approximately the same level of bond fixation (23%, 53%, 48%, 48%, 49%, shortest bond 1.358 Å, longest bond 1.456 Å). The interplanar angles between consecutive six- and four-membered rings starting from the terminus are 1.31, 2.98, 3.61, 4.67, 3.84, 5.47, 4.50, and 4.99°, a smoother progression than that of **3a**, likely due to the absence of crystal lattice forces.[14] The closest contact is between H1 and C22f (2.99 Å), the terminal ring centroids are separated by 7.48 Å, with an interplanar angle of 33.2°. Taking the central six-membered ring as a reference, the inner helix climbs 5.07 Å and turns in plane by 415.7°.

Are heliphenes **3** and **4** sufficiently extended to render their enantiomers amenable to resolution? The answer is provided by variable-temperature NMR experiments carried out on derivatives **3b** and **4b**. Remarkably, decoalescence of the potentially diastereotopic methylene hydrogens of the substituent in **3b** occurred only on cooling, providing $\Delta G^{\ddagger}_{-4.5\,^{\circ}\mathrm{C}} = 13.4 \pm 0.4\ \mathrm{kcal\,mol^{-1}}$ (400 MHz, $\Delta\nu_{\max} = 12.6$ Hz, [D$_8$]toluene). This value is less than 1 kcal mol^{-1} higher than that of the corresponding [7]heliphene **2**.[1] To our further surprise, [9]heliphene **4b** did not show any change in the shape of the corresponding methylene singlet signal down to the (solubility) limiting temperature of −45 °C (400 MHz, [D$_8$]toluene), suggesting a lower barrier to enantiomerization, less than around 12 kcal mol^{-1}. As proposed previously,[1,15] it appears that steric activation of the helical ground state toward unwinding the helix is responsible for the observed dynamic behavior. Structural elements, such as additional stereocenters biasing the helix or steric blockers locking it, will have to be introduced to render the heliphene frame configurationally robust. Finally, it is evident that extensions of the "stitching" procedures outlined in Schemes 1–3 should provide access to even higher members of the heliphene series. Such is the focus of future research.

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A New Pd^0–Cu$^{\mathrm{I}}$ Bimetallic Catalyst for the Synthesis of Indoles from Isocyanates and Allyl Carbonates[**]

Shin Kamijo and Yoshinori Yamamoto[*]

In the research field of transition-metal-catalyzed organic synthesis, one of the modern trends is to use a bimetallic catalyst system to explore not only more efficient but also entirely new transformations. Representative examples of such bimetallic catalysis in palladium-catalyzed reactions[1] are the following: 1) cat.Pd^0/Cu$^{\mathrm{I}}$ in the Sonogashira coupling reaction, in which a catalytic amount of Cu salts activate terminal acetylenes to form copper–acetylide species;[2] 2) cat Pd^0/Cu$^{\mathrm{I}}$ in the Stille coupling reaction, in which organostannanes are transmetalated to give organocoppers which

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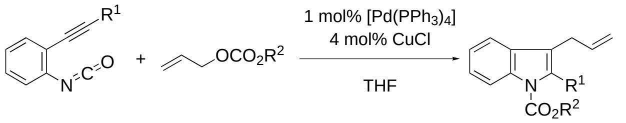
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

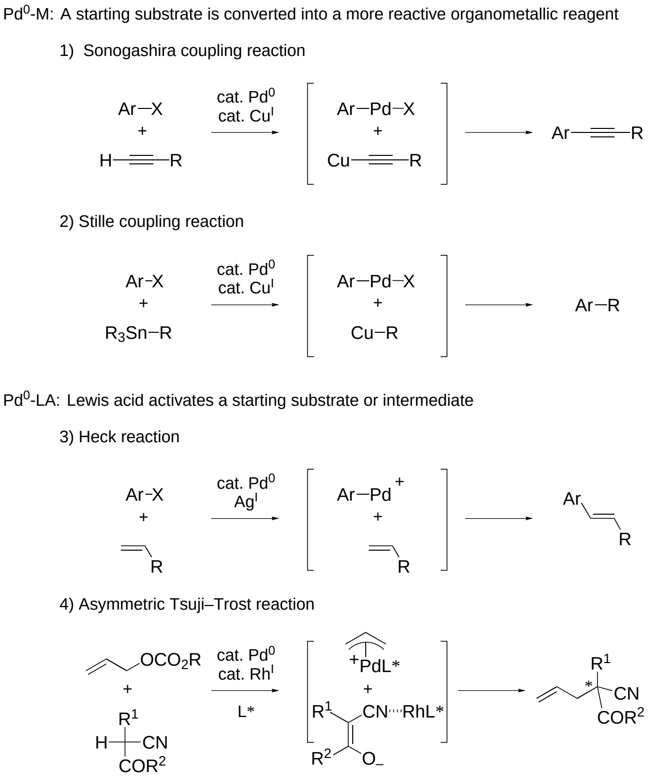
accelerate the coupling;[3] 3) cat.Pd^0/excess Ag^I in the Heck reaction, in which Ag salts abstract the halide ion to produce a reactive cationic Pd intermediate;[4] 4) cat.Pd^0/Rh^I in the asymmetric Tsuji–Trost reaction, in which Rh activates pronucleophiles by coordinating to a cyano group.[5] Accordingly, the above examples 1) and 2) are categorized into the Pd^0–M group, while examples 3) and 4) belong to the Pd^0–LA family (LA = Lewis acid, Scheme 1). We now report that the coupling of the (2-alkynyl)phenylisocyanate **1** and the allyl carbonate **2** proceeds using a palladium–copper bimetallic catalyst system to afford indoles **3**[6–9] in high yields [Eq. (1)],



(1)

1 **2** **3**

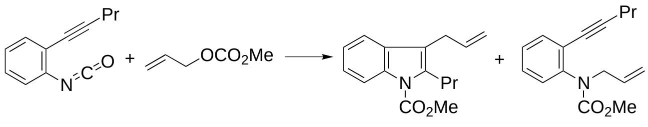
in which Cu^I ions most probably act as π-coordinative Lewis acids.[10]



Scheme 1. Bimetallic catalyst systems in Pd-Catalyzed Reactions. Pd^0–M: A starting material is converted into a more reactive organometallic complex. 1) Sonogashira coupling reaction; 2) Stille coupling reaction. Pd^0–LA: LA acts as a Lewis acid to activate a starting substrate or an intermediate. 3) Heck reaction; 4) Asymmetric Tsuji–Trost reaction.

We first investigated several catalytic systems for the reaction of **1** with **2**. The results are summarized in Table 1. The reaction of 2-(1-pentynyl)phenyl-1-isocyanate (**1a**) and allyl methyl carbonate (**2a**) in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ gave the *N*-allylaniline derivative **4aa** in 83 % yield (entry 1). After intensive investigations, we found that Cu^I species effectively catalyze the cyclization to form the indole **3aa**. Of the additives we tested, CuCl showed the best catalytic activities and gave the desired indole **3aa** in 73 % yield (entry 2), while CuBr showed a comparable activity to CuCl (entry 3). Other Cu^I catalysts such as CuI, $[(CuOTf)_2{\cdot}C_6H_6]$, and CuOAc gave lower yields of **3aa** (entries 4–6) and Cu_2O displayed no catalytic activity for the cyclization (entry 7). However, Cu^{II} catalysts inhibited the formation of both **3aa** and **4aa** (entry 8). Among the other metal-based catalysts, $ZnCl_2$ was found to catalyze the cyclization to form **3aa** in 62 % yield and did not give **4aa** at all (entry 9). AgCl and $PdCl_2$ did not catalyze the cyclization and gave only **4aa** (entries 10 and 11). LiCl inhibited the formation of both **3aa** and **4aa** and resulted in the recovery of the starting material **1a** in 69 % yield (entry 12), while tetrabutylammonium chloride did not yield **3aa** (entry 13). We found after further optimization of the reaction conditions that the reaction proceeds efficiently in THF by using 1 mol % of $[Pd(PPh_3)_4]$ and 4 mol % of CuCl as cocatalysts [Eq. (1)].

Table 1. Effect of the additive.[a]



1a **2a** **3aa** **4aa**

Entry	Additive	NMR yield (isolated) [%][b]	
		3aa	**4aa**
1	none	0	89 (83)
2	CuCl	78 (73)	0
3	CuBr	70	trace
4	CuI	27	20
5	$[(CuOTf)_2{\cdot}C_6H_6]$[c]	37	0
6	CuOAc	26	37
7	Cu_2O	0	69
8[d]	$CuCl_2$	0	0
9	$ZnCl_2$	62	0
10	AgCl	0	70
11	$PdCl_2$	0	74
12[e]	LiCl	0	0
13	nBu$_4$NCl	0	80

[a] **2a** (2 equiv) was added to a solution of **1a**, $[Pd(PPh_3)_4]$ (5 mol %), and additive (20 mol %) in THF, and the mixture was heated at 100 °C for 1 h. [b] Yields were determined by ^1H NMR spectroscopy with *p*-xylene as an internal standard (yield is shown in parentheses). [c] 10 mol % additive was used. [d] The starting material **1a** was recovered in 29 % yield, as suggested by NMR spectroscopy. [e] The starting material **1a** was recovered in 69 % yield, as suggested by NMR studies.

We investigated the scope and limitations of the indole synthesis based on the bimetallic catalyst system. We first treated the (2-alkynyl)phenylisocyanate **1a** [R^1 = Pr in Eq. (1)] with various allyl carbonates **2** (Table 2). The reaction of **1a** and allyl methyl carbonate (**2a**) was conducted in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ (1 mol %) and CuCl (4 mol %) in THF (1 M) at 100 °C for 1 h. The desired 3-allyl-*N*-(methoxycarbonyl)-2-propylindole (**3aa**) was obtained in 81 % yield (entry 1). The reaction with bulky allyl carbonates **2b** and **2c** also proceeded smoothly to give the corresponding indoles **3ab** and **3ac** in 69 and 72 % yields, respectively (entries 2 and 3). Even allyl phenyl carbonate

Table 2. Indole synthesis from **1a** and various allyl carbonates.[a]

Entry	**2**	R^2	**3**	Yield [%]
1	**2a**	Me	**3aa**	81
2	**2b**	*i*Pr	**3ab**	69
3	**2c**	*t*Bu	**3ac**	72
4	**2d**	Ph	**3ad**	86
5	**2e**	Bn	**3ae**	83

[a] **2** (1.2 equiv) was added to a solution of **1a**, [Pd(PPh$_3$)$_4$] (1 mol%), and CuCl (4 mol%) in THF, and the mixture was stirred at 100°C for 1 h.

(**2d**) and allyl benzyl carbonate (**2e**) gave the corresponding indoles **3ad** and **3ae** in good yields (entries 4 and 5).

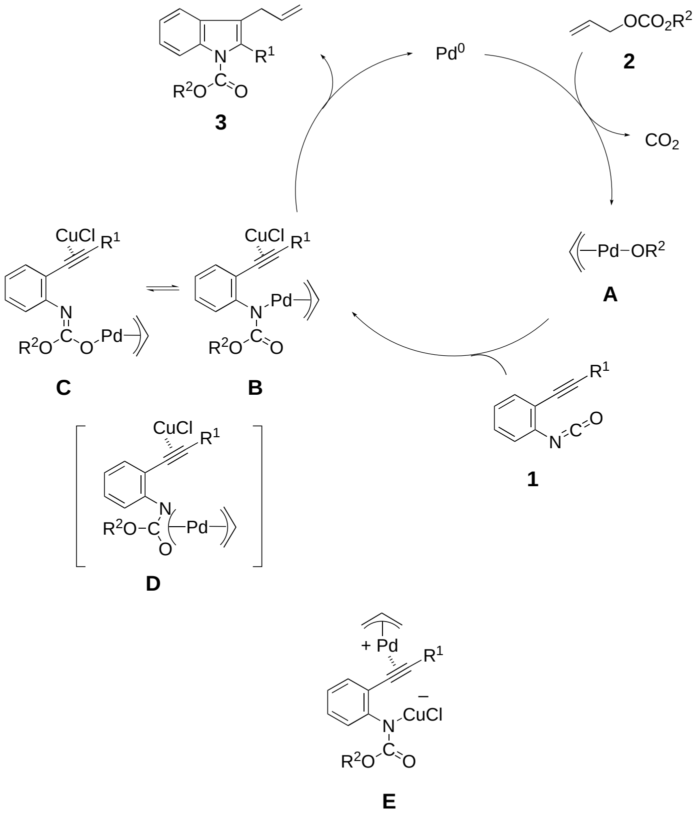
We next treated allyl methyl carbonate (**2a**) [R^2 = Me in Eq. (1)] with isocyanate **1** having various acetylenic terminal groups (Table 3). The isocyanates with propyl (**1a**) and cyclopentyl (**1b**) substituents afforded the corresponding indoles **3aa** and **3ba** in 81 and 74%, respectively (entries 1 and 2). However, the isocyanate with a terminal *tert*-butyl group (**1c**) afforded the corresponding *N*-allylaniline derivative **4ca** in 42% yield and did not give the corresponding indole **3ca** at all (entry 3). The phenyl-substituted isocyanates **1d**–**1f** gave the corresponding indoles **3da**–**3fa** in good yields (entries 4–6). The above results indicate that the reaction proceeds irrespective of the electronic nature of the aromatic ring.

Table 3. Indole synthesis from **2a** and various isocyanates.[a]

Entry	**1**	R^1	Reaction time [h]	**3**	Yield [%]
1	**1a**	Pr	1	**3aa**	81
2[b]	**1b**	cyclopentyl	3	**3ba**	71
3	**1c**	*t*Bu	5	**3ca**	0[c]
4[b]	**1d**	Ph	2	**3da**	62
5[d]	**1e**	*P*-MeOC$_6$H$_4$	6	**3ea**	62
6[d]	**1f**	*p*-CF$_3$C$_6$H$_4$	7	**3fa**	65

[a] The reaction was conducted with **1** and **2a** (1.2 equiv) in the presence of [Pd(PPh$_3$)$_4$] (1 mol%) and CuCl (4 mol%) in THF (1 M) at 100°C for the time displayed in Table 3. [b] The reaction was conducted in 0.5 M THF solution. [c] **4ca** was obtained in 42% yield. [d] Two equivalents of **2a** were used.

A proposed mechanism is shown in Scheme 2. Initially, the Pd^0 center reacts with allyl carbonates **2** to give the π-allylpalladium alkoxide complex **A** with extrusion of CO$_2$. Then, the insertion of isocyanates **1** into complex **A** would form the π-allylpalladium intermediate **B**. This intermediate, with Pd–N bonding, could be in equilibrium with the Pd–O-bonded intermediate **C**, which should more probably be represented as the bis-π-allylpalladium analogue **D**.[11] Insertion of the alkyne then occurs to form indole **3** and the Pd^0 species is regenerated. The key step in this proposed mechanism is the insertion of the alkyne into the π-allylpalladium intermediates **B**–**D**, which occurs to give the *trans* indoles **3**. The role of CuCl is not understood completely at present, but we believe that the Cu^I center behaves as a Lewis acid for the C≡C bond to activate the alkyne through π coordination and catalyze the insertion of the alkyne into intermediates **B**–**D**, that is, it acts as a catalyst for the carboamination of the alkyne.[12] An alternative mechanism through the intermediate **E** can be proposed, in which copper activates the nitrogen nucleophile and the alkyne bond coordinates to a π-allylpalladium cationic species.[17] At the present time, it is impossible to distinguish between the two mechanisms; the alkyne bond is activated by copper or by palladium species. It should be emphasized that no carboamination takes place at all in the absence of CuCl.



Scheme 2. Proposed mechanism for the formation of indoles.

In conclusion, we have developed a new [Pd(PPh$_3$)$_4$]/CuCl bimetallic catalyst system for the synthesis of indoles **3** from isocyanates **1** and allyl carbonates **2**. This is the first example of a palladium-catalyzed indole syntheses from isocyanates. Various kinds of indoles are now available, and deprotection of the alkoxycarbonyl group is relatively easy.[18] Further studies on synthetic applications and a mechanistic investigation are now in progress.

Experimental Section

Allyl methyl carbonate (**2a**, 69 μL, 0.6 mmol) was added to a solution 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) in THF (0.5 mL) under an argon atmosphere, and the mixture was stirred at 100°C for 1 h. 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/ethyl acetate 100/1 to 20/1) to afford 3-allyl-*N*-(methoxycarbonyl)-2-propylindole (**3aa**) in 81% yield (104.2 mg).

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Fluorescence Enhancement through Enzymatic Cleavage of Internally Quenched Dendritic Peptides: A Sensitive Assay for the AspN Endoproteinase**

John M. Ellard, Thomas Zollitsch, W. Jon Cummins, Alan L. Hamilton, and Mark Bradley*

Fluorescence resonance energy transfer (FRET) systems in which a peptide sequence contains both a fluorophore and an internal quencher are amongst the best methods available for protease analysis and characterization. Numerous proteases have been studied using this method, including trypsin which cleaves the FRET-based system Dabcyl-Gly-Pro-Ala-Lys-Leu-Ala-Ile-Gly-Edans,[1] cathepsin B which cleaves Abz-Lys-Leu-X-Phe-Ser-Lys-Gln-EDDnp (where X is Cys(SBz), Thr(OBz), or Ser(OBz) and EDDnp is 2,4-dinitrophenylethylenediamine),[2] leukotriene D$_4$ hydrolase which cleaves ε-DNP-L-Lys-D-Amp[3] (where Amp is 2-amino-3-(7-methoxy-4-coumaryl)propanoic acid) and caspase 1 and 3 which cleave the FRET systems BFP-Tyr-Val-Ala-Asp-GFP and BFP-Asp-Glu-Val-Asp-GFP, respectively (where BFP is blue fluorescent protein and GFP is green fluorescent protein)[4] to name but a few. A host of methods have been developed using this methodology to determine the most appropriate substrate for a particular protease. For example, Meldal et al. have reported a powerful general method for the use of a split-and-mix approach to libraries of FRET-based peptides for on-bead screening to determine optimal substrates for a range of proteases including subtilisin carlsberg,[5] FRET-based hexapeptide libraries have been used to map the S′-subsite specificity of serine proteases using solution-based assays,[6] and a positional scanning substrate library has been used to determine the specificity of ICE (= interleukin-converting enzyme).[7]

In this paper a new method for the detection of proteolytic activity is presented using internal fluorescence quenching between fluorophores of the same type. These are attached to a dendrimer-type structure, thereby giving a high local concentration of fluorophore needed for quenching yet eliminating the need for a separate quenching moiety. This method simplifies the synthesis of substrates for assay compared to traditional FRET, while being very sensitive due to the amplification nature of the assay as multiple

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