from these intermediates **C**−**E**, several possibilities are conceivable. We would like to propose that the transmetalation between Pd and Cu would take place to produce the intermediate **F**.[36] The reasons for this proposal are as follows. (1) The palladium-catalyzed reaction of **1a** with **2a** gave the *N*-allylaniline derivative **4a**, indicating that the methoxyallylation of NCO proceeded only with the palladium catalyst and the assistance of the copper catalyst was not needed (Table 1, entry 10). Without the palladium catalyst, the reaction did not take place at all, and therefore, the reaction proceeds via the intermediate **G**. (2) The copper catalyst was needed to give the indole **3a** (Table 1, entry 1), and therefore, the major role of the copper catalyst lies in a step of the cyclization for producing indole framework.[37] (3) If aminopalladation to the triple bond of **C** takes place, the addition must proceed in a *cis* manner. However, *trans*-aminopallada-

(35) For the chemistry on bis-π-allylpalladium complexes, see: (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641−6647. (b) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113−8114. (c) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729−731. (d) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413−4421. (e) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372−377. (f) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9453−9454. (g) Solin, N.; Narayan, S.; Szabó, K. J. *Org. Lett.* **2001**, *3*, 909−912. (h) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2002**, *4*, 1563−1566.

(36) Anionic cyclization of 2-alkynylaniline derivatives is well-known; see: (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845−1847. (b) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823−1828. (c) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305−1308. (d) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741−2746. (e) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511. (f) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529−534. (g) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488−2490.

(37) The complexation between alkyne and CuCl was reported nearly two decades ago by Macomber and Rausch,[38] and more recently such complexation has been applied to the synthesis of alkynylcoppers.[39,40] Moreover, ZnX_2-alkyne complexes have been isolated.[41]

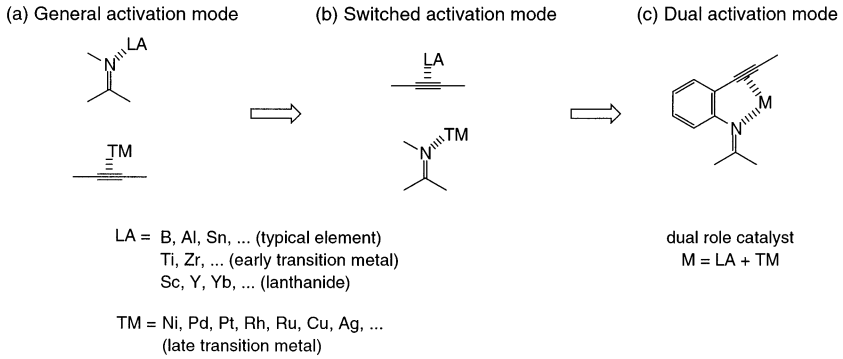
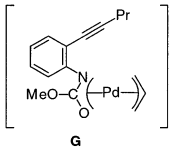


FIGURE 2. Activation of unsaturated bonds.

tion is needed to give **3**, leading to a proposal including the intermediate **F**.[42]



G

A Dual Role Catalyst for the Synthesis of *N*-(Alkoxycarbonyl)indoles from 2-(Alkynyl)phenylisocyanates and Alcohols. In general, Lewis acid (LA) is used to activate the C=X (heteroatom) unsaturated bonds through σ-coordination,[43] whereas a transition metal (TM) is used to activate the C=C multiple bonds through π-coordination (Figure 2a, general activation mode).[44] Typical elements, early transition metals, and lanthanides[45] are frequently used as LA, and late transition metals show very often the activity as TM. On the other hand, in recent years, we have some examples that certain LA catalysts activate C=C multiple bonds through π-coordination and TM catalysts activate C=X unsaturated bonds through σ-coordination (Figure 2b, switched activation mode). For example, the LA catalysts such as B, Al, and Hf promote the carbosilylation and the hydrosilylation of alkynes,[46] and the TM catalysts such as Ag, Cu, Rh, and Pd, bearing chiral ligands, exhibit good enantioselectivities in the addition reaction of nucleophiles to C=X unsaturated bonds.[47] However, the dual activation of a C=C multiple bond and a C=X unsaturated bond by a single metal complex M is rare (Figure 2c, dual activation mode).[48] In the previous section, we mentioned about the bimetallic catalyst, Pd^0–Cu^I, which activates the π-electrons of C=C multiple bond and σ-electrons of NCO bond in **1**. We found that the coupling reaction of the 2-(alkynyl)phenylisocyanates **1** and alcohols **5** proceeds under palladium or platinum catalysts to afford the indoles **6** in good to high yields, in which a single metal catalyst, Pd or Pt, most probably acts as a dual role catalyst; it activates simultaneously isocyanate as a LA and alkyne as a TM.

(38) Macomber, D. W.; Rausch, M. D. *J. Am. Chem. Soc.* **1983**, *105*, 5325−5329.

(39) Ito, H.; Arimoto, K.; Sensui, H.-o.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977−3980.

(40) (a) Ikegashita, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, 1039−1040. (b) Nishihara, Y.; Ikegashita, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233−1234. (c) Nishihara, Y.; Ikegashita, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075−4078. (d) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780−1787. (e) Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282−286.

(41) Lang, H.; Mansilla, N.; Rheinwald, G. *Organometallics* **2001**, *20*, 1592−1596.

(42) The reaction of the *N*-allylaniline derivative **4a** in the presence of $Pd(PPh_3)_4$ (1 mol %) and CuCl (4 mol %) in THF at 100 °C for 1 h, a similar condition as shown in Table 2, did not afford the indole **3a**. A significant amount of the starting material **4a** was recovered, indicating that the existence of the intermediates **C**−**F** in the catalytic cycle is important for the formation of the indole.

(43) For reviews, see: (a) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: New York, 1996. (b) *Lewis Acid Reagents*; Yamamoto, H., Ed.; Oxford University: Oxford, 1999. (c) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York, 2000; Vol. 2.

(44) (a) Reference 27c. (b) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277−4278. (c) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845−4852. (d) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323−5326. (e) Uanagihara, N.; Lamberet, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753−2754. (f) Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297−300.

(45) (a) *Lanthanides in Organic Synthesis*; Imamoto, T., Ed.; Academic: London, 1994. (b) *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Anwander, R., Dowdy, E. C., Groger, H., Eds.; Springer: New York, 1999.

(46) For Lewis acid-catalyzed reactions of alkynes, see: (a) Imamura, K.-i.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081−1084. (b) Jung, I. N.; Yoo, B. R. *Synlett* **1999**, 519−528 and references therein. (c) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071−1087 and references therein. (d) Yoshikawa, E.; Kasahara, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 4499−4502.

(47) (a) Reference 43 and references cited therein. [Ag]: (b) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723−4724. (c) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319−9320. (d) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701−3703. (e) Ohkouch, M.; Yamaguchi, M.; Yamagishi, T. *Enantiomer* **2000**, *5*, 71−81. (f) Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Kageyama, H.; Yamamoto, H. *Synlett* **2001**, 69−72. [Cu]: (g) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837−838. (h) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. (i) Evans, D. A.; Kozlowski, M. S.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (j) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739−8746. [Rh]: (k) Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5517−5520. (l) Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793−796. (m) Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3122−3131. (n) Motoyama, Y.; Narusawa, H.; Nishiyama, H. *Chem. Commun.* **1999**, 131−132. [Pd]: (o) Reference 35a. (p) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (q) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. [Pt]: (r) Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032−10039. (s) Motoyama, Y.; Mikami, Y.; Kawakami, H.; Aoki, K.; Nishiyama, H. *Organometallics* **1999**, *18*, 3584−3588.

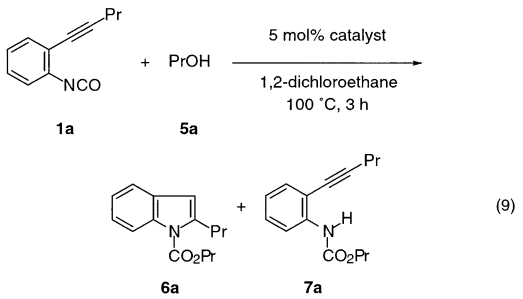
(48) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764−765. (b) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328−4331.

TABLE 3. Investigation for Effective Dual Role Catalyst[a]

entry	catalyst	yield,[b] % 6a	yield,[b] % 7a
1	Na_2PdCl_4	70 (74)	0
2	$PdCl_2$	68 (63)	0
3	$PdCl_2(CH_3CN)_2$	67	0
4	$PdCl_2(PPh_3)_2$	4.1	67
5	$Pd(OAc)_2$	1.6	85
6	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	0	82
7	$Pd(PPh_3)_4$	0	47
8	$Pd_2(dba)_3{\cdot}CHCl_3$	0	96
9	$NiCl_2$	0	60
10	$PtCl_2$	62	0
11	$NaAuCl_4{\cdot}2H_2O$	41	40
12	$AuCl_3$	57	32
13	AgCl	0	86
14	CuCl	trace	75
15	$CuCl_2$	trace	67
16	$ZnCl_2$	trace	77
17[c]	none	0	91 (80)

[a] Unless otherwise noted, the reaction of **1a** with **5a** (2 equiv) was carried out in the presence of the catalyst (5 mol %) in 1,2-dichloromethane (0.5 M) at 100 °C for 3 h. [b] Yields were determined by ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yields are shown in parentheses. [c] The reaction time was 6 h.

We first examined the reaction of 2-(1-pentynyl)-phenylisocyanate **1a** with propanol **5a** under various metal catalysts (eq 9). The results are summarized in Table 3. Na_2PdCl_4 catalyst showed the best catalytic activity as a dual role catalyst to form the indole **6a**[49] in high yield (entry 1). The other Pd^{II} catalysts, such as $PdCl_2$ and $PdCl_2(CH_3CN)_2$, showed similar catalytic activities (Table 3, entries 2 and 3). Interestingly, it was not necessary to carry out the reaction under Ar atmosphere. It seems that the catalytic activity is high for a few hours even in the presence of O_2. The use of $PdCl_2$-$(PPh_3)_2$, $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and the Pd^0 catalysts gave the aniline derivative **7a** either exclusively or very predominantly (Table 3, entries 4−8). Among the other transition metals we tested, Pt^{II} and Au^{III} also showed a catalytic activity to form the indole **6a** either in good yield or predominantly (Table 3, entries 9−16). Even without the catalysts, the reaction of the isocyanate **1a** with **5a** proceeded at 100 °C to give the aniline derivative **7a** in a high yield; however, a longer time (6 h) was needed to complete the reaction (entry 17), indicating that the palladium and other catalysts accelerate the addition of **5a** to the NCO group of **1a** (Table 3, entries 4−9 and 13−16).



(9)

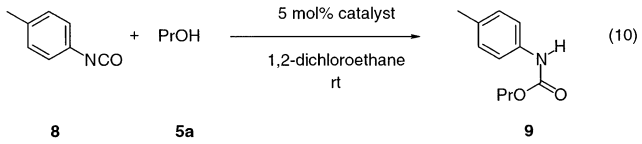
(49) The indole synthesis from 2-alkynyl-*N*-(alkoxycarbonyl)aniline derivatives has been reported but a cyclization with complete retention of the alkoxycarbonyl group is rare; see: (a) Reference 13a. (b) Reference 15b.

TABLE 4. Reaction of *p*-Tolyl Isocyanate 8 and Propanol 5a[a]

entry	catalyst	reaction time, h	yield,[b] %
1	none	24	98
2	Na_2PdCl_4	4	100 (97)
3	$PtCl_2$	16	100

[a] The reaction of **8** with **5a** (2 equiv) was carried out in the presence of the catalyst (5 mol %) in 1,2-dichloroethane (0.5 M) at room temperature for the time shown in Table 4. [b] Yields were determined by ^{1}HNMR with CH_2Br_2 as an internal standard. The isolated yield is shown in parentheses.

We further examined the reaction of *p*-tolyl isocyanate **8** with propanol **5a** at room temperature to clarify the role of Na_2PdCl_4 and $PtCl_2$ as a Lewis acid catalyst (Table 4).[33] The reactions in the presence of a catalytic amount of Na_2PdCl_4 (Table 4, entry 2) and $PtCl_2$ (Table 4, entry 3) gave the corresponding carbamate **9** in shorter reaction times compared with the reaction without the catalyst (Table 4, entry 1), indicating that the Pd^{II} and Pt^{II} catalysts exhibit a Lewis acidic property and enhance the reactivity of the isocyanate by coordination. Since the cyclization of the aniline derivative **7a** leading to the indole **6a** was promoted by Na_2PdCl_4 and $PtCl_2$ catalyst,[13a,50] it is clear that these catalysts act as a dual role catalyst which activates both π- and σ-electrons simultaneously.



(10)

We investigated the scope and limitations of the indole synthesis under the dual role catalysts (Table 5). We first carried out the reaction of propanol **5a** with isocyanates **1** having various substituents R^1 at the terminal of acetylenic bond. The reaction of 2-(1-pentynyl)phenyl-isocyanate **1a** with **5a** was conducted in the presence of a catalytic amounts of Na_2PdCl_4 (5 mol %) in 1,2-dichloroethane (0.5 M) at 100 °C for 1.5 h. *N*-(Propoxy-carbonyl)-2-propylindole **6a** was obtained in 74% yield (Table 5, entry 1). Even when the bulkiness of the substituent R^1 increased from propyl **1a** to cyclopentyl **1b** and *tert*-butyl group **1c**, the reaction proceeded smoothly to produce the corresponding indoles **6a**−**c** in good to excellent yields (Table 5, entries 1−3). The aromatic substituents such as phenyl **1d**, *p*-methoxyphenyl **1e**, and *p*-trifluoromethylphenyl group **1f** gave the corresponding indoles **6d**−**f** in allowable yields (Table 5, entries 4−6). The isocyanate having terminal acetylenic group **1g** also gave the indole **6g** in 45% yield by using $PtCl_2$ catalyst (Table 5, entry 7). The use of Na_2PdCl_4 catalyst for the reaction of **1g** resulted in the formation of a complex mixture of unidentified products. We next carried out the reaction of 2-(1-pentynyl)phenylisocyanate **1a** with various alcohols **5**. Although longer reaction times were needed along with the increase of bulkiness

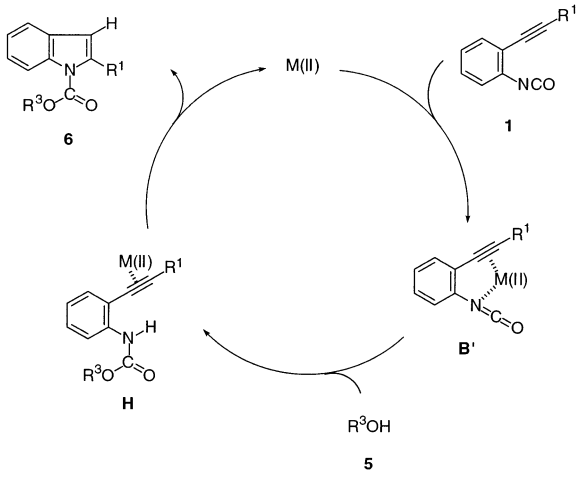
(50) The cyclization of the aniline derivative **7a** was carried out in the presence of Na_2PdCl_4 and $PtCl_2$ (5 mol %) in 1,2-dichloroethane at 100 °C for 1 h, a condition similar to that shown in Table 5. The corresponding indole **6a** was obtained in 74% NMR yield in the case of Pd^{II} and in 78% NMR yield in the case of Pt^{II}, respectively.

TABLE 5. *N*-(Alkoxycarbonyl)indole 6 from 2-(Alkynyl)phenylisocyanates 1 and Alcohols 5[a]

entry	1	R^1	5	R^3	reaction time, h	6	yield,[b] %
1	**1a**	Pr	**5a**	Pr	1.5	**6a**	74
2	**1b**	cyclopentyl	**5a**	Pr	1.5	**6b**	83
3	**1c**	*t*-Bu	**5a**	Pr	2	**6c**	89
4	**1d**	Ph	**5a**	Pr	1.5	**6d**	59
5	**1e**	*p*-$MeOC_6H_4$	**5a**	Pr	1.5	**6e**	58
6	**1f**	*p*-$CF_3C_6H_4$	**5a**	Pr	1.5	**6f**	55
7[c]	**1g**	H	**5a**	Pr	2	**6g**	45
8	**1a**	Pr	**5b**	Me	1.5	**6h**	65
9	**1a**	Pr	**5c**	*i*-Pr	2	**6i**	67
10[c]	**1a**	Pr	**5d**	*t*-Bu	24	**6j**	56
11	**1a**	Pr	**5e**	Bn	3	**6k**	64
12[c]	**1a**	Pr	**5f**	CH_2═$CHCH_2$	4	**6l**	85

[a] Unless otherwise noted, the reaction of **1** with **5** (2 equiv) was conducted in the presence of Na_2PdCl_4 (5 mol %) in 1,2-dichloroethane (0.5 M) at 100 °C for the time shown in Table 5. [b] Isolated yield. [c] $PtCl_2$ (5 mol %) was used instead of Na_2PdCl_4.

SCHEME 2. Proposed Mechanism for the Formation of *N*-(Alkoxycarbonyl)indoles under a Dual Role Catalyst



of the alcohols MeOH **5b**, *i*-PrOH **5c**, and *t*-BuOH **5d**, the corresponding indoles **6h**, **6i**, and **6j** were formed in good yields (Table 5, entries 8−10). In the case of bulky *tert*-butyl alcohol **5d**, $PtCl_2$ showed higher catalytic activity than that of Na_2PdCl_4, giving the indole **6j** in an allowable yield. Benzyl alcohol **5e** and allyl alcohol **5f** gave the corresponding indoles **6k** and **6l** in 64% and 85% yields, respectively (Table 5, entries 11 and 12). In the case of allyl alcohol, only $PtCl_2$ showed catalytic activity and Na_2PdCl_4 did not afford the desired indole **6l**.

A proposed mechanism for the formation of indoles **6** under a dual role catalyst is shown in Scheme 2. Initially, the catalyst M^{II} coordinates both alkynyl group and isocyanate group of the starting material **1** to form the activated intermediate **B′**. The addition of the alcohol **5** to the isocyanate is facilitated by the coordination of Lewis acidic M^{II} to give the carbamate intermediate **H**. Successive aminometalation and regeneration of the catalyst M^{II} afford the indole **6**. The aminometalation proceeds through the activation of alkyne by the typical transition metal nature of the catalyst M^{II}.[13,44]

Conclusions

Novel tandem reactions for the synthesis of 3-allyl-*N*-(alkoxycarbonyl)indoles **3** and *N*-(alkoxycarbonyl)indoles **6** were developed. The bimetallic catalyst, $Pd(PPh_3)_4$−CuCl, is effective for the formation of 3-allyl-*N*-(alkoxycarbonyl)indoles **3** from 2-(alkynyl)phenylisocyanates **1** and allyl carbonate **2**. The dual role catalyst, Na_2PdCl_4 or $PtCl_2$, works effectively for the formation of *N*-(alkoxycarbonyl)indoles **6** from 2-(alkynyl)phenylisocyanates **1** and alcohols **5**. The cooperative action of a Lewis acidic and transition metallic nature of catalysts in the catalytic cycles is a key to promote the tandem reactions. The present indole synthesis allows us to prepare variously substituted indoles, and the deprotection of alkoxycarbonyl group on the nitrogen atom in the indole ring is quite easy.[51]

Experimental Section

Representative Procedure for the Synthesis of 3-Allyl-*N*-(alkoxycarbonyl)indole under the Pd^0−Cu^I Bimetallic Catalyst. To a THF solution (0.5 mL) of 2-(1-pentynyl)phenyl-1-isocyanate **1a** (92.7 mg, 0.5 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol), and CuCl (2.0 mg, 0.02 mmol) was added allyl methyl carbonate **2a** (69 μL, 0.6 mmol) under an argon atmosphere. The solution was stirred at 100 °C for 1 h in a tightly capped 5 mL microvial. The reaction mixture was cooled to room temperature, filtered through a short Florisil pad, and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 100:1−20:1) yielding 3-allyl-*N*-(methoxycarbonyl)-2-propylindole **3a** in 81% yield (104.2 mg).

Representative Procedure for the Synthesis of *N*-(Alkoxycarbonyl)indole under the Palladium Catalyst. To a 1,2-dichloroethane solution (1 mL) of 2-(1-pentynyl)-phenyl-1-isocyanate **1a** (92.7 mg, 0.5 mmol) and Na_2PdCl_4 (7.4 mg, 0.025 mmol) was added propanol **5a** (75 μL, 1 mmol) under air. The solution was stirred at 100 °C for 1.5 h in a tightly capped 5 mL microvial. The reaction mixture was cooled to room temperature, filtered through a short Florisil pad, and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 100:1−20:1) to afford *N*-(propoxycarbonyl)-2-propylindole **6a** in 74% yield (90.7 mg).

Acknowledgment. We thank faculty members in the Instrumental Analysis Center for Chemistry at Tohoku University for measurements of mass spectra and elemental analyses.

Supporting Information Available: Characterization data of the compounds **1g**, **2k**, **6a**−**l,** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034254P

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