Isoxazolinoisoquinoline Heterocycles via Solid-Phase Reissert and Suzuki Reactions

Beth A. Lorsbach, Jeffrey T. Bagdanoff, R. Bryan Miller,* and Mark J. Kurth*

Department of Chemistry, University of California, Davis, California 95616

Received November 3, 1997

A traceless solid-phase synthesis strategy has been developed that delivers novel isoxazolinoisoquinoline heterocycles. The process consists of solid-phase Reissert formation (isoquinoline → **I**), Suzuki coupling lithiation, and subsequent C1-alkylation (**I** → **II**), and exo-olefin selective 1,3-dipolar nitrile oxide cycloaddition followed by Reissert hydrolysis (**II** → **III**) to liberate the targeted heterocycle.

Introduction

In a recent paper, we reported the Reissert-based solid-phase synthesis of several isoxazolinoisoquinoline heterocycles.[1] Our interest in the novel combination of these two structural features within a single framework stemmed from the observation that isoquinoline and isoxazoline substructures both exhibit significant biological activities: isoquinolines, substituted at C1 with basic-containing substituents including N and O heterocycles, have shown a wide variety of bioactivity,[2] and the isoxazoline heterocycle has been used extensively to modify a variety of other biologically active systems.[3] An efficient method for incorporating substitution at the isoquinoline C1 position is through use of Reissert intermediates that take advantage of the increased C1-acidity of the 2-acyl-1,2-dihydroisoquinaldonitriles.[4,5] This type of chemistry has been used in the polymer area for both production of monomers for subsequent polymerization and polymerization of Reissert compounds themselves.[6] These observations, plus the importance of methodological developments in solid-phase[7] and combinatorial strategies,[8] led us[9] to investigate a "traceless" solid-phase approach for construction of the isoxazolinoisoquinoline heterocyclic system. The success of our preliminary studies with the Reissert-based solid-phase synthesis of these heterocycles[1] encouraged us to pursue the incorporation of a polymer-bound Suzuki coupling reaction to further enhance compound diversity.[10]

There are numerous examples of the Suzuki coupling reactions both in solution as well as on a solid support.[11,12] Typically, Suzuki coupling involves the palladium-catalyzed coupling of an aryl or alkenyl halide with an aryl- or alkenyl boronic acid. The catalytic cycle proceeds via oxidative addition, transmetalation, and reductive elimination.[13] While Suzuki coupling strategies provide an effective method for C−C formation, to our knowledge there has been no report of Suzuki couplings performed on Reissert intermediates. We report herein the solution- and solid-phase Suzuki coupling of a Reissert halide with aryl boronic acids as well as incorporation of Suzuki couplings in the synthesis of isoxazolinoisoquinoline derivatives.

Results and Discussion

In our preliminary paper,[1] we validated the solid-phase synthetic strategy outlined in Figure 1. The hallmarks of this study were that (i) solid-phase Reissert formation can be effected such that the resulting Reissert intermediate provides coincident substrate-resin linkage (isoquinoline → **I**), (ii) the resulting solid-phase Reissert complex can be C1-allylated (**I** → **II**), and (iii) nitrile oxide reagents undergo chemoselective *exo*-olefin 1,3-dipolar cycloaddition (vs *endo*-enamide 1,3-dipolar cycloaddition; see **II**). Once the Reissert complex had been successfully exploited for linker, activation (C1), and nitrile oxide chemoselection, hydrolysis deconvoluted the Reissert complex delivering the targeted heterocycle **III** and thus constituted a "traceless"[14] solid-phase route to isoxazolinoisoquinoline heterocycles (**III**).

(1) Lorsbach, B. A.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1996**, *61*, 8716−17.

(2) (a) Brossi, A. *Heterocycles* **1978**, *11*, 521−47. (b) Shuster, H. F.; Kathawala, F. *Chem. Heterocycl. Comp.* **1995**, *38*, 1−224.

(3) (a) Khalil, M. A.; Mapaonya, M. F.; Ko, D.-H.; You, Z.; Oriaku, E. T.; Lee, H. J. *Med. Chem. Res.* **1996**, *6*, 52−60. (b) Groutas, W. C.; Venkataraman, R.; Chong, L. S.; Yoder, J. E.; Epp, J. B.; Stanga, M. A.; Kim, E.-H. *Bioorg. Med. Chem.* **1995**, *3*, 125−8.

(4) Reissert, A. *Chem. Ber.* **1905**, *38*, 1603.

(5) Reviews: (a) Popp, F. D. In *Quinolines;* Jones, G., Ed.; J. Wiley and Sons: New York, 1982; Part II, pp 353−375. (b) Popp, F. D. *Bull. Soc. Chim. Belg.* **1981**, *90*, 609−13.

(6) (a) Gibson, H. W.; Guilani, B. *Polym. Commun.* **1991**, *32*, 324−8. (b) Gibson, H. W.; Pandya, A.; Guilani, B. *Polym. Prepr.* **1988**, *29*, 154−4.

(7) (a) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135−44. (b) Leznoff, C. C. *Chem. Soc. Rev.* **1974**, *3*, 65−85. (c) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327−33.

(8) (a) Ellman, J. A.; *Acc. Chem. Res.* **1996**, *29*, 132−43. (b) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144−54. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.

(9) (a) Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2. (b) Kurth, M. J.; Ahlberg Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang, R.; Nakatsu, T.; Green, C. *J. Org. Chem.* **1994**, *59*, 5862−4.

(10) Stavenuiter, J.; Hamzink, M.; van der Hulst, R.; Zomer, G.; Westra, G. Kriek, E. *Heterocycles* **1987**, *26*, 2711−16.

(11) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981** *11*, 513. (b) Sato, M.; Miyaura, N. Suzuki, A. *Chem. Lett.* **1989**, 1405. (c) Takayuki, O.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (d) Miyaura, N.; Suzuki, A. *Terahedron Lett.* **1979**, 3437. (e) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, 2865. (c) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866. (f) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(12) (a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177−9180. (b) Backes, J. A.; Ellman, J. A. *J. Am. Soc. Chem.* **1994**, *116*, 11171−11172. (c) Guile, J. W.; Johnson, S. G.; Murray, W. V. *Abstracts of Papers*, 211th Nathional Meeting of the American Chemical Society, New Orleans, Spring 1996; American Chemical Society: Washington, DC, 1996; Abstract 126.

(13) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995** *95*, 2457−2483.

S0022-3263(97)02014-8 CCC: $15.00 © 1998 American Chemical Society
Published on Web 03/11/1998

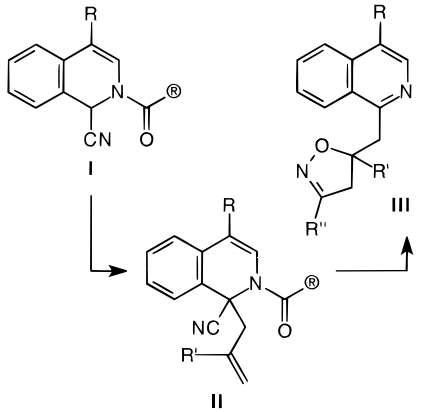
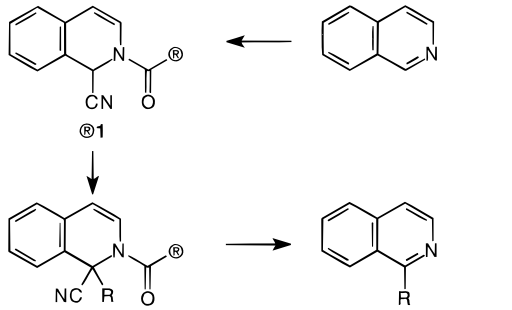


Figure 1. Solid-phase Reissert approach to isoxazolinoisoquinoline heterocycles (® = 2% DVB-polystyrene).

Scheme 1. C1-Alkylation of the Solid-Phase Reissert Complex (® = 2% DVB-Polystyrene)



®**2a**; R = CH_3
®**2b**; R = CH_2CH_3
®**2c**; R = $CH_2C_6H_5$
®**2d**; R = $CH_2CH{=}CH_2$

3a; R = CH_3
3b; R = CH_2CH_3
3c; R = $CH_2C_6H_5$
3d; R = $CH_2CH{=}CH_2$

While solution-phase Reissert alkylations traditionally use NaH for activation,[15] solid-phase Reissert ®**1** (®**1** denotes Reissert substrate **1** supported on 2% DVB-polystyrene) formed by treating polymer-bound benzoyl chloride [®$C_6H_4C(=O)Cl$][7b,c] with isoquinoline and trimethylsilyl cyanide (TMSCN) required the soluble base LDA for C1-alkylation. Addition of methyl iodide at −78 °C followed by warming to ambient temperature (48 h) gave resin ®**2a** (Scheme 1). This resin, having been exposed to four synthetic transformations (carbonylation, acid chloride formation, Reissert condensation, and C1-alkylation), was swollen in THF and treated with aqueous KOH to effect Reissert hydrolysis. Subsequent filtration and ether wash followed by normal aqueous workup of the organic layer delivered 1-methylisoquinoline (**3a**; 56% overall yield from ®$C_6H_4CO_2H$). In a similar fashion, C1-substituted isoquinolines **3b** and **3c** were prepared from ethyl iodide (59% overall yield) and benzyl bromide (50% overall yield), respectively. GC analysis of each crude Reissert/C1-alkylation/hydrolysis reaction mixture showed nearly complete C1-alkylation; in all cases, only a trace (<5%) of unalkylated isoquinoline could be detected.

Once we verified that we could form and alkylate solid-phase Reissert ®**1**, the question of olefin selectivity in the 1,3-dipolar cycloaddition step became our next problem. Our previous experience with both solution-[16] and solid-phase[17] nitrile oxide cycloaddition reactions[18] established that steric and electronic factors influence olefin selectivity in 1,3-dipolar cycloadditions,[19] suggesting that C1-allylated Reissert compound **II** was a good candidate for olefin-selective cycloaddition. In our first test of this *exo*-olefin versus *endo*-enamide competition in the Reissert series, we felt it was prudent to bias the system toward exo-addition by placing a bulky substituent at the isoquinoline C4-position. Thus, 4-phenylisoquinoline[20] was selected and Reissert formation (®**4**) followed by LDA-mediated C1-allylation delivered ®**5a**. We found that in situ generation of $CH_3CH_2C{\equiv}N^+O^-$ (nitropropane + PhNCO + Et_3N) resulted in concomitant 1,3-dipolar cycloaddition with complete exo-selectivity based on analysis of the crude hydrolysis product.[1] That is, only isoxazolinoisoquinoline **6a** was obtained (27% overall yield from ®$C_6H_4CO_2H$).[21] This was impressive given that 5 equiv of $CH_3CH_2CN^+O^-$ were employed! Moreover, alkylation of ®**4** with methallyl bromide delivered ®**5b**, which, despite increased steric hindrance at the exo-olefin, also underwent only exo-1,3-dipolar cycloaddition, giving **6c** on hydrolysis (24% overall yield from ®$C_6H_4CO_2H$) (Scheme 2). Finally, the exo-olefin selectivity found in the reaction of $CH_3CH_2C{\equiv}N^+{-}O^-$ with ®**5a** was also observed in the reaction $C_6H_5C{\equiv}N^+O^-$ with ®**5a**; again, only exo-cycloadduct **6b** was obtained (23% overall yield from ®$C_6H_4CO_2H$).[21b]

We returned to resin ®**1**, encouraged by the exo-olefin selectivity in the 1,3-dipolar cycloaddition step, and C1-alkylated it with allyl bromide to give resin ®**2e** (see Scheme 3).[22] Thus, the 1,3-dipolar cycloaddition confronted a much less hindered enamide C=C and brought to the fore the question of whether exo-selectivity would still prevail. Treating resin ®**2e** with excess $CH_3CH_2C{\equiv}N^+O^-$ or excess $C_6H_5C{\equiv}N^+O^-$ followed by Reissert hydrolysis delivered only the exo-cycloadducts **7a** and **7b** (25% and 26% overall yield from ®$C_6H_4CO_2H$)![21b] The resin does not mediate endo-/exo-olefin selectivity as the solution-phase variant of this reaction also gives only exo-cycloaddion (**2e** → **2e′**; 1.9:1 ratio of diastereomers; 82% unoptimized) leading to **7a** upon Reissert hydrolysis. One final probe of the exo-selectivity was to alkylate ®**1** with methallyl bromide, thus adding steric hindrance to the exo-olefin. Again, when resin ®**2f** was treated with excess $CH_3CH_2C{\equiv}N^+O^-$, only exo-cycloadduct **7c** (21% overall yield) was obtained.

(14) (a) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006−7. (b) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999−12000. (c) Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703−6.

(15) Boekelheide, V.; Weinstock, J. *J. Am. Chem. Soc.* **1952**, *74*, 660−3.

(16) (a) Beebe, X.; Chiappari, C. L.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1993**, *58*, 7320−1. (b) Kim, H. R.; Kim, H. J.; Duffy, J. L.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259−62. (c) Kurth, M. J.; Olmstead, M. M.; Rodriguez, M. J. *J. Org. Chem.* **1990**, *55*, 283−8. (d) Kurth, M. J.; Rodriguez, M. J. *Tetrahedron* **1989**, *45*, 6963−8. (e) Kurth, M. J.; Rodriguez, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7577−8.

(17) (a) Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204−12. (b) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1995**, *60*, 4196−203. (c) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061−2.

(18) Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261−327.

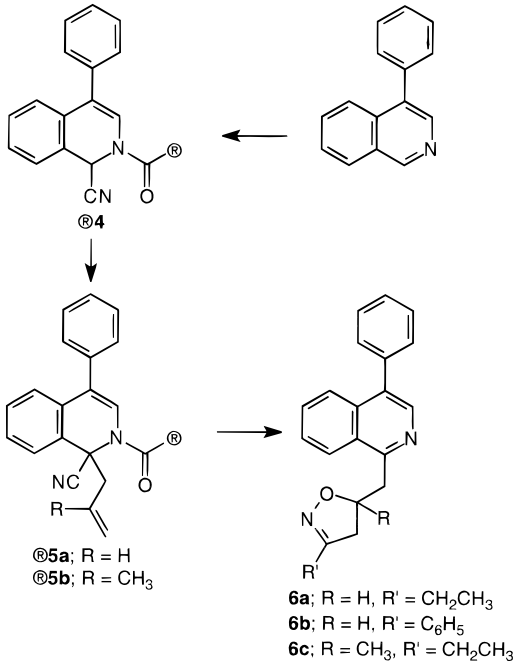
(19) Rodriguez, M. J. Ph.D. Thesis, UCD, 1989 (Avail.: University Microfilms Int., Order No. DA8903740).

(20) Miller, R. B.; Svoboda, J. J. *Synth. Commun.* **1994**, *24*, 1187−93.

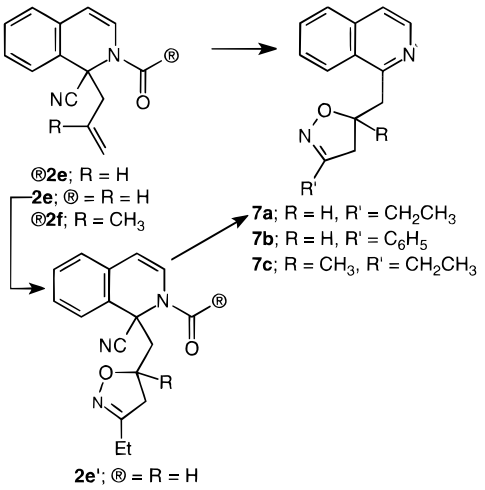
(21) (a) The crude ^1H NMR show no evidenced of a second isoxazoline-containing product. (b) The purity of the crude product was judged to be 90% by ^1H NMR analysis.

(22) Hydrolysis of this Reissert compound is complicated by the fact that a fair degree of olefin isomerization occurs, leading to a 1:4 mixture of 1-(2-propenyl)isoquinoline and 1-(1-propenyl)isoquinoline.

Scheme 2. Preparation of C4-Substituted Isoxazolinoisoquinoline Heterocycles (® = 2% DVB-Polystyrene)



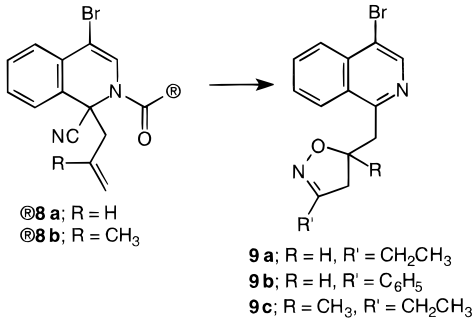
Scheme 3. Preparation of C4-Unsubstituted Isoxazolinoisoquinoline Heterocycles (® = 2% DVB-Polystyrene in ®2e and ®2f; ® = H in 2e and 2e′)



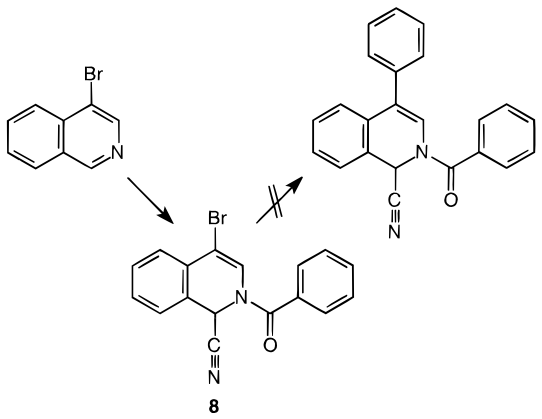
These results, especially with excess nitrile oxide, suggest that the Reissert enamide C═C is electronically deactivated for 1,3-dipolar cycloaddition. AM1 semiempirical calculations support this conclusion.[23]

When 4-bromoisoquinoline was put through the solid-phase Reissert → C1-allylation → 1,3-dipolar cycloaddition → hydrolysis sequence, isoxazolinoisoquinolines **9a**, **9b**, and **9c** were obtained in 26%, 24%, and 23% overall yield, respectively, from ®$C_6H_4CO_2H$ (Scheme 4).[21b] Since these results were as expected, we set out to use commercially available 4-bromoisoquinoline in our investigation of the Suzuki coupling reaction, which is well established as an active halide for Suzuki couplings.[24]

Scheme 4. C4-Bromo Substituted Isoxazolinoisoquinolines (® = 2% DVB-Polystyrene)



Scheme 5. Suzuki Coupling of a Reissert-Derived Enamide Bromide (8)

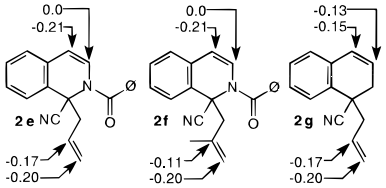


4-Bromoisoquinoline readily undergoes solution-phase Reissert formation when treated with TMSCN and benzoyl chloride (Scheme 5). However, Suzuki coupling of the vinyl bromide in **8** with phenylboronic acid fails to deliver the desired product (starting material recovered), suggesting that this electron-rich enamide bromide is not conducive to the Suzuki coupling protocol.

In light of this failure, we next prepared 6-bromo-5,8-dimethylisoquinoline (**10**)[25] in the hope that the corresponding Reissert intermediate, now possessing a fully aromatic halide, would retain normal Suzuki reactivity. As an initial foray, we carried out the solution-phase Suzuki coupling of **10** with phenylboronic acid [catalytic $Pd(PPh_3)_4$ in 2 M aqueous Na_2CO_3 plus DME] (Scheme 6; ® = H).

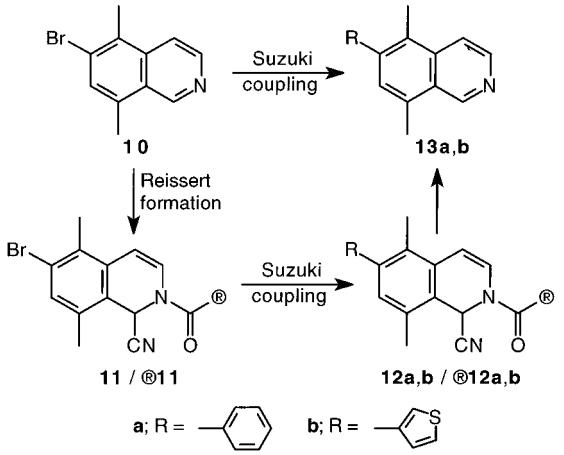
After heating at 80 °C for 12 h, the reaction was quenched with aqueous NH_4OAc and yielded 5,8-dimethyl-6-phenylisoquinoline (**13a**) in 89% yield. Having thus prepared an authentic product sample, we next synthesized Reissert derivative **11** (93% yield) and subjected this to Suzuki coupling conditions. To our delight, Suzuki coupling proceeded nicely, delivering Reissert **12a**

(23) Mulliken population analysis, obtained by AM1 semiempirical calculations comparing **2e**/**f** and hypothetical compound **2g**, indicates that the *exo*-olefin is unaffected by the amide moiety whereas the *endo*-olefin is deactivated.



(24) Miller, R. B.; Dugar, S. *Tetrahedron Lett.* **1989**, *30*, 297−300.
(25) Miller, R. B.; Moock, T. *Tetrahdedron Lett.* **1980**, *21*, 3319−22.

Scheme 6. Solution- and Solid-Phase Suzuki Coupling of a Reissert Intermediate (® = H for Solution-Phase Studies; ® = 2% DVB-Polystyrene for Solid-Phase Studies)



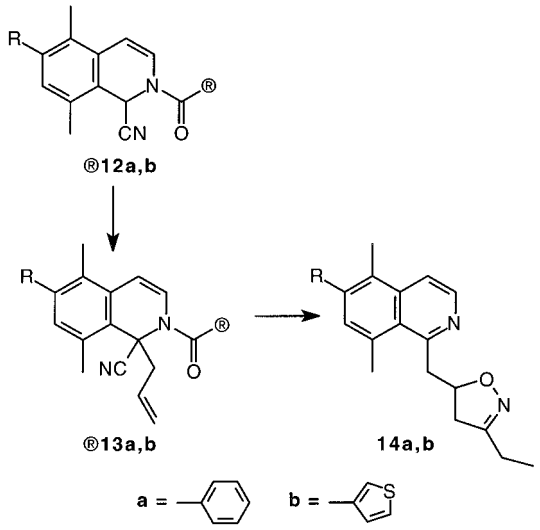
in 75% yield overall from **10**. Subsequent treatment of **12a** with aqueous KOH (100 °C, 12 h, solvent) effected Reissert hydrolysis and produced 5,8-dimethyl-6-phenylisoquinoline (**13a**; 89% overall yield from **10**), identical to the authentic sample prepared by direct Suzuki coupling of **10**.

Having established that the aryl bromide of Reissert **11**, unlike the enamide bromide of Reissert **8**, participates in the Suzuki coupling reaction, we next explored using a heteroaromatic boronic acid in place of phenylboronic acid. Indeed, palladium-mediated coupling of solution-phase Reissert intermediate **11** with 3-thiopheneboronic acid delivered Reissert **12b** in 77% overall yield from **10**. Subsequent Reissert hydrolysis gave 5,8-dimethyl-6-(3-thiophene)isoquinoline (**13b**; 69% overall yield), which was identical to the product obtained by direct Suzuki coupling of isoquinoline **10** with 3-thiopheneboronic acid (**10** → **13b**). These solution results with Reissert **11** → **13a**/**13b** set the stage for exploring the solid-phase variant.

Solid-phase Reissert ®**11** was subjected to Suzuki coupling as follows (Scheme 6; ® = 2% DVB-polystyrene). First, ®**11** was swollen in DME, and a catalytic amount of $Pd(PPh_3)_4$ was added and the mixture stirred gently at ambient temperature for 30 min. Phenylboronic acid and 2 M aqueous Na_2CO_3 were added, and the solution was heated to 80 °C for 36 h (monitoring this reaction proved unworkable by FT-IR). The cooled reaction mixture, which was filtered and washed with DME/H_2O [(1:1), 40 mL], H_2O (2 × 20 mL), 1 M HCl (2 × 15 mL), H_2O (2 × 30 mL), DME (2 × 20 mL), THF (2 × 40 mL), and Et_2O (2 × 25 mL), gave solid-phase ®**12a**, which was treated with aqueous KOH to effect Reissert hydrolysis with concomitant cleavage of **13a** from the polymer (19% overall yield in four steps from ®$C_6H_5CO_2H$; ~66% yield per solid-phase step). In a similar manner, **13b** was prepared in a 17% overall yield using 3-thiopheneboronic acid in the coupling reaction with ®**11**. With these results, we were poised to incorporate the Suzuki coupling reaction in the synthesis of isoxazolinoisoquinolines derivatives.

To incorporate the Suzuki coupling reaction in our solid-phase synthesis of isoxazolinoisoquinoline derivatives, resin ®**11** was subjected to Suzuki coupling conditions to deliver resins ®**12a** and ®**12b** which were then

Scheme 7. C6-Substituted Isoxazolinoisoquinolines via Suzuki Coupling (® = 2% DVB-Polystyrene)



treated with LDA and alkylated at C1 with allyl bromide (see Scheme 7). Alkylated resins ®**13a** and ®**13b** were in turn treated with excess $CH_3CH_2C{\equiv}N^+O^-$ to deliver only the exo-cycloadducts **14a** and **14b** in 19% and 17% yield, respectively, after Reissert hydrolysis.

Conclusion

In summary, we have developed a traceless solid-phase strategy for the synthesis of novel isoxazolinoisoquinoline heterocycles. We have established the viability of the solid-supported Reissert reaction, demonstrated that the polymer-bound Reissert compound can be C1-alkylated, and determined that the 1,3-dipolar cycloaddition reaction of nitrile oxides is selective for the exo-olefin. Finally, we have shown that Reissert intermediates can accommodate a Suzuki coupling reaction to give an additional pathway for diversity. Currently, we are looking to extend this methodology to other heterocycles.

Experimental Section

General Experimental Procedures. All reactions were run under a N_2 atmosphere. Reagents and solvents were purified as follows: dichloromethane was distilled from P_2O_5, benzene and THF were distilled from sodium/benzophenone, cyclohexane was distilled from CaH_2, and diisopropylamine was distilled from KOH. All other reagents were used as received. Infrared spectra were determined on a Galaxy 3000 series Mattson FT-IR. NMR spectra were run using a General Electric QE-300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). Elemental analyses were performed at Midwest MicroLabs.

For reactions involving a polymer support, the polymer was swollen in the reaction solvent for 30 min prior to addition of other reagents. The reaction workup for the polymer substrate included suction filtration using a sintered glass funnel and washing with solvents of varying polarity, usually three times each with water, THF, and hexane. The polymer was then dried overnight under vacuum and an IR spectrum obtained of a KBr pellet of a crushed sample of the polymer. IR bands that are assigned to the polymer support are 3026, 2922, 1601, 1493, 1453, 759, and 698 cm^{-1}. All other bands reported are indicative of the new functionality attached to the polymer. Reactions were monitored by the appearance and/or disappearance of absorbances ascribed to functional group transformations occurring where possible. In the case where the

new functionality is indistinguishable from the previous IR spectrum, a small amount of the polymer was subjected to appropriate cleavage conditions and an ^{1}H NMR spectrum taken.

Polymer-Supported Benzoic Acid.[7b,c] Following Leznoff's procedure, unfuctionalized polystyrene−2% divinylbenzene copolymer (20 g) was suspended in cyclohexane (80 mL) and *n*-BuLi (1.6 M, 150 mL) at ambient temperature over 1 h. The orange mixture was heated to 60 °C, allowed to stir at this temperature for 12 h, and cooled, and the cyclohexane was cannulated out, and the resin was washed three times with dry THF (150 mL). The lithiated polymer was swollen in THF (150 mL), and dry CO_2 was bubbled in for 2−3 h. As CO_2 addition proceeded, the resin changed color from orange to yellow and finally back to orange. The resulting polymer was collected by filtration, washed and dried as described in the general experimental procedures. Polymer loading was determined by titration to be 1.5 mequiv/g: FTIR (KBR) 1698 cm^{-1}.

Polymer-Supported Benzoyl Chloride.[7b,c] Polymer-supported benzoic acid (15 g) was swollen in $SOCl_2$ (200 mL) at ambient temperature for 30 min. A catalytic amount of DMF (1 mL) was added, and the mixture was refluxed for 2−3 h. The polymer was filtered and washed with $CHCl_3$, CH_2Cl_2, THF, and Et_2O. The polymer was dried in a vacuum desiccator overnight: FTIR (KBR) 1760 cm^{-1}.

General Polymer-Supported Reissert Procedure. To a mixture of the acid chloride resin 1 (1.5 g, loading 1.5 mmol/g) in CH_2Cl_2 (30 mL) was added isoquinoline (1.45 g, 11.2 mmol). The mixture was allowed to stir at ambient temperature for 20 min, at which time TMSCN (1.12 g, 10.1 mmol) was added. The resulting mixture was stirred for an additional 48 h, filtered, and washed with CH_2Cl_2 (1 × 50 mL), aqueous HCl (1 × 75 mL), water (1 × 75), aqueous $NaHCO_3$, (1 × 75 mL), water (1 × 75 mL), and THF (2 × 50 mL). The resin was dried in a desiccator for 5 h. All polymer-supported Reissert compounds were made in this fashion from the appropriate isoquinolines: FTIR (KBR) 1680 cm^{-1}.

General Polymer-Supported Alkylation Procedure. The resin obtained from the Reissert reaction was placed in a round-bottom flask (100 mL) with dry THF (20 mL) and cooled to −78 °C. LDA (1.20 g, 11.12 mmol) was added, and the mixture was stirred for 30 min. Methyl iodide (0.90 mL, 84.0 mmol) was added dropwise, and the mixture was allowed to warm to ambient temperature, stirred for 48 h, and collected by filtration. The resin was washed with THF (1 × 50 mL), aqueous HCl/THF (1:1; 2 × 50 mL), water (2 × 50 mL), and THF (2 × 50 mL). The resin was dried in a desiccator for 8 h. Since FTIR could not establish the completeness of the alkylation, the Reissert was hydrolyzed to determine alkylation efficiency by ^{1}H NMR of the crude isoquinoline reaction mixture (>95% C1-alkylated).

General Polymer-Supported Cleavage Procedure. The alkylated resin was placed in a round-bottom flask (25 mL), and THF (10 mL) plus 1 M KOH (10 mL) were added. The mixture was refluxed for 12 h, cooled to ambient temperature, filtered, and washed with Et_2O (2 × 25 mL). The filtrate was placed in a separatory funnel and the aqueous layer discarded. The organic layer was washed with water (2 × 50 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (90:10 hexane/EtOAc to 25:75 hexane/EtOAc) to give the alkylated isoquinoline. Note: this cleavage procedure was also used to liberate isoxazolinoisoquinoline derivatives.

1-Methylisoquinoline (3a):[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H), 7.50 (d, J = 5.76 Hz, 1H), 7.60 (m, 2H), 7.80 (d, J = 7.79 Hz, 1H), 8.11 (d, J = 7.62 Hz, 1H), 8.38 (d, J = 5.79 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.42, 119.25, 125.62, 127.01, 127.19, 129.91, 134.85, 141.81, 158.59; 56% yield; trace unalkylated isoquinoline by GC.

1-Ethylisoquinoline (3b):[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.53 Hz, 3H), 3.30 (q, J = 7.56 Hz, 2H), 7.49 (d, J = 5.76 Hz, 1H), 7.59 (m, 2H), 7.81 (d, J = 7.93 Hz, 1H), 8.15 (d, J = 8.39 Hz, 1H), 8.43 (d, J = 5.71 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.02, 28.90, 119.57, 125.64, 127.36, 127.80, 130.27, 135.27, 142.33, 163.56, 183.79; 59% yield; trace unalkylated isoquinoline by GC.

1-Benzylisoquinoline (3c):[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,21 (s, 3H), 7.15 (m, 5H), 7.46 (m, 3H), 7.63 (d, J = 8.90 Hz, 1H), 7.99 (d, J = 7.60 Hz, 1H), 8.36 (d, J = 5.75 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.05, 119.76, 125.79, 126.21, 127.16, 127.32, 128.48, 128.57, 128.59, 129.80, 136.58, 139.44, 142.01, 160.13; 50% yield; trace unalkylated isoquinoline by GC.

General Polymer-Supported 1,3-Dipolar Cycloaddition Procedure. The alkylated resin (1.5 g, 1.5 mequiv/g) was placed in two-necked flask (100 mL) with dry benzene (40 mL). Nitropropane (844 mg, 11.3 mmol) and PhNCO (2.67 g, 22.5 mmol) were added followed by a catalytic amount of Et_3N (22.7 mg, 0.2 mmol). The mixture was heated to reflux for 36 h and cooled to ambient temperature, water (10 mL) was added, and the resulting mixture was stirred for 10 min. The resin was collected by filtration and washed with THF (2 × 50 mL), water (8 × 50 mL), and THF (4 × 50 mL). The resin was dried in a desiccator for 5 h.

1-[(3-Ethyl-4,5-dihydro-5-isoxazolyl)methyl]isoquinoline (7a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.59 Hz, 3H), 2.25 (q, J = 7.49 Hz, 2H), 2.80 (ddd, J = 7.03 Hz, 1H), 2.87, (ddd, J = 9.92 Hz, 1H), 3.32 (ddd, J = 8.14 Hz, 1H), 3.73 (ddd, J = 5.26 Hz, 1H), 5.12 (m, 1H), 7.47, (d, J = 5.75 Hz, 1H), 7.53 (m, 2H), 7.74, (d, J = 7.70 Hz, 1H), 8.12 (d, J = 7.93 Hz, 1H), 8.36 (d, J = 5.71 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.19, 21.63, 40.16, 42.27, 79.47, 120.14, 125.56, 127.54, 127.73, 127.86, 130.39, 136.43, 141.85, 157.75, 160.72; FTIR ($CDCl_3$) 3060, 2975, 2939, 1623, 1586, 1561, 1502, 1434, 1384, 1367, 1297, 908 cm^{-1}; 25% yield; pale yellow oil.

1-[(4,5-Dihydro-3-phenyl-5-isoxazolyl)methyl]isoquinoline (7b): mp 131−132 °C (recrystallized from EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (ddd, J = 7.34 Hz, 1H), 3.41 (m, 2H), 3.83 (ddd, J = 5.27 Hz, 1H), 5.37 (m, 1H), 7.30 (m, 3H), 7.50 (d, J = 5.87 Hz, 1H), 7.58 (m, 4H), 7.75 (d, J = 7.59 Hz, 1H), 8.12 (d, J = 8.48 Hz, 1H), 8.37 (d, J = 5.74 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.75, 40.14, 80.42, 119.82, 125.07, 126.63, 127.26, 127.43, 127.52, 128.54, 129.64, 129.88, 130.05, 136.09, 141.60, 156.89, 157.20; FTIR ($CDCl_3$) 3053, 2953, 2926, 1623, 1586, 1563, 1502, 1447, 1391, 1355, 909 cm^{-1}; 26% yield. Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.71. Found: C, 79.04; H, 5.66; N, 9.94.

1-[(3-Ethyl-5-methyl-5-oxazolyl)methyl]isoquinoline (7c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87t, J = 7.54 Hz, 3H), 1.30 (s, 3H), 2.05 (q, J = 7.48 Hz, 2H), 2.63 (dd, J = 17.13 Hz, 1H), 3.39 (dd, J = 17.08 Hz, 1H), 3.49 (dd, J = 13.915, 1H), 3.64 (dd, J = 13.91 Hz, 1H), 7.45, (d, J = 5.75 Hz, 1H), 7.57 (m, 2H), 7.70, (d, J = 7.61 Hz, 1H), 8.26 (d, J = 8.12 Hz, 1H), 8.35 (d, J = 3.23 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.38, 20.98, 26.16, 43.74, 46.06, 85.86, 119.24, 126.25, 126.24, 126.80, 128.00, 129.62, 135.95, 140.80, 157.75, 160.72; FTIR ($CDCl_3$) 3154, 2977, 1793, 1560, 1463, 1380, 1097 cm^{-1}; 21% yield; light brown oil.

1-[(3-Ethyl-4,5-dihydro-5-isoxazolyl)methyl]-4-phenylisoquinoline (6a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 4.80 Hz, 3H), 2.26 (q, J = 7.55 Hz, 2H), 2.84 (ddd, J = 7.10 Hz, 1H), 3.01 (ddd, J = 9.95 Hz, 1H), 3.34 (ddd, J = 8.05, 1H), 3.77 (ddd, J = 5.33 Hz, 1H), 5.16 (m, 1H), 7.36, (m, 5H), 7.55 (m, 2H), 7.81, (d, J = 7.73 Hz, 1H), 8.17 (d, J = 7.96 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$)_δ 11.36, 21.81, 40.45, 42.55, 79.69, 125.91, 125.98, 127.66, 127.70, 128.27, 128.97, 130.56, 130.60, 132.89, 135.03, 137.55, 141.78, 157.24, 160.92; FTIR ($CDCl_3$) 3058, 3024, 2972, 2918, 2879, 2850, 1678, 1638, 1599, 1492, 1451, 1340, 1263, 1242, 1065 cm^{-1}; 27% yield; light brown oil.

1-[(4,5-Dihydro-3-phenyl-5-isoxazolyl)methyl]-4-phenylisoquinoline (6b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (ddd, J = 7.52 Hz, 1H), 3.46 (m, 2H), 3.88 (ddd, J = 5.43 Hz, 1H), 5.37 (m, 1H), 7.30 (m, 3H), 7.42 (m, 5H), 7.60 (m, 4H), 7.85 (d, J = 3.21 Hz, 1H), 8.19 (d, J = 4.34 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.81, 40.38, 80.60, 125.48, 125.66, 126.58, 126.91, 127.14, 127.31, 126.76, 127.39, 127.91,

127.96, 128.56, 128.64, 130.16, 131.34, 135.39, 137.07, 141.12, 156.61; FTIR ($CDCl_3$) 3058, 3031, 2962, 2917, 1615, 1556, 1507, 1498, 1445, 1392, 1355, 1260, 1074, 1029, 909 cm^{-1}; 23% yield; pale yellow oil.

1-[(3-Ethyl-5-methyl-5-oxazolyl)methyl]-4-phenylisoquinoline (6c): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.54 Hz, 3H), 1.51 (s, 3H), 2.10 (q, J = 7.48 Hz, 2H), 2.63 (dd, J = 17.13 Hz, 1H), 3.39 (dd, J = 17.08 Hz, 1H), 3.49 (dd, J = 13.915, 1H), 3.64 (dd, J = 13.91 Hz, 1H), 7.39, (m, 5H), 7.54 (m, 2H), 7.78, (d, J = 3.67 Hz, 1H), 8.30 (s, 1H), 8.34 (d, J = 3.18 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.84, 21.40, 26.57, 44.24, 46.40, 86.34 125.14, 126.80, 126.97, 127.76, 127.96, 128.50, 130.04, 130.13, 132.38, 134.61, 137.28, 141.08, 157.15, 160.73; FTIR ($CDCl_3$) 3058, 3031, 2962, 2917, 1617, 1556, 1507, 1498, 1445, 1392, 1355, 1260, 1074, 1029, 1020, 909 cm^{-1}; 24% yield; brown oil.

4-Bromo-1-[(3-ethyl-4,5-dihydro-5-isoxazolyl)methyl-]isoquinoline (9a): ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 4.33 Hz, 3H), 2.23 (q, J = 7.60 Hz, 2H), 2.76 (ddd, J = 7.66 Hz, 1H), 3.01 (ddd, J = 6.99 Hz, 1H), 3.35 (ddd, J = 5.31, 1H), 3.71 (ddd, J = 5.35 Hz, 1H), 5.11 (m, 1H), 7.46, (m, 2H), 8.12, (d, J = 4.44 Hz, 1H), 8.34 (d, J = 5.75 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.90, 21.35, 39.76, 42.05, 78.92, 118.62, 125.73, 126.64, 128.33, 128.83, 131.31, 134.79, 143.40, 157.12, 160.42; FTIR ($CDCl_3$) 3082, 3058, 3023, 3000, 2970, 2920, 2848, 1716, 1683, 1675, 1635, 1600, 1309, 1288, 1261, 1241, 1208, 1179, 1113, 1064 cm^{-1}; 26% yield; brown oil.

4-Bromo-1-[(4,5-dihydro-3-phenyl-5-isoxazolyl)methyl-]isoquinioline (9b): ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (ddd, J = 7.28 Hz, 1H), 3.46 (m, 2H), 3.89 (ddd, J = 5.39 Hz, 1H), 5.38 (m, 1H), 7.33 (m, 3H), 7.51 (m, 5H), 7.58 (m, 4H), 7.85 (d, J = 3.21 Hz, 1H), 8.19 (d, J = 4.34 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 29.66, 40.25, 80.48, 119.93, 125.19, 125.47, 126.60, 127.23, 127.52, 128.16, 128.29, 128.41, 128.51, 129.87, 129.92, 130.22, 143.35, 156.89, 157.17; FTIR ($CDCl_3$) 3154, 2960, 2901, 1617, 1567, 1469, 1382 cm^{-1}; 24% yield; light brown oil.

4-Bromo-1-[(3-ethyl-5-methyl-5-oxazolyl)methyl]isoquinoline (9c): ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 6.79 Hz, 3H), 1.45 (s, 3H), 2.11 (q, J = 7.54 Hz, 2H), 2.60 (dd, J = 17.17 Hz, 1H), 3.29 (dd, J = 17.14 Hz, 1H), 3.41 (dd, J = 14.01, 1H), 3.55 (dd, J = 14.01 Hz, 1H), 7.60, (t, J = 1.23 Hz, 1H), 7.68, (t, J = 1.12 Hz, 1H), 8.07 (d, J = 7.97 Hz, 1H), 8.25 (d, J = 8.48 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.21, 21.81, 26.93, 44.45, 46.88, 86.42, 119.11, 126.69, 127.55, 128.51, 130.04, 131.68, 135.30, 143.45, 157.88, 161.08; FTIR ($CDCl_3$) 3154, 2977, 2938, 1816, 1617, 1567, 1461, 1380, 1097 cm^{-1}; 23% yield; yellow oil.

General Solution Suzuki Coupling Procedure. $Pd(PPh_3)_4$ (115.5 mg, 0.133 mmol) was added to 2-benzoyl-6-bromo-1-cyano-5,8-dimethyl-1,2-dihydroisoquinoline (**11**; 1.0 g, 2.66 mmol) in benzene (20 mL), and the solution was stirred for 30 min. Phenylboronic acid (0.649 g, 5.32 mmol) and 2 M aqueous Na_2CO_3 (3.0 mL, 5.85 mmol) were added, and the mixture was heated to 80 °C for 20 h. The solution was cooled to ambient temperature, diluted with 25% aqueous NH_4OAc (10 mL) and stirred for 5 min. The organic layer was separated from the aqueous layer. The aqueous layer was washed with EtOAc (2 × 10 mL), and the washings were combined with the organic layer. The combined organic layers were washed with DME/H_2O (1:1, 10 mL), water (2 × 10 mL), 1 M HCl (2 × 5 mL), and water (2 × 15 mL) and then dried with $MgSO_4$. The solvent was removed in vacuo. This procedure was followed for all solution Suzuki coupling reactions.

General Solution Reissert Hydrolysis Procedure. A THF (10 mL) solution of 2-benzoyl-6-phenyl-1-cyano-5,8-dimethyl-1,2-dihydroisoquinoline (**12**; 0.50 g, 1.33 mmol) was treated with 1 M aqueous KOH (10 mL, 0.01 mol). The solution was refluxed for 12 h and cooled to ambient temperature, and the organic layer was separated from the aqueous layer. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), and the washings were combined with the organic layer. The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. This procedure was followed for all solution Reissert hydrolysis reactions.

2-Benzoyl-6-bromo-1-cyano-5,8-dimethyl-1,2-dihydroisoquinoline (11): mp 175−177 °C (recrystallized from EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 6H), 6.21 (d, J = 7.96 Hz, 1H), 6.59 (s, 1H), 6.70 (d, J = 1.53 Hz, 1H), 7.41 (s, 1H), 7.41−7.61 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.06, 18.46, 42.39, 107.86, 115.49, 122.89, 126.69, 126.98, 128.63, 129.20, 129.39, 130.18, 130.84, 130.91, 132.09, 132.21, 133.61, 133.69, 168.59; FTIR ($CDCl_3$) 2951, 1667, 1631, 1452, 1348, 1270, 908 cm^{-1}; 93% yield. Anal. Calcd for $C_{19}H_{15}N_2OBr$: C, 62.14; H, 4.12; N, 7.63. Found: C, 62.08; H, 4.12; N, 7.66.

2-Benzoyl-1-cyano-5,8-dimethyl-6-phenyl-1,2-dihydroisoquinoline (12a): ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.41 (s, 3H), 6.20 (d, J = 7.72 Hz, 1H), 6.63 (m, 2H), 7.00 (s, 1H), 7.21−7.67 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.42, 18.69, 43.20, 108.88, 116.46, 123.41, 126.29, 127.65, 128.66, 129.09, 129.13, 129.32, 129.56, 129.61, 129.71, 130.04, 132.21, 132.24, 132.32, 132.98, 141.84, 144.46, 169.12; FTIR ($CDCl_3$) 2957, 1669, 1632, 1468, 1378, 1271, 1154, 1042, 908 cm^{-1}; 75% yield; pale yellow oil.

2-Benzoyl-1-cyano-5,8-dimethyl-6-(3-thiophene)-1,2-dihydroisoquinoline (12b): ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.38 (s, 3H), 6.17 (d, J = 7.76 Hz, 1H), 6.60 (s, 1H), 7.04 (m, 2H), 7.38 (m, 1H), 7.41−7.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.95, 18.16, 42.59, 108.23, 115.90, 122.88, 122.98, 125.26, 125.80, 128.56, 128.77, 129.10, 129.19, 131.65, 131.75, 131.86, 132.27, 138.59, 141.43, 168.58; FTIR ($CDCl_3$) 2957, 1669, 1632, 1468, 1378, 1271, 1154, 1042, 908 cm^{-1}; 77% yield; pale yellow oil.

5,8-Dimethyl-6-phenyl-1-isoquinoline (13a): ^1H NMR (300 MHz, $CDCl_3$) 2.53 (s, 3H), 2.78(s, 3H), 7.41−7.50 (m, 6H), 7.84 (d, J = 5.35 Hz, 1H), 8.61 (d, J = 5.96 Hz, 1H), 9.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.34, 18.24, 117.67, 126.86, 127.18, 127.99, 128.15, 129.35, 130.36, 132.54, 136.09, 141.71, 142.79, 143.26, 149.57; FTIR ($CDCl_3$) 2951, 2924, 1613, 1602, 1465, 1389, 1036, 907 cm^{-1}; 89% yield; pale yellow oil.

5,8-Dimethyl-6-(3-thiophene)-1-isoquinoline (13b): ^1H NMR (300 MHz, $CDCl_3$) δ 2.59, (s, 3H), 2.76 (s, 3H), 7.18 (m, 1H), 7.28 (m, 1H), 7.35 (s, 1H), 7.43 (m, 1H), 7.81 (d, J = 5.10 Hz, 1H), 8.60 (d, J = 5.97 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.37, 18.18, 117.60, 123.55, 125.30, 126.80, 128.35, 129.02, 130.20, 132.56, 136.09, 137.44, 141.91, 143.23, 149.47; FTIR ($CDCl_3$) 2949, 2918, 1614, 1587, 1481, 1465, 1444, 1411, 1384, 1247, 1035, 907 cm^{-1}; 69% yield; pale yellow oil.

General Polymer-Supported Suzuki Coupling Procedure.[11a] Polymer-supported Reissert resin (1.5 g, 1.5 mequiv/g) was swollen in CH_2Cl_2 (30 mL) and treated with $Pd(PPh_3)_4$ (173.3 mg, 0.15 mmol). After 30 min, phenylboronic acid (731.5 mg, 6.0 mmol) and 2 M aqueous Na_2CO_3 (1.65 mL, 6.6 mmol, 4.4 equiv) were added, and the mixture was heated to 80 °C for 72 h. The mixture was cooled to ambient temperature, diluted with 25% aqueous NH_4OAc (10 mL), stirred for 5 min, and filtered. The resin was washed with CH_2Cl_2/H_2O (1:1, 40 mL), water (2 × 20 mL), 1 M aqueous HCl (2 × 15 mL), water (2 × 30 mL), CH_2Cl_2 (2 × 20 mL), THF (2 × 40 mL), and Et_2O (2 × 25 mL) and dried in a desiccator for 8 h.

5,8-Dimethyl-1-[(3-ethyl-4,5-dihydro-5-isoxazolyl)methyl]-6-phenyl-1-isoquinoline (14a): ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 3.55, 3H), 2.28 (q, J = 7.43 Hz, 2H), 2.45 (s, 3H), 2.65 (ddd, J = 9.18 Hz, 1H), 2.70 (s, 3H), 3.11, (ddd, J = 7.0 Hz, 1H), 3.50 (ddd, J = 7.32 Hz, 1H), 4.07 (ddd, J = 4.39 Hz, 1H), 5.18 (m, 1H), 7.29 (m, 5H), 7.76 (d, J = 5.98 Hz, 1H), 8.54 (d, J = 5.82 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.96, 15.37, 18.27, 21.45, 26.05, 42.69, 44.86, 80.04, 117.70, 127.24, 128.04, 128.20, 129.40, 130.40, 132.59, 132.62, 133.29, 137.95, 141.19, 141.78, 143.35, 149.65, 158.12, 160.64; 23% yield; pale yellow oil.

5,8-Dimethyl-1-[(3-ethyl-4,5-dihydro-5-isoxazolyl)methyl]-6-(3-thiophene)-1-isoquinoline (14b): ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.52, 3H), 2.36 (q, J = 7.60 Hz, 2H), 2.59 (s, 3H), 2.76 (ddd, J = 7.60 Hz, 1H), 2.87, (ddd, J = 9.92 Hz, 1H), 2.94 (s, 3H), 3.32 (ddd, J = 8.14 Hz, 1H), 3.73

(ddd, J = 5.26 Hz, 1H), 5.12 (m, 1H), 7.18 (d, J = 3.73, 1H), 7.29 (m, 1H), 7.38 (s, 1H), 7.44, (m, 1H), 7.76 (d, J = 5.92, 1H), 8.42 (d, J = 5.92 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.32, 16.65, 21.82, 26.35, 43.07, 45.22, 80.44, 117.10, 123.97, 125.76, 129.47, 129.66, 133.07, 133.57, 141.59, 158.49; 25% yield; pale yellow oil.

Acknowledgment. We are grateful to the National Science Foundation and the DuPont Educational Aid Program for financial support of this research.

Supporting Information Available: ^{1}H NMR spectra for **3a**−**c**, **6a**−**c**, **7a**−**c**, **9a**−**c**, **11**, **12a,b**, **13a,b**, and **14a,b**; ^{13}C NMR spectra for **3a**−**c**, **6a**−**c**, **7a**−**c**, **9a**−**c**, **11**, **12a,b**, **13a,b**, and **14a,b** (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9720142