JOC*Article*

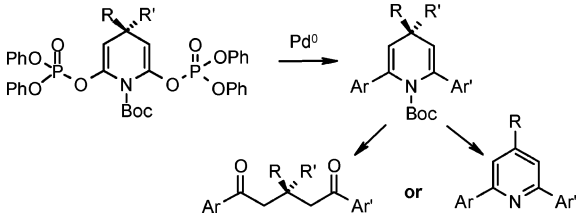
Synthesis and Reactivity of Imide-Derived Bisvinyl Phosphates. Reactivity of 2,6-Disubstituted 1,4-Dihydropyridines

Deborah Mousset, Isabelle Gillaizeau,* Andréa Sabatié, Pascal Bouyssou, and Gérard Coudert*

ICOA, UMR 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France

isabelle.gillaizeau@univ-orleans.fr; gerard.coudert@univ-orleans.fr.

Received April 6, 2006



Symmetrical and unsymmetrical 2,6-disubstituted dihydropyridines were prepared in high yields under mild conditions using the Suzuki and Stille Pd-catalyzed coupling reactions of imide-derived bisvinyl phosphates with a range of aryl, heteroaryl, and alkenyl moieties. The alkylation reaction at C-4 easily afforded original tri- and tetrasubstituted dihydropyridines. Hydrolysis of the latter under acidic condition provided efficiently either open-chain 1,5-diketones or di- or trisubstituted pyridines.

Introduction

Enol phosphates represent versatile intermediates in the construction of complex organic molecules.[1] The ability to easily convert enol phosphates into a myriad of functional motifs of synthetic relevance is well-known. In particular, this moiety has proved to be a robust and versatile partner for cross-coupling reactions mediated by Pd(0) and Ni(0). Enol phosphates have in fact, in a few cases, proved to work better in such reactions than their triflate counterparts owing to higher stability, higher reaction yield, and easier work up. The ability of enol phosphates to undergo these cross-coupling reactions in the presence of various heteroatoms makes them attractive functional groups for the construction of various substituted heterocyclic systems. Enol phosphates were used in Suzuki,[1i,1e,2] Stille,[1h,2d,3] Sonogashira,[4] Negishi,[5] and Kumada-Tamao[6] reactions and were also applied in total synthesis.[7]

In a recent paper,[8] using a methodology developed in our group, we described an efficient synthesis of 2,6-disubstituted dihydropyridines under mild conditions using the Suzuki and Stille Pd-catalyzed coupling reactions of imide-derived bisvinyl phosphates with a range of aryl, heteroaryl, and alkenyl moieties. As part of our interest in using readily available enol phosphates in the synthesis of new heterocyclic compounds, we wish to report herein a general methodology for the synthesis of

(1) (a) Nicolaou, K. C.; Shi, G. Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467−5468. (b) Buon, C.; Chacun-Lefevre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605−614. (c) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889−1911. (d) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205−4208. (e) Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969−6975. (f) Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 7875−7878. (g) Moraes, D. N.; Barrientos-Astigarraga, R. E.; Castelani, P.; Comasseto, J. V. *Tetrahedron* **2000**, *56*, 3327−3337. (h) Bouyssou, C. B.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 701−702. (i) Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321−3324. (j) Fugami, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 2203−2206. (k) Takai, K.; Sato, M.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, 57, 108−115. (l) Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609−1612. (m) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531−2534.

(2) (a) Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360−6368. (b) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471−473. (c) Campbell, I. B.; Guo, J.; Jones, E.; Steel, P. G. *Org. Biomol. Chem.* **2004**, *2*, 2725−2727. (d) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett.* **2005**, 46, 4261−4263.

(3) (a) Nicolaou, K. C.; Shi, G. Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757−1758.

(4) cf. References 2a and 3a.

(5) Jiang, J. L.; Devita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593−594.

(6) (a) Liao, Y.; Hu, Y. H.; Wu, H.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, 10, 2285−2316. (b) Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, 66, 7875−7878. (c) Miller, J. A. *Tetrahedron Lett.* **2002**, *43*, 7111−7114. (d) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199−1205. (e) Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001−1002.

(7) (a) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, 2771−2774.

(8) Mousset, D.; Gillaizeau, I.; Hassan, J.; Lepifre, F.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **2005**, *46*, 3703−3705 and references cited herein.

10.1021/jo0607360 CCC: $33.50
Published on Web 07/08/2006

polysubstituted dihydropyridines and/or pyridines which are of great interest as intermediates in medicinal chemistry.[9] Dihydropyridines (DHPs) exhibit interesting features that make them attractive for use in organic synthesis. Furthermore, only a few examples of 2,6-disubstituted dihydropyridines have been described so far, and most of them have been synthesized from the corresponding pyridine or pyridinium salt.[10]

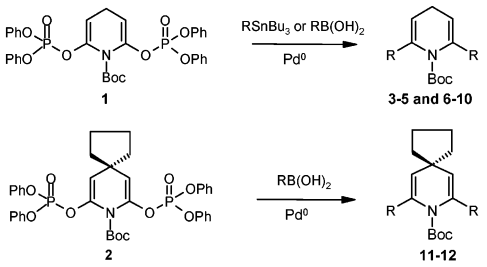
In this paper, we give a full account of our investigations which focus primarily on the preparation of 2,6-disubstituted dihydropyridines derivatives symmetrical or not by using Pd-catalyzed coupling reactions. Second, we also investigated the reactivity of the dihydropyridine by performing functionalization reactions at C-4 and by applying hydrolysis conditions.

Results and Discussion

As previously described,[8] the cross-coupling reactions of bisenolphosphates **1** and **2**, obtained from the corresponding glutarimides via the bislithium enolate, afforded the 2,6-disubstituted dihydropyridines **3**−**12** in high yields. Table 1 summarizes the most significant experiments of this study. The boronic acids or tin reagents are commercially available except for 2-methylstannylbenzodioxine (entry 2, Table 1).[3b] The *N*-Boc group was initially used as an electron withdrawing protecting group since it is easily removable under acidic conditions.

After the successful preparation of symmetrical 2,6-disubstituted dihydropyridines, we turned our attention to more interesting unsymmetrical dihydropyridine derivatives. To achieve this goal, we first investigated the two-step Suzuki−Miyaura reactions. The key step was the selective monocoupling reaction. Unfortunately, by reducing first the quantity of boronic acid under the same conditions as above (1.1 equiv $PhB(OH)_2$, 5 mol % $PdCl_2(PPh_3)_2$, 2 equiv Na_2CO_3 (2M), EtOH, reflux 30 min) or by applying Hirao and Sakurai conditions[12] on bisvinyl phosphate **2** (110 mol % $PhB(OH)_2$, 1.5 mol % $Pd_2(dba)_3$, 3.6 mol % Cy_3P, 200 mol % Cs_2CO_3 in dioxane at 85 °C during 24 h) we were not able to isolate the desired monosubstituted dihydropyridine derivative. After only 1 h, we recovered bissubstituted product **11** (in 40% yield) accompanied by unreacted starting material **2** (in 50% yield). The monosubstituted dihydropyridine derivative appeared indeed to be more reactive than the starting bisvinyl phosphate **2**. Thus, we decided to introduce both substituents successively (Scheme 1. To this aim, we first prepared monovinyl phosphate **14** by treatment of the *N*−Boc glutarimide **13**[8] with LiHMDS (1.2 equiv) at −78 °C followed by the addition of diphenyl chlorophosphate. After workup and purification by chromatography, compound **14** was isolated in 74% yield. It should be noted that we selected the spiro derivative **13** for its greater stability than its nonspiro counterpart. We then attempted the first Suzuki coupling reaction under similar conditions. The monosubstituted derivative **15** was then isolated in 77% yield. Starting from the latter, and by using the same protocol, enol phosphate **16** was synthesized in 78% yield. A second Suzuki coupling reaction enabled us to obtain the desired unsymmetrical 2,6-dihydropyridines **17a**−**f** in remarkably high yields (cf. Table 2). In the case of compounds **17a**,**b**, we also had the opportunity to test a new palladium catalyst prepared by Nolan's group.[13] Under these conditions (1.1 equiv $PhB(OH)_2$, 10 mol % (IMes)Pd(η^3-2-methylallyl)-

TABLE 1. Suzuki and Stille Coupling Reactions on Bisvinyl Phosphates 1 and 2[d]



Entry	bis-vinyl-phosphate	Reagents	Products	Yield (%)
1[a]	**1**	Bu_3Sn	**3**	**88**
2[a]	**1**	Me_3Sn	**4**	**66**
3[a]	**1**	Bu_3Sn C_4H_9	**5**	**54**
4[b]	**1**	$(OH)_2B$	**6**[c]	**88**
5[b]	**1**	$(OH)_2B$ S	**7**	**83**
6[b]	**1**	$(OH)_2B$ O	**8**	**25**
7[b]	**1**	$(OH)_2B$ S	**9**	**60**
8[b]	**1**	$(OH)_2B$ O	**10**	**61**
9[b]	**1**	$(OH)_2B$	**3**	**54**
10[b]	**2**	$(OH)_2B$	**11**	**85**
11[b]	**2**	$(OH)_2B$ S	**12**	**70**

[a] Conditions: 10 mol % $Pd(PPh_3)_4$, 4 equiv $RSnBu_3$, 3 equiv LiCl, THF, 3 h, reflux.[11] [b] Conditions: (i) 10 mol % $PdCl_2(PPh_3)_2$ THF, RT, 10 min; (ii) 3 equiv $RB(OH)_2$, 2 equiv Na_2CO_3 2 M, EtOH, reflux, 3 h. [c] Reaction time: 30 min. [d] All the compounds were fully characterized by analytical and spectroscopic methods.

(9) Chhillar, A. K.; Arya, P.; Mukherjee, C.; Kumar, P.; Yadav, Y.; Sharma, A. K.; Yadav, V.; Gupta, J.; Dabur, R.; Jha, H. N.; Watterson, A. C.; Parmarn V. S.; Prasad, A. K.; Shrama, G. *Bioorg. Med. Chem.* **2006**, *14*, 973−981.

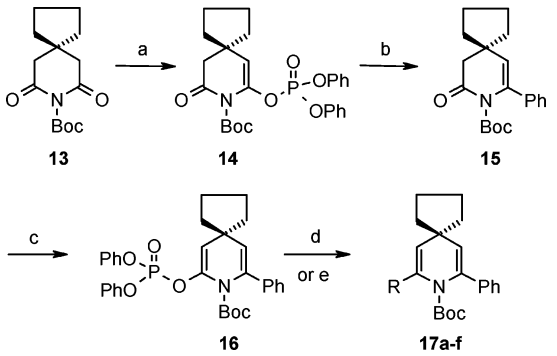
(10) (a) For dihydropyridines chemistry reviews see Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156. (b) Lounasmaa, M.; Tolvanen, A. In *Comprehensive Heterocyclic Chemistry II*; Katrisky, A. R., Rees, C. W., Scriven, E. F. V.; Eds.; Pergamon: Oxford, U.K., 1996; Vol. 5, p 135. (c) Charrette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830. (d) Lavilla, R.; Bernabeu, M. C.; Carranco, I.; Diaz, J. L. *Org. Lett.* **2003**, *5*, 717−720. (e) Ishar, M. P. S.; Kumar, K.; Kaur, S.; Kumar, S.; Girdhar, N. K.; Sachar, S.; Marwaha, A.; Kapoor, A. *Org. Lett.* **2001**, *3*, 2133-2136. (f) Jakubowicz, K; Wong, Y.-S.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *J. Org. Chem.* **2005**, *70*, 7780−7783.

(11) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

(12) Mao, L.; Sakurai, H.; Hirao, T. *Synthesis* **2004**, 2535−2539.

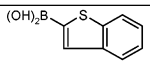
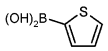
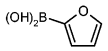
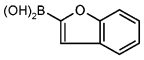
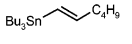
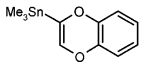
(13) Navarro, O.; Oonishi, Y.; Kelly, R. A.; Stevens, E. D.; Briel, O.; Nolan, S. P. *J. Organomet. Chem.* **2004**, 689, 3722−3727 and references cited therein.

SCHEME 1[a]



[a] (a) (i) 1.2 equiv LiHMDS, THF, −78 °C, 1.5 h; (ii) 1.2 equiv $ClP(O)(OPh)_2$, −78 °C, 2 h (74%). (b) (i) 5 mol % $PdCl_2(PPh_3)_2$, THF, TA, 10 min; (ii) 2.5 equiv $PhB(OH)_2$, 2 equiv Na_2CO_3 (2 M), EtOH, reflux 2 h (77%). (c) (i) 1.2 equiv LiHMDS, THF, −78 °C, 1.5 h; (ii) 1.2 equiv $ClP(O)(OPh)_2$, −78 °C, 1 h (78%). (d) (i) 5 mol % $PdCl_2(PPh_3)_2$, THF, TA, 10 min; (ii) 2.5 equiv $RB(OH)_2$, 2 equiv Na_2CO_3 (2 M), EtOH, reflux 2 h. (e) 5 mol % $Pd(PPh_3)_4$, 2 equiv $RSnBu_3$ or $RSnMe_3$, 1.5 equiv LiCl, THF, 2 h, reflux. (cf. Table 2).

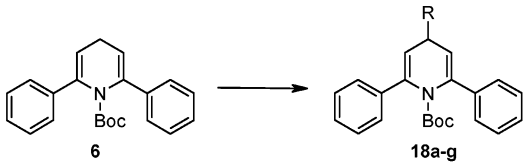
TABLE 2. Synthesis of Unsymmetrical 2,6-Dihydropyridine Derivatives 17a−f from the Monovinyl Phosphate 16

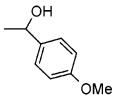
Entry	Reagents	Products	Yield (%)
1		**17a**	**80**
2		**17b**	**100**
3		**17c**	**79**
4		**17d**	**48**
5		**17e**	**50**
6		**17f**	**52**

Cl,[12] 2 equiv Na_2CO_3 (2M), EtOH, reflux 30 min) we successfully obtained the desired substituted dihydropyridines **17a** and **17b**, respectively, in 75% and 70% yield. To the best of our knowledge, it is the first application of this catalyst in the palladium coupling reaction onto a vinyl phosphate moiety.

Our next aim was then to functionalize the C-4 position. Creating variations of these 1,4-dihydropyridines is an important task. To the best of our knowledge, there is no literature precedent for the direct alkylation of 1,4-dihydropyridines at the C-4 position. Some alkylations are described on the piperidine skeleton but in each case via the 2-methoxy-1,2,5,6-tetrahydropyridine moiety. Matsumura et al. reported the regioselective introduction of substituents at C-4 of a piperidine ring by using the addition of a Grignard reagent in the presence of CuBr[14] or by the stereoselective addition of dimethyl alkylmalonate in the presence of $TiCl_4$ in Et_3N/CH_2Cl_2.[15] Torii et al. also described an easy access to 4-hydroxy-1,2,3,4-tetrahydropyridines by an acid-catalyzed rearrangement under mild conditions.[16]

TABLE 3. FunctionalizAtion Reactions at C-4 of Dihydropyridine 6[a]



Entry	Electrophiles	R	Products	Yield (%)
1	Methyl iodide	$-CH_3$	**18a**	**97**
2	Allyl bromide		**18b**	**74**
3	Benzaldehyde		**18c**	**75**
4	Acetone		**18d**	**100**
4	4-Methoxy-benzaldehyde		**18e**	**65**
5	Cyclohexanone		**18f**	**80**
6	Methyl vinyl ketone		**18g**	**41**

[a] Reagents and conditions: (i) 1.1 equiv *n*-BuLi, THF, −78 °C, 5 min; (ii) 3 equiv electrophile, −78 °C, 2 h; (iii) NH_4Cl sat.

Hence, we decided to introduce various substituents at C-4 by preparing the 4-lithio derivative of 2,6-diphenyl-1,4-dihydropyridine **6**, chosen as a model compound. The best results were obtained using 1.1 equiv of *n*-BuLi at −78 °C for only 5 min. The 4-lithio derivative was trapped with a range of electrophiles (3 equiv) leading to the required 4-substituted derivatives **18a−g** in high yields (cf. Table 3). The use of another base such as LDA resulted in a dramatic decrease of the yield because of unreacted starting material. Compound **6** was found to be quite sensitive to basic conditions. Thus, if reaction times were superior to 5 min, it also resulted in lower overall yields.

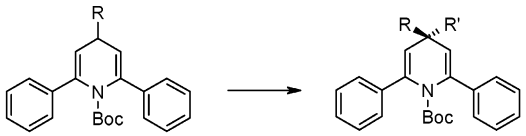
Encouraged by these promising results, we then explored the bisfunctionalization reaction at the C-4 position. A first attempt was made starting from the 4-methyl derivative **18a**. Optimal conditions were determined to be 1.1 equiv of *t*-BuLi at −78 °C for only 5 min, followed by the addition of the second electrophile (3 equiv). In this case, using iodomethane as the electrophile, 4,4-dimethyl-2,6-diphenyl-dihydropyridine **19a** was isolated in quantitative yield (cf. Table 4). However, variations in the nature of the electrophile had a dramatic influence on

(14) Shono, T.; Terauchi, J.; Ohki, Y.; Matsumura, Y. *Tetrahedron Lett.* **1990**, *31*, 6385−6386.

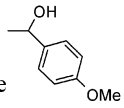
(15) Matsumura, Y.; Yoshimoto, Y.; Horikawa, C.; Maki, T.; Watanabe, M. *Tetrahedron Lett.* **1996**, *37*, 5715−5718.

(16) Torii, S.; Inokuchi, T.; Akahosi, F.; Kubota, M. *Synthesis* **1987**, 242−245.

TABLE 4. Second Functionalization at C-4 of Dihydropyridines 18A and 18b[a]

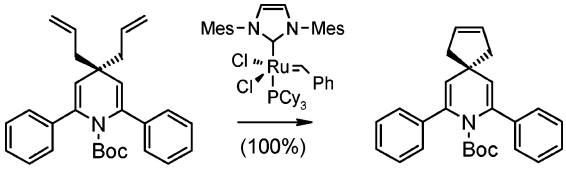


18a or 18b 19a-e

Entry	R	Electrophiles	R'	Pdcts	Yield (%)
1	$-CH_3$	Methyl iodide	$-CH_3$	**19a**	**100**
2	$-CH_3$	Allyl bromide		**19b**	**34**
3	$-CH_3$	Acetone		**19c**	**10**
4		CH_3I	$-CH_3$	**19b**	**100**
5		Allyl bromide		**19d**[b]	**100**
6		4-Methoxy-benzaldehyde		**19e**	**88**

[a] Reagents and conditions: (i) 1.1 equiv *t*-BuLi, THF, −78 °C, 5 min; (ii) 3 equiv electrophile, 2 h, −78 °C; (iii) NH_4Cl sat. [b] The bisallylic compound **19d** could also be obtained by using a "one pot" procedure without isolation of the monocoupling derivative **18b** (cf. experimental part).

SCHEME 2. Metathesis Cyclization Reaction on the Bisallylic Compound 19d[a]



19d 20

[a] Conditions and reagents: Ruthenium catalyst[16] (10 mol %), toluene, 60 °C, 15 h.

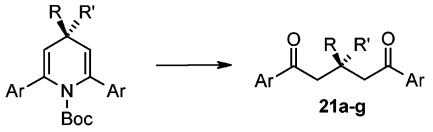
the reactivity of these dihydropyridine derivatives (cf. Table 4, entries 2−3). For more hindered groups, the best strategy was to carry out the first step with the allyl group for example. (Table 4, entries 4−6).

As we had it in hand, we decided to perform a ring-closing metathesis reaction on bisallylic compound **19d**. Treatment of the latter using a second generation ruthenium catalyst[17] afforded the desired cyclized derivative **20** in quantitative yield (cf. Scheme 2). Finally starting from commercially available glutarimide, the original unsaturated spiro derivative **20**, an unsaturated analogue of compound **11,** was obtained in only five steps and in 48% global yield.

With the goal of valorising these substituted dihydropyridines, we then examined their behavior under acidic conditions.

(17) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678.

TABLE 5. Hydrolysis of Dihydropyridine Derivatives[a]



21a-g

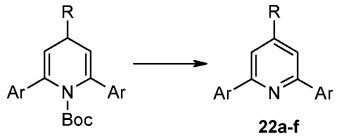
Entry	Cpds	Products	Yield (%)
1	**6**	**21a**[18]	**100**
2	**9**	**21b**[19]	**100**
3	**7**	**21c**	**95**
4	**11**	**21d**	**94**
5	**12**	**21e**	**82**
6	**18b**	**21f**	**77**
7	**19a**	**21g**	**100**

[a] Reagents and conditions: 3 N HCl/EtOAc, RT, 4 h.

Treatment of various dihydropyridines with 3 N HCl in ethyl acetate promoted ring opening and gave the corresponding open-chain diketones in very good yields (Table 5). This methodology provides easy access to original 1,5-diketones not described yet or not otherwise easily accessible. In addition, treatment of dihydropyridines derivatives with anhydrous TFA afforded the corresponding di- or trisubstituted pyridines **22a**−**f** in high yields (See Table 6).

In conclusion, we demonstrated the usefulness of synthesizing enol phosphates derived from imides. These compounds are versatile starting materials for palladium catalyzed cross-coupling reactions giving efficient access to a range of 2,6-disubstituted 1,4-dihydropyridines. On the latter's C-4 position, selective mono- or bissubstitution was achieved in good yield. This work demonstrates the potential of our methodology. Moreover, hydrolysis under acidic conditions of the dihydropyridine derivatives provides a direct and efficient route either to original 1,5-diketones or to various di- or trisubstituted pyridines. Because different patterns of substitution on the heterocycle are compatible with the reaction conditions, the proposed methodology could be very useful for the synthesis of natural products and biologically active compounds containing piperidine moieties. Indeed, the application of this methodology to the synthesis of more complex heterocyclic structures is currently under investigation in our laboratory via the study of the reactivity of the enamide double bond.

TABLE 6. Di- or Trisubstituted Pyridines 22a−f[a]



Entry	Cpds	Products	Yield (%)
1	**6**	**22a**[20]	**95**
2	**7**	**22b**	**100**
3	**9**	**22c**[21]	**55**
4	**10**	**22d**[22]	**50**
5	**18d**	**22e**	**80**
6	**18f**	**22f**	**85**

[a] Reagents and conditions: 6.4 equiv TFA, CH_2Cl_2, RT, 4 h.

Experimental Section

Only representative procedures and characterizations of the products are described here. Full details can be found in the Supporting Information.

Author: The chemical abbreviation P.E. was used in the paragraphs below. If this is not polyethylene (PE), please define

General Procedure (A) for the Stille Coupling Reaction. 1-(*tert*-Butoxycarbonyl)-2,6-di-(1,4-benzodioxin-2-yl)-1,4-dihydropyridine (4). To a stirred solution of bisvinyl phosphate **1** (0.74 mmol, 500 mg) in THF (2.5 mL), trimethyl(benzodioxin)tin (3.69 mmol, 1.09 g) and anhydrous lithium (4.43 mmol, 188 mg) were added under argon, then the flask was evacuated and backfilled with argon three times. Under argon, $Pd(PPh_3)_4$ (0.074 mmol, 51 mg) was added, and the mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with water; ethyl acetate was then added. The organic layer was separated and dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 8:2) to afford **4** (66% yield) as a yellow solid: mp 99−100 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.44 (s, 9H); 2.75 (t, 2H, J = 5 Hz); 5.93 (t, 2H, J = 5 Hz); 6.17 (s, 2H); 6.67−7.00 (m, 8H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.1, 28.1, 82.5, 116.2, 116.3, 117.3, 124.1, 124.2, 124.4, 134.2, 134.6, 142.2, 142.7, 152.3. IR ν_{max} (KBr): 2926, 2854, 1751, 1600, 1494, 1463. MS (IE): m/z 446 $[M + H]^+$.

General Procedure (B) for the Suzuki Coupling Reaction. 1-(*tert*-Butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine (6). To a solution of bisvinyl phosphate **1** (0.74 mmol, 500 mg) in THF (2.5 mL) under argon, $PdCl_2(PPh_3)_2$ (0.074 mmol, 51 mg) was added. The flask was evacuated and backfilled with argon three times, and the mixture was stirred during 15 min. Then, phenylboronic acid (3.69 mmol, 449 mg), 2M Na_2CO_3 (aqueous solution) (1.25 mL), and few drops of EtOH were added. The mixture was refluxed for 30 min. After cooling, ethyl acetate was added; the organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography (silica gel, PE then PE/EtOAc 8:2) to afford **6** (88% yield) as a white solid: mp 126−127 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.03 (s, 9H); 2.94 (t, 2H, J = 5 Hz); 5.78 (t, 2H, J = 5 Hz); 7.24−7.40 (m, 6H); 7.52−7.57 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.9, 27.6, 81.3, 116.4, 125.4, 127.3, 128.3, 138.9, 142.6, 152.3. IR ν_{max} (KBr): 2971, 2930, 2812, 1716, 1670, 1629, 1598. MS (IE): m/z 354.50 $[M + H]^+$. HRMS (IE): m/z calcd for $[C_{22}H_{23}-CO_2-t\text{-}Bu]^+$, 232.1126; found, 232.1112.

1-(*tert*-Butoxycarbonyl)-2,6-dithianaphten-2-yl-1,4-dihydropyridine (7). The Suzuki coupling reaction was carried out as described in the general procedure (B) by using thianaphtene-2-boronic acid. The reaction was completed in 3 h. After purification by flash column chromatography (silica gel, PE then PE/EtOAc 9:1), the desired compound **7** was isolated as a yellow solid (83% yield): mp 149−150 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.82 (s, 9H); 3.08 (t, 2H, J = 5 Hz); 5.83 (t, 2H, J = 5 Hz); 7.32−7.44 (m, 4H); 7.49 (s, 2H); 7.85−7.88 (m, 2H); 8.08−8.11 (m, 2H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.7, 27.5, 81.2, 116.9, 120.7, 122.2, 122.8, 122.9, 123.1, 123.3, 124.3, 124.4, 124.7, 124.8, 135.1, 136.4, 137.9, 140.2, 141.0, 152.1. IR ν_{max} (KBr): 3018, 2976, 2938, 1700, 1640, 1571, 1545. MS (IE): m/z 344.05 $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$. HRMS (IE): m/z $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$ calcd for $C_{21}H_{14}NS_2$, 344.0567; found, 344.0562.

8-(*tert*-Butoxycarbonyl)-7,9-diphenyl-8-aza-spiro[4.5]deca-6,9-diene (11). The Suzuki coupling reaction was carried out as described in the general procedure (B) by using phenylboronic acid. The reaction was completed in 3 h. After purification by flash column chromatography (silica gel, PE then PE/EtOAc 9:1), the desired compound **11** was isolated as a white solid (85% yield): mp 137−138 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.03 (s, 9H); 1.74−1.82 (m, 8H); 5.67 (s, 2H); 7.25−7.40 (m, 6H); 7.54−7.57 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.0; 27.6; 40.8; 45.6; 81.1; 125.5; 126.4; 127.2; 128.2; 139.0; 140.5; 152.3. IR ν_{max} (KBr): 3017, 2956, 2874, 1707, 1520, 1494, 1450. MS (IE): m/z 286.50 $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$. HRMS (IE): m/z $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$ calcd for $C_{21}H_{20}N$, 286.1595; found, 286.1576.

8-(*tert*-Butoxycarbonyl)-7,9-dithianaphten-2-yl-8-aza-spiro-[4.5]deca-6,9-diene (12). The Suzuki coupling reaction was carried out as described in the general procedure (B) by using thianaphtene-2-boronic acid. The reaction was completed in 3 h. After purification by flash column chromatography (silica gel, PE then PE/EtOAc 8:2), the desired compound **11** was isolated as an orange solid (70% yield): mp 142−143 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.17 (s, 9H); 1.82 (s, 8H); 5.98 (s, 2H); 7.28−7.37 (m, 4H); 7.42 (s, 2H); 7.74−7.82 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.3, 27.8, 40.4, 46.4, 82.1, 119.7, 123.3, 123.6, 124.3, 124.4, 124.9, 128.8, 135.8, 139.2, 140.1, 152.0. IR ν_{max} (KBr): 3077, 2963, 2874, 1718, 1593, 1489, 1457. MS (IE): m/z 401.50 $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$. HRMS (IE): m/z $[M-{}^{\bullet}CO_2t\text{-}Bu]^+$ calcd for $C_{25}H_{20}NS_2$, 398.1037; found, 398.1008.

9-{(Phenyloxy)-[bisphosphoryl]oxy}-8-(*tert*-butoxycarbonyl)-8-aza-spiro[4.5]deca-9-en-7-one (14). To a solution of 8-(*tert*-butoxycarbonyl)-7,9-dioxo-8-aza-spiro[4.5]decane **13**[8] (0,75 mmol, 200 mg) in THF (7 mL) at −78 °C under argon, LiHMDS (0.9 mmol, 1 M in THF, 0.9 mL) was added dropwise. After being stirred for 1.5 h at −78 °C, a solution of diphenyl chlorophosphate (0.9 mmol, 0.186 mL) in THF (3 mL) was added. After 1 h at −78 °C, the reaction was quenched by the slow addition of H_2O. Ethyl acetate was then added, the organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica

gel, toluene/EtOAc 9:1 with 0.5% Et_3N) to afford the monovinyl phosphate **13** (74%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.49 (s, 9H); 1.50−1.65 (m, 8H); 2.41 (s, 2H); 5.27 (d, 1H, J = 2.2 Hz); 7,22−7,26 (m, 6H); 7,33−7,39 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 23.7, 27.7, 38.5, 41.1, 44.0, 85.3, 103.6, 103.7, 120.1, 120.2, 126.0, 130.1, 138.5, 150.4, 168.8. IR ν_{max} (NaCl film): 3017, 2962, 2875, 1780, 1741, 1698, 1489, 1456, 1343. MS (IS): m/z 500.51 $[M + H]^+$.

8-(*tert*-Butoxycarbonyl)-9-phenyl-8-aza-spiro[4.5]deca-9-en-7-one (15). To a solution of monovinyl phosphate **14** (1.8 mmol, 900 mg) in THF (10 mL) under argon, $PdCl_2(PPh_3)_2$ (0.18 mmol, 75 mg) was added. The flask was evacuated and backfilled with argon three times, and the mixture was stirred during 15 min. Then, phenylboronic acid (4.51 mmol, 550 mg), 2 M Na_2CO_3 (aqueous) (2.9 mL), and a few drops of EtOH were added. The mixture was refluxed for 2 h. After the mixture cooled, ethyl acetate was added, and the organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography (silica gel, PE then PE/EtOAc/DCM 8:1:1) to afford **14** (77% yield) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.14 (s, 9H); 1.67−1.78 (m, 8H); 2.54 (s, 2H); 5.48 (s, 1H); 7,30−7,36 (m, 5H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.1, 27.3, 38.2, 42.4, 44.7, 84.0, 122.7, 125.9, 126.0, 128.3, 128.6, 132.4, 137.5, 138.4, 150.3, 170.7. IR ν_{max} (NaCl film): 3060, 2980, 2847, 1771, 1698, 1493, 1447. MS (IS): m/z 328.50 $[M + H]^+$.

7-{(Phenyloxy)-[bisphosphoryl]oxy}-8-(*tert*-butoxycarbonyl)-9-phenyl-8-aza-spiro[4.5]deca-6,9-diene (16). To a solution of compound **15** (0,31 mmol, 100 mg) in THF (8 mL) at −78 °C under argon, LiHMDS (0.52 mmol, 1 M in THF, 0.52 mL) was added dropwise. After stirring for 1.5 h at −78 °C, a solution of diphenyl chlorophosphate (0.46 mmol, 0.95 mL) in THF (3 mL) was added. After 2 h at −78 °C, the reaction was quenched by the slow addition of H_2O. Ethyl acetate was then added, the organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, toluene/EtOAc 9:1) to afford the vinyl phosphate **16** (78% yield) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.18 (s, 9H); 1.66−1.71 (m, 8H); 5.26 (d, 1H, J = 2 Hz); 5.60 (s, 1H); 7,16−7,45 (m, 15H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 21.5, 23.9, 27.8, 40.5, 45.2, 45.3, 111.5, 111.6, 82.3, 120.2, 120.3, 125.3, 125.5, 125.6, 126.2, 127.3, 128.1, 128.2, 129.1, 129.8, 137.8, 137.9, 140.4, 141.4, 141.6, 150.6, 150.7, 151.8, 151.9. IR ν_{max} (NaCl film): 2956, 2872, 1731, 1691, 1489, 1456, 1345. MS (IS): m/z 560.60 $[M + H]^+$.

General Procedure (C) for the Suzuki Coupling Reaction. 7-(Thianaphten-2-yl)-8-(*tert*-butoxycarbonyl)-9-phenyl-8-aza-spiro[4.5]deca-6,9-diene (17a). To a solution of monovinyl phosphate **16** (0.18 mmol, 100 mg) in THF (1.5 mL) under argon, $PdCl_2(PPh_3)_2$ (0.02 mmol, 7.5 mg) was added. The flask was evacuated and backfilled with argon three times, and the mixture was stirred during 15 min. Then, thianaphtene-2-boronic acid (0.36 mmol, 64 mg), 2 M Na_2CO_3 (aqueous) (0.5 mL), and a few drops of EtOH were added. The mixture was refluxed for 3 h. After the mixture cooled, ethyl acetate was added, and the organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography (silica gel, PE then PE/EtOAc 8:2) to afford **17a** (80% yield) as an orange solid: mp 64−65 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.02 (s, 9H); 1.70−1.74 (m, 8H); 5.64 (s, 2H); 5.88 (s, 1H); 7,14−7,34 (m, 6H); 7,48−7,52 (m, 2H); 7,64−7,73 (m, 2H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 24.2, 27.7, 40.6, 46.1, 81.6, 119.4, 122.3, 123.6, 124.2, 124.4, 125.6, 126.6, 127.5, 128.3, 128.7, 135.5, 138.7, 139.2, 140.1, 140.9, 142.7, 152.5. IR ν_{max} (KBr): 3022, 2968, 2864, 1715, 1616, 1502, 1456. MS (IS): m/z 444.50 $[M + H]^+$. HRMS (IE): m/z $[M\text{-}^{\bullet}CO_2t\text{-}Bu]^+$ calcd for $C_{23}H_{20}NS$, 342.1316; found, 342.1332.

General Procedure (D) for the Functionalization Reaction on the C-4 Position of Dihydropyridine (6). 1-(*tert*-Butoxycarbonyl)-4-methyl-2,6-diphenyl-1,4-dihydropyridine (18a). To a solution of the 1-(*tert*-butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine (**6**) (0.45 mmol, 150 mg) in THF (3 mL) at −78 °C under argon, *n*-BuLi (0.49 mmol, 1.6 M in hexane, 310 μL) was added dropwise. After the mixture was stirred for 5 min at −78 °C, methyl iodide (1.35 mmol, 0.84 mL) was added dropwise, and the mixture was stirred for 2 h at −78 °C. The reaction was quenched by the slow addition of H_2O. Ethyl acetate was then added, the organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 9:1) to afford **18a** (97% yield) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.02 (s, 9H); 1.28 (d, 3H, J = 7 Hz); 3.10−3.22 (m, 1H); 5.62 (d, 2H, J = 3.5 Hz); 7.24−7.41 (m, 6H); 7.54−7.57 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 20.7, 27.6, 30.2, 81.2, 123.1, 125.5, 125.9, 127.4, 128.3, 138.9, 141.4, 152.2. IR ν_{max} (NaCl film): 2977, 2930, 2872, 1717, 1600, 1578, 1557. MS (IS): m/z 348.30 $[M + H]^+$. HRMS (IE): m/z $[M\text{-}HCO_2t\text{-}Bu]^{+\bullet}$ calcd for $C_{18}H_{15}N$, 245.1204; found, 245.1178.

4-Allyl-1-(*tert*-butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine (18b). The functionalization reaction was carried out as described in the general procedure (D) by using allyl bromide. After purification by flash column chromatography (silica gel, PE/EtOAc 9:1), the desired compound **18b** was isolated as a yellow solid (74% yield): mp 128−129 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.02 (s, 9H); 2.35 (t, 2H, J = 7 Hz); 3.13−3.20 (m, 1H); 5.08−5.16 (m, 2H); 5.67 (d, 2H, J = 3.5 Hz); 5.78−5.95 (m, 1H); 7.24−7.41 (m, 6H); 7.54−7.57 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 27.6, 35.1, 39.3, 81.3, 117.2, 120.7, 125.6, 127.4, 128.3, 135.7, 138.9, 142.1, 152.1. IR ν_{max} (KBr): 2976, 2925, 2889, 1711, 1675, 1634, 1593. MS (IS): m/z 374.30 $[M + H]^+$. HRMS (IE): m/z $[M\text{-}^{\bullet}C_3H_5]^+$ calcd for $C_{22}H_{22}NO_2$, 332.1650; found, 332.1640.

General Procedure (E) for the second Functionalization Reaction on the C-4 Position of Dihydropyridine (18). 1-(*tert*-Butoxycarbonyl)-4,4-dimethyl-2,6-diphenyl-1,4-dihydropyridine (19a). To a solution of the 1-(*tert*-butoxycarbonyl)-4-methyl-2,6-diphenyl-1,4-dihydropyridine (**18a**) (0.30 mmol, 104 mg) in THF (2 mL) at −78 °C under argon, *t*-BuLi (0.33 mmol, 1.7 M in hexane, 200 μL) was added dropwise. After the solution was stirred for 5 min at −78 °C, methyl iodide (0.90 mmol, 600 μL) was added, and the mixture was stirred for 2 h at −78 °C. The reaction was quenched by the slow addition of H_2O. Ethyl acetate was then added, the organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 8:2) to afford **19a** (100% yield) as a white solid: mp 106−107 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.02 (s, 9H); 1.24 (s, 6H); 5.60 (s, 2H); 7.24−7.40 (m, 6H); 7.56 (d, 4H, J = 7 Hz). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 27.6, 29.1, 34.1, 81.1, 123.1, 125.6, 127.4, 128.2, 138.9, 139.0, 140.4, 141.4, 152.3. IR ν_{max} (KBr): 2969, 2918, 2874, 1707, 1507, 1469, 1450. MS (IS): m/z 362.00 $[M + H]^+$. HRMS (IE): m/z $[M\text{-}CH_3\text{-}CO_2t\text{-}Bu]^{+\bullet}$ calcd for $C_{18}H_{15}N$, 245.1204; found, 245.1219.

1-(*tert*-Butoxycarbonyl)-4-allyl-4-methyl-2,6-diphenyl-1,4-dihydropyridine (19b). Starting from the compound **18a**, the second functionalization reaction was carried out as described in the general procedure (E) by using allyl bromide. After purification by flash column chromatography (silica gel, PE/EtOAc 9.5:0.5), the desired compound **19b** was isolated (34% yield).

Starting from the compound **18b**, the reaction was carried out as described in the general procedure (E) by using methyl iodide. After purification by flash column chromatography, the desired compound **19b** was isolated (100% yield) as a beige oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.01 (s, 9H); 1.23 (s, 3H); 2.27 (d, 2H, J = 7 Hz); 5.07 (m, 2H); 5.51 (s, 2H); 5.75−5.92 (m, 1H); 7.25−7.40 (m, 6H$_r$); 7.54−7.56 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 27.6, 29.6, 37.6, 46.5, 81.1, 118.0, 125.3, 125.6, 127.1, 127.4, 128.2, 128.8, 134.3, 139.0, 141.1, 152.1. IR ν_{max} (KBr): 2960, 2924, 2846, 1721, 1598, 1574, 1550. MS (IS): m/z

388.50 $[M + H]^+$. HRMS (IE): *m*/*z* $[M-{}^{\bullet}C_3H_5]^+$ calcd for $C_{23}H_{24}NO_2$, 346.1807; found, 346.1826.

8-(*tert*-Butoxycarbonyl)-7,9-diphenyl-8-aza-spiro[4.5]deca-2,6,9-triene (20). A solution of bisallylic compound **19d** (213 mg, 0.51 mmol) and Nolan's ruthenium catalyst[16] (43 mg, 0.05 mmol) in degassed toluene was refluxed for 15 h (until TLC shows complete conversion of the substrate). Evaporation of the solvent followed by flash chromatography (silica gel, PE/EtOAc 9.5/0.5) provides compounds **20** (100% yield) as a yellow solid: mp 120−121 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.03 (s, 9H); 2.55-(s, 4H); 5.76 (s, 2H); 5.80 (s, 2H); 7.25−7.40 (m, 6H); 7.54−7.58 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 27.7, 48.0, 44.5, 81.3, 125.0, 125.6, 125.8, 127.6, 127.7, 128.3, 128.4, 129.4, 139.0, 140.6, 152.4. MS (IS): *m*/*z* 386.5 $[M + H]^+$. HRMS (IE): *m*/*z* $[M]^{+\bullet}$ calcd for $C_{26}H_{27}NO_2$, 385.2041; found, 385.2049.

General Procedure (F) for the Hydrolysis Reaction. 1,5-Diphenyl-pentane-1,5-dione (21a).[18] To a solution of the 1-(*tert*-butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine (**6**) (0.30 mmol, 100 mg) in EtOAc (2 mL) at room temperature under argon, a 3 N solution of hydrochloric acid (1 mL) was added, and the mixture was stirred for 2 h. The mixture was diluted with H_2O (5 mL), EtOAc (4 mL) was added, and the organic layer was washed with a solution of saturated aqueous Na_2CO_3. The organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, PE/EtOAc 9:1) to afford **21a** (100% yield) as a white solid: mp 65−66 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 2.15−2.26 (m, 2H); 3.13 (t, 4H, J = 7 Hz); 7.43−7.59 (m, 6H); 7.97−8.00 (m, $4H_r$). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 18.8, 37.7, 128.2, 128.7, 133.2, 136.9, 197.4. IR ν_{max} (KBr): 2970, 2938, 2900, 1692, 1576, 1449. MS (IS): *m*/*z* 253.00 $[M + H]^+$.

General Procedure (G) for the Aromatization Reaction. 2,6-Diphenyl-pyridine (22a).[20] To a solution of the 1-(*tert*-butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine **6** (0.15 mmol, 50 mg) in dry DCM (0.5 mL) at room temperature under argon, trifluoroacetic acid (1.28 mmol, 100 μL) was added dropwise. The mixture was stirred for 4 h at room temperature. The reaction was quenched with an aqueous solution of saturated Na_2CO_3; dichloromethane was then added. The organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The crude solid was washed with petroleum ether, then filtrated to afford the desired disubstituted pyridine **22a** (95% yield) as a yellow solid: mp 80−81 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.39−7.57 (m, 6H); 7.66−7.69 (m, 2H); 7.77−7.83 (m, 1H); 8.12−8.17 (m, 4H). ^{13}C NMR (250 MHz; $CDCl_3$): δ (ppm) 118.8, 127.1, 128.8, 129.1, 137.6, 139.6, 157.0. IR ν_{max} (KBr): 2964, 2924, 2872, 1589, 1598, 1567. MS (IS): *m*/*z* 232.5 $[M + H]^+$.

Acknowledgment. The authors thank gratefully Professor Steve Nolan (New Orleans, USA) for his gift of ruthenium metathesis catalyst and palladium catalyst.

Supporting Information Available: Detailed experimental procedures, full characterization of new compounds, ^{1}H and ^{13}C NMR spectra for compounds **1**−**12** and **14**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0607360

(18) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681.
(19) Owsley, D. C.; Nelke, J. M.; Bloomfield, J. J. *J. Org. Chem.* **1973**, *38*, 901−903.
(20) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2005**, 485−492.
(21) Meth-Cohn, O.; Jiang, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3737−3745.
(22) Oda, K.; Nakagami, R.; Niszonohi, N.; Machida, M. *Chem. Commun.* **1999**, 2371−2372.