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Solid-Phase Synthesis of Indolecarboxylates Using Palladium-Catalyzed Reactions

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Polymer-supported, palladium-catalyzed cyclization reactions effectively synthesized indolecarboxylates. Palladium-catalyzed carbon−carbon bond-forming reactions of immobilized enaminoesters followed by transesterification yielded indole 2- or 3-carboxylates with various functional groups on the benzene ring. Indolecarboxylates were efficiently cyclized via an intramolecular palladium-catalyzed amination reaction of immobilized N-substituted dehydrohalophenylalanines, and immobilized *N*-acetyl-dehydroalanines were efficiently converted into indolecarboxylates via tandem Heck−amination reactions.

Introduction

A major aspect of solid-phase chemistry is synthesizing heterocyclic compounds from various methods.[1] In particular, low molecular weight heterocyclic compounds are used in pharmaceutical lead compounds because they are highly functionalizable scaffolds, and indoles have received a lot of attention in solution- and solid-phase chemistry.[2,3] The reported solid-phase indole syntheses can be classified into several categories by reaction type. These methods provide indoles with a variety of substituted patterns, and indoles that have substituents at the C-2 and C-3 positions are critical to biological activity. Fischer indolization of immobilized ketones with phenylhydrazines should ensure diversity at the C-2 and the C-3 positions, as well as on the benzene ring. However, this reaction has limitations: such electron-deficient para-substituted hydrazines cannot cyclize, and meta-substituted phenylhydrazines usually yield a mixture of 4- and 6-substituted indoles.[3a] In addition, under strongly acidic conditions, an acid-stable linker[3a,l] is required. Palladium-catalyzed coupling reactions have the potential to completely control the substitution position on the benzene ring, which seems to be adequate since combinatorial chemistry has recently moved from using mixture libraries to single compounds. Although several solid-phase indole syntheses using palladium-catalyzed reactions are reported, more research is expected in order to improve solid-phase methodologies for synthesizing diverse heterocyclic compounds. Therefore, we have examined novel methods for obtaining several immobilized intermediates and palladium-catalyzed cyclizations. This paper reports the results of the solid-phase synthesis of indoles and related heterocyclic compounds[4] (Figure 1). While the manuscript was being prepared, two alternative solid-phase syntheses of 2,3-disubstituted indoles using a modified Madelung indole synthesis and a modified Bischler indole synthesis have appeared in the literature.[3r,s] High diversity at the C-2 or the C-3 positions can be introduced using the typical building blocks and one of these methods.

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(1) (a) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61−91. (b) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369−418. (c) Franzén, R. J. *J. Comb. Chem.* **2000**, *2*, 195−214. (d) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998. (e) Czarnik, A. W.; DeWitt, S. H. *A Practical Guide to Combinatorial Chemistry*; American Chemical Society: Washington, DC, 1997. (f) Wilson, S. R., Czarnik, A. W., Eds. In *Combinatorial Chemistry*; John Wiley & Sons: New York, 1997.

(2) For recent review of indole synthesis, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045−1075 and references therein.

(3) (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869−4872. (b) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189−7192. (c) Hughes, I. *Tetrahedron Lett.* **1996**, *37*, 7595−7598. (d) Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804−1809. (e) Fagnola, H. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307−2310. (f) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439−2442. (g) Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963−7966. (h) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449−4452. (i) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317−8320. (j) Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799−5802. (k) Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett.* **2000**, *41*, 6253−6257. (l) Yang, L. *Tetrahedron Lett.* **2000**, *41*, 6981−6984. (m) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89−92. (n) Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751−4754. (o) Wu, T. Y. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett.* **2001**, *3*, 3827−3830. (p) Macleod, C.; Hartley, R. C.; Hamprecht, W. *Org. Lett.* **2002**, *4*, 75−78. (q) Willoughby, C. A.; Hutchins, S. M.; Rosauer, K. G.; Dhar, M. J.; Chapman, K. T.; Chicchi, G. G.; Sadowski, S.; Weinberg, D. H.; Patel, S.; Malkowitz, L.; Salvo, J. D.; Pacholok, S. G.; Cheng, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 93−96. (r) Wacker, D. A.; Kasireddy, P. *Tetrahedron Lett.* **2002**, *43*, 5189−5191. (s) Lee, S.-H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Comb. Chem.* **2003**, *5*, 188−196.

(4) Portion of this work has been previously communicated: (a) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2002**, *4*, 191−192. (b) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210−211. (c) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2137−2138.

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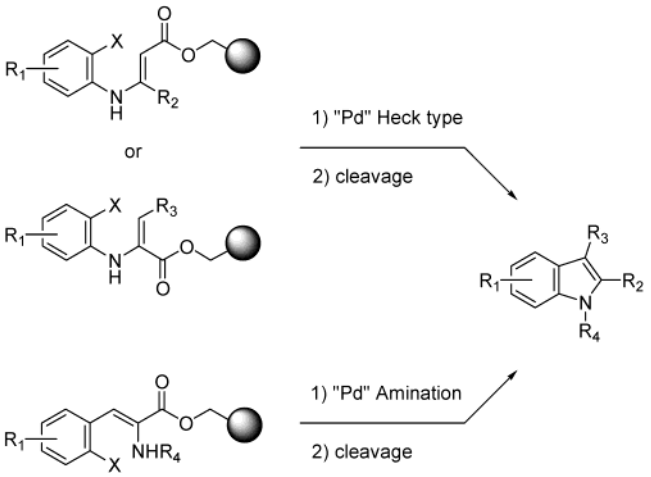
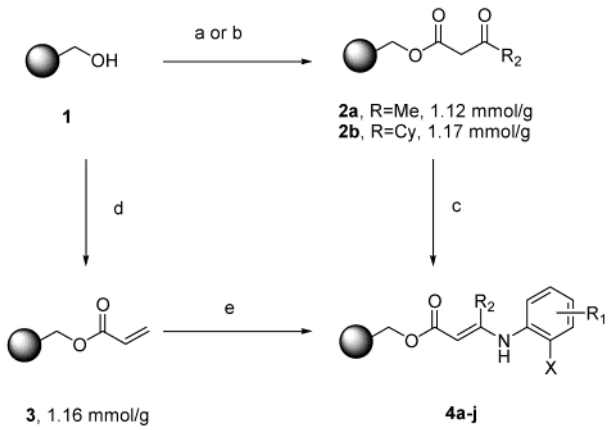


FIGURE 1.

SCHEME 1[a]



[a] (a) *tert*-Butyl acetoacetate (10 equiv), toluene, 100 °C, 4 h; (b) 5-acyl-Meldrum's acid adduct (5 equiv), THF, reflux, 5 h; (c) 2-haloanilines (1.5 equiv), *p*-TsOH (2 mol %), benzene, reflux, 4 h, Dean Stark apparatus; (d) acryloyl chloride (8.6 equiv), DIEA (8.6 equiv), THF, rt, 5 h; (e) $PdCl_2(CH_3CN)_2$ (20 mol %), 1,4-benzoquinone (2 equiv), LiCl (20 equiv), 2-haloanilines (2.0 equiv), THF, 50 °C, 24 h.

Results and Discussion

Preparation of Immobilized *β*-(2-Halophenyl)-amino-Substituted α,*β*-Unsaturated Esters (Scheme 1). Previously, indole-3-carboxylates were synthesized in solution via an intramolecular palladium-catalyzed cyclization of *β*-(2-halophenyl)amino-substituted α,*β*-unsaturated esters,[5] and we first applied this methodology to solid-phase indole synthesis. In solution, the most straightforward method for synthesizing *β*-enaminoesters is to condense an amine with a *β*-ketoester. Immobilized *β*-ketoesters **2a** and **2b** were prepared according to a literature procedure.[6−8] The reactions were followed by monitoring the ketone (1717 cm^{-1}) and ester (1742 cm^{-1}) ATR FT-IR peaks. After washing and drying, the loading of **2a** and 2**b** were determined from the yield of 3-alkyl-3-pyrazolin-5-one, which was cleaved and isolated from the resin by treatment with 5% hydrazine in EtOH. Although azeotropic water had to be removed, acid-catalyzed condensation of resin **2a** with 2-iodoaniline in benzene proceeded smoothly to yield the corresponding immobilized enaminoester, **4a**. The strong peak at 1611 cm^{-1}, which is the absorption of the double bond in the enaminoester, indicated the formation of resin **4a**. Immobilized enaminoesters, **4b**−**d**, were obtained with reasonable loading according to a similar procedure. Unfortunately, a lower conversion was obtained when resin **2b** was used under acid-catalyzed conditions. The lower conversion is probably due to the lower reactivity of the sterically hindered carbonyl group.

TABLE 1. Immobilized *β*-(2-Halophenyl)amino-Substituted α,*β*-Unsaturated Esters

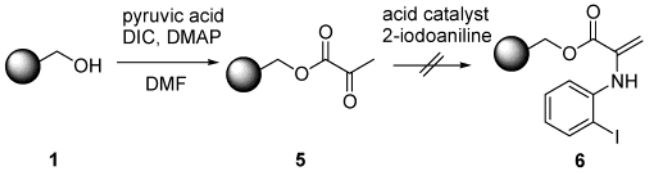
4	X	R_1	R_2	method	loading (mmol/g)
a	I	H	Me	A	0.78
b	Br	H	Me	A	0.86
c	Br	4-Me	Me	A	0.93
d	Br	5-CF_3	Me	A	0.77
e	I	H	H	B	0.98
f	Br	H	H	B	1.06
g	Br	4-Me	H	B	0.68
h	Br	4-CF_3	H	B	0.81
i	Br	5-NO_2	H	B	0.82
j	Br	5-CF_3	H	B	0.88

An alternate procedure for producing the unsubstituted enaminoesters **4e**−**j** (R_1 = H) was investigated. Many oxidative transformations have been achieved using a palladium(II) catalyst in the presence of oxidizing agents in solution.[9] However, a palladium(II)−chloride-catalyzed oxidative amination reaction between REM (regeneratable Michael linker) resin **3**[10] and haloanilines has not been reported. To prepare a halophenylamino-substituted REM resin, initially a palladium-catalyzed oxidative amination was performed by agitating REM resin **3**, 2 equiv of 2-iodoaniline, 20 mol % $PdCl_2(CH_3CN)_2$, 2 equiv of 1,4-benzoquinone, and a large excess of LiCl in THF at room temperature for 24 h. Resin **4e** exhibited a strong IR peak at 1623 cm^{-1}, which is typical of enaminoesters, but there was also a weak peak at 1723 cm^{-1} (REM resin), which indicted that resin **3** was not completely converted into **4e**. When the reaction was conducted at 50 °C for 24 h, the FT-IR spectrum indicated that the reaction went to completion. Analyzing the nitrogen on the polymer bead gave estimations of the loading of **4a**−**j** (Table 1). Under these conditions, both electron-donating and electron-withdrawing substituted anilines could be used.

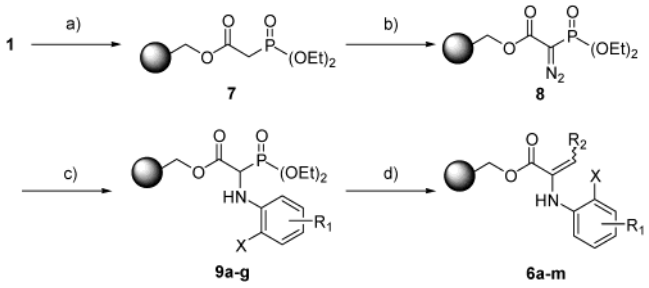
Preparation of Immobilized α-(2-Halophenyl)-amino-Substituted α,*β*-Unsaturated Esters. Acid-catalyzed condensation was reexamined to prepare immobilized α-enaminoesters (Scheme 2). Thus, condensation of hydroxymethyl polystyrene resin with pyruvic acid was

(5) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215−219.
(6) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667−668.
(7) Tietze, L. F.; Steinmetz, A. Balkenhohl, F. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1303.
(8) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem*. **1978**, *43*, 2087−2088.
(9) (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books; Sausalito, CA, 1999. (b) Bozell, J. J.; Hegedus, L. S. *J. Org. Chem*. **1981**, *46*, 2561−2563. (c) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 927−928.
(10) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc*. **1997**, *119*, 3288−3295.

SCHEME 2



SCHEME 3[a]



[a] (a) Diethylphosphonoacetic acid (3 equiv), 2,6-dichlorobenzoyl chloride (3 equiv), pyridine (6 equiv), DMF, rt, 16 h; (b) *p*-$C_{12}H_{25}PhSO_2N_3$ (3 equiv), DBU (3 equiv), toluene, rt, 4 h; (c) 5 mol % $Rh_2(OAc)_4$, 2-haloanilines (5 equiv), toluene, 80 °C; (d) R_2CHO (3 equiv), DBU (3 equiv), THF, rt, 12 h.

conducted in standard DIC-coupling conditions followed by several acid-catalyzed condensation of immobilized α-keto-ester **5** with 2-iodoaniline. However, the reactions were unsuccessful and only gave the starting polymer **5**.

Various alternatives for preparing α-enaminoesters were considered, and a rhodium-catalyzed N−H insertion reaction on immobilized α-diazophosphonoacetate with aniline, followed by the Horner−Emmons reaction, was attempted. Recently, carbene and carbenoid species insertion reactions have been widely used in organic chemistry.[11] Moody and co-workers reported the N−H insertion reaction of rhodium carbenoids, which effectively functionalized amides, carbamates, and anilines.[12] Although rhodium carbenoid insertion reactions are already used to construct several heterocyclic compounds and cyclopropane derivatives in solid-phase chemistry,[13] N−H insertion reaction of α-diazophosphonoacetate on a polymer support has not been reported. Immobilized diethylphosphonoacetate was prepared by reaction of a hydroxymethyl polystyrene resin with diethylphosphonoacetic acid according to the mixed anhydride method[14] (Scheme 3). When resin **7** was formed, the FT-IR spectrum displayed a strong peak at 1735 cm^{-1}. Diazo transfer to resin **7** was achieved by treating **7** with *p*-dodecylbenzenesulfonyl azide using DBU as the base in toluene. The resulting immobilized α-diazophosphonoacetate showed characteristic absorptions at 2124 and 1702 cm^{-1}, which indicated diazo and ester functions, respectively. The loading of resin **8**, which was estimated by nitrogen elemental analysis of the polymer beads, was 1.1−1.2 mmol/g. On the basis of the loading of **1**, the measured values indicated a smooth and reasonable transformation. Next, a rhodium-catalyzed insertion reaction with haloanilines was investigated. Treating **8** with 2-iodoaniline in the presence of rhodium acetate (5 mol %) in toluene at 80 °C for 40 h yielded **9a**, the N−H insertion product. Resin **9a** shows an absorption peak at 1737 cm^{-1}. During the reaction, the characteristic diazo absorption peak completely disappeared, which is consistent with the elemental analysis of polymer **9a** and suggested a high conversion yield. A catalytic amount of phenol was used as an additive to improve the reactivity of 2-iodoaniline, since a previous report suggested an additive effect of phenol[12c] and the rate was vastly accelerated. However, adding phenol was not necessary for 2-bromoaniline derivatives because the reaction was completed within 24 h for both the electron-donating and the electron-withdrawing groups on the benzene ring with high loading (0.85−1.04 mmol/g). The subsequent solid-phase Horner−Emmons reactions[14,15] of **9a**−**g** with aromatic and aliphatic aldehydes (3 equiv) using DBU[16] (3 equiv) as a base proceeded smoothly, and a broad range of aldehydes were applicable to the reaction, as shown in Table 2. The reaction was monitored by the disappearance of the peak at 1737 cm^{-1} and the new absorption of **6a** at 1702 cm^{-1}.

TABLE 2. Immobilized α-(2-Halophenyl)amino-Substituted α,β-Unsaturated Esters

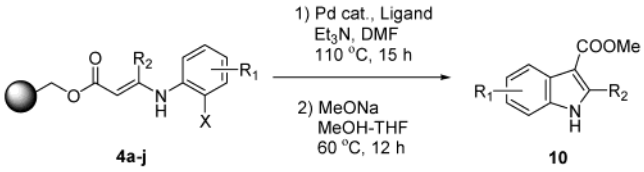
6	X	R_1	R_2	loading (mmol/g)[a]
a	I	H	Ph	1.00
b	Br	H	Ph	1.04
c	I	H	4-$MeOC_6H_4$	0.94
d	Br	H	2-pyridyl	0.90
e	I	H	2-thienyl	0.93
f	I	H	cyclohexyl	0.98
g	I	H	*n*-pentyl	1.10
h	Br	4-Me	Ph	0.92
i	Br	5-OMe	Ph	1.06
j	Br	4-CF_3	Ph	0.93
k	Br	5-CF_3	Ph	0.89
l	Br	5-NO_2	Ph	0.75
m	Br	4,6-diF	Ph	0.42

[a] Loading values of **6a**−**m** were estimated by elemental analysis of nitrogen on the polymer beads.

Solid-Phase Synthesis of Indolecarboxylates Using Palladium-Catalyzed Intramolecular Coupling (Table 3). The palladium-catalyzed cyclization was investigated using immobilized enaminoester, **4**. Resin **4a** was heated at 110 °C for 15 h in the presence of 15 mol % $Pd(OAc)_2$ and triethylamine in DMF. Then transesterification of the immobilized indole carboxylate using MeONa in MeOH−THF at 60 °C resulted in a 27% yield of methyl indole 3-carboxylate, **10a**, based on the loading of **4a** after SiO_2 column chromatography. Adding P(2-Tol)$_3$ to the reaction mixture increased the isolated yield from 27 to 63%. For aryl-bromide substrate, **4b**, $Pd_2(dba)_3$·

(11) Ye, T.; McKervey, M. A. *Chem. Rev*. **1994**, *94*, 1091.
(12) (a) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879−2884. (b) Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885−2888. (c) Haigh, D. *Tetrahedron* **1994**, *50*, 3177−3194. (d) Moody, C, J.; Ferris, L.; Haigh, D.; Swann, E. *Chem. Commun*. **1997**, 2391−2392.
(13) (a) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett*. **2001**, *3*, 2173-2176. (b) Iso, Y.; Shindo, H.; Hamana, H. *Tetrahedron* **2000**, *56*, 5353−5361. (c) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett*. **1997**, *38*, 6973−6976. (d) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett*. **1997**, *38*, 7139−7142. (e) Cano, M.; Camps, F.; Joglar, J. *Tetrahedron Lett*. **1998**, *39*, 9819−9822.
(14) Salvino, J. M.; Kiesow, T. J.; Darnbrough, S.; Labaudiniere, R. *J. Comb. Chem*. **1999**, *1*, 134−139.
(15) Wipf, P.; Henninger, T. C. *J. Org. Chem*. **1997**, *62*, 1586−1587.
(16) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A. Mangold, R.; Meyer, R. Riedl, B. *Synthesis* **1992**, 487.

TABLE 3. Palladium-Catalyzed Intramolecular Cyclization Reactions



4	X	10	R_1	R_2	Pd catalys	ligand	purity (%)[a]	yield (%)[b]
a	I	**a**	H	Me	$Pd(OAc)_2$	none	91	27
a	I	**a**	H	Me	$Pd(OAc)_2$	$P(2\text{-Tol})_3$	90	63
b	Br	**a**	H	Me	$Pd(OAc)_2$	$P(2\text{-Tol})_3$	93	35
b	Br	**a**	H	Me	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	92	53
c	Br	**b**	5-Me	Me	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	93	43
d	Br	**c**	6-CF_3	Me	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	93	32
e	I	**d**	H	H	$Pd_2(dba)_3$	none	83	74
e	I	**d**	H	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	87	78
f	Br	**d**	H	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	90	69
g	Br	**e**	5-Me	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	nd	57
h	Br	**f**	5-CF_3	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	nd	65
i	Br	**g**	6-NO_2	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	90	39
j	Br	**h**	6-CF_3	H	$Pd_2(dba)_3$	$P(2\text{-Tol})_3$	82	66

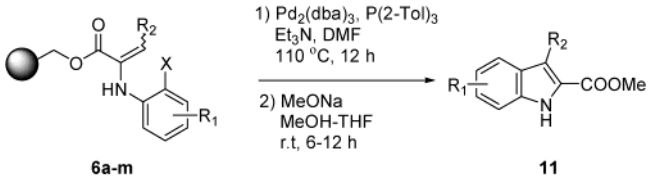
[a] Purity determined by HPLC at 254 nm of crude product. [b] Isolated yields (>95% pure as judged by NMR and HPLC analysis) of **10** after SiO_2 column chromatography were based on the loading of **4a**−**j**.

$CHCl_3$ worked better than $Pd(OAc)_2$. Table 3 summarizes the optimized conditions for **4c**−**j**. Under optimum conditions, 2-unsubstituted 3-indolecarboxylates generally produced better results than 2-methyl 3-indolecarboxylates. The main reason for the lower yield of 2-methyl 3-indolecarboxylates is probably the lower stability of the immobilized enaminoesters under the coupling conditions. In a preliminary study in solution, benzyl *β*-(2-iodophenyl) amino-α-methyl acrylate was completely decomposed into 2-iodoaniline and benzyl acetoacetate in $CDCl_3$. However, the purity of the 2-methyl 3-indolecarboxylates was very high (>90% by HPLC analysis).

In a similar fashion, the palladium-catalyzed reactions for the polymers, **6a**−**m**, also yielded the 3-substituted indole 2-carboxylates, **11a**−**l**, and Table 4 summarizes the yields. After heating the *p*-methoxy-substituted resin **6i** for 40 h, the corresponding indolecarboxylate, **11h**, and a considerable amount of uncyclized enamine were obtained. The reaction was significantly improved by replacing $P(2\text{-Tol})_3$ with *t*-Bu_3PHBF_4,[17] and **11h** was obtained in 67% yield.

Intramolecular Horner−Emmons Reaction on a Polymer Support. α-Diazophosphonates in solution are versatile building blocks,[11,12,18] and we have extended this chemistry to include polymer-supported reactions. Treating **8** with 2-substituted anilines or 2-substituted benzoic acid in the presence of rhodium acetate (5 mol %) in toluene at 80 °C yielded the N−H or O−H insertion products. The FT-IR spectrum indicated that the diazo function was completely consumed, although using 2′-aminobenzophenone required a longer reaction time. The intramolecular Horner−Emmons reaction and subsequent cleavage yielded indolecarboxylates and isocoumarins (Table 5). For the isocoumarins, after cleaving, the reduced methylene compound from the α-diazophosphonate was detected in the crude product. The side reaction caused the low yield of the O−H insertion reaction.

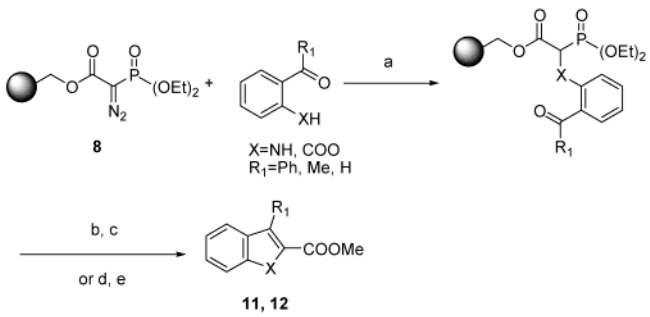
TABLE 4. Palladium-Catalyzed Intramolecular Cyclization Reactions



6	X	11	R_1	R_2	purity (%)[a]	yield (%)[b]
a	I	**a**	H	Ph	70	48
b	Br	**a**	H	Ph	82	52
c	I	**b**	H	4-$MeOC_6H_4$	52	40
d	Br	**c**	H	2-pyridyl	65	54
e	I	**d**	H	2-thienyl	55	31
f	I	**e**	H	cyclohexyl	nd	72
g	I	**f**	H	*n*-pentyl	nd	60
h	Br	**g**	5-Me	Ph	88	62
i	Br	**h**	6-OMe	Ph	nd	25, 67[c]
j	Br	**i**	5-CF_3	Ph	nd	56
k	Br	**j**	6-CF_3	Ph	nd	62
l	Br	**k**	6-NO_2	Ph	nd	60
m	Br	**l**	5,7-diF	Ph	69	40

[a] Purity determined by HPLC at 254 nm of crude product. [b] Isolated yields (>95% pure as judged by NMR and HPLC analysis) of **11** after SiO_2 column chromatography were based on the loading of **6a**−**m**. [c] $Pd_2(dba)_3{\cdot}CHCl_3$ (7.5 mol %), 30 mol % *t*-Bu_3PHBF_4, and 3 equiv of Cy_2NMe were used.

TABLE 5. Rhodium-Catalyzed Insertion and Intramolecular Horner−Emmons Reactions[a]



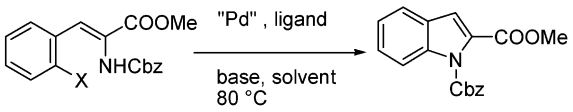
compd	X	R_1	purity (%)[b]	yield (%)[c]
11a	N	Ph	84	75
11m	N	Me	95	87
12a	COO	Ph	87	27
12b	COO	Me	76	21
12c	COO	H	42	15

[a] Reaction conditions: (a) $Rh_2(OAc)_4$ (5 mol %), toluene, 80 °C, 12−42 h; (b) DBU (5 equiv), THF, rt, 12 h; (c) MeONa (5 equiv), MeOH, THF, rt, 8 h, for indoles; (d) DBU (3 equiv), CH_2Cl_2, rt, 12 h. (e) Et_3N, MeOH, THF, 70 °C, 15 h, for isocoumarins. [b] Purity determined by HPLC at 254 nm of the crude product. [c] Isolated yield.

Intramolecular Palladium-Catalyzed Amination Reaction on a Polymer Support. Intramolecular animation reactions have synthesized a wide variety of nitrogen-containing heterocyclic compounds.[18b,19−20] To date, intramolecular amination in solid-phase reactions

(17) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.
(18) Recently, some applications for aniline insertion to indole synthesis were reported. (a) Moody, C. J.; Swann, E. *Synlett* **1998**, 135−136. (b) Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623. (c) Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4*, 2317−2320.

TABLE 6. Intramolecular Palladium-Catalyzed Amination of *N*-Cbz-Dehydrophenylalanine[a]



13a: X=Br
13b: X=OTf

14

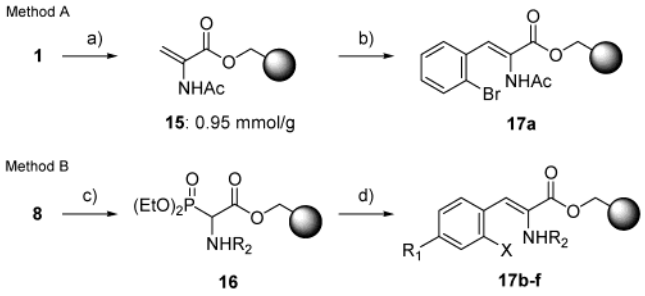
entry	X	"Pd"	ligand	base	solvent	yield (%)
1	Br	$PdCl_2(dppf)$[b]	none	KOAc	DMF	0
2	Br	$Pd_2(dba)_3$	*t*-Bu_3P[c]	Cs_2CO_3	toluene	40
3	Br	$Pd_2(dba)_3$	*t*-Bu_3P	Cy_2NMe	toluene	98
4[d]	OTf	$Pd_2(dba)_3$	*t*-Bu_3P	Cy_2NMe	toluene	0
5	OTf	$Pd_2(dba)_3$	*t*-Bu_3P	Cy_2NMe	DMF	53
6[e]	OTf	$Pd_2(dba)_3$	*t*-Bu_3PHBF_4	Cy_2NMe	DMF	87

[a] Catalyst loading was not minimized. [b] $PdCl_2(dppf)$ (6 mol %) and 3.3 equiv of KOAc were used at 90 °C. [c] Stock solution of *t*-Bu_3P (0.5 M) in toluene was used. $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), 20 mol % *t*-Bu_3P, and 1.2 equiv of base were used for entries 2−5. [d] **13b** was recovered in 80% after 12 h. [e] $Pd_2(dba)_3$·$CHCl_3$ (3 mol %), 12 mol % *t*-Bu_3PHBF_4 and 1.2 equiv of Cy_2NMe were used at 100 °C for 13 h.

is unprecedented in the literature, although a few palladium-catalyzed amination reactions have been applied to the solid-phase synthesis of arylamines using immobilized aryl halides.[21] Therefore, we applied these methodologies to create diverse libraries using solid-phase combinatorial approaches by examining the cyclization reaction on a polymer support. In solution, Brown demonstrated that the intramolecular palladium-catalyzed annulation of dehydrohalophenylalanine can produce N-substituted 2-indolecarboxylate derivatives in excellent yields.[18b] However, using these reported conditions on a polymer support did not successfully cyclize the aryl bromide substrates. Thus, the catalytic system for the transformation was improved and evaluated for general use. Phosphine ligands were screened for the cyclization of **13a** in solution, and *t*-Bu_3P[22] gave the best results, as shown in Table 6. Other phosphine ligands such as P(2-Tol)$_3$, P(2-furyl)$_3$, and 2-(di-*tert*-butylphosphino)biphenyl yielded unidentified products. Using Cy_2NMe[23] instead of Cs_2CO_3 as a base dramatically improved the yield, and the reaction was completed within 15 min (entry 3). If this reaction could convert aryl triflate substrates into indoles, then this method could have general applications since phenolic intermediates are readily available and easily converted to aryl triflates.[24] Therefore, the amination reaction with an aryl triflate substrate was examined.[25] However, intramolecular amination of aryl triflate substrate, **13b**, under the same reaction conditions was unsuccessful (entry 4). Adding LiCl and using Cs_2CO_3 were also ineffective, but changing the solvent to DMF or THF improved the results. Although the cyclization reaction was slower than with the aryl bromide substrates, S−O cleavage of the triflate was not observed under these reaction conditions.

On the basis of the above results, solid-phase, intramolecular palladium-catalyzed amination reactions were investigated. The substrates for the amination reaction, **17a**−**f**, were prepared by one of two methods, shown in Scheme 4.

SCHEME 4[a]



[a] (a) 2-Acetoamideacrylic acid (5 equiv), 40% DEAD in toluene (5 equiv), PPh_3 (5 equiv), THF, rt, 24 h; (b) 1-bromo-2-iodobenzene (3 equiv), 7.5 mol % $Pd_2(dba)_3$·$CHCl_3$, Et_3N (15 equiv), DMF, 100 °C, 24 h; (c) R_2NH_2 (3−10 equiv), 5−10 mol % $Rh_2(OAc)_4$, toluene, 100 °C, 7−20 h; (d) ArCHO (3 equiv), DBU (3 equiv), THF, rt, 3−12 h.

In method A, a Heck reaction of immobilized *N*-acetyldehydroalanine **15**[26] with 3 equiv of 1-bromo-2-iodobenzene was performed under the Heck coupling conditions for the REM resin.[27]

In method B, a rhodium-catalyzed insertion reaction of immobilized α-diazophosphonoacetate with benzylcarbamate or substituted anilines yielding the immobilized N-substituted-α-phosphonylglycine, **16**, which was used in a Horner−Emmons reaction. Table 7 summarizes the loading of **17a**−**f**. The values indicate that the transformation progresses smoothly and reasonably.

Palladium-catalyzed intramolecular amination was performed using reaction conditions similar to the solution-phase procedure. Thus, immobilized *N*-acetyl- or *N*-Cbz-dehydrobromophenylalanine, **17a**−**f**, were heated at 80 °C for 12 h in the presence of a palladium catalyst, a ligand, and a base in toluene, which was followed by the transesterification of immobilized indolecarboxylate using MeONa in MeOH−THF. Table 8 summarizes the

(19) For recent reviews of amination reaction, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

(20) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (c) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068−3073. (d) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893−1895. (e) Deboves, H. J. C.; Hunter, C.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 733−736.

(21) (a) Ward, Y.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993−6996. (b) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181−7184. (c) Saha, A. K.; Liu, L.; Marichal, P.; Odds, F. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2735−2739. (d) Saha, A. K.; Liu, L.; Simoneaux, R. L. *J. Comb. Chem.* **2001**, *3*, 181−188.

(22) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (c) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504.

(23) (a) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107−3112. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(24) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

(25) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264−1267. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (c) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273.

(26) (a) Barbaste, M.; Rolland-Fulcrand, V.; Roumestant, M.-L.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 6287−6290. (b) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535−4538.

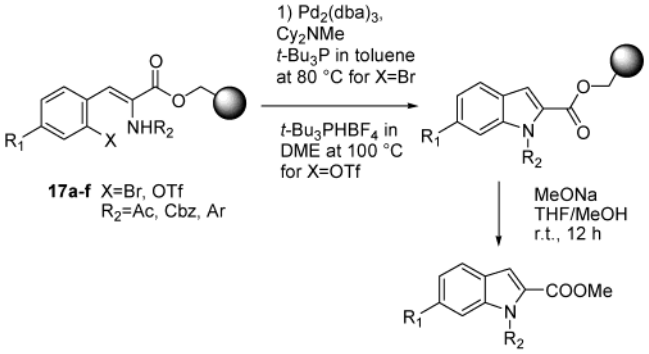
(27) Kondo, Y.; Inamoto, K.; Sakamoto, T. *J. Comb. Chem.* **2000**, *2*, 232−233.

TABLE 7. Immobilized α-Amino-Substituted α,β-Unsaturated Esters

17	X	R_1	R_2	loading (mmol/g)[a]
a	Br	H	Ac	0.51
b	Br	H	Cbz	0.79
c	OTf	H	Cbz	0.90
d	OTf	OMe	Cbz	1.13
e	Br	H	2-MeC_6H_4	0.84
f	Br	H	4-$CF_3C_6H_4$	0.79

[a] Loading value of **17a** was determined from the yields after cleavage using Et_3N/MeOH at 50 °C. The loading values of **17b**−**f** were estimated by elemental analysis of nitrogen on the polymer beads.

TABLE 8. Intramolecular Palladium-Catalyzed Amination of Immobilized *N*-Substituted Dehydrobromophenylalanine



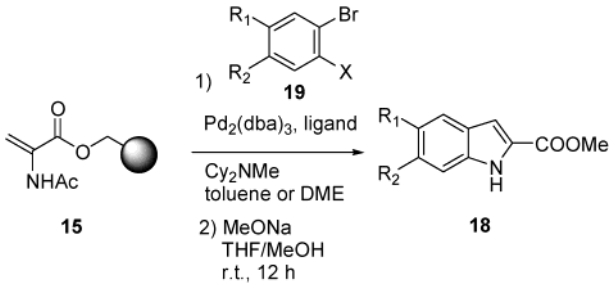
17	X	18	R_1	R_2	yield (%)[a]
a	Br	**a**	H	H	99
b	Br	**a**	H	H	62
c	OTf	**a**	H	H	48
d	OTf	**b**	OMe	H	43
e	Br	**c**	H	2-MeC_6H_4	44
f	Br	**d**	H	4-$CF_3C_6H_4$	48

[a] Isolated yield of **18a**−**d** after SiO_2 column chromatography based on the loading of **17a**−**f**.

yield of methyl 2-indolecarboxylates, **18a**−**d**. Under optimal reaction conditions, good results for aryl bromide substrates were obtained. Aryl triflate substrates were also used, but the reaction conditions need to be further modified. *N*-Aryl indoles, **18c** and **18d**, were also obtained in moderate yields.

Palladium-Catalyzed Tandem C,N-Arylation of Immobilized Enamine. We investigated an indole one-pot synthesis on a polymer support using optimal reaction conditions, and the $Pd_2(dba)_3$/*t*-Bu_3P/Cy_2NMe was quite similar to the Heck reaction reported by Fu et al.[23b] (Table 9). Palladium-catalyzed one-pot syntheses with good yields have been reported such as a palladium-catalyzed annulation reaction between *o*-iodoanilines and cyclic ketones[28a] and palladium-catalyzed tandem amination−Heck reactions between 1,2-dibromobenzene and an enaminone.[28b] In the latter case, the initial step was the amination reaction followed by a Heck-type cyclization to yield 2,3-disubstituted indoles, but a second addition of palladium catalyst and ligand was required. In our approach, the initial step is Heck coupling followed by an amination reaction to yield the indoles.

TABLE 9. Palladium-Catalyzed Tandem C,N-Arylation[a]



19	R_1	R_2	X	18	R_1	R_2	yield (%)[b]
a	H	H	I	**a**	H	H	46
b	H	H	Br	**a**	H	H	78
c	H	H	OTf	**a**	H	H	41
d	Me	Me	Br	**e**	Me	Me	82
e	OMe	H	Br	**f**	OMe	H	39
				b	H	OMe	31

[a] A 0.5 M stock solution of *t*-Bu_3P in toluene was used for **19a**,**b**, and *t*-Bu_3PHBF_4 was used for **19c**−**e**. DME was used for **19c**. [b] Isolated yield of **18** after SiO_2 column chromatography based on the loading of **15**.

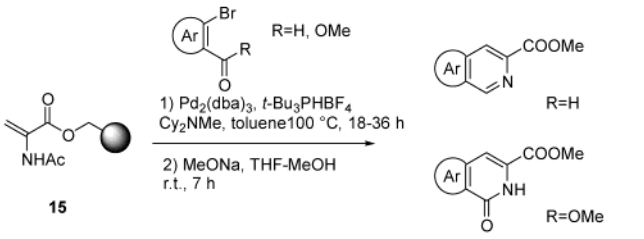
Initially, the immobilized *N*-acetyl-dehydroalanine, **15**, with excess 1-bromo-2-iodobenzene, **19a**, resulted in a mixture of Heck coupling compounds and a small amount of the cyclization product, **18a**. After careful optimization, it was determined that reducing the amount of **19a** significantly improved the isolated yield of **18a**, which increased to 46%. Further optimization by replacing **19a** with 1,2-dibromobenzene, **19b**, at 100 °C led to indolecarboxylate in good yields after transesterification. A similar result was obtained when a symmetric dibromo derivative, **19d**, was used, and additional palladium catalyst or ligand was not required to complete the reaction. However, a problematic result was obtained when the asymmetrical dibromo derivative, **19e**, was used and the reaction of resin **15** with **19e** yielded a mixture of 5-methoxy-2-indolecarboxylate, **18f**, and 6-methoxy-2-indolecarboxylate, **18b**. The overall yield for **18b** and **18f** was acceptable, but the reaction was not selective. The low selectivity for the tandem C,N-arylation of asymmetrical substrates suggests that, at this point, this methodology may be limited to symmetric substrates.

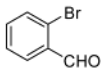
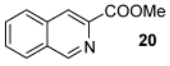
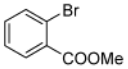
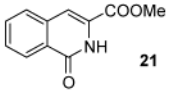
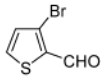
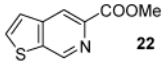
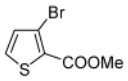
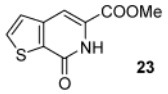
As an extension of the Heck reaction on the immobilized dehydroalanate, the synthesis of isoquinolines[29] and related compounds were examined (Table 10). The Heck reactions of immobilized *N*-acetyl-dehydroalanine with 2-bromobenzaldehyde or methyl 2-bromobenzoate followed by a transesterification resulted in the isoquinoline-3-carboxylates, **20** or **21**, in moderate yields. Employing the above method afforded thieno[2,3-*c*]pyridines, **22** and **23**, in moderate yields. Naphthyridine synthesis was tried using bromopyridinecarbaldehydes under the same reaction conditions; however, no successful result has been obtained at this moment.

(28) For palladium-catalyzed one-pot indole syntheses in solution, see: (a) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676−2677. (b) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109−1112.

(29) Most recently, similar solution-phase chemistry for isoquinoline-3-carboxylates was reported. Chattopadhyay, S. K.; Maity, S.; Pal, B. K.; Panja, S. *Tetrahedron Lett.* **2002**, *43*, 5079−5081.

TABLE 10. Heck Reaction of Immobilized Dehydroalanate 15



entry	Ar-X	product	yield (%)
1		 **20**	56
2		 **21**	60
3		 **22**	52
4		 **23**	62

Conclusions

In summary, new methods for solid-phase indole syntheses were demonstrated. Palladium catalysts on a solid support oxidatively formed enaminoesters. Enaminoesters were also prepared in a solid-phase, rhodium-catalyzed N−H insertion into immobilized carbenoids, which were generated from the immobilized α-diazophosphonoacetate followed by a Horner−Emmons reaction. Intramolecular palladium-catalyzed cyclization of the α- or *β*-(2-halophenyl)amino-substituted α,*β*-unsaturated esters was effective in the solid-phase synthesis of indole 2- and 3-carboxylates with various functional groups on the benzene ring. Moreover, the intramolecular palladium-catalyzed amination route was a useful strategy and the palladium-catalyzed tandem C,N-arylation also provided a new one-pot method for solid-phase indole synthesis.

Experimental Section

General Comments. All reactions were carried out under an argon atmosphere. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an argon atmosphere. Other dry solvents and reagents were purchased from commercial sources and used without further purification. Hydroxymethyl polystyrene resin (1% divinylbenzene) was used. Aryl triflate substrates,[24] 3,4-dibromoanisole[30] and 3-bromothiophene-2-carbaldehyde[31] were prepared according to a literature procedure. The overlapped quaternary carbon in ^{13}C NMR was confirmed by the JEOL QUAT[32] method. Melting points (mp) are uncorrected.

Procedure for the Preparation of Immobilized *β*-Keto Ester (2a).[6] A mixture of hydroxymethyl polystyrene resin (7.5 g, 9.3 mmol), *tert*-butyl acetoacetate (10.8 g, 93 mmol), and toluene (75 mL) was heated at 100 °C for 4 h. After cooling, the resin was washed with toluene (50 mL × 3), THF (50 mL × 5), and MeOH (50 mL × 3) and the resin was dried under reduced pressure at 40 °C. The loading was determined from the isolated yield of 3-methyl-3-pyrazolin-5-one cleaved from resin by the treatment with 5% hydrazine in EtOH as 1.12 mmol/g.

General Procedure for the Preparation of Immobilized *β*-(2-Halophenyl)amino-Substituted α,*β*-Unsaturated Ester (4). A mixture of immobilized *β*-keto ester **2a** (1 g, 1.12 mmol), 2-haloaniline (1.5 equiv), *p*-toluenesulfonic acid hydrate (2%), and benzene (10 mL) was refluxed for 4 h using a Dean Stark apparatus. After cooling, the resin was washed with toluene (10 mL × 3), H_2O (10 mL × 3), THF (10 mL × 3), and MeOH (10 mL × 3), and the resin was dried under reduced pressure at 40 °C. The loading of resin **4** was estimated by elemental analysis for nitrogen.

General Procedure for the Preparation of Immobilized *β*-(2-Halophenyl)amino-Substituted α,*β*-Unsaturated Ester (4) from REM Resin. A mixture of REM resin **3** (1 g, 1.39 mmol), $PdCl_2(CH_3CN)_2$, (72 mg, 0.278 mmol), LiCl (1.18 g, 27.8 mmol), 1,4-benzoquinone (300 mg, 2.78 mmol), and THF (10 mL) was stirred at room temperature. After 10 min, 2-haloaniline (2 equiv) was added, and then the mixture was stirred for 24 h at 50 °C. The resin was filtered and washed with THF (10 mL × 3), 5% $NaHCO_3$ (10 mL × 3), H_2O (10 mL × 3), DMF (10 mL × 3), THF (5 mL × 3), and MeOH (5 mL × 3), and the resin was dried under reduced pressure at 40 °C. The loading of resin **4** was estimated by elemental analysis for nitrogen.

Procedure for the Preparation of Immobilized α-Diazophosphonoacetate (8). A mixture of hydroxymethyl polystyrene resin **1** (11 g, 13.64 mmol) and DMF (110 mL) was stirred at room temperature. After 20 min, diethylphosphonoacetic acid (6.58 mL, 40.93 mmol), pyridine (6.6 mL, 81.84 mmol), and 2,6-dichlorobenzoyl chloride (5.86 mL, 40.92 mmol) were added consecutively, and then the mixture was stirred for 15 h at room temperature. The resin was filtered and washed with DMF (100 mL × 4), THF (100 mL × 2), CH_2Cl_2 (100 mL × 2), and MeOH (100 mL × 2), and the resin was dried under reduced pressure at 40 °C to give 13.5 g of resin **7**. A mixture of resin **7** (6 g, 6.06 mmol), *p*-dodecylbenzenesulfonyl azide (6.4 g, 18.18 mmol), and toluene (60 mL) was stirred at room temperature. DBU (2.72 mL, 18.18 mmol) was added at room temperature and the mixture continued to stir for 4 h. The resin was filtered and washed with toluene (60 mL × 3), DMF (60 mL × 3), THF (60 mL × 3), CH_2Cl_2 (60 mL × 3), and MeOH (60 mL × 3), and the resin was dried under reduced pressure at 40 °C to give 6.1 g of resin **8**. The loading of resin **8** was estimated by elemental analysis for nitrogen as 1.1 mmol/g (N, 3.08%).

General Procedure for the Rhodium-Catalyzed Insertion Reaction. A mixture of resin **8** (1.5 g, 1.8 mmol), 2-haloaniline (5 equiv), $Rh_2(OAc)_4$ (5 mol %), and toluene (15 mL) was heated at 80 °C for 12−40 h. The resin was filtered and washed with toluene (15 mL × 3), DMF (15 mL × 3), THF (15 mL × 3), CH_2Cl_2 (15 mL × 3), and MeOH (15 mL × 3), and the resin was dried under reduced pressure at 40 °C. The loading of **9** was estimated by elemental analysis for nitrogen.

General Procedure for the Horner−Emmons Reaction. DBU (0.11 mL, 0.75 mmol) was added to a suspension of resin **9** (0.25 mmol) in THF (3 mL) and the mixture agitated for 5 min; aldehyde (3 equiv) was added and the mixture agitated for 12 h at room temperature. The resin was washed with THF (3 mL × 3), DMF (3 mL × 3), THF (3 mL × 3), CH_2Cl_2 (3 mL × 3), and MeOH (3 mL × 3), and the resin was dried under reduced pressure. The loading of **6** was estimated by elemental analysis for nitrogen.

(30) Andersh, B.; Murphy, D. L.; Olson, R. J. *Synth. Commun.* **2000**, *30*, 2091−2098.
(31) Fuller, L. S.; Iddon, B.; Smith, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3465−3470.
(32) Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Johns, S. R.; Willing, R. I. *J. Chem. Soc., Chem. Commun.* **1982**, 1138−1140.

Palladium-Catalyzed Cyclization of Resin 4 and Cleavage from Resin Using NaOMe. A mixture of resin **4b** (0.39 g, 0.33 mmol), $Pd_2(dba)_3$·$CHCl_3$ (23 mg, 0.025 mmol), P(*o*-Tol)$_3$ (30 mg, 0.1 mmol), Et_3N (0.69 mL, 4.95 mmol), and DMF (3 mL) was heated at 110 °C for 15 h. The resin was washed with DMF (5 mL × 3), DMF/H_2O 1:1 (5 mL × 3), DMF (5 mL × 3), THF (5 mL × 3), and MeOH (5 mL × 3), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (107 mg, 1.98 mmol) in THF (3 mL) and MeOH (1.5 mL) was agitated at 60 °C for 12 h. The resin was separated by filtration and washed with ethyl acetate; the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) to afford 33 mg (53%) of **10a**.

Methyl 2-Methyl-3-indolecarboxylate (10a).[33] Mp 164−165 °C (diethyl ether−hexane) (lit. 162−163 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.75 (3H, s), 3.94 (3H, s), 7.18−7.35 (3H, m), 8.05−8.12 (1H, m), 8.36 (1H, brs). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.18 (CH_3), 50.78 (CH_3), 104.47 (C), 110.49 (CH), 121.24 (CH), 121.70 (CH), 122.35 (CH), 127.09 (C), 134.46 (C), 144.01 (C), 166.54 (C). IR ν (cm^{-1}): 3265, 1663, 1198. MS (EI) *m*/*z*: 189 (M^+). HRMS: calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0775.

Palladium-Catalyzed Cyclization of Resin 6 and Cleavage from Resin Using NaOMe. A mixture of resin **6a** (0.23 g, 0.23 mmol), $Pd_2(dba)_3$·$CHCl_3$ (16 mg, 0.0173 mmol), P(*o*-Tol)$_3$ (21 mg, 0.069 mmol), Et_3N (0.48 mL, 3.45 mmol), and DMF (2 mL) was heated at 110 °C for 12 h. The resin was washed with DMF (3 mL × 3), DMF/H_2O 1:1 (3 mL × 3), DMF (3 mL × 3), THF (3 mL × 3), and MeOH (3 mL × 3), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (75 mg, 1.38 mmol) in THF (2 mL) and MeOH (1 mL) was agitated at room temperature for 6 h. The resin was separated by filtration and washed with ethyl acetate; the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (6:1) to afford 28 mg (48%) of **11a**.

Methyl 3-Phenyl-2-indolecarboxylate (11a).[34] Mp 137−139 °C (MeOH) (lit. 138−139 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.82 (3H, s), 7.12−7.19 (1H, m), 7.33−7.50 (5H, m), 7.54−7.59 (2H, m), 7.64 (1H, d, J = 8.3 Hz), 9.00 (1H, brs). ^{13}C NMR ($CDCl_3$) δ (ppm): 51.81 (CH_3), 111.70 (CH), 120.94 (CH), 121.82 (CH), 122.38 (C), 124.43 (C), 125.93 (CH), 127.28 (CH), 127.89 (2CH, C), 130.56 (2CH), 133.37 (C), 135.73 (C), 162.40 (C). IR ν (cm^{-1}): 3323, 1669, 1251. MS *m*/*z*: 251 (M^+). HRMS: calcd for $C_{16}H_{13}NO_2$, 251.0946; found, 251.0966. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.37; H, 5.37; N, 5.64.

Intramolecular Horner−Emmons Reaction. DBU (0.22 mL, 1.47 mmol) was added to a suspension of resin **12b** (525 mg, 0.49 mmol) in THF (5 mL), and the mixture was agitated for 12 h at room temperature. The resin was washed with THF (5 mL × 3), DMF (5 mL × 3), THF (5 mL × 3), CH_2Cl_2 (5 mL × 3), and MeOH (5 mL × 3), and the resin was dried under reduced pressure. A mixture of the above resin and NaOMe (159 mg, 2.94 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 8 h. The resin was separated by filtration and washed with ethyl acetate; filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) to afford 81 mg (87%) of methyl 3-methyl-2-indolecarboxylate[35] **11m**. Mp 147−148 °C (MeOH) (lit. 148 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.61 (3H, s), 3.95 (3H, s), 7.10−7.18 (1H, m), 7.29−7.40 (2H, m), 7.67 (1H, d, J = 8.0 Hz), 8.71 (1H, brs). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.93 (CH_3), 51.70 (CH_3), 111.63 (CH), 119.95 (CH), 120.39 (C), 120.81 (CH), 123.19 (C), 125.66 (CH), 128.51 (C), 135.90 (C), 163.06 (C). IR ν (cm^{-1}): 3308, 1676, 1254. MS *m*/*z*: 189 (M^+). HRMS: calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0747.

Methyl *N*-Benzyloxycarbonyl-2-indolecarboxylate (14). To a solution of **13a** (195 mg, 0.5 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (23 mg, 0.025 mmol) in toluene (3 mL) was added 0.5 M toluene solution of tri-*tert*-butylphosphine (0.2 mL, 0.1 mmol) and *N*,*N*-dicyclohexyl-*N*-methylamine (0.13 mL, 0.6 mmol) at room temperature. The whole mixture was stirred for 30 min at 80 °C and then poured into water. The organic phase was separated, and the aqueous phase was extracted with EtOAc (two times). The combined extracts were washed with water (two times) and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude material was purified by chromatography on silica gel using diethyl ether/hexane (5:1) to afford 152 mg (98%) of **14** as a colorless viscous oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.73 (3H, s), 5.42 (2H, s), 7.14 (1H, s), 7.26−7.46 (7H, m), 7.61 (1H, d, J = 8.5 Hz), 8.09 (1H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.32 (CH_3), 69.66 (CH_2), 115.05 (CH), 115.71 (CH), 122.27 (CH), 123.66 (CH), 127.10 (CH), 127.63 (C), 128.71 (2CH), 128.77 (2CH), 128.82 (CH), 130.32 (C), 134.45 (C), 137.62 (C), 150.69 (C), 162.22 (C). IR ν (cm^{-1}): 1727, 1202. MS *m*/*z*: 309 (M^+). HRMS: calcd for $C_{18}H_{15}NO_4$, 309.1001; found, 309.1033.

Immobilized *N*-Acetyl-dehydroalanine (15).[26] To a mixture of hydroxymethyl polystyrene resin (4.8 g, 7 mmol), 2-acetamidoacrylic acid (4.52 g, 35 mmol), and triphenylphosphine (9.2 g, 35 mmol) in THF (72 mL) was added dropwise at room temperature a 40% solution of diethyl azodicarboxylate (16 mL, 35 mmol) in toluene. The mixture was gently stirred for 24 h at room temperature. The resin was collected by filtration and washed with THF (three times), CH_2Cl_2 (three times), MeOH (three times), CH_2Cl_2 (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. The loading was determined from the isolated yield of methyl 2-acetamidoacrylate cleaved from the resin by the treatment with 10% triethylamine in MeOH at 50 °C for 8 h as 0.95 mmol/g. IR ν (cm^{-1}): 3398, 1717, 1696.

Methyl 2-Acetamidoacrylate.[36] Mp 47−49 °C (lit. 49−51 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.13 (3H, s), 3.85 (3H, s), 5.88 (1H, s), 6.60 (1H, s), 7.73 (1H, brs), 7.95 (1H, s), 8.00 (1H, d, J = 8.0 Hz). IR ν (cm^{-1}): 3361, 1706, 1673, 1507. MS *m*/*z*: 143 (M^+). HRMS: calcd for $C_6H_9NO_3$, 143.0582; found, 143.0544.

Immobilized α-Acetamido-*β*-(2-bromophenyl)-acrylate (17a). To a mixture of immobilized 2-acetamidoacrylate **15** (2 g, 1.9 mmol), $Pd_2(dba)_3$·$CHCl_3$ (130 mg, 0.14 mmol), and triethylamine (4 mL, 28.5 mmol) in DMF (18 mL) was added 1-bromo-2-iodobenzene (0.74 mL, 5.7 mmol) at room temperature. The whole mixture was gently stirred for 24 h at 100 °C. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. The loading was determined from the isolated yield of methyl-α-acetamido-*β*-(2-bromophenyl)-acrylate cleaved from the resin by the treatment with 10% triethylamine in MeOH at 50 °C for 12 h as 0.51 mmol/g. IR ν (cm^{-1}): 3024, 2921, 1700, 1684, 1239.

Methyl α-Acetamido-*β*-(2-bromophenyl)-acrylate.[37] Mp 138−139 °C (diethyl ether) (lit. 142−144 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04 (3H, brs), 3.88 (3H, s), 7.02 (1H, brs), 7.18−7.44 (4H, m), 7.62 (1H, d, J = 8.0 Hz). IR ν (cm^{-1}): 3147, 3000, 1719, 1654. MS *m*/*z*: 297 (M^+). HRMS: calcd for $C_{12}H_{12}BrNO_3$, 297.0001; found, 296.9959.

(33) Kaneko, C.; Naito, T.; Hashiba, M.; Fujii, H.; Somei, M. *Chem. Pharm. Bull.* **1979**, *27*, 1813−1819.
(34) Sohda, T.; Yamazaki, I.; Kawamura, N. EP 449196, 1991.
(35) Elvidge, J. A.; Spring, F. S. *J. Chem. Soc.* **1949**, S135−140.
(36) Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Kataoka, K.; Shidori, K.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 832−838.
(37) Wagaw. S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

Immobilized α-*N*-Cbz-*β*-(2-bromophenyl)-acrylate 17b. A mixture of immobilized α-diazophosphonoacetate **8** (1.0 g, 1.1 mmol), benzyl carbamate (831 mg, 5.5 mmol), $Rh_2(OAc)_4$ (23 mg, 0.055 mmol), and toluene (10 mL) was heated at 100 °C for 7 h. The resin was collected by filtration and washed with toluene (three times), DMF (three times), THF (three times), CH_2Cl_2 (three times), and MeOH (three times) and the resin was dried under reduced pressure at 40 °C. The loading of **16** was estimated by elemental analysis for nitrogen as 0.87 mmol/g (N, 1.22%).

DBU (0.49 mL, 3.3 mmol) was added to the above resin **16** in THF (10 mL), and the mixture was agitated for 5 min. Then, 2-bromobenzaldehyde (0.39 mL, 3.3 mmol) was added, and the mixture was again agitated for 12 h at room temperature. The resin was collected by filtration and washed with THF (three times), DMF (three times), THF (three times), CH_2Cl_2 (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. The loading of **17b** was estimated by elemental analysis for nitrogen as 0.79 mmol/g (N, 1.1%). IR ν (cm^{-1}): 3021, 2919, 1719.

Methyl 2-Indolecarboxylate 18a Using Resin 17a.[38] To a mixture of resin **17a** (400 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (19 mg, 0.02 mmol), and *N*,*N*-dicyclohexyl-*N*-methylamine (0.13 mL, 0.6 mmol) in toluene (4 mL) was added 0.5 M toluene solution of tri-*tert*-butylphosphine (0.16 mL, 0.08 mmol), and the mixture was then heated at 80 °C for 12 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (11 mg, 0.2 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 12 h. The resin was separated by filtration and washed with ethyl acetate, and the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) to afford 36 mg (99%) of **18a** as a colorless solid. Mp 150−151 °C (ethyl acetate−hexane) (lit. 148−150 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.95 (3H, s), 7.14−7.45 (4H, m), 7.70 (1H, d, J = 8.0 Hz), 8.89 (1H, brs). IR ν (cm^{-1}): 3330, 1696, 1684. MS *m*/*z*: 175 (M^+). HRMS: calcd for $C_{10}H_9NO_2$, 175.0633; found, 175.0609.

Methyl 2-Indolecarboxylate 18a Using Resin 17c. To a mixture of resin **17c** (300 mg, 0.27 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (51 mg, 0.055 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (64 mg, 0.22 mmol), and *N*,*N*-dicyclohexyl-*N*-methylamine (0.24 mL, 1.1 mmol) in DME (2.8 mL) was heated at 100 °C for 38 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (30 mg, 0.55 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 12 h. The resin was separated by filtration and washed with ethyl acetate, and the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) to afford 20 mg (48%) of **18a** as a colorless solid.

Tandem Procedure for Methyl 2-Indolecarboxylate 18a on a Polymer Support. To a mixture of resin **15** (300 mg, 0.285 mmol), 1,2-dibromobenzene (0.051 mL, 0.428 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (39 mg, 0.043 mmol), and *N*,*N*-dicyclohexyl-*N*-methylamine (0.18 mL, 0.855 mmol) in toluene (3 mL) was added 0.5 M toluene solution of tri-*tert*-butylphosphine (0.34 mL, 0.17 mmol), and the mixture was then heated at 100 °C for 24 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (15 mg, 0.285 mmol) in THF (3 mL) and MeOH (1.5 mL) was agitated at room temperature for 16 h. The resin was separated by filtration and washed with ethyl acetate; the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) to afford 39 mg (78%) of **18a** as a colorless solid.

Methyl 3-Isoquinolinecarboxylate (20).[39] A mixture of resin **15** (500 mg, 0.475 mmol), 2-bromobenzaldehyde (0.17 mL, 1.425 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (33 mg, 0.036 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (41 mg, 0.143 mmol), and *N*,*N*-dicyclohexyl-*N*-methylamine (0.31 mL, 1.43 mmol) in toluene (4 mL) was heated at 100 °C for 18 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (26 mg, 0.475 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 7 h. The resin was separated by filtration and washed with ethyl acetate, and the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (1:1) to afford 50 mg (56%) of **20** as a colorless solid. Mp 77−79 °C (diethyl ether−hexane) (lit. 70−71 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 4.08 (3H, s), 7.73−7.85 (2H, m), 7.99 (1H, d, J = 7.7 Hz), 8.08 (1H, d, J = 7.7 Hz), 8.62 (1H, s), 9.35 (1H, s). IR ν (cm^{-1}): 1723, 1437, 1291, 1094. MS *m*/*z*: 187 (M^+). HRMS: calcd for $C_{11}H_9NO_2$, 187.0633; found, 187.0592.

Methyl 3-Isoquinolonecarboxylate[40] (21). A mixture of resin **15** (500 mg, 0.475 mmol), methyl 2-bromobenzoate (1.425 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (33 mg, 0.036 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (41 mg, 0.143 mmol), and *N*,*N*-dicyclohexyl- *N*-methylamine (0.31 mL, 1.425 mmol) in toluene (4 mL) was heated at 100 °C for 24 h. The resin was collected by filtration and washed with DMF (three times), DMF/H_2O 1:1 (three times), DMF (three times), THF (three times), and MeOH (three times), and the resin was dried under reduced pressure at 40 °C. A mixture of the above resin and NaOMe (26 mg, 0.475 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 6 h. The resin was separated by filtration and washed with ethyl acetate, and the filtrate was washed with saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (1:1) to afford 58 mg (60%) of **21** as a colorless solid. Mp 160−162 °C (ethyl acetate−hexane) (lit. 158−159.5 °C). ^{1}H NMR ($CDCl_3$) δ (ppm): 4.00 (3H, s), 7.38 (1H, s), 7.61−7.77 (3H, m), 8.47 (1H, d, J = 8.0 Hz), 9.17 (1H, brs). IR ν (cm^{-1}): 3166, 3056, 2954, 1725, 1656. MS *m*/*z*: 203 (M^+). HRMS: calcd for $C_{11}H_9O_3N$, 203.0582; found, 203.0607.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) Hamel, P.; Zajact, N.; Atkinson, J. G.; Girard, Y. *Tetrahedron Lett*. **1993**, *34*, 2059−2062.

(39) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem*. **1982**, *25*, 1081−1091.

(40) Nunami, K.; Suzuki, M.; Yoneda, N. *J. Org. Chem*. **1979**, *44*, 1887−1888.