JOC Article
pubs.acs.org/joc

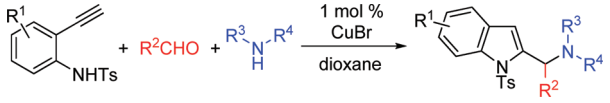
Construction of Nitrogen Heterocycles Bearing an Aminomethyl Group by Copper-Catalyzed Domino Three-Component Coupling−Cyclization

Yusuke Ohta, Hiroaki Chiba, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

hohno@pharm.kyoto-u.ac.jp; nfujii@pharm.kyoto-u.ac.jp

Received June 25, 2009



A direct approach to 2-(aminomethyl)indoles by copper-catalyzed domino three-component coupling−cyclization of 2-ethynylanilines with a secondary amine and aldehyde has been developed. By use of a cyclic or acyclic secondary amine and aldehyde (paraformaldehyde, aliphatic or aromatic aldehydes) in the presence of 1 mol % of CuBr, 2-ethynylanilines were converted to a variety of substituted 2-(aminomethyl)indoles in good to excellent yields. Utilizing this domino reaction and C−H functionalization at the indole C-3 position, polycyclic indoles were readily synthesized. Construction of benzo[*e*][1,2]thiazine and indene motifs by the reaction of sulfonamide and malonate congeners is also presented.

Introduction

Development of efficient and practical methods that minimize requisite reagents, cost, byproducts, time, and separation processes[1] for the desired transformation is of growing interest in modern organic chemistry. For diversity-oriented synthesis of structurally complex molecules, it is desirable to convert easily available materials to the target compounds by multibond forming processes with simple operation. While considerable attention has been focused on the multicomponent reaction (MCR),[2] a catalytic cascade reaction[3] including MCR would be more valuable to accomplish these tasks.

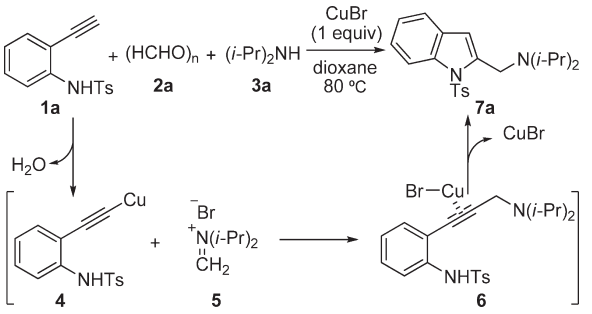
The indole nucleus is a prominent structural motif found in numerous natural and unnatural products with vital biological activities.[4] Particularly, the 2-(aminomethyl)-indole motif represents the key structures that exist in several biologically active indole alkaloids[5] as well as synthetic compounds[6] including calindol.[7] Most of the existing synthetic routes to 2-(aminomethyl)indoles start from the functionalized indoles such as indole-2-carboxylic acid or its derivatives, which limit the structural diversity of the target molecules that can be readily synthesized.[8]

During the course of our efforts directed toward the development of useful transformations of allenic

(1) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.
(2) For recent reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484–491. (d) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108.
(3) For recent reviews, see: (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.
(4) For recent reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920.
(5) For recent reviews, see: (a) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587–596. (b) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559–590. (c) Leonard, J. *Nat. Prod. Rep.* **1999**, *16*, 319–338. (d) Lobo, A. M.; Prabhakar, S. *J. Heterocycl. Chem.* **2002**, *39*, 429–436. (e) Takayama, H. *Chem. Pharm. Bull.* **2005**, *52*, 916–928. (f) Takayama, H.; Kitajima, M.; Kogure, N. *Curr. Org. Chem.* **2005**, *9*, 1445–1464. (g) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655–8681.
(6) For recent examples, see: (a) Morón, J. A.; Campillo, M.; Perez, V.; Unzeta, M.; Pardo, L. *J. Med. Chem.* **2000**, *43*, 1684–1691. (b) Spadoni, G.; Balsamini, C.; Diamantini, G.; Tontini, A.; Tarzia, G. *J. Med. Chem.* **2001**, *44*, 2900–2912. (c) Rivara, S.; Mor, M.; Silva, C.; Zuliani, V.; Vacondio, F.; Spadoni, G.; Bedini, A.; Tarzia, G.; Lucini, V.; Pannacci, M.; Fraschini, F.; Plazzi, P. V. *J. Med. Chem.* **2003**, *46*, 1429–1439. (d) Stewart, A. O.; Cowart, M. D.; Moreland, R. B.; Latshaw, S. P.; Matulenko, M. A.; Bhatia, P. A.; Wang, X.; Daanen, J. F.; Nelson, S. L.; Terranova, M. A.; Namovic, M. T.; Donnelly-Roberts, D. L.; Miller, L. N.; Nakane, M.; Sullivan, J. P.; Brioni, J. D. *J. Med. Chem.* **2004**, *47*, 2348–2355. (e) Rivara, S.; Lorenzi, S.; Mor, M.; Plazzi, P. V.; Spadoni, G.; Bedini, A.; Tarzia, G. *J. Med. Chem.* **2005**, *48*, 4049–4060. (f) Brands, M.; Ergüden, J.-K.; Hashimoto, K.; Heimbach, D.; Schröder, C.; Siegel, S.; Stasch, J.-P.; Weigand, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4201–4205.
(7) (a) Kessler, A.; Faure, H.; Petrel, C.; Ruat, M.; Dauban, P.; Dodd, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3345–3349. (b) Petrel, C.; Kessler, A.; Dauban, P.; Dodd, R. H.; Rognan, D.; Ruat, M. *J. Biol. Chem.* **2004**, *279*, 18990–18997. (c) Ray, K.; Tisdale, J.; Dodd, R. H.; Dauban, P.; Ruat, M.; Northup, J. K. *J. Biol. Chem.* **2005**, *280*, 37013–37020.
(8) For recent synthesis of 2-(aminomethyl)indoles by another approach, see: (a) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083–2086. (b) Pedras, M. S. C.; Suchy, M.; Ahiahonu, P. W. K. *Org. Biomol. Chem.* **2006**, *4*, 691–701.

Published on Web 08/12/2009 DOI: 10.1021/jo901328q

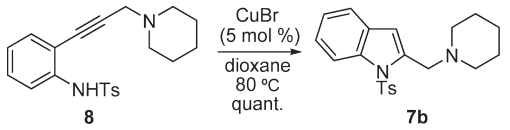
SCHEME 1. Domino Three-Component Coupling−Cyclization



compounds,[9,10] we found that the reaction of *N*-tosylated 2-ethynylaniline **1a** with paraformaldehyde **2a** and diisopropylamine **3a** in dioxane in the presence of copper(I) bromide (Crabbé conditions)[11] afforded a 2-(aminomethyl)indole derivative **7a** in 92% yield (Scheme 1) without forming the expected [2-(*N*-tosylamino)phenyl]allene. This reaction can be rationalized by Mannich-type MCR followed by indole formation through intramolecular hydroamination toward the activated alkyne moiety of a plausible intermediate **6**. Actually, the reaction of the identically prepared propargyl amine **8**[12] with CuBr (5 mol %) gave the expected indole **7b** in quantitative yield (Scheme 2).

To develop an atom-economical, direct synthetic method to 2-(aminomethyl)indoles without producing any salts as byproducts,[13−15] we conducted a careful survey of the above indole formation. Herein we report full details of our investigation into the copper(I)-catalyzed domino three-component coupling−cyclization reaction of 2-ethynylaniline derivatives.[16] Two-step construction of polycyclic indoles by combination with palladium-catalyzed C−H functionalization at the indole C-3 position, scope and limitation of the asymmetric three-component indole

SCHEME 2. Indole Formation from the Proposed Intermediate 8



formation, and synthesis of benzo[*e*][1,2]thiazine derivatives and indene-1,1-dicarboxylate are also presented.

Result and Discussion

Synthesis of 2-(Aminomethyl)indoles with Use of Several Amines and Aldehydes. To improve the original reaction conditions using a stoichiometric amount of CuBr and 3 equiv of $(i\text{-Pr})_2$NH (Scheme 1), our initial attempt was made by reacting *N*-tosyl-2-ethynylaniline **1a**, paraformaldehyde **2a** (2 equiv), piperidine **3b** (1.1 equiv), and CuBr (100 mol %) in the presence of Et_3N (2 equiv), which would decrease the loading of piperidine (Table 1, entry 1).[17] The reaction proceeded rapidly to give the desired 2-(aminomethyl)indole **7b** in 71% yield. While use of a catalytic amount of CuBr (10 or 1 mol %) with respect to **1a** increased the yield of **7b** (entries 2 and 3), the reaction without CuBr led to the recovery of **1a**. The reaction in the absence of Et_3N also showed efficient conversion into **7b** (entry 4). This result can be explained by the plausible reaction mechanism depicted in Scheme 1, in which the sulfonamide proton is presumably transferred to the 3-position of indole. This step could be mediated by piperidine or the basic substituent in the product and/or intermediate. The decreased use of **2a** also produced the desired indole **7b**, although a prolonged reaction time (1−12 h) was necessary (entries 5 and 6). Use of $CuBr_2$, CuCl, or CuI as the catalyst was also tolerated in this three-component indole formation (entries 7−9).

Next, we examined the scope of the 2-(aminomethyl)-indole formation with various symmetrical secondary amines (Table 2) under the optimized conditions (Table 1, entry 4). The reaction of 2-ethynylaniline **1a** with bulky diisopropylamine **3a** (1.1 equiv) and paraformaldehyde **2a** (2 equiv) in the presence of CuBr (1 mol %) gave the expected indole derivatives **7a** in 81% yield (entry 1). Pyrrolidine **3c** also showed efficient conversion into the corresponding indoles **7c** (entry 3). The use of volatile diethylamine **3d** successfully afforded **7d**, although 2 equiv of Et_2NH was needed (entry 4). Secondary amines containing removable allyl and benzyl groups **3e** and **3f**, respectively, were also acceptable as amine components when the reactions were conducted with a prolonged reaction time (entries 5 and 6).[18]

We also investigated the three-component synthesis of 2-(aminomethyl)indoles using various aldehyde components

(9) For our recent studies on allene chemistry, see: (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749–1753. (b) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647–2650. (c) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744–8754. (d) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513–1517. (e) Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113–5115. (f) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, *8*, 947–950. (g) Ohno, H.; Aso, A.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6325–6328. (h) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821–4824. (i) Okano, A.; Mizutani, T.; Oishi, S.; Tanaka, T.; Ohno, H.; Fujii, N. *Chem. Commun.* **2008**, 3534–3536. (j) Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 5239–5242.

(10) For recent reviews, see: (a) Ohno, H. *Chem. Pharm. Bull.* **2005**, *53*, 1211–1226. (b) Ohno, H. *Yakugaku Zasshi* **2005**, *125*, 899–925.

(11) Searles, S.; Nassim, Y.; Li, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747–751.

(12) For the preparation of **8**, see the Supporting Information.

(13) For indole synthesis with dihaloarenes, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439–442. (b) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311–11316.

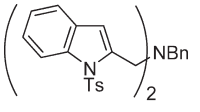
(14) For indole synthesis with haloanilines, see: (a) Olivi, N.; Spruyt, P.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2004**, *45*, 2607–2610. (b) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271–3274. (c) Sanz, R.; Guilarte, V.; Pérez, A. *Tetrahedron Lett.* **2009**, *50*, 4423–4426.

(15) For two-component indole synthesis via a Sonogashira-type reaction, see: (a) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846. (b) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307–3310.

(16) A portion of this study (several reactions in Tables 1, 2, and 5, and Scheme 3) was already reported in a preliminary communication: Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298.

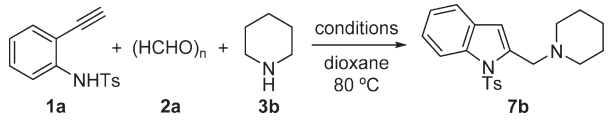
(17) We consider decreasing the amount of amine component is important and economical especially when using more valuable amines such as **11** (Scheme 4).

(18) When benzylamine was used instead of a secondary amine, dimeric compound **18** was produced in 82% yield (100 °C, 3 h, then reflux, 1 h).



18

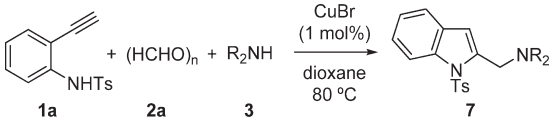
TABLE 1. Optimization of Reaction Conditions with Use of Ethynylaniline 1a and Piperidine 3b[a]



entry	CuX (mol %)	$(HCHO)_n$ equiv	additive (equiv)	time (h)	yield[b] (%)
1	CuBr (100)	2.0	Et_3N (2)	0.25	71
2	CuBr (10)	2.0	Et_3N (2)	0.25	84
3[c]	CuBr (1)	2.0	Et_3N (2)	0.25	92
4	CuBr (1)	2.0		0.25	87
5	CuBr (1)	1.5		1	75
6	CuBr (1)	1.1		12	70
7	$CuBr_2$ (1)	2.0		0.25	79
8	CuCl (1)	2.0		0.25	87
9	CuI (1)	2.0		0.25	83

[a]Unless otherwise stated, reaction was carried out with **1a** (0.18 mmol, 1 equiv), **2a** (equivalents shown), **3b** (1.1 equiv), and a copper salt (catalyst amount shown) in 1,4-dioxane (3 mL) at 80 °C. [b]Yields of isolated products. [c]The reaction was conducted on 1.25 mmol scale.

TABLE 2. Reactions with Various Amines[a]



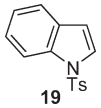
entry	amine **3**	time (h)	product	yield[c] (%)
1	$(i\text{-Pr})_2NH$ (**3a**)	0.25	**7a**	81
2	piperidine (**3b**)	0.25	**7b**	87
3	pyrrolidine (**3c**)	0.25	**7c**	89
4	Et_2NH (**3d**)[b]	0.25	**7d**	89
5	$(allyl)_2NH$ (**3e**)	0.5	**7e**	78
6	Bn_2NH (**3f**)	2	**7f**	78

[a]Unless otherwise stated, reactions were carried out with **1a** (0.18 mmol), **2a** (2.0 equiv), amine **3** (1.1 equiv), and CuBr (1 mol %) in 1,4-dioxane (3 mL) at 80 °C. [b]2 equiv of amine **3d** was used. [c]Yields of isolated products.

(Table 3). The reaction of 2-ethynylaniline **1a** with *n*-butyraldehyde **2b** and piperidine **3b** in the presence of CuBr efficiently gave the indole **7g** bearing a branched substituent in excellent yield (quant., entry 1). The bulky isobutyraldehyde **2c** required an elevated reaction temperature and prolonged reaction time leading to a slightly decreased yield of **7h** (77%, entry 2). Benzaldehyde **2d** was tolerated for this indole formation (entry 3). Similarly, use of a variety of substituted aryl aldehydes afforded the desired indoles **7j**–***l*** in good yields (entries 4–6).[19]

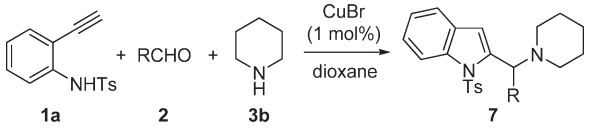
We expected that a reaction with a chiral ligand that coordinates to a copper atom could produce optically active 2-(aminomethyl)indoles. Knochel recently developed a

(19) When acetone was used instead of an aldehyde, Mannich-type reaction did not proceed and compound **19** was produced.



19

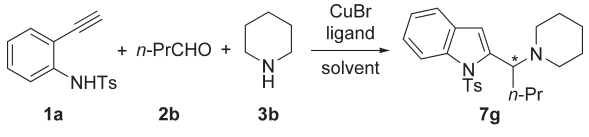
TABLE 3. Reactions with Various Aldehydes[a]

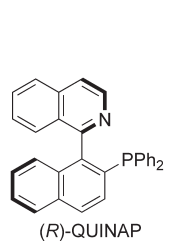


entry	aldehyde **2**	conditions	product (%yield)[b]
1	*n*-PrCHO (**2b**)	80 °C for 0.25 h	**7g** [R = *n*-Pr] (quant.)
2	*i*-PrCHO (**2c**)	reflux for 3 h	**7h** [R = *i*-Pr] (77)
3	PhCHO (**2d**)	reflux for 10 h	**7i** [R = Ph] (70)
4	(4-CO_2Me) C_6H_4CHO (**2e**)	reflux for 3 h	**7j** [R = (4-CO_2Me)C_6H_4] (76)
5	(4-Me) C_6H_4CHO (**2f**)	reflux for 3 h	**7k** [R = (4-Me)C_6H_4] (85)
6	(2-Br) C_6H_4CHO (**2g**)	reflux for 4 h	***7l*** [R = (2-Br)C_6H_4] (65)

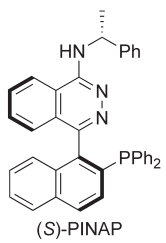
[a]Reactions were carried out with **1a** (0.18 mmol), **2** (2.0 equiv), amine **3b** (1.1 equiv), and CuBr (1 mol %) in 1,4-dioxane (1.5 mL) at 80 °C. [b]Yields of isolated products.

TABLE 4. Asymmetric Synthesis of 2-(Aminomethyl)indoles[a]





(*R*)-QUINAP



(*S*)-PINAP

entry	ligand	solvent	conditions	yield[b] (%)	product (% ee)[c]
1	(*R*)-QUINAP	dioxane	rt, 24 h	quant.	(+)-**7g** (47)
2	(*R*)-QUINAP	THF	rt, 72 h	86	(+)-**7g** (30)
3	(*R*)-QUINAP	benzene	rt, 72 h	86	(+)-**7g** (43)
4	(*R*)-QUINAP	toluene	rt, 72 h	94	(+)-**7g** (22)
5	(*S*)-PINAP	dioxane	rt, 10 h	quant.	(−)-**7g** (59)
6	(*S*)-PINAP	toluene	rt, 120 h	93	(−)-**7g** (56)
7	(*S*)-PINAP	benzene	rt, 120 h	quant.	(−)-**7g** (63)

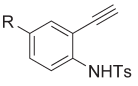
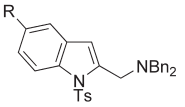
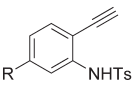
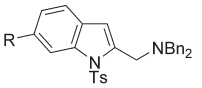
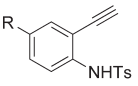
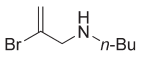
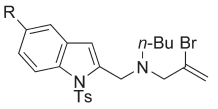
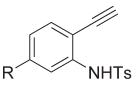
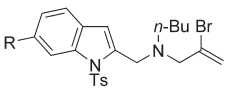
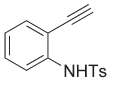
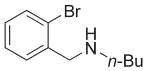
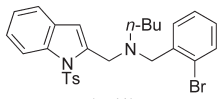
[a]Reactions were carried out with 2-ethynylaniline **1a**, CuBr (5 mol %), and ligand (5.5 mol %) in solvent (2 mL). [b]Yields of isolated products. [c]Determined by chiral HPLC (CHIRALCEL OD-H).

novel asymmetric synthesis of chiral propargylic amines with excellent ee values through a copper-catalyzed asymmetric Mannich-type reaction of alkynes with an aldehyde and a secondary amine using QUINAP as a chiral ligand (up to 98% ee).[20] Carreira reported the similar synthesis of propargylic amine in up to 99% ee with PINAP.[21] We initially examined the asymmetric three-component construction of

(20) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766. (b) Gommerman, N.; Knochel, P. *Chem. Commun.* **2004**, 2324–2325. (c) Gommerman, N.; Knochel, P. *Chem. Commun.* **2005**, 4175–4177.

(21) (a) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973. (b) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437–2440.

TABLE 5. Synthesis of Variously Substituted 2-(Aminomethyl)indoles[a]

entry	2-ethynylaniline	amine	conditions	product (yield[d])
		Bn_2NH		
1	**1b** (R = CF_3)	**3f**	80 °C, 3 h	**7m** (R = CF_3, 90%)
2	**1c** (R = CO_2Me)		80 °C, 5 h	**7n** (R = CO_2Me, 91%)
3	**1d** (R = Me)		80 °C, 5 h, then reflux, 1 h	**7o** (R = Me, 78 %)
				
4	**1e** (R = CF_3)	**3f**	80 °C, 3 h	**7p** (R = CF_3, 61%)
5	**1f** (R = CO_2Me)		80 °C, 5 h	**7q** (R = CO_2Me, 79%)
				
6[b]	**1a** (R = H)	**3g**	80 °C, 3 h, then reflux,[c] 1 h	**7r** (R = H, 98%)
7[b]	**1b** (R = CF_3)		80 °C, 3 h	**7s** (R = CF_3, 91%)
8[b]	**1c** (R = CO_2Me)		80 °C, 3 h	**7t** (R = CO_2Me, 98%)
9[b]	**1d** (R = Me)		80 °C, 3 h, then reflux,[c] 3 h	**7u** (R = Me, 98%)
				
10[b]	**1e** (R = CF_3)	**3g**	80 °C, 3 h, then reflux, 1 h	**7v** (R = CF_3, 94%)
11[b]	**1f** (R = CO_2Me)		80 °C, 3 h, then reflux, 1.5 h	**7w** (R = CO_2Me, 99%)
				
12	**1a**	**3h**	80 °C, 3 h, then reflux, 1 h	**7x** (80%)

[a]Unless otherwise stated, reactions were carried out with 2-ethynylaniline (0.18 mmol), **2a** (2.0 equiv), amine (1.1 equiv), and CuBr (1 mol %) in 1,4-dioxane (3 mL). [b]0.37 mmol scale. [c]4 equiv of Et_3N was added before reflux. [d]Yields of isolated products.

the 2-(aminomethyl)indole motif with *n*-butyraldehyde **2b** in dioxane in the presence of CuBr (5 mol %) and QUINAP (5.5 mol %) (Table 4). The reaction proceeded smoothly even at room temperature to give the desired **7g** in a quantitative yield but with only 47% ee (entry 1).[22] Screening of the reaction solvent did not improve the asymmetric induction (entries 2−4). When the reaction was carried out with PINAP in dioxane, **7b** was obtained with a slightly higher ee (59%, ee, entry 5). Use of PINAP in benzene gave the most promising result (63% ee), although a prolonged reaction time was necessary (entry 7). These results suggest that 2-ethynylaniline **1a** is a less effective alkyne component for an asymmetric Mannich reaction.[23]

Synthesis of Substituted 2-(Aminomethyl)indoles with Use of Various Ethynylanilines and Secondary Amines. Various substituted 2-ethynylanilines and asymmetrical secondary amines were then applied to the domino three-component coupling−cyclization (Table 5). 2-Ethynylanilines **1b** and **1c** substituted by an electron-withdrawing trifluoromethyl or methoxycarbonyl group at the para position to the amino group were reacted with paraformaldehyde **2a** and dibenzylamine **3f** in the presence of CuBr (1 mol %) to yield indoles **7m** (90% yield) and **7n** (91% yield), respectively (entries 1 and 2). Ethynylaniline **1d** bearing an electron-donating methyl group at the para position to the amino group also showed efficient compatibility leading to the corresponding indole **7o**. The reactions with 2-ethynylanilines **1e** and **1f** containing an electron-withdrawing group such as a trifluoromethyl or methoxycarbonyl group at the meta position were similarly converted into the corresponding indoles **7p** (61% yield) and **7q** (79% yield), respectively (entries 4 and 5). The asymmetrical 2-bromoallylamine **3g** and 2-bromobenzylamine **3h** were also applicable to this indole formation with use of various 2-ethynylanilines (entries 6−12), although Et_3N was necessary for the cyclization step when using 2-ethynylanilines **1a** and **1d** (entries 6 and 9).

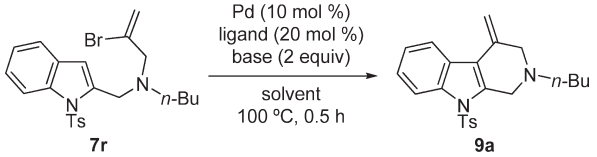
Construction of Polycyclic Indoles by Palladium-Catalyzed C−H Functionalization. A polycyclic indole motif is an important core framework that is widely found in biologically active compounds.[24] Therefore, development of a

(22) It was reported that the copper-catalyzed Mannich reaction of alkynes in the presence of (*R*)-QUINAP gave (*S*)-propargylamines, while the reaction with (*S*)-PINAP gave the corresponding (*R*)-isomers, see refs 20 and 21.

(23) Knochel and Carreira reported that phenylacetylene is a good component for enantioselective synthesis of propargylic amine with QUINAP or PINAP, see refs 20 and 21.

(24) For biologically active polycyclic indoles having a 2-(aminomethyl) moiety, see: (a) Espada, A.; Jiménez, C.; Debitus, C.; Riguera, R. *Tetrahedron Lett.* **1993**, *34*, 7773–7776. (b) Rashid, M. A.; Gustafson, K. R.; Boyd, M. R. *J. Nat. Chem.* **2001**, *64*, 1454–1456. (c) Glennon, R. A.; Grella, B.; Tyacke, R. J.; Lau, A.; Westaway, J.; Hudson, A. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 999–1002. (d) Liu, C.; Masuno, M. N.; MacMillan, J. B.; Molinski, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5941–5945. (e) Sonnenschein, R. N.; Farias, J. J.; Tenney, K.; Mooberry, S. L.; Lobkovsky, E.; Clardy, J.; Crews, P. *Org. Lett.* **2004**, *6*, 779–782.

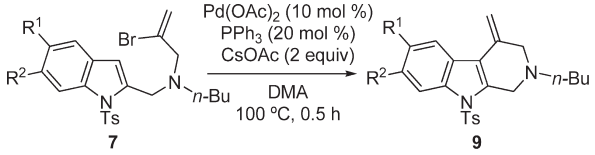
TABLE 6. Palladium-Catalyzed C−H Olefination[a]



entry	catalyst	ligand	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	CsOAc	DMF	47
2	$Pd(OAc)_2$	PPh_3	CsOAc	DMA	65
3	$Pd(PPh_3)_4$		CsOAc	DMA	7
4	$Pd(OAc)_2$	PPh_3	KOAc	DMA	35
5	$Pd(OAc)_2$	dppm	CsOAc	DMA	32

[a]Reactions were carried out with 2-(aminomethyl)indole **7r**, palladium catalyst (10 mol %), ligand (20 mol %), and base (2 equiv) in solvent (2 mL) at 100 °C for 0.5 h. [b]Yields of isolated products.

TABLE 7. Palladium-Catalyzed C−H Olefination with Use of Substituted 2-Ethynylanilines[a]



entry	R^1	R^2	indole	product	yield[b] (%)
1	CF_3	H	**7s**	**9b**	64
2	CO_2Me	H	**7t**	**9c**	54
3	CH_3	H	**7u**	**9d**	62
4	H	CF_3	**7v**	**9e**	62
5	H	CO_2Me	**7w**	**9f**	77

[a]Reactions were carried out with 2-(aminomethyl)indole **7**, $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and CsOAc (2 equiv) in DMA (2 mL) at 100 °C for 0.5 h. [b]Yields of isolated products.

convenient and reliable method for the construction of these frameworks is strongly required.[25] We expected that the present synthesis of 2-(aminomethyl)indoles via domino three-component coupling−cyclization would bring about an extremely useful synthetic route to this class of compounds. Thus, we surveyed the construction of polycyclic indole skeletons by three-component indole formation followed by palladium-catalyzed C−H functionalization at the C-3 position of indoles. First, 2-(aminomethyl)indole **7r** synthesized by the three-component indole formation (Table 5, entry 6) was subjected to $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and CsOAc (2 equiv) in DMF (Table 6, entry 1). The reaction proceeded cleanly to afford tetrahydropyridine-fused indole **9a** in 47% yield. When DMA was used as the reaction solvent, a higher yield of **9a** was observed (65%, entry 2). Further investigation of the palladium catalyst, ligand, and base (entries 3−5) revealed that the conditions shown in entry 2 were most effective. Encouraged by this result, we investigated the reaction with several 2-(aminomethyl)indoles containing an electron-withdrawing and -donating group to obtain variously substituted tetrahydropyridine-fused indoles **9b−f** in moderate to good yields (Table 7).

We next examined construction of polycyclic indoles by palladium-catalyzed C−H arylation using 2-(aminomethyl)-indole **7x**, which was prepared from ethynylaniline **1a** and amine **3h** (Table 5, entry 12). By treatment with 20 mol % of $Pd(OAc)_2$ and 40 mol % of PPh_3, dihydrobenzazepine-fused indole **10** was efficiently obtained in 80% yield over 2 steps (Scheme 3). One-pot three-component indole formation/Pd-catalyzed C−H arylation also provided polycyclic indole **10** in 84% yield from **1a**.

Synthetic Application to Calindol, Benzo[*e*][1,2]thiazines, and Indene. Calindol (**13**), which contains a 2-(aminomethyl)-indole motif, is a positive modulator of the human Ca^{2+} receptor showing a calcimimetic activity.[4] This compound could be easily synthesized by using our domino three-component indole formation (Scheme 4). As we expected, the reaction of 2-ethynylaniline **1a** with paraformaldehyde **2a** and 1-(1-naphthyl)ethylamine **11**[26] in the presence of CuBr directly produced a protected calindol **12**. The allyl and tosyl groups on the nitrogen atoms of **12** were easily removed by successive treatment with $Pd(PPh_3)_4$ (2 mol %)/NDMBA and TBAF to give calindol **13** in 90% yield over two steps.

We next envisioned the preparation of benzothiazine-1,1-dioxide derivatives **15** through domino MCR and cyclization. Since benzo[*e*][1,2]thiazine-1,1-dioxides are widely found in biologically active compounds including nonsteroidal anti-inflammatory drugs (NSAIDs),[27] various approaches to construct this structure have been reported.[28] We expected that the use of such a sulfonamide as **14**, an aldehyde, and a secondary amine in the presence of a copper catalyst would bring about a Mannich-type reaction followed by 6-*endo-dig* cyclization[29] to afford a benzo[*e*][1,2]thiazine **15**. The reaction of *N*-methyl- and *N*-ethylsulfonamides **14a** and

(25) For recent synthesis of polycyclic indoles, see: (a) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592–11593. (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425. (c) Kuroda, N.; Takahashi, Y.; Yoshinaga, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 1843–1845.

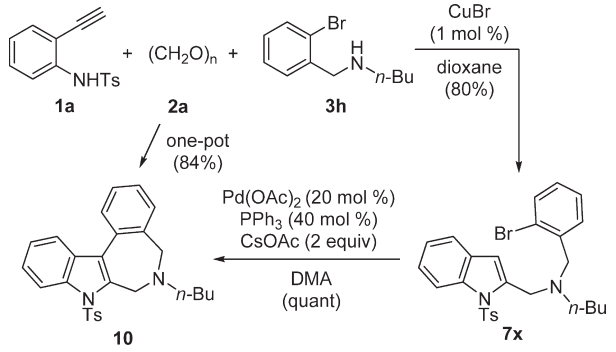
(26) For the preparation of **11**, see the Supporting Information.

(27) (a) Lombardino, J. G.; Wiesman, E. H. *J. Med. Chem.* **1971**, *14*, 973–977. (b) Lombardino, J. G.; Wiesman, E. H.; McLamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171–1175. (c) Lombardino, J. G.; Wiesman, E. H. *J. Med. Chem.* **1972**, *15*, 848–849. (d) Zinnes, H.; Lindo, N. A.; Sircar, J. C.; Schwartz, M. L.; Shavel, J., Jr. *J. Med. Chem.* **1973**, *16*, 44–48. (e) Zinnes, H.; Sircar, J. C.; Lindo, N.; Schwartz, M. L.; Fabian, A. C.; Shavel, J., Jr.; Kasulanis, C. F.; Genzer, J. D.; Lutomski, C.; DiPasquale, G. *J. Med. Chem.* **1982**, *25*, 12–18. (f) Kwon, S.-K.; Park, M.-S. *Arch. Pharm. Res.* **1992**, *15*, 251–255. (g) Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel, W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, *40*, 980–989. (h) Lee, E. B.; Kwon, S. K.; Kim, S. G. *Arch. Pharm. Res.* **1999**, *22*, 44–47.

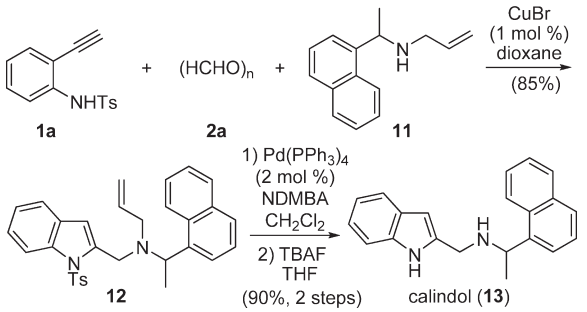
(28) (a) Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919–926. (b) Lombardino, J. G.; Kuhla, D. E. *Adv. Heterocycl. Chem.* **1981**, *28*, 73–126. (c) Motherwell, W. B.; Pennell, A. M. K. *J. Chem. Soc., Chem. Commun.* **1991**, 877–879. (d) Nemazanyi, A. G.; Volovenko, Y. M.; Neshchadimenko, V. V.; Babichev, F. S. *Chem. Heterocycl. Compd.* **1992**, *28*, 220–222. (e) Manjarrez, N.; Pérez, H. I.; Sorís, A.; Luna, H. *Synth. Commun.* **1996**, *26*, 585–591. (f) Manjarrez, N.; Pérez, H. I.; Sorís, A.; Luna, H. *Synth. Commun.* **1996**, *26*, 1405–1410. (g) Takahashi, M.; Morimoto, T.; Isogai, K.; Tsuchiya, S.; Mizumoto, K. *Heterocycles* **2001**, *55*, 1759–1769. (h) Layman, W. J.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem.* **2005**, *70*, 9147–9155. (i) Vidal, A.; Madelmont, J.-C.; Mounetou, E. *Synthesis* **2006**, 591–593. (j) Aliyenne, A. O.; Kraiem, J.; Kacem, Y.; Hassine, B. B. *Tetrahedron Lett.* **2008**, *49*, 1473–1475. (k) Zia-ur-Rehman, M.; Choudary, J. A.; Elsegood, M. R. J.; Siddiqui, H. L.; Khan, K. M. *Eur. J. Med. Chem.* **2009**, *44*, 1311–1316.

(29) Related synthesis of thiazines already has been reported, see: (a) Barange, D. K.; Batchu, V. R.; Gorja, D.; Pattabiraman, V. R.; Tatini, L. K.; Babu, J. M.; Pal, M. *Tetrahedron* **2007**, *63*, 1775–1789. (b) Barange, D. K.; Nishad, T. C.; Swamy, N. K.; Bandameedi, V.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Pal, M. *J. Org. Chem.* **2007**, *72*, 8547–8550.

SCHEME 3. Palladium-Catalyzed C−H Arylation and One-Pot Formation of Polycyclic Indoles from Ethynylaniline

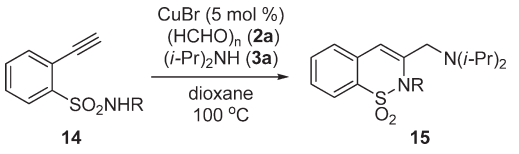


SCHEME 4. Synthesis of Calindol[a]



[a]NDMBA = *N*,*N*′-dimethylbarbituric acid.

TABLE 8. Synthesis of Benzo[*e*][1,2]thiazine-1,1-dioxide Motif by Three-Component Coupling and Cyclization[a]



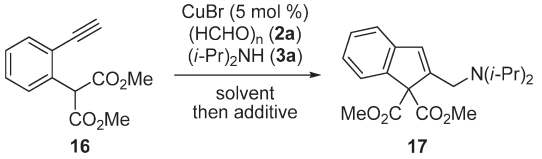
entry	R	time (h)	product	yield[b] (%)
1	Me (**14a**)	16	**15a**	34
2	Et (**14b**)	22	**15b**	37
3	(4-CH_3)C_6H_4 (**14c**)	3.5	**15c**	90
4	Ph (**14d**)	4	**15d**	92
5	(4-MeO)C_6H_4 (**14e**)	3.5	**15e**	89
6	(4-Cl)C_6H_4 (**14f**)	3	**15f**	95

[a]Reactions were carried out with **2a** (2.0 equiv) and **3a** (1.2 equiv) in the presence of CuBr (5 mol %) in 1,4-dioxane (3 mL) at 100 °C. [b]Yields of isolated products.

14b under standard conditions gave the desired benzothiazines **15a** and **15b**, respectively, but in low yields (34% and 37%, respectively, entries 1 and 2, Table 8). Considering that acidity of the amide proton in **14a** and **14b** would be insufficient for the cyclization step, we next examined the reaction of sulfonanilide derivatives bearing a related structure to 2-ethynylanilines **1**. As we expected, the reaction of sulfonanilide **14c** gave the benzothiazine **15c** in high yield (90%, entry 3). Other sufonanilides **14d**−**f** were also good reactants in this three-component thiazine synthesis (entries 4−6).

Finally, we investigated the synthesis of 2-(aminomethyl)-indene-1,1-dicarboxylate **17** using this domino Mannich-type reaction/cyclization strategy (Table 9). Disappointingly, the reaction of malonate derivative **16** with $(HCHO)_n$ **2a** and $(i\text{-Pr})_2NH$ **3a** in dioxane in the presence of CuBr (5 mol %) did not afford the desired indene **17**, only giving the Mannich adduct in 90% yield (entry 1). A careful evaluation of the reaction conditions revealed that the use of more polar DMF as the solvent converted **16** into the desired 2-(aminomethyl) indene **17** in 39% yield. Addition of $(i\text{-Pr})_2NEt$ after completion of the Mannich reaction efficiently promoted the indene formation leading to **17** in 70% yield.

TABLE 9. Synthesis of 2-(Aminomethyl)indene 17[a]



entry	solvent	additive[b]	temp (°C)	time (h)	yield[c] (%)
1	dioxane		80	2	0
2	DMF		150	5	39
3	DMF	$(i\text{-Pr})_2NEt$	110	10	70

[a]Reactions were carried out with **2a** (2.0 equiv) and **3a** (1.2 equiv) in solvent (2 mL) in the presence of CuBr (5 mol %). [b]Added after completion of the Mannich type reaction (ca. 30 min, monitored by TLC). [c]Yields of isolated products.

Conclusions

We have developed a novel synthesis of 2-(aminomethyl)-indoles through a copper-catalyzed domino three-component coupling−cyclization. This domino reaction forming two carbon−nitrogen bonds and one carbon−carbon bond is the first catalytic multicomponent indole construction producing water as the only theoretical waste. The use of the chiral ligand PINAP in the reaction with alkyl aldehydes produced the corresponding indole bearing a branched substituent **7g** with moderate ee values. This reaction is synthetically useful for diversity-oriented synthesis of not only 2-(aminomethyl)indoles but also tetrahydropyridine- and benzazepine-fused indoles, using readily available reaction components. The benzo[*e*][1,2]thiazine and indene motif can also be constructed by using a similar domino three-component coupling and cyclization strategy.

Experimental Section

General Procedure for Synthesis of 2-(Aminomethyl)indole: Synthesis of 2-[(*N*,*N*-Diisopropylamino)methyl]-1-tosylindole (7a). To a stirred mixture of 2-ethynylaniline **1a** (50.0 mg, 0.18 mmol), $(HCHO)_n$ (11.1 mg, 0.37 mmol), and CuBr (0.3 mg, 0.0018 mmol) in dioxane (3.0 mL) was added diisopropylamine **3a** (28.6 μL, 0.20 mmol) at room temperature under argon, and the reaction mixture was stirred at 80 °C for 15 min. Concentration under reduced pressure followed by column chromatography purification over silica gel with hexane−EtOAc (10:1) afforded the indole **7a** (57.3 mg, 81%) as a colorless solid: mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 12H, 4 × CHCH_3), 2.33 (s, 3H, ArCH_3), 3.01−3.11 (m, 2H, 2 × CH), 3.92 (d, J = 1.5 Hz, 2H, CH_2), 6.79 (s, 1H, 3-H), 7.18−7.25 (m, 4H, Ar), 7.41−7.43 (m, 1H, Ar), 7.64−7.67 (m, 2H, Ar), 8.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (4C), 21.5, 44.4, 49.3 (2C), 110.1, 114.4, 120.2, 123.3, 123.5, 126.3 (2C),

129.8 (2C), 129.9, 136.4, 137.8, 144.4, 144.6; MS (FAB) *m*/*z* (%) 385 (MH^+, 100), 284 (75); HRMS (FAB) calcd for $C_{22}H_{29}N_2O_2S$ (MH^+) 385.1950, found 385.1953.

General Procedure for Synthesis of Tetrahydropyridine-Fused Indole: Synthesis of 2-Butyl-4-methylene-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (9a). The mixture of indole **7r** (50.0 mg, 0.11 mol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), PPh_3 (5.5 mg, 0.021 mmol), and CsOAc (40.4 mg, 0.021 mmol) in DMA (2 mL) was stirred at 100 °C for 0.5 h under argon. Concentration under reduced pressure followed by column chromatography purification over silica gel with hexane−AcOEt (4:1) gave **9a** (26.8 mg, 65%) as an yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.30−1.38 (m, 2H, CH_2CH_3), 1.53−1.59 (m, 2H, NCH_2CH_2), 2.33 (s, 3H, $ArCH_3$), 2.53−2.56 (m, 2H, NCH_2CH_2), 3.38 (s, 2H, NCH_2), 4.16 (s, 2H, NCH_2), 5.10 (s, 1H, C=CH*H*), 5.59 (s, 1H, C=C*H*H), 7.20 (d, J = 8.6 Hz, 2H, Ar), 7.26−7.33 (m, 2H, Ar), 7.67 (d, J = 8.6 Hz, 2H, Ar), 7.76−7.78 (m, 1H, Ar), 8.18 (d, J = 8.1 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.6, 21.5, 29.6, 51.5, 55.8, 57.7, 108.6, 114.4, 116.5, 120.4, 124.0, 124.4, 126.4 (2C), 127.3, 130.0 (2C), 135.5, 135.7, 136.1, 136.6, 145.1; MS (FAB) *m*/*z* (%) 395 (MH^+, 100); HRMS (FAB) calcd for $C_{23}H_{27}N_2O_2S$ (MH^+) 395.1793, found 395.1804.

General Procedure for Synthesis of Benzo[*e*][1,2]thiazine-1,1-dioxide: 3-[(*N*,*N*-Diisopropylamino)methyl]-2-methyl-2*H*-benzo-[*e*][1,2]thiazine-1,1-dioxide (15a). To a stirred mixture of **14a** (50.0 mg, 0.26 mmol), $(HCHO)_n$ (15.4 mg, 0.51 mmol), and CuBr (1.8 mg, 0.013 mmol) in dioxane (3 mL) was added diisopropylamine (43.1 μL, 0.31 mmol) at room temperature under argon. The reaction mixture was stirred at 100 °C for 16 h. Concentration under reduced pressure followed by column chromatography purification over silica gel with hexane−EtOAc (8:1) gave **15a** as a pale yellow solid (27.2 mg, 34%): mp 94.5−98.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, J = 6.9 Hz, 12H, 4 × $CHCH_3$), 3.11−3.19 (m, 2H, 2 × CH), 3.40 (s, 3H, NCH_3), 3.50 (s, 2H, NCH_2), 6.51 (s, 1H, 4-H), 7.32 (d, J = 8.0 Hz, 1H, Ar), 7.39−7.42 (m, 1H, Ar), 7.52−7.55 (m, 1H, Ar), 7.84 (d, J = 8.0 Hz, 1H Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4 (4C), 30.9, 47.5 (2C), 48.4, 109.0, 121.5, 126.3, 126.8, 130.5, 131.7, 132.9, 143.5. Anal. Calcd for $C_{16}H_{24}N_2O_2S$: C, 62.30; H, 7.84; N, 9.08. Found: C, 62.09; H, 7.57; N, 8.88.

Dimethyl 2-[(*N*,*N*-Diisopropylamino)methyl]indene-1,1-dicarboxylate (17). To a stirred mixture of **16** (51.0 mg, 0.22 mmol), $(HCHO)_n$ **2a** (13.2 mg, 0.44 mmol), and CuBr (1.58 mg, 0.011 mmol) in DMF (2 mL) was added diisopropylamine **3a** (34.0 μL, 0.24 mmol) at room temperature under argon. After the reaction mixture was stirred at 110 °C for 30 min, diisopropylethylamine (77.0 μL, 0.44 mmol) was added to the mixture. The mixture was additionally stirred at 110 °C for 9.5 h. Concentration under reduced pressure followed by column chromatography purification over alumina with hexane−EtOAc (20:1) gave **17** (52.8 mg, 70%) as a brown oil: IR (neat) 1732 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, J = 14.0 Hz, 12H, 4×CCH_3), 3.06−3.11 (m, 2H, 2 × NCH), 3.50 (d, J = 1.1 Hz, 2H, NCH_2), 3.73 (s, 6H, 2 × OCH_3), 7.00 (s, 1H, 3-H), 7.15−7.18 (m, 1H, Ar), 7.24−7.31 (m, 2H, Ar), 7.57 (d, J = 7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7 (4C), 43.8, 48.7, 53.0 (2C), 70.3, 120.8, 124.8, 125.1, 128.7, 131.6, 141.0, 144.3, 149.4, 168.9 (2C); MS (FAB) *m*/*z* 346 (MH^+, 100), 286 (35), 245 (60); HRMS (FAB) calcd for $C_{20}H_{28}NO_4$ (MH^+) 346.2018, found 346.2008.

Acknowledgment. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (A) (H.O.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the program for the Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO), and the Targeted Proteins Research Program. Y.O. is grateful to Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

Supporting Information Available: Experimental procedure, full characterization, ^{1}H and ^{13}C NMR spectra of all new compounds, and COSY spectra of **7a**, **9a**, **15a**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.