ORGANIC LETTERS

2002
Vol. 4, No. 4
623−626

Palladium-Catalyzed Stereocontrolled Vinylation of Azoles and Phenothiazine

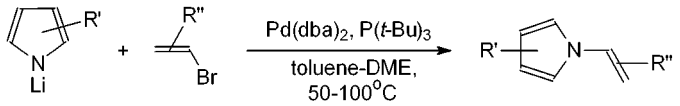
Artyom Y. Lebedev, Vyatcheslav V. Izmer, Denis N. Kazyul'kin, Irina P. Beletskaya, and Alexander Z. Voskoboynikov*

Department of Chemistry, Moscow State University, V-234, Moscow 119899, Russian Federation

voskoboy@org.chem.msu.su

Received December 15, 2001

ABSTRACT



Vinylation of various azoles (pyrrole, indole, carbazole, and their derivatives) and phenothiazine with vinyl bromides catalyzed by palladium–phosphine complexes results in the respective *N*-vinylazoles in 30–99% yields. This reaction with *cis*- and *trans*-β-bromostyrenes is stereospecific giving the respective products with *full retention of configuration*.

For the past several years we have seen a vigorous growth of the chemistry of palladium-catalyzed coupling reactions due to the discovery and application of new phosphine and carbene ligands, particularly for Pd-catalyzed arylation of amines.[1−4] Although the palladium-catalyzed arylation of azoles is used for the synthesis of *N*-arylazoles,[2c,5] the respective reaction with vinyl halides has not yet been realized. *N*-Vinylazoles have been shown to serve as monomers for the synthesis of poly(*N*-vinylazoles),[2c,6] which can be used as semiconductors and photosensitive materials. However, so far, only a few methods of the synthesis of *N*-vinylazoles have been described.[6b,7] These procedures are rather limited in scope and selectivity. For example, while *Z*-adducts can be prepared, the respective *E*-isomers were altogether inaccessible. Therefore a straightforward palladium-catalyzed vinylation of azoles by vinyl halides is undoubtedly an attractive alternative for the known methods. Beyond other advantages this reaction, as other Pd-catalyzed cross-coupling reactions, should be stereospecific to give pure *Z*- and *E*-enamines, as soon as pure diastereomers of vinyl halides with desired stereochemistry are readily available.

The main problem in realizing Pd-catalyzed vinylation of amines is competitive elimination. A common procedure for Buchwald−Hartwig Pd-catalyzed amination of arylhalides suggests the use of an excess of strong bases, such as *t*-BuOM (M = Na, K). Even in the course of arylation in

(1) For reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(2) For applications of P(*t*-Bu)$_3$, see: (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (d) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.

(3) For applications of other bulky, electron-rich phosphines, see: (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (c) Zhao, S. H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463. (d) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369 and references therein. (f) Alt, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560 and references therein.

(4) For applications of carbene ligands, see: (a) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (c) Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617−618*, 635.

(5) (a) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481. (b) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618. (c) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403.

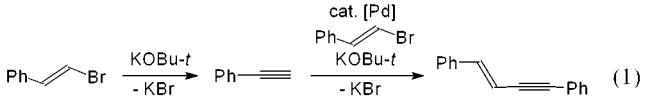
(6) (a) Trofimov, B. A.; Mikhaleva, A. I.; Morozova, L. V. *Russ. Chem. Rev.* **1985**, *54*, 1034. (b) Brustolin, F.; Castelvetro, V.; Ciardelli, F.; Ruggeri, G.; Colligiani, A. *J. Polym. Sci., A: Polym. Chem.* **2001**, *39*, 253.

(7) (a) Reppe, W. *Liebigs Ann. Chem.* **1956**, *132*, 601. (b) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (c) Shostakovsky, M. F.; Skvortsova, G. G.; Domnina, E. S. *Russ. Chem. Rev.* **1969**, 38, 892. (d) Trofimov, B. A.; Mikhaleva, A. I. *Chem. Heterocycl. Compds. (Rus.)* **1980**, 1299.

10.1021/ol0172370 CCC: $22.00
Published on Web 01/24/2002

some cases a side elimination-addition route including benzyne intermediates can compete with the Pd-catalyzed route to give mixtures of isomeric anilines.[8] For vinyl halides, the elimination by *t*-BuOM should occur readily to give the respective alkynes.[9]

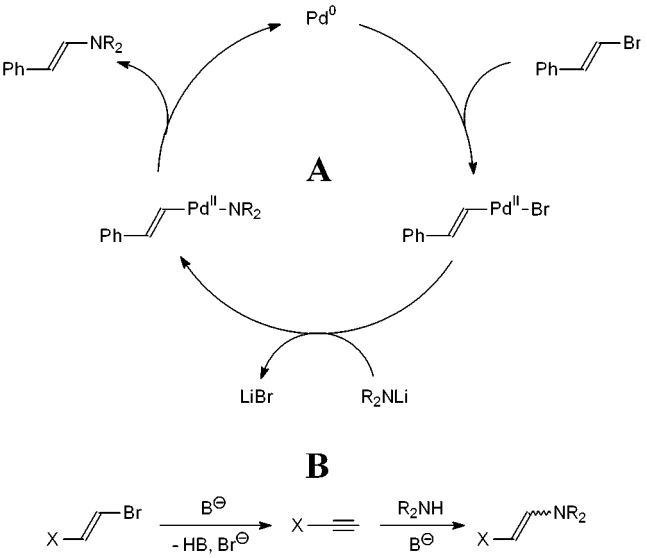
Nevertheless, we have found that indole and *trans*-β-bromostyrene in the presence of 2 equiv of KOBu-*t* and 4 mol % of Pd(dba)$_2$/2*t*-Bu$_2$PC$_6$H$_4$Ph-*o* give 1-[(*E*)-2-phenylethenyl]-1*H*-indole in 84% yield upon 20 h at 80 °C. No starting *trans*-β-bromostyrene was recovered, but a side product, [(3*E*)-4-phenyl-3-buten-1-ynyl]benzene (**1**), was isolated in 6% yield. In a separate experiment we have found that, in the absence of indole, *trans*-β-bromostyrene gives **1** under the same conditions in almost quantitative yield (eq 1).[10,11] These observations, as well as the result of a control



(1)

experiment showing that *trans*-β-bromostyrene amination does not take place without Pd-catalyst, favor a reaction mechanism including an addition of vinyl bromides to Pd^0 (pathway A, Scheme 1) rather than noncatalytic pathways.

Scheme 1. Catalytic and Noncatalytic Pathways for Amination of Nonactivated Vinyl Bromides



The alternative pathway, including an addition of amine to the activated double bond and successive elimination of HBr, can be realized only for activated Michael-type olefins BrCH=CMeR bearing electron-withdrawing substituents, such as R = CN, COOMe.[12] A more common alternative, pathway B, includes an elimination-addition sequence. Phenylacetylene is well-known for the ability to add an amine molecule in the presence of base.[7b] However, in our reaction this is not the case, since on the evidence of HPLC, only phenylacetylene was formed in the absence of Pd-catalyst and the addition had not taken place.

Despite the success of palladium-catalyzed vinylation of indole, the attempts to extend this protocol to vinylation of other azoles, such as of 2,4-dimethylpyrrole, carbazole, and pyrrole gave **1** as the only product. The same occurred with readily available P(*t*-Bu)$_3$ ligand in place of expensive *t*-Bu$_2$-PC$_6$H$_4$Ph-*o*, as with the former even indole failed to react.

Naturally, we expected that the competition between elimination and Pd-catalyzed route could be resolved in favor of the latter by a judicious choice of basic reagent. For this study we have chose indole as NH-reagent since it gave a positive result even in the presence of *t*-BuOK, and we employed P(*t*-Bu)$_3$ as a more practical ligand.

Table 1. Vinylation of Indole Derivatives by *trans*-β-Bromostyrene Catalyzed by Pd(dba)$_2$/P(*t*-Bu)$_3$[a]

entry	indole derivative	yield (%) of *trans*-β-*N*-indolylstyrene
1	[indolyl]K	<1[b]
2	[indolyl]Na	9
3	[indolyl]Li	99[b]
4	[indolyl]MgBr	65
5	indole, K$_3$PO$_4$	64
6	indole, K$_2$CO$_3$	8
7	[*N*-indolyl]SnEt$_3$	22

[a] 1 mol % Pd(dba)$_2$/2P(*t*-Bu)$_3$, toluene−DME, 2.5 h, 82 °C. [b] Also for equimolar mixture of indole and *t*-BuOM, where M = K, Li.

Table 2. Vinylation of Indolyllithium by *trans*- and *cis*-β-Bromostyrene Catalyzed by Pd(dba)$_2$/Phosphine[a]

entry	phosphine ligand	[Pd], mol. %	time, min	yield, %
	trans-β-bromostyrene			
1	PPh$_3$	1.0	150	0.8
2	DPPP	1.0	150	1.6
3	*rac*-BINAP	1.0	150	4.6
4	DPPF	1.0	15	39
5	DPPF	1.0	150	76
6	P(*t*-Bu)$_3$	1.0	15	47
7	P(*t*-Bu)$_3$	2.0	15	68
8	P(*t*-Bu)$_3$	4.0	15	87
9	P(*t*-Bu)$_3$	1.0	150	99
10	*t*-Bu$_2$PC$_6$H$_4$Ph-*o*	1.0	15	99
	cis-β-bromostyrene			
11	DPPF	1.0	30	83
12	P(*t*-Bu)$_3$	1.0	30	86
13	*t*-Bu$_2$PC$_6$H$_4$Ph-*o*	1.0	30	99

[a] Pd(dba)$_2$/phosphine (Pd/P = 1/2), toluene−DME; 85 °C.

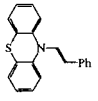
(8) (a) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3389. (c) Beller, M.; Breindl, C.; Riermeier, T. H., Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403.

(9) Huntsman, W. D. In *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; pp 553−620.

(10) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1997; p 2.

(11) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabyashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.

Table 3. Catalytic Vinylation[a] of Azoles and Phenothiazine

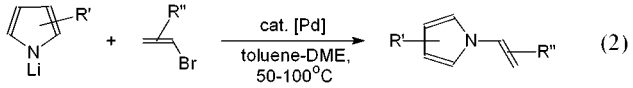
entry	vinyl bromide	azole or amine	product	time, temp.	yield, convers.
1				7 h, 50°C	30%,[b] 63%[c]
2				9 h, 70°C	91%, 99%[c]
3				9 h, 70°C	68%,[d] 89%[c]
4				1.5 h, 85°C	99%, 99%[c]
5				10.5 h, 70°C	54%, 60%[c]
6				11.5 h, 60°C	75%, 79%[c]
7				8 h, 85°C	99%, 99%[c]
8				10 h, 100°C	96%, 99%[c]
9				2 h, 85°C	99%, 99%[c]
10				8.5 h, 90°C	33%,[e] 45%[c]
11				7 h, 85°C	99%, 99%[c]
12				10 h, 100°C[f]	83%,[g] 99%[c]
13				2.5 h, 85°C	61%, 65%[h]
14				2 h, 90°C	59%, 65%[h]
15				2.5 h, 65°C	58%, 67%[h]
16				3 h, 85°C	35%,[i] 65%[h]

[a] 4 mol % Pd(dba)$_2$/2P(*t*-Bu)$_3$, toluene−DME. [b] Byproducts of this reaction were not identified. [c] Conversion of vinyl bromide (HPLC). [d] This reaction produces also [(3*E*)-4-phenyl-3-buten-1-ynyl]benzene (6%) and 2,5-dimethyl-3-[(*E*)-2-phenylethenyl]-1*H*-pyrrole (4%). [e] This reaction produces also 9-[(*E*)-2-phenylethenyl]-9*H*-carbazole (2%) and 9-vinyl-9*H*-carbazole (3%). [f] In toluene−dioxane. [g] The formation of 1-[(*E*)-2-phenylethenyl]-1*H*-indole (10%) was also observed. [h] Conversion of azole (HPLC). [i] The following byproducts are formed: 9-[(1*E*)-prop-1-enyl]-9*H*-carbazole (15%), 9-[(1*Z*)-prop-1-enyl]-9*H*-carbazole (5%), 9-allyl-9*H*-carbazole (5%).

We showed that the addition of coordinating solvent DME to toluene favors the indole vinylation reaction. Surprisingly, we found that either preformed indolyllithium or indole/*t*-BuOLi were the most reactive and selective reagents, resulting in 1-[(*E*)-2-phenylethenyl]-1*H*-indole in almost quantitative yield in the presence of Pd(dba)$_2$/2P(*t*-Bu)$_3$ under the conditions studied (Table 1). Indolylpotassium and -sodium as well as indole/K_2CO_3, on the other hand, gave poor results, while the soluble base K_3PO_4 gave the desired product in 64% yield. Good yield was also observed with indolylmagnesium bromide, which is, similarly to *N*-lithioindole, a covalent compound. A covalent nonbasic *N*-indolyltriethyltin[13] gives the desired product in low yield. Thus, it is evident that a proper choice of basicity, neither too strong nor too weak, is a key to success.

The screening of phosphine ligands (Table 2) confirmed the preliminary result that Pd(dba)$_2$/2*t*-Bu$_2$PC$_6$H$_4$Ph-*o* is the most active catalytic system for indole vinylation by *trans*-*β*-bromostyrene and also by *cis*-*β*-bromostyrene. Catalysts based on P(*t*-Bu)$_3$ and DPPF ligands possess lower activity, though good to high yields can be achieved with these readily available ligands. The reaction with both *Z*- or *E*-bromostyrenes were stereospecific, giving the respective products with *full retention of configuration*.

We then proceeded to study the scope of vinylation of other azoles employing a readily available Pd(dba)$_2$/2P(*t*-Bu)$_3$ system (Table 3, eq 2). As is evident from the presented data the reaction is general in the series of common



(2)

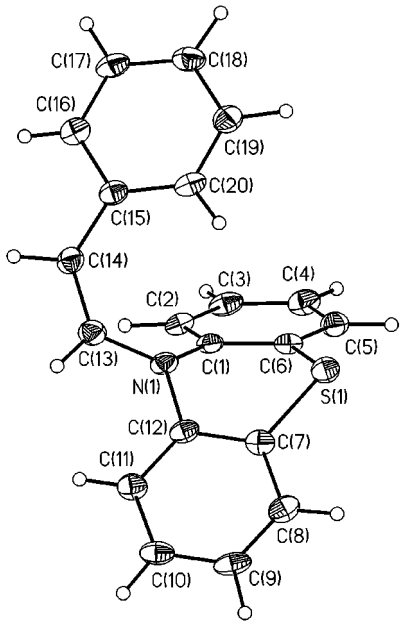


Figure 1. Molecular structure of 10-[(*Z*)-2-phenylethenyl]-10*H*-phenothiazine, showing the 50% thermal ellipsoids and atom labeling scheme. Selected bond lengths (Å) are N(1)−C(13) 1.396(4), N(1)−C(1) 1.420(4), N(1)−C(12) 1.432(4), C(14)−C(13) 1.338(5), C(14)−C(15) 1.462(5); selected bond angles (deg) are C(13)−N(1)−C(1) 121.5(3), C(13)−N(1)−C(12) 119.8(3), C(1)−N(1)−C(12) 116.2(3), C(13)−C(14)−C(15) 131.1(3), C(14)−C(13)−N(1) 128.3(3).

(12) Texier, F.; Bourgois, J. *Bull. Soc. Chim. Fr.* **1976**, 487.

azoles including pyrrole, indole, carbazole, and their derivatives. Moreover, in all cases the reaction was stereospecific to give pure diastereomers of *N*-2-phenylethenylazoles, the configuration of which was controlled by the configuration of starting bromostyrene.[14] No isomerization of the starting bromostyrenes and the resulted vinylazoles was observed under reaction conditions. Besides azoles, the reaction is applicable to phenathiazine. For example, this substrate and *cis*-*β*-bromostyrene gave 10-[(*Z*)-2-phenylethenyl]-10*H*-phenathiazine in almost quantitative yield. The molecular structure of this compound, established by X-ray crystal structure analysis,[15] corresponds to *cis*-enamine (Figure 1).

The vinylation of indole by geminal bromoolefins such as α-bromostyrene and 2-bromopropene is accompanied by a partial isomerization. The amination of CH_2═CHBr is not as smooth and quantitative as the reaction with bromostyrenes. The respective products, 1-vinyl-1*H*-indole and 9-vinyl-9*H*-carbazole, turned out to be thermally unstable compounds that polymerized readily. However, we succeeded in developing mild conditions for their synthesis by carefully controlling time and temperature and deliberately stopping the reaction, not allowing it to run to quantitative conversions. Thus, the desired *N*-vinylazoles were successfully obtained in 61% and 59% yields (on 65% conversion of azoles), respectively.

Because *N*-vinylazoles are widely used as building blocks for photosensitive and photoelectronic polymers and composites, the Pd-catalyzed vinylation of azoles is an appealing method, suitable for industrial application. It can be a good alternative to the direct hydroamination of acetylene,[6a,b,10] since the latter method can lead to a formation of explosive byproducts in industrial equipment. It should be noted that the above-described Pd-catalyzed reaction for azoles and phenathiazine, i.e., for substrates with low nucleophilicity, gives enamines that cannot be prepared by the routine condensation of amines with aldehydes or ketones. Moreover, this method for *cis*- and *trans*-*β*-bromostyrenes provides *a predictable and controlled stereoselectivity*.

Acknowledgment. Financial support from the Russian Foundation for Basic Research (grant 01-03-32474a), International Science and Technology Center (grant 1036/99), INTAS (grant 2000-00841), and ExxonMobil Chemical Company is gratefully acknowledged.

Supporting Information Available: Synthetic procedures, analytical and spectral data for all compounds newly synthesized, and results of crystal structure analysis of 10-[(*Z*)-2-phenylethenyl]-10*H*-phenathiazine. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0172370

(13) For the palladium-catalyzed reaction of *cis*-*β*-bromostyrene with *n*-Bu_3SnNEt_2, see: Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Nippon Kagaku Kaishi* **1985**, *3*, 547; *Chem. Abstr.* **1985**, *104*, 129990.

(14) The reaction of 2,5-dimethylpyrrole with *cis*-*β*-bromostyrene gives 2,5-dimethyl-1-[(*E*)-2-phenylethenyl]-1*H*-pyrrole (17%), 2,5-dimethyl-3-[(*E*)-2-phenylethenyl]-1*H*-pyrrole (31%), and [(3*E*)-4-phenyl-3-buten-1-ynyl]benzene (5%) but not the desired 2,5-dimethyl-1-[(*Z*)-2-phenylethenyl]-1*H*-pyrrole.

(15) Crystal data: monoclinic, *P*2(1)/*a*, $a = 15.502(9)$ Å, $b = 5.792(4)$ Å, $c = 16.587(10)$ Å, $\beta = 97.569(16)°$, $V = 1476.3(15)$ Å^3, $Z = 4$.