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Probing the Stereoselectivity of the Heck Arylation of Endocyclic Enecarbamates with Diazonium Salts. Concise Syntheses of (2*S*,5*R*)-Phenylproline Methyl Ester and Schramm's C-Azanucleoside

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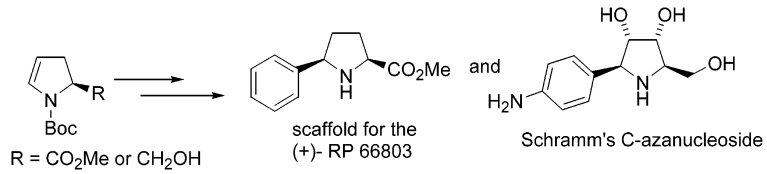
ABSTRACT



The diastereoselectivity of the Heck arylation of several chiral, nonracemic, five-membered endocyclic enecarbamates with aryldiazonium tetrafluoroborates was evaluated. The cis selectivity observed for some enecarbamates bearing coordinating groups was explored in the concise synthesis of the (2*S*,5*R*)-(+)-phenylproline methyl ester, a scaffold for the nonpeptide cholecystokinin antagonist (+)-RP 66803, and in the synthesis of Schramm's potent antiprotozoan C-azanucleoside.

The palladium-catalyzed Heck reaction is an extremely valuable reaction in modern organic synthesis. This pivotal C−C coupling reaction has been attracting considerable interest in recent decades due to its growing versatility and still unlimited scope and synthetic potential.[1]

The phosphine-free Heck arylations employing aryldiazonium salts are among the earliest Heck arylations reported, but its application to organic synthesis has been rather limited despite its outstanding ability for installating electron-rich aromatic rings, a major challenge when using aryl halides.[1a] Recently, interest in the use of aryldiazonium salts as electrophiles in the synthesis of complex natural products resurged, demonstrating the feasibility of these Heck arylations.[2]

Our interest in the Heck arylation of electron-rich olefins stems from the prominent display of an α-aryl heterocyclic framework in the core structure of several natural and nonnatural compounds (Figure 1). Many of these heterocyclic compounds exhibit pharmacological activity and are important synthetic targets. The natural compounds (−)-codonopsine **1**[3] and the green tea constituent (−)-epigallo-

(1) For recent reviews on the Heck reaction consult: (a) Whitcombe, N. J.; Hii, M.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (d) Crisp, G. *Chem. Soc. Rev.* **1998**, *27*, 427. (e) Shibasaki, M.; Boden, D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(2) (a) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079. (b) Brunner, H.; Le Cousturier de Courcy, N.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815. (c) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083. (d) Mehta, G.; Sengupta, S. *Tetrahedron Lett.* **1996**, *37*, 8625. (e) Beller, M.; Kuhlein, K. *Synlett* **1995**, 441.

(3) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5393.

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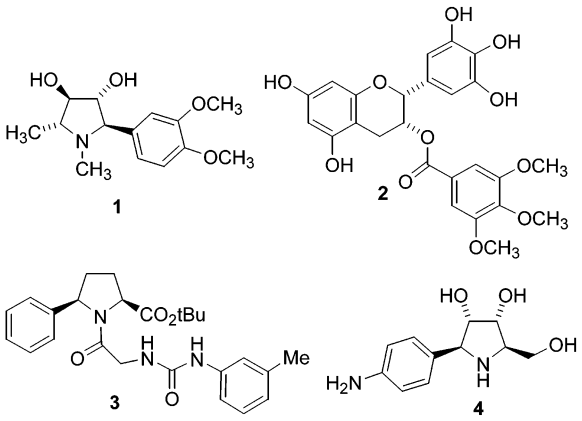


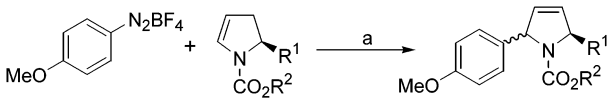
Figure 1. Compounds containing an α-aryl heterocycle.

catechin-3-gallate (EGCG) **2**[4] display hypotensive and cancer preventive properties, respectively. The nonnatural compound *cis*-5-phenylproline forms the basic scaffold for the nonpeptide cholecystokinin antagonist (+)-RP 66803 **3**,[5] while the *p*-aminophenyl C-azanucleoside **4** described by Schramm and co-workers[6] shows very promising trypanosomal activity.

A few years ago we reported the Heck arylation of five-membered endocyclic enecarbamates employing aryldiazonium tetrafluoroborates as the key step in the total synthesis of codonopsinine.[7] In a follow-up study to determine the factors controlling the diastereoselectivity of arylation of chiral five-membered enecarbamates, we noticed wide fluctuations in the diastereomeric ratio, depending on the nature of the functional group at the chiral center and, to a lesser extent, on the reaction conditions. These results are presented in Table 1.

As anticipated, bulky functional groups at C-5 provided the 2,5-trans Heck adduct as the major product, in ratios that correlated with the steric bulk of the groups. The highest trans diastereomeric ratios were those obtained with *tert*-butyldiphenylsilane (TBDPS) and triphenylmethyl (trityl) groups (Table 1, entries 1 and 3). In general, a slightly higher diastereoselectivity is observed with the *t*-butoxycarbonyl (Boc) group on the pyrrolidine nitrogen. Somewhat surprising was the modest stereoselectivity observed for the methyl and *tert*-butyl esters of dehydroprolines (entries 9, 10, and 13). Replacement of the ester groups by more coordinating groups such as amide or alcohol led to a sharp decrease in the trans selectivity, as observed for the Weinreb amide enecarbamate (entry 12) and for the prolinol enecarbamate bearing a hydroxymethyl group at C-5 (entries 6−8). Coordinating effects are evident when we compare the results of entries 5 and 6 of Table 1. A decrease in the expected selectivity toward the trans adduct was also observed when using an alternative Heck protocol in ethanol (Table 1, entries 2, 7, and 10). It is worthwhile pointing out that a moderate reversal in diastereoselectivity was observed with enecarbamate **5** when we replaced acetonitrile with NMP, DMF, or DMA as the reaction solvent (Table 2), although these changes in the reaction conditions also led to a concurrent decrease in yields, which is probably related to the decomposition of the diazonium salts in these solvents.[8] The results presented in Tables 1 and 2 for the esters, amide, and hydroxymethyl

Table 1. Diastereoselectivity for the Heck Arylation with Aryldiazonium Tetrafluoroborates

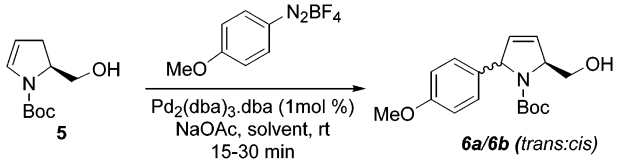


a) $Pd_2(dba)_3$.dba (1mol %), AcONa, MeCN, rt., 15-30 min

entry	R^1	R^2	trans:cis[a]	yield (%)[b]
1	$CH_2OTBDPS$	*t*-Bu	92:08	92
2[c]	$CH_2OTBDPS$	*t*-Bu	80:20	92
3	CH_2OTr	*t*-Bu	90:10	96
4	CH_2OTr	Me	87:13	90
5	CH_2OAc	*t*-Bu	88:12	67
6	CH_2OH	*t*-Bu	48:52	95
7[c]	CH_2OH	*t*-Bu	40:60	60
8	CH_2OH	Me	52:48	92
9	CO_2Me	Me	75:25	93
10[c]	CO_2Me	Me	63:37	95
11	CO_2Me	*t*-Bu	86:14	90
12	CONMe(OMe)	*t*-Bu	49:51	82
13	CO_2*t*-Bu	*t*-Bu	82:18	98

[a] Ratio determined by capillary GC. [b] Isolated yields. [c] Using 10 mol % $Pd(OAc)_2$, di-*tert*-butylmethylpyridine, EtOH, 55 °C, 15 min.

Table 2. Effect of the Solvent on the Diastereoselectivity of the Heck Arylation of Enecarbamate **5**



5 — $Pd_2(dba)_3$.dba (1mol %), NaOAc, solvent, rt, 15-30 min — ***6a/6b*** *(trans:cis)*

solvent[a]	**6a**/**6b** (trans:cis)[b]	yield (%)[c]
CH_3CN	48:52	95
NMP	28:72	40
DMF	34:66	50
DMA	36:64	51

[a] Ethanol, acetone, and THF led to low conversions. [b] Ratio was determined by capillary GC. [c] Isolated yields.

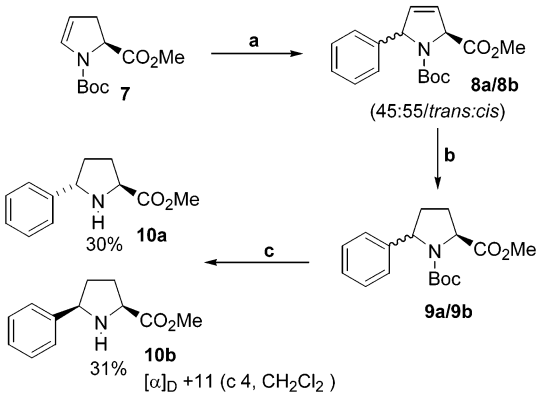
(4) Zaveri, N. T. *Org. Lett.* **2001**, *3*, 843.
(5) Manfré, F.; Pulicani, P. *Tetrahedron: Asymmetry* **1994**, *5*, 235.
(6) Miles, R. W.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Parkin, D. W.; Schramm, V. L. *Biochemistry* **1999**, *38*, 13147.
(7) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039.
(8) Diazonium salts are rather unstable in NMP and DMF, which might explain the low yields. For a previous study of the stability of the diazonium salts, see: (a) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (b) Lahoti, R. J.; Parameswaran, V.; Wagle, D. R. *Ind. J. Chem.* **1981**, *20B*, 767.

groups at the chiral center seem to suggest some degree of coordination of the ligand-free cationic palladium intermediate to the potentially coordinating groups at C-5.[9]

Despite the present low stereoselectivity, a quick access to 2,5-cis aryl prolinols and prolines (entries 7, 8, and 12) by these Heck arylations opens new routes to synthetically relevant intermediates that are otherwise difficult to prepare.

In the specific case of arylation of endocyclic enecarbamate **7**, this opens the way to the synthesis of (2*S*,5*R*)-phenyl proline methyl ester, a known precursor of the nonpeptide cholecystokinin antagonist (+)-RP 66803 **3** in a very concise manner.[10] A straightforward synthesis of the (2*S*,5*R*)-phenylproline methyl ester is presented in Scheme 1. Heck

Scheme 1. Synthesis of the (2*S*,5*R*), and (2*S*,5*S*)-Phenyl Proline Methyl Esters from Enecarbamate **7**



(a) $C_6H_4N_2BF_4$, Pd_2dba_3 (4 mol %), NaOAc, MeCN, 30 °C, 30 min (85%). (b) H_2, 10%−Pd/C, 15 h, rt (100%). (c) HCl/MeOH, rt, 1 h (61%).

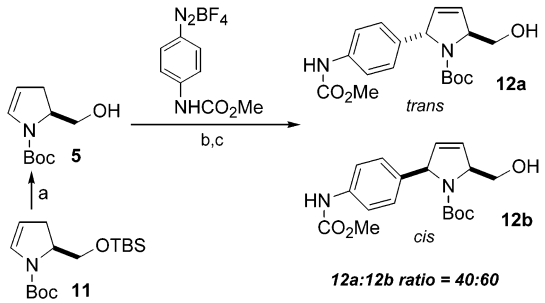
arylation of enecarbamate **7** using phenyldiazonium tetrafluoroborate required 4 mol % $Pd_2(dba)_3$ and a reaction temperature of ∼30 °C to attain good yields of the Heck adducts. The arylation proceeded with an unexpected low stereoselectivity (compare with entries 9−11, Table 1) providing a 45:55 (trans/cis) inseparable mixture of 5-phenyl dehydroprolines **8a**/**8b**, indicating a further dependence of the stereoselectivity on the diazonium salt substitution pattern. The mixture of 3,4-dehydroprolines underwent catalytic hydrogenation to give a ∼1:1 mixture of Boc-5-phenylprolines **9a**,**b**, which were deprotected with HCl/MeOH to give the diastereomeric phenylproline methyl esters in an overall yield of 48%. Flash chromatography provided the two diastereomers **10a** and **10b** in pure form. Overall, the desired (2*S*,5*R*)-phenylproline methyl ester **10b** was obtained in three steps with an overall yield of 26% from enecarbamate **7**.[11]

Another illustrative application of the cis Heck adduct obtained from the arylation of the hydroxy enecarbamate **5** was the total synthesis of the antiprotozoan C-azanucleoside **4**. Protozoan parasite infections such as malaria and trypanosomiasis are among the most important tropical diseases, causing a heavy toll in lives and productivity in developing and underdeveloped countries.[12] A key characteristic of these parasites is the lack of a de novo pathway for purine biosynthesis, and as a result, these organisms need to salvage purines from the host for the synthesis of their own DNA and RNA.[13] For this purpose, the parasites produce a family of nucleoside N-ribosyl hydrolases that are not found in mammalian cells, thus making the N-ribosyl hydrolases suitable targets for inhibition and creating viable therapeutic control of the disease.[14]

Recently, Schramm and Tyler reported on 1-aryliminoribitols, which bind tightly to nonspecific nucleoside hydrolases such as inosine-uridine nucleoside hydrolase (IU-NH) and to specific nucleoside hydrolases such as the inosine-adenosine-guanosine nucleoside hydrolase (IAG-NH).[15] The trypanosomal nucleoside hydrolase IU-NH involved in purine salvage pathways is strongly inhibited by the *p*-aminophenyliminoribitol **4** with a dissociation constant of 30 nM.[16]

Heck arylation of prolinol enecarbamate **5** provided a new and concise route to the synthesis of Schramm's C-azanucleoside **4**. The first stage involved the preparation of the hydroxy enecarbamate **5** from the silyloxy enecarbamate **11** with TBAF (Scheme 2). Heck arylation of the hydroxy

Scheme 2. Synthesis of the Arylpyrroline Precursor of Schramm's C-Azanucleoside



(a) TBAF 1M, THF, 0 °C, 1 h (93%); (b) $Pd_2(dba)_3$·dba (1 mol %), MeCN, NaOAc, 30 min, rt (80%); (c) chromatographic separation.

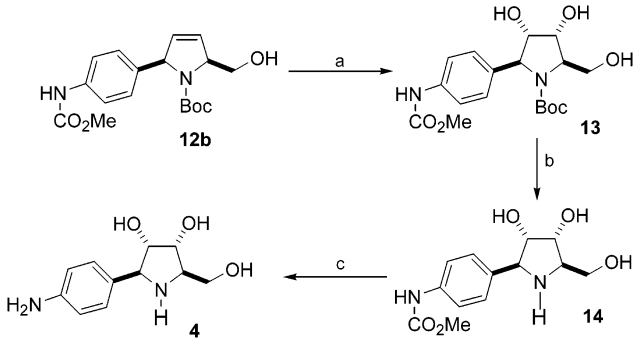
enecarbamate **5** gave the Heck adducts with a modest stereoselectivity in favor of the cis adduct in good yield (80% yield; 60:40 diastereomeric ratio).

(9) There are many precedents for the stereocontrolled Heck arylation of olefins promoted by proximal functional groups. For some representative examples, see: (a) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544. (b) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (c) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7235. (d) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (e) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129. (f) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; K. T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604. (g) Madin, A.; Overman, L. *Tetrahedron Lett.* **1992**, *33*, 4859.

(10) Previous synthesis of the (2*S*,5*R*)-phenylproline methyl ester: (a) ref 5. (b) Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (c) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (d) Momotake, A.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (e) Betsbrugge, J. V.; Nest, W. V. D.; Verheyden, P.; Tourwé, D. *Tetrahedron* **1998**, *54*, 1753. (f) Zaluski, M. C. F.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J. B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594.

The hydroxymethyl arylpyrrolines **12a** and **12b** were readily separated by flash chromatography and the cis adduct **12b** converted to the C-azanucleoside using the sequence described in Scheme 3. Sharpless dihydroxylation of **12b** occurred smoothly to provide the triol **13** in 89% yield. Removal of the Boc group was performed with acetyl chloride in methanol to give the triol **14**, followed by the acidic hydrolysis of the aryl carbamate to afford the nucleoside **4** in 88% yield as the corresponding hydrochloride.[17]

Scheme 3. Completion of the Synthesis of Azanucleoside **4**



(a) $K_2OsO_4 \cdot 2H_2O$ (cat.), NMO, acetone:H_2O:*t*-BuOH; 3:6:1; rt, 30 min-1 h (89%); (b) AcCl, MeOH, 0 °C, 30 min (100%); (c) HCl, EtOH, reflux, 30 h (88%).

This strategy allowed the synthesis of C-azanucleoside **4** in four steps from enecarbamate **5** in an overall yield of 37% and is amenable to the synthesis of analogues.

In conclusion, the stereoselectivity of the Heck arylation of five-membered enecarbamates depends significantly on the nature of the functional group at C-5. Noncoordinating, bulky groups favor trans aryl insertion, whereas coordinating groups such as the Weinreb amide and hydroxymethyl seem to slightly favor cis aryl insertion, thereby counterbalancing steric effects.

Exploration of the synthetic potential of 2,5-cis Heck adducts permitted the concise synthesis of (2*S*,5*R*)-phenylproline methyl ester **10b** in three steps in an overall yield of 25% and the synthesis of antiprotozoan C-azanucleoside **4** in four steps in an overall yield of 37% from the respective endocyclic enecarbamates.

Other chiral five-membered endocyclic enecarbamates bearing potentially complexing groups are under evaluation, aimed at increasing the Heck cis selectivity and to further applications of these intermediates in synthesis. These results will be reported in due course.

Acknowledgment. We thank FAPESP for financial support and CNPq and CAPES for fellowships.

Supporting Information Available: Experimental procedure for the Heck arylations and spectroscopic characterization of compounds **5**, **6a**, **6b**, **10a**, **10b**, **12a**, **12b**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Yields were not optimized. The synthesis can be accomplished in two steps by using Cbz instead of Boc as the protecting group.

(12) Morel, C. *Parasitol. Today* **2000**, *16*, 2.

(13) (a) Hammond, D. J.; Gutteridge, W. E. *Mol. Biochem. Parasitol.* **1984**, *13*, 243. (b) Estupiñán, B.; Schramm, V. L. *J. Biol. Chem.* **1994**, *269*, 23068.

(14) (a) Gopaul, D. N.; Meyer, S.; Degane, M.; Sachettini, J. C.; Schramm, V. L. *Biochemistry* **1996**, *35*, 5963. (b) Parkin, D. W.; Limberg, G.; Tyler, P. C.; Furneaux, R. H.; Chen, X.-Y.; Schramm, V. L. *Biochemistry* **1997**, *36*, 3528.

(15) (a) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915. (b) Miles, R. W.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Parkin, D. W.; Schramm, V. L. *Biochemistry* **1999**, *38*, 13147.

(16) Degano, M.; Almo, S.; Sacchettini, J. C.; Schramm, V. L. *Biochemistry* **1998**, *37*, 6277.

(17) Acidic hydrolysis of triol **13** provided **4** (hydrochloride), albeit in lower yields. Filtration through Dowex gave **4** as a free base, the spectroscopic data of which were in good agreement with those described in ref 15. The structure of triol **13** was also confirmed by X-ray diffraction.