ORGANIC LETTERS

2012
Vol. 14, No. 9
2254–2257

Palladium-Catalyzed Asymmetric Allylic Alkylation of Electron-Deficient Pyrroles with *Meso* Electrophiles

Barry M. Trost,* Maksim Osipov, and Guangbin Dong

Department of Chemistry, Stanford University, Stanford, California 94305, United States

bmtrost@stanford.edu

Received March 14, 2012

ABSTRACT

Pyrroles can serve as competent nucleophiles with *meso* electrophiles in the Pd-catalyzed asymmetric allylic alkylation. The products from this transformation were obtained as a single regio- and diastereomer in high yield and enantiopurity. A nitropyrrole-containing nucleoside analogue was synthesized in seven steps to demonstrate the synthetic utility of this transformation.

The assembly of organic molecules in an enantioselective fashion remains an important synthetic challenge. The Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) is a powerful method for the construction of several different bond types, including C–C, C–N, C–O, and C–S bonds.[1] Typically, the Pd-AAA requires the use of soft, stabilized nucleophiles, such as malonates or imides. Recently, less stabilized nucleophiles have been successfully employed in the Pd-AAA.[2]

The importance of nitrogen-containing compounds makes the stereoselective construction of C–N bonds an important synthetic endeavor. Pyrrole-substituted nucleoside analogues have been shown to act as universal nucleosides in PCR amplification of DNA.[3] This activity has been attributed to the electronic distribution of the pyrrole nucleus, which interacts equally well with all four natural nucleoside bases. Further, due to the broad-spectrum antiviral activity observed in the drug ribavirin, pyrrole-containing nucleoside analogues have been studied as isosteres for their potential antiviral properties and other useful biological activities (Figure 1).[3] Likewise, these nucleoside analogues have been used to study the mechanism of action of ribavirin.[4]

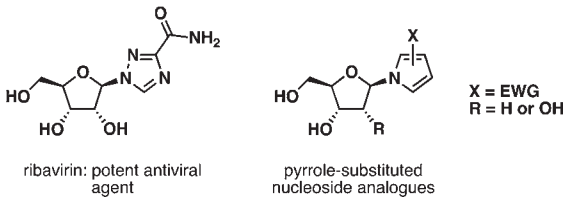


Figure 1. Representative compounds.

(1) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (d) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (e) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59.

(2) For some examples, see: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Trost, B. M.; Zhang, T. *Org. Lett.* **2006**, *8*, 6007. (c) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (d) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439.

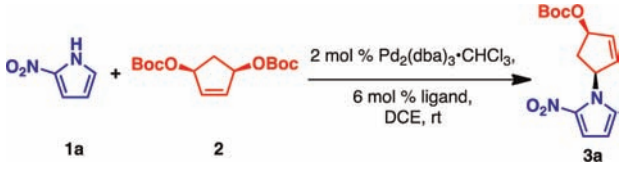
(3) (a) Nichols, R.; Andrews, P. C.; Zhang, P.; Bergstrom, D. E. *Nature* **1994**, *369*, 492. (b) Bergstrom, D. E.; Zhang, P.; Toma, P. H.; Andrews, P. C.; Nichols, R. *J. Am. Chem. Soc.* **1995**, *117*, 1201. (c) Klewer, D. A.; Hoskins, A.; Zhang, P.; Davisson, V. J.; Bergstrom, D. E.; LiWang, A. C. *Nucleic Acids Res.* **2000**, *28*, 4514. (d) Harki, D. A.; Graci, J. D.; Korneeva, V. S.; Ghosh, S. K. B.; Hong, Z.; Cameron, C. E.; Peterson, B. R. *Biochemistry* **2002**, *41*, 9026.

(4) Sanghvi, Y. S.; Bhattacharya, B. K.; Kini, G. D.; Matsumoto, S. S.; Larson, S. B.; Jolley, W. B.; Robins, R. K.; Revanker, G. R. *J. Med. Chem.* **1990**, *33*, 336.

10.1021/ol3006584
Published on Web 04/16/2012

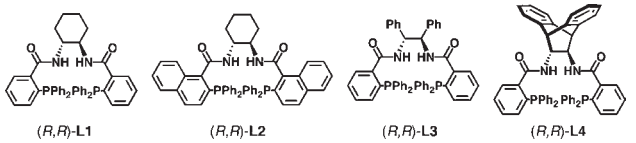
While nucleoside analogues have a wealth of applications, traditional syntheses of these compounds are limited by their reliance on chiral pool strategies. These strategies only provide access to the natural enantiomer of ribose. Recently, some L-nucleoside analogues have been shown to have higher potency and lower toxicity when compared to their D-enantiomer.[5] As a result, processes that provide access to both enantiomers are desirable. Inspired by the wealth of biological activity present in pyrrole-substituted nucleoside analogues, we sought to develop a general method to utilize these nitrogen heterocycles as nucleophiles in the Pd-AAA. While pyrroles have been shown to act as competent nucleophiles in the Pd-AAA with vinyl aziridines,[6] and in the context of a total synthesis,[7] the generality of utilizing *meso* electrophiles with pyrroles has not been studied. By employing a *meso* starting material, both D- and L-enantiomers of ribose can be accessed simply by switching the chiral ligand used in the enantiodetermining Pd-AAA.

Table 1. Selected Optimization Studies[a]



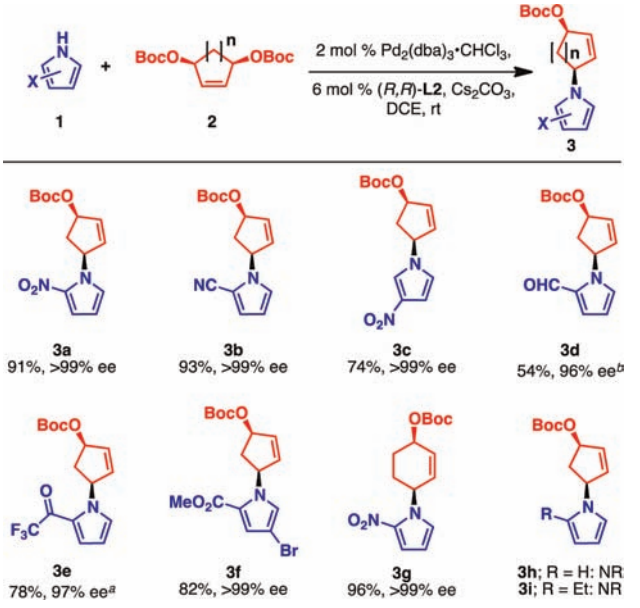
entry	ligand	additive	% yield[b]	% ee[c]
1	(*R*,*R*)-**L1**	none	55	83
2	(*R*,*R*)-**L2**	none	80	98
3	(*R*,*R*)-**L3**	none	78	90
4	(*R*,*R*)-**L4**	none	62	82
5	(*R*,*R*)-**L2**	HOAc	–	–
6	(*R*,*R*)-**L2**	NEt_3	75	97
7	(*R*,*R*)-**L2**	K_2CO_3	94	98
8	(*R*,*R*)-**L2**	Cs_2CO_3	90	>99

[a] All reactions were performed with 1.0 equiv of **1a**, 1.1 equiv of **2**, and 1.1 equiv of the indicated additive at ambient temperature, 0.25 M in DCE for 24 h. [b] Isolated yield. [c] % ee determined by chiral HPLC.



Our initial studies examined the reaction between 2-nitro-1*H*-pyrrole (**1a**) and *meso*-cyclopentene dicarbonate **2** in the presence of 2 mol % $Pd_2(dba)_3$•$CHCl_3$ and 6 mol % chiral ligand (Table 1). Employing (*R*,*R*)-**L1** as the ligand facilitated the desired alkylation reaction in a promising 53% yield and 83% enantiomeric excess (entry 1). Switching to (*R*,*R*)-**L2**, which contains a bulkier naphthyl phosphine, improved the reaction yield to 80% and the enantiomeric excess to 98% (entry 2). Employing (*R*,*R*)-**L3** provided the alkylated pyrrole **3a** in 78% yield and 90% enantiomeric excess (entry 3). Finally, using (*R*,*R*)-**L4** as the chiral ligand delivered the product in 62% yield and an 82% enantiomeric excess (entry 4). With an optimal ligand in hand, the effects of various additives were studied to further improve the reactivity (entries 5−8). The addition of acetic acid had a detrimental effect on the reaction, and none of the desired product could be observed. In general, adding base to the reaction medium had a positive effect on the reactivity. Triethylamine (entry 6) showed comparable results to the case with no additives; however, potassium carbonate improved the reaction to afford the product **3a** in 94% with >98% enantiomeric excess (entry 7). Changing to the softer cesium counterion delivered the product **3b** in 90% yield as a single observable enantiomer by chiral HPLC (entry 8).

Scheme 1. Scope of Pd-AAA of Pyrroles with Cyclopentene Dicarbonate **2**[a]



[a] All reactions were performed with 1.0 equiv of pyrrole nucleophile (**1**), 1.1 equiv of *meso* electrophile **2**, and 1.1 equiv of Cs_2CO_3 at ambient temperature, 0.25 M in DCE for 24 h. Yield refers to isolated yield. % ee determined by chiral HPLC. [b] (*R*,*R*)-**L1** was used.

With the optimized conditions in hand, the scope of the desymmetrization was explored by varying the pyrrole nucleophile (Scheme 1). A number of functional groups were tolerated at either the 2- or 3-position of the pyrrole nucleus, including nitro groups (**3a** and **3c**), nitriles (**3b**), aldehydes (**3d**), ketones (**3e**), esters (**3f**), and halides (**3f**). The reaction also proceeded smoothly using a six-membered cyclohexyl dicarbonate, providing the desired

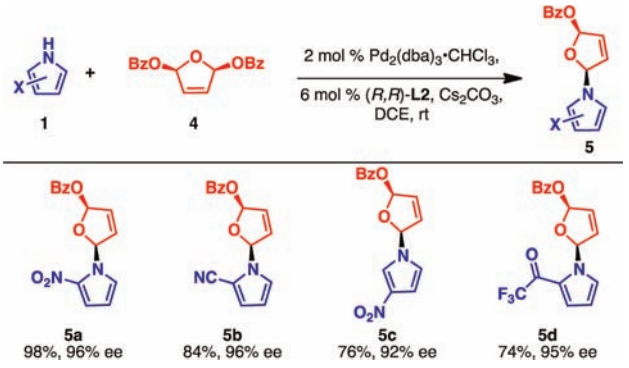
(5) (a) Jahnke, T. S.; Nair, V. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017. (b) Gosselin, G.; Mathé, C. *Antiviral Res.* **2006**, *71*, 276.

(6) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800.

(7) (a) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054. (b) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357. (c) Trost, B. M.; Dong, G. *Chem.—Eur. J.* **2009**, *15*, 6910.

cyclohexyl-substituted pyrrole **3g** in quantitative yield as a single observed enantiomer. The presence of an electron-withdrawing group was necessary to facilitate the transformation, and only starting materials were observed after 24 h when electron-rich or -neutral pyrroles were used (**3h** and **3i**). Employment of a weaker electron-withdrawing group, such as an aldehyde or ester, led to diminished yields while retaining high levels of enantioselectivity. The presence of an electron-withdrawing group was likely needed to increase the acidity of the pyrrole N−H as well as to make the anionic nucleophile softer and more compatible with the soft π-allyl Pd electrophile. In all cases examined, the desymmetrized product was observed as a single regio- and diastereomer, and only unreacted starting materials were isolated in cases where lower yields were observed.

Scheme 2. Scope of Pd-AAA of Pyrroles with Dihydrofuran **4**[a]



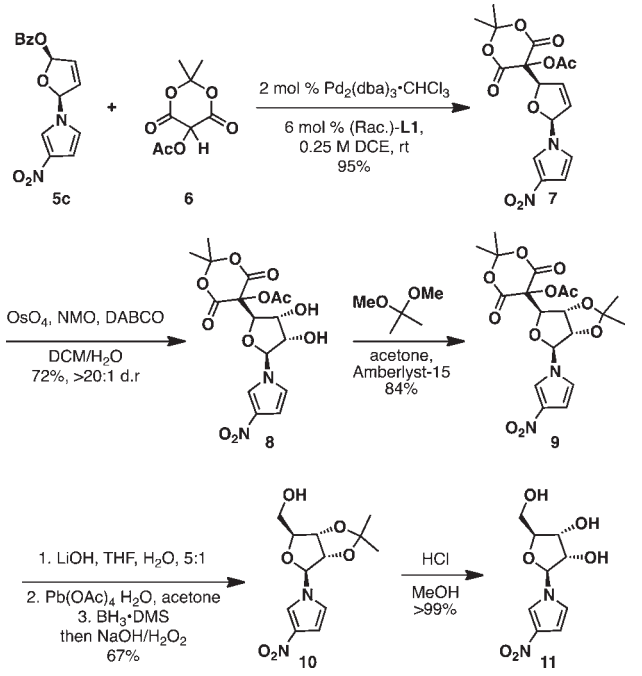
[a] All reactions were performed with 1.0 equiv of pyrrole nucleophile (**1**), 1.1 equiv of **4**, and 1.1 equiv Cs_2CO_3 at ambient temperature, 0.25 M in DCE for 24 h. Yield refers to isolated yield. % ee determined by chiral HPLC.

To expand the scope of this transformation, *meso* dihydrofuran **4** was utilized as an electrophile in the transformation (Scheme 2). Dihydrofuran **4** is a more challenging system due to its high propensity to undergo elimination/aromatization under basic conditions leading to the undesired, achiral furan product. To our delight, dihydrofuran **4** could serve as an electrophile to afford the alkylated product without any observed aromatization of the product to the undesired furan. Electron-deficient pyrroles substituted at either the 2- or 3-position served as nucleophiles to provide chiral dihydrofurans **5a**−**d** in good yield and with excellent levels of enantioselectivity. These products were observed exclusively with recovered starting materials accounting for the remainder of the mass balance.

To demonstrate the synthetic utility of this process, dihydrofuran **5c** was elaborated into a pyrrole-substituted nucleoside analogue **11** (Scheme 3). Previously, nitropyrrole-substituted nucleoside analogues were reported to act as universal bases in DNA transcription.[3] Unfortunately, prior syntheses of these compounds started from carbohydrate precursors, which are available only as the natural D-enantiomer, and require extensive use of protecting groups.

To introduce the hydroxymethylene functionality, benzoate **5c** was substituted with acetoxy Meldrum's acid (**6**) using a Pd-catalyzed diastereoselective substitution, which afforded dihydrofuran **7** in 95% yield as a single diastereomer.[8] Being substrate controlled, this reaction was conducted using (Rac.)-**L1**, which is far more cost-effective than the chiral variant of the same ligand. Previous work has demonstrated that using (Rac.)-**L1** in place of an achiral ligand can improve the outcome of a diastereoselective allylic substitution.[7c] Os-catalyzed dihydroxylation of dihydrofuran **7** provided diol **8** as a >20:1 mixture of diastereomers in 72% yield. Conversion of the free diol to the subsequent acetonide **9** proceeded in 84% yield. Without isolation or purification, acetonide **9** was converted to primary alcohol **10**. First, acetonide **9** was treated with LiOH in THF/H_2O, which chemoselectively hydrolyzed the Meldrum's acid acetonide in the presence of the diol acetonide and furnished a dicarboxylic acid intermediate. This dicarboxylic acid was treated with lead(IV) acetate in acetone to effect the oxidative double decarboxylation and unmask the monocarboxylic acid. This monocarboxylic acid was then reduced using BH_3•DMS providing the primary alcohol **10** in 67% yield. Finally, removal of the acetonide in methanolic HCl afforded the desired nucleoside analogue (**11**) in >99% yield without the need for purification. Characterization data for **11** were in agreement with previous reports.[3d,9]

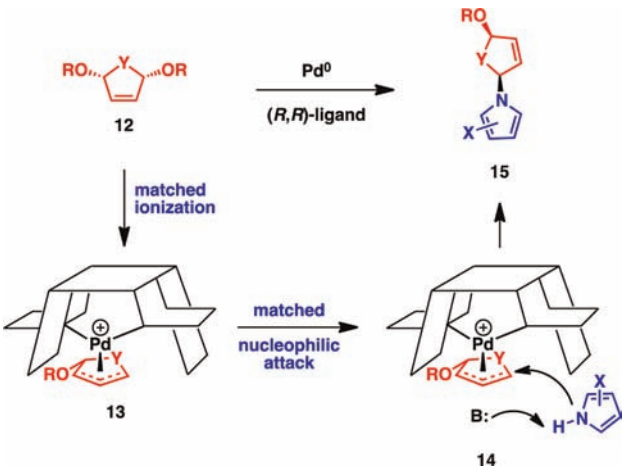
Scheme 3. Synthesis of Pyrrole-Substituted Ribonucleoside Analogue **11**



(8) Previous studies showed that acetoxy Meldrum's acid is a versatile acyl anion equivalent in the Pd-AAA: Trost, B. M.; Osipov, M.; Kaib, P. S. J.; Sorum, M. T. *Org. Lett.* **2011**, *13*, 3222.

(9) Absolute configuration was assigned by analogy to previous reports. See ref 7a, 7b.

Scheme 4. Mechanistic Rationale for Observed Stereochemistry



To rationalize the observed absolute configuration of the products obtained from the Pd-AAA of pyrrole with *meso* electrophiles, we propose the following explanation based on the wall-and-flap model we have previously disclosed (Scheme 4).[1d,10] Matched ionization from one of the prochiral faces of the *meso* electrophile **12** proceeds as the enantiodetermining step with inversion such that the leaving group (OR) departs from underneath the "flap" of the (*R*,*R*)-Pd-ligand complex **13**. Nucleophilic attack proceeds in a matched manner under the flap of the (*R*,*R*)-Pd-ligand complex **14** with another inversion, on the same face that ionization occurred delivering product **15**. The absolute configuration of **11** as well as other systems are in agreement with this model.

In conclusion, we have demonstrated that pyrroles can act as nucleophiles in the Pd-AAA with *meso* electrophiles. Both cyclopentene dicarbonates and dihydrofuran dibenzoates were used as electrophiles in the transformation. The reaction proceeded with high chemoselectivity and tolerated a variety of functional groups on the pyrrole nucleus. The products of this transformation were obtained in high yield and enantiomeric excess, as single regio- and diastereomers. To demonstrate the synthetic utility, a pyrrole-containing ribonuceloside analogue was synthesized in eight steps and 30% overall yield using minimal protecting groups. Unlike other strategies, both natural and unnatural enantiomers of the nucleoside analogues could be readily accessed.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health (GM33049) for their generous support of our programs. M.O. is a John Stauffer Memorial Fellow. M.O. and G.D. are Stanford Graduate Fellows. Palladium salts were generously supplied by Johnson-Matthey.

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

(10) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

The authors declare no competing financial interest.