Tetrahedron Letters, Vol. 34, No. 15, pp. 2437-2440, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

COMBINED DIRECTED METALATION - CROSS COUPLING STRATEGIES. A REGIOSPECIFIC ROUTE TO HETERORING-ANNELATED *ortho*-NAPHTHOQUINONES AND A SHORT SYNTHESIS OF β-LAPACHONE

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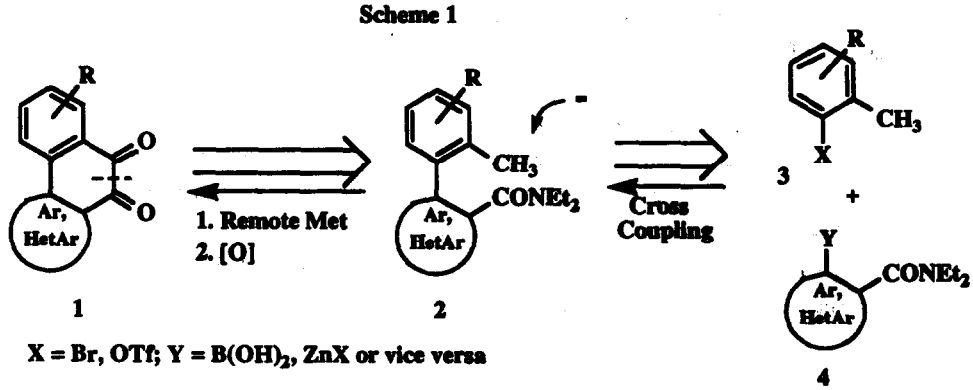
Abstract: *A general combined metalation - cross coupling methodology (Scheme 1) for the regiospecific construction of heteroring fused o-naphthoquinones 8 is described and its application to a short synthesis of the antimalarial/antitumor natural product β-lapachone (14) is demonstrated.*

We report on a new general method for the construction of heteroring-annelated *ortho*-naphthoquinones **1** by thematic variation of three inter-connecting synthetic methodologies recently cultivated in our laboratories (**Scheme 1**): a) directed *ortho* metalation to construct precursor *ortho*-Br or -ZnX heterocyclic amides **4**; b) transition metal catalyzed cross coupling of **4** with *ortho*-methyl aryl halides or triflates **3** to give intermediate heterobiaryls **2**; and c) remote metalation - cyclization of **2** to furnish target systems **1**.[1,2] We further describe the application of this sequence, in modified form, to a short and effective synthesis of the antitumor and antimalarial natural product, β-lapachone[3,4] (**Scheme 2**). The significance of the reported methodology derives from the inadequacy of regioselective methodologies for the preparation of polycyclic *o*-quinones,[5] their utility as intermediates for a variety of highly condensed systems,[6] and the large number of biologically active *o*-quinonoid natural products.[7]

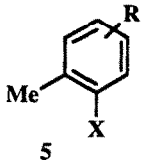
Scheme 1



1 **2**

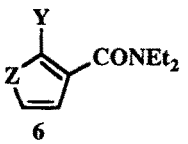
X = Br, OTf; Y = B(OH)$_2$, ZnX or vice versa

In contrast to the aromatic precedent,[2c] cross coupling of *o*-bromotoluene (**5a**) with the furan (**6a**) and thiophene (**6b**) boronic acid amides under standard $Pd(PPh_3)_4$-catalyzed aq Na_2CO_3/DME or DME/EtOH/reflux conditions[8] led to poor yields of products **7a** and **7b** respectively (Table, entries 1,2) with substantial amounts (70-72%) of protodeboronation products **6** (Z = O, S; Y = H). However, inversion of the X,Y substituents on the reacting partners and coupling **5b** with **6c** and **6d**[9] respectively under the aq Na_2CO_3/DME/reflux conditions in the presence of cat $Pd(PPh_3)_4$ led to 80-82% yields of products **7a** and **7b** respectively (entries 3,4).[10] To circumvent the protodeboronation problem, the Negishi cross coupling regimen[11] was tested. Thus treatment of **5a** with the furan and thiophene amide organozincs, **6e** and **6f**[12] using $Pd(PPh_3)_4$ catalyst in refluxing THF for 16 h furnished the heterobiaryls **7a** and **7b** respectively in 72-75% yields thus offering a viable and perhaps more general alternative to the Suzuki process for cases involving sensitive boronic acid partners. As gleaned from the Table, the Suzuki and Negishi cross coupling methods generally afford comparable yields of products. To extend the scope, **6f** was cross coupled with 2-bromo-3-methylpyridine to give the thiophenylpyridine **7f** (entry 8) and compound **5b** was coupled with N,N-diethyl 2-bromonicotinamide[13] to afford the corresponding azabiaryl **7g** (entry 9) in good yields.



5

	X	R
5a	Br	H
5b	$B(OH)_2$	H
5c	Br	5-Cl
5d	$B(OH)_2$	5-Cl
5e	Br	4,5-OCH_2O
5f	$B(OH)_2$	4,5-OCH_2O



6

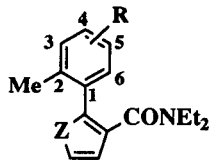
	Y	Z
6a	$B(OH)_2$	O
6b	$B(OH)_2$	S
6c	Br	O
6d	Br	S
6e	ZnBr	O
6f	ZnBr	S

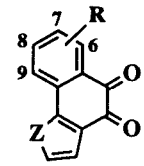
The results of LDA-mediated cyclization - oxidation of heterobiaryls **7a-e** to the fused *ortho*-naphthoquinones **8a-e** are summarized in the Table. While standard conditions for the remote metalation-cyclization (LDA/THF/0°C/3h)[14] were used, the subsequent oxidation step of the normally unstable, and therefore not purified, intermediate phenols was effected under several conditions which are given in the Table as optimized for each substrate.

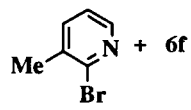
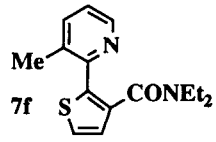
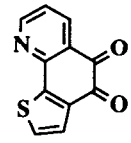
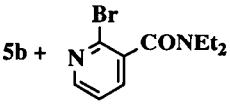
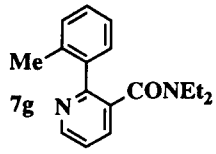
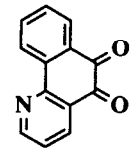
The short synthesis of β-lapachone (**14**) (**Scheme 2**) was initiated by conventional conversion of δ-valerolactone (**9**) into its trimethyl derivative (**10**) in good overall yield.[15] Application of the conditions of Murai and coworkers[16] for enol triflate preparation gave **11** which upon cross coupling with the boronic acid benzamide **12**[17] smoothly afforded the cross coupling product **13**. Exposure of **13** to excess LDA followed by $FeCl_3$ oxidation,[3] afforded β-lapachone (**14**) in modest yield.[18]

In summary, a new combined metalation (*ortho*, remote) and cross coupling methodology has been developed for the construction of heteroring-annelated *o*-naphthoquinones **8** and has been applied for the rapid assemblage of the antimalarial/antitumor β-lapachone (**14**). The deficiencies of the Suzuki cross coupling for π-excessive heterocyclic boronic acids (**6a-b**) have been noted and a preliminary comparison of the organoboron (**5b** + **6c-d**) and organozinc (**5a** + **6e-f**) coupling pathways to heterobiaryls **7** has been provided. This work offers a further demonstration of the versatility of integrated metalation - cross coupling technology in synthetic aromatic and heteroaromatic chemistry.[19,20]

Table. Synthesis of Heterobiaryls and *o*-Naphthoquinones

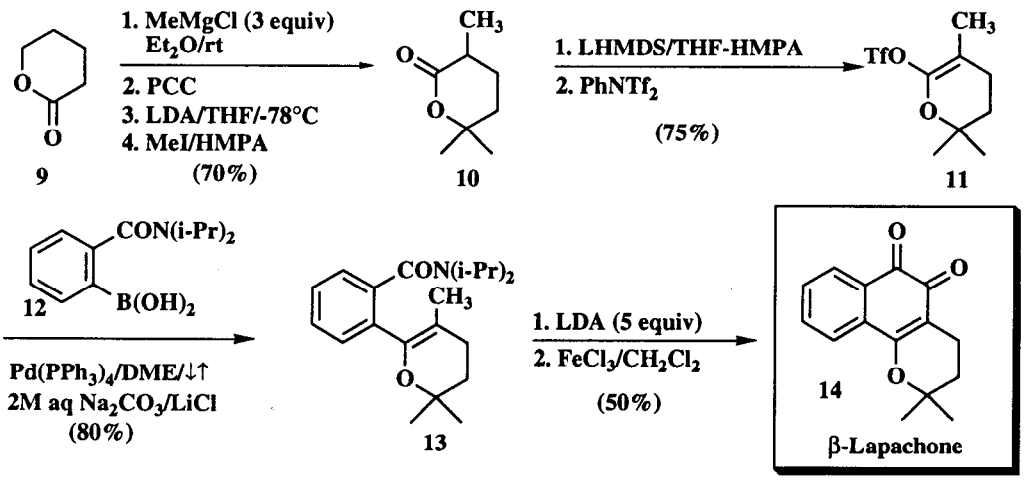




Entry	Coupling Partners [a]	Biaryl 7	yld, %[a]	Quinone 8	yld, %
1	5a + 6a	7a (Z = O, R = H)	28	8a (R = H)	50[b]
2	5a + 6b	7b (Z = S, R = H)	26	8b (Z = S, R = H)	55[b]
3	5b (5a) + 6c (6e)	7a	80 (72)		
4	5b (5a) + 6d (6f)	7b	82 (75)		
5	5d (5c) + 6c (6e)	7c (Z = O, R = 5-Cl)	88 (70)	8c (Z = O, R = 7-Cl)	[c]
6	5d (5c) + 6d (6f)	7d (Z = S, R = 5-Cl)	95 (75)	8d (Z = S, R = Cl)	67[d]
7	5f (5d) + 6c (6e)	7e (Z = O, R = 4,5-OCH_2O)	70 (73)	8e (Z = O, R = 7,8-OCH_2O)	[c]
8			75		74[d]
9			85		60[b]

[a] Structure numbers and yields without and with parentheses refer to Suzuki and Negishi coupling respectively. [b] $CrO_3/H_2O/SiO_2$ oxidation (Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* **1978**, 534). [c] Extensive decomposition, no product isolated. [d] O_2/salcomine/DMF oxidation (Kamikawa, T.; Isao, K. *Synthesis* **1986**, 431).

Scheme 2



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9. **6c-d** were prepared in 70-75% yield from the corresponding amides by treatment with *s*-BuLi/ TMEDA/THF/-78°C followed by BrCN quench.
10. For analogous observations, see: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.-H. *J. Heterocyclic Chem.* **1986**, *26*, 311.
11. Negishi, E.-i.; Luo, F.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.
12. Prepared from the corresponding amides by 1. *s*-BuLi/TMEDA/THF/-78°C; 2. $ZnBr_2$/THF.
13. Prepared in 80% yield from 2-bromonicotinic acid by treatment with $ClCONEt_2$/MeCN/reflux, see Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 5277.
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18. mp 152-154°C, lit mp 151-152°C; IR, NMR, MS spectral data identical with those reported (Joshi, K.C.; Prakash, L.; Singh, P. *Phytochemistry* **1973**, *12*, 942).
19. All new compounds show combustion analysis and spectroscopic data (IR, ^1H and ^{13}C NMR, HRMS) consistent with the given structures.

20. We are grateful to Carlos Zani for preliminary observations, NSERC Canada for financial support, and to CNPq, Brazil, for a scholarship to M.A.F.B.

(Received in USA 31 December 1992; accepted 5 February 1993)