ORGANIC LETTERS

2007
Vol. 9, No. 23
4901−4904

An Organocatalytic Oxidative Coupling Strategy for the Direct Synthesis of Arylated Quaternary Stereogenic Centers

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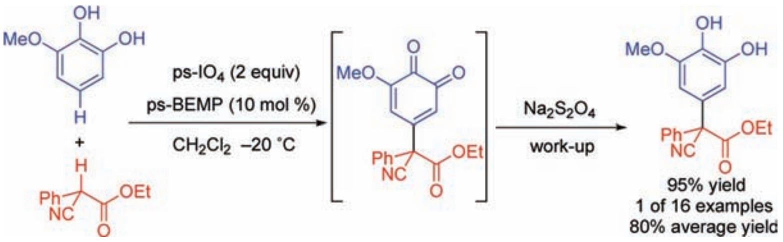
Received September 19, 2007

ABSTRACT



A broadly applicable oxidative coupling strategy of 3-substituted catechols and carbon-centered pro-nucleophiles for the construction of arylated quaternary stereogenic centers has been developed. Pivoting on a base-catalyzed addition of a carbon-centered acid to an in situ generated *o*-benzoquinone, the method is general and atom-economical and provides remarkably efficient access to one of the most challenging structural motifs. Furthermore, use of chiral bifunctional organocatalysts allows the process to be rendered asymmetric (up to 81% ee).

A number of biologically important natural products and pharmaceutical compounds contain derivatives of 1,2-dihydroxylated aromatic rings (catechol derivatives) covalently attached to all-carbon quaternary stereogenic centers; examples include the calcium channel antagonist verapamil[1] and the paraherquamide family of antiparasitic alkaloids (Figure 1).[2−4]

Common though this motif is, its direct construction, and the direct construction of the quaternary carbon−aryl bond in general, remains a significant synthetic challenge.[5] Some of the most attractive synthetic solutions include Friedel−Crafts alkylations,[6] intramolecular Heck couplings,[7] S$_N$Ar reactions of 1,3-dicarbonyl compounds with *p*-fluoronitrobenzenes,[8] and transition-metal-catalyzed coupling reactions of carbon-centered nucleophiles to aryl halides. The

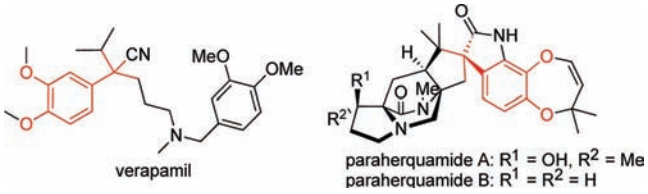


Figure 1. Pharmaceutical compounds and natural products containing arylated quaternary stereogenic centers.

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(1) (a) Steidle, W.; Dengel, F. GB1101479, 1968. (b) Singh, B. N.; Chew, C. Y. C.; Josephson, M. A.; Packer, M. *Am. J. Cardiol*. **1982**, *50*, 886. (c) For a stereospecific synthesis, see: Theodore, L. J.; Nelson, W. L. *J. Org. Chem*. **1987**, *52*, 1309.

(2) (a) Lopez-Gresa, M. P.; Gonzalez, M. C.; Ciavatta, L.; Ayala, I.; Moya, P.; Primo, J. *J. Agric. Food. Chem.* **2006**, *54*, 2921 and references cited therein. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127.

(3) Other examples include the Amaryllidaceae alkaloid family; for a review, see: Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606.

(4) The motif is also present in the mastigophorenes, see: (a) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin. Trans. 1* **1991**, 2737. (b) For asymmetric total syntheses, see: Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762.

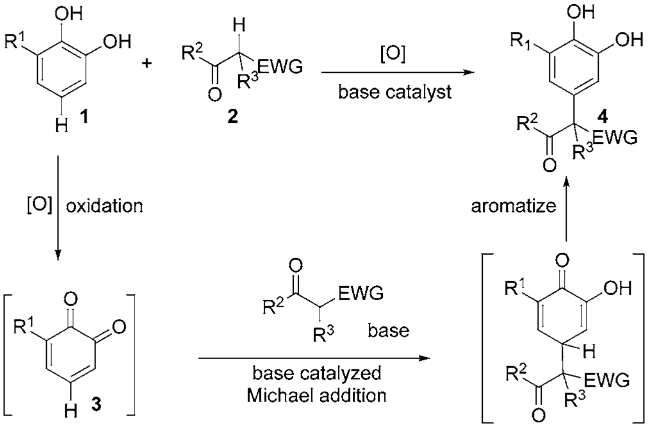
10.1021/ol702277v CCC: $37.00

latter approach, first reported by Buchwald in 1998, is arguably the most powerful to date allowing efficient and sometimes highly enantioselective arylation reactions to be performed with a range of transition metals and ligands.[9,10] Recently, enantioselective arylation reactions of β-keto esters using commercially available 1,4-quinones as electrophiles were reported.[11,12]

The abundance of attractive target molecules containing all-carbon quaternary stereogenic centers attached to functionalized aromatic ring systems and the possibility of developing a new, broadly applicable and metal free method for their construction was appealing.

Our planned strategy, based on a formal oxidative coupling of a 5-unsubstituted catechol **1** with a suitably acidic carbon-centered pro-nucleophile **2** in the presence of a base catalyst, is shown in Scheme 1. In situ oxidation of a catechol would generate an electrophilic *o*-benzoquinone intermediate **3** primed for attack[13] by the conjugate base of the carbon-centered acid. Following Michael addition, aromatization would generate the catechol product **4** substituted at the 5-position as desired. As 3-substituted catechols can be readily prepared[14] or are commercially available and the intermediate *o*-benzoquinone reagents are highly reactive and often unstable, this strategy would provide a powerful and general route to compounds containing arylated quaternary stereogenic centers.

Scheme 1. Concept: An Oxidative Coupling Strategy for the Construction of Arylated Quaternary Stereogenic Centers



Initially, ^{1}H NMR studies were performed to demonstrate the necessity for the in situ generation of the *o*-benzoquinone intermediates. A range of 3-substituted catechols were oxidized in $CDCl_3$ using a polymer supported periodate oxidant (ps-IO_4)[15] and their half-lives monitored. Figure 2 clearly demonstrates that whereas commercially available 1,2-naphthoquinone[16] is stable indefinitely, 3-substituted *o*-benzoquinone reagents rapidly degrade even when bulky or electron-donating substituents are present.[17]

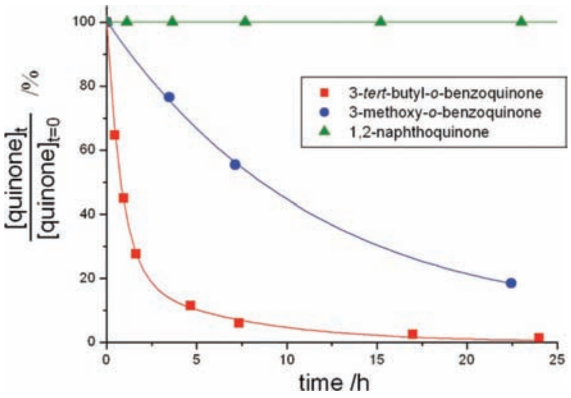


Figure 2. Decomposition of 3-substituted *o*-benzoquinones in $CDCl_3$ compared with stable 1,2-naphthoquinone, measured against an internal standard; see the Supporting Information for details.

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(5) For a review on the enantioselective construction of all carbon quaternary centers, see: Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369.

(6) For the use of Friedel–Crafts alkylations to form arylated quaternary centers, see: (a) Grundl, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429. (b) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348.

(7) (a) For a review, see: Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453 and references 39–44 therein. (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261. For the application of intramolecular Heck coupling in synthesis, see: (c) Tietze, L. F.; Wiegand, J. M.; Vock, C. A. *Eur. J. Org. Chem.* **2004**, *20*, 4107. (d) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.

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(9) (a) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (c) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (d) Hamada, T.; Chieffe, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

(10) For Ni-catalyzed coupling, see: Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500. For Cu-catalyzed coupling, see: Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.

(11) For selected reviews on organocatalysis, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem*. **2007**, *11*, 1701. (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (c) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (d) List, B. *Chem. Commun*. **2006**, *8*, 819. (e) Dalko, P. I.; Moisan L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (f) *Acc. Chem. Res.* **2004**, *37*, special issue on organocatalysis. (g) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

(12) Alemán, J.; Richter, B.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5515.

(13) *o*-Benzoquinones are notoriously unstable, and as a result (in contrast to *p*-quinones), examples of their use as Michael acceptors, particularly toward carbon-centered nucleophiles, are rare. For additions of allylstannanes, see: (a) Maruyama, K.; Takuwa, A.; Naruta, Y.; Satao, K.; Soga, O. *Chem. Lett.* **1981**, 47. (b) Nishigaichi, Y.; Takuwa, A. *Chem. Lett.* **1990**, 1575. (c) Nishigaichi, Y.; Yoshida, N.; Matsuura, M.; Takuwa, A. *Chem. Lett.* **1999**, 803. For additions of silyl enol ethers, see: (d) Sagawa, Y.; Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1988**, 1105. For a review on nucleophilic additions to quinones, see: (e) Kutyrev, A. A. *Tetrahedron* **1991**, *47*, 8043. (f) Nematollahi, D.; Alimoradi, M.; Rafiee, M. *J. Phys. Org. Chem.* **2007**, *20*, 49.

(14) (a) Hansen, T. V.; Skattebøl, L. *Tetrahedron Lett.* **2005**, *46*, 3357. (b) Berberian, V.; Allen, C. C. R.; Sharma, N. D.; Boyd, D. R.; Hardacre, C. *Adv. Synth. Catal.* **2007**, *349*, 727.

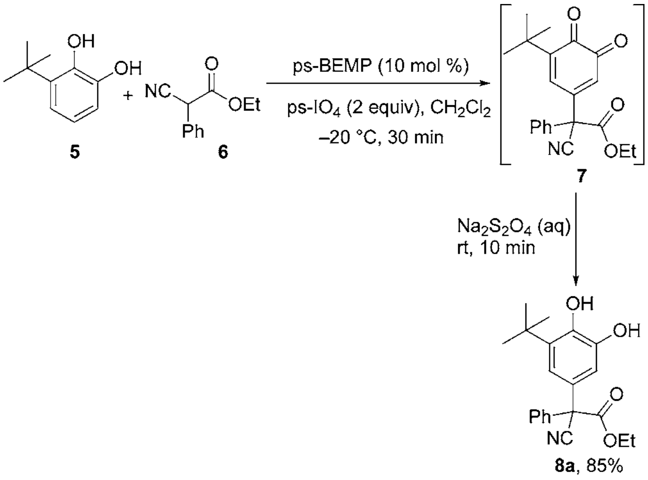
(15) Harrison, C. R.; Hodge, P. *J. Chem. Soc., Perkin. Trans. 1* **1982**, 509.

(16) 1,2-Naphthoquinones are unusually stable compared with *o*-benzoquinones and their use as Michael acceptors is better established. For additions of β-dicarbonyl compounds, see: (a) Grinev, A. N.; Arsenichev, I. K.; Nikolaeva I. S.; Golovanova, L. A.; Pushkina, T. V.; Okinskevich, O. V.; Fomina, A. N.; Pershin, G. N. *Khim. Farm. Zh.* **1985**, *19*, 699. (b) Grinev, A. N.; Arsenichev, I. K. *Zh. Org. Khim.* **1985**, *21*, 1315. (c) Christoffers, J.; Mann, A. *Eur. J. Org. Chem.* **1999**, 2511. For an isolated example of a quinine-catalyzed addition to 1,2-naphthoquinone leading to a 4-substituted-1,2-naphthoquinone, see ref 12.

With the necessity for in situ generation of the *o*-benzoquinone intermediate demonstrated, proof of principle studies were required to probe the feasibility of the organocatalytic oxidative coupling strategy. 3-*tert*-Butylcatechol **5** and ethyl phenylcyanoacetate **6** were chosen as representative quinone precursor and pro-nucleophile, respectively, and their coupling using a range of base catalysts and conditions in conjunction with ps-IO_4 was investigated. Feasibility was readily established, optimization followed, and the best reaction conditions employed 1 equiv each of **5** and **6** and 2 equiv of ps-IO_4 in the presence of 10 mol % of polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (ps-BEMP) in CH_2Cl_2 at −20 °C.

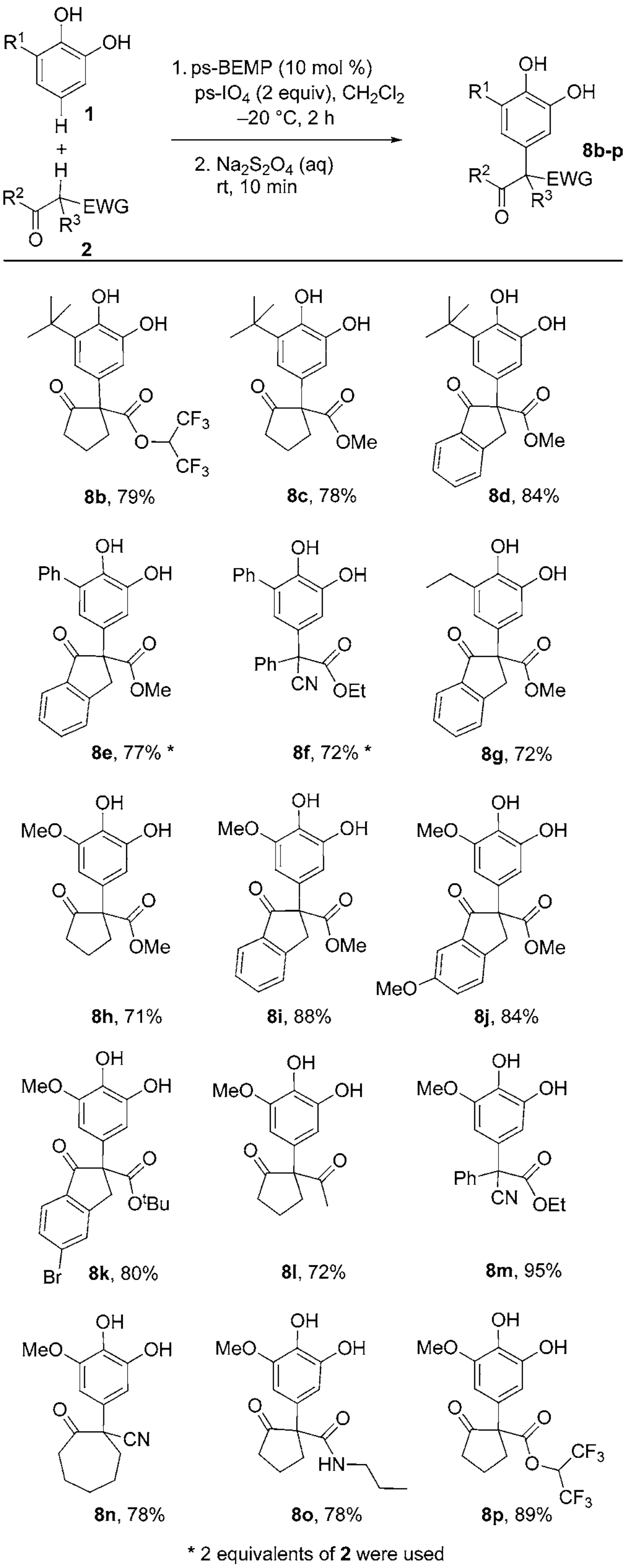
After 30 min, complete consumption of the starting materials and production of quinone intermediate **7** was observed. Following a sodium hydrosulfite reductive workup, the desired arylated product **8a** was afforded in 85% overall yield (Scheme 2).

Scheme 2. Proof of Principle Studies: Oxidative Coupling of 3-*tert*-Butylcatechol and Ethyl Phenylcyanoacetate



The scope of the reaction with respect to the 3-substituted catechol was then investigated. *tert*-Butyl-, ethyl-, phenyl-, and methoxy-substituted catechols were all found to be effective substrates. The scope of the reaction with respect to the pro-nucleophile was also found to be broad; *β*-ketoesters, *β*-diketones, *β*-ketoamides, α-cyano ketones, and α-cyano acetates were all found to be effective. In most cases, equimolar amounts of pro-nucleophile and catechol were employed, and in all cases, the addition was rapid, completely regioselective, and high yielding (Scheme 3).

Scheme 3. Scope of the Organocatalytic Oxidative Couplings of Catechols with Pro-nucleophiles



* 2 equivalents of **2** were used

Although optimized for the production of racemates, the oxidative coupling strategy was readily modified to allow an efficient asymmetric organocatalytic variant. Thus, replacement of ps-BEMP with a cinchona alkaloid-derived bifunctional organocatalyst allowed the formation of the arylated product with high levels of enantiocontrol. For example, oxidative coupling of equimolar amounts of

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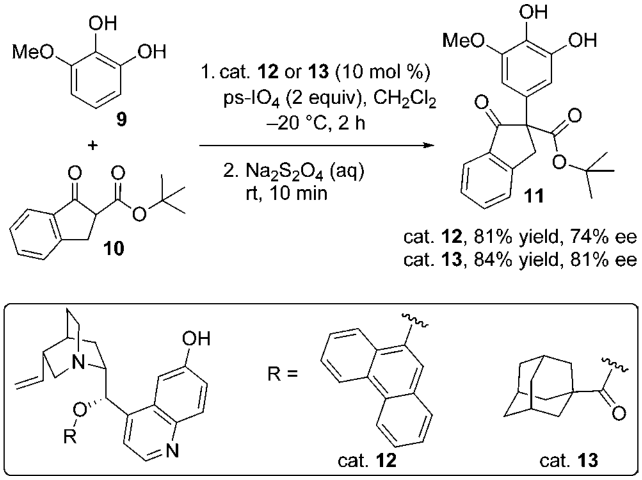
(17) After 24 h, a complex mixture of products was obtained in the case of 3-methoxy- and 3-*tert*-butylquinones. *o*-Benzoquinone is known to decompose through dimerization and polymerization pathways; see: Harley-Mason, J.; Laird, A. H. *J. Chem. Soc.* **1958**, 1718.

Scheme 4. Asymmetric Organocatalytic Oxidative Coupling



3-methoxycatechol **9** and *tert*-butyl 1-oxoindan-2-carboxylate **10** in CH$_2$Cl$_2$ at −20 °C in the presence of known quinidine-derived catalyst **12**[18] (10 mol %) afforded arylated product **11** in 81% isolated yield and 74% ee. A repeat of the reaction in the presence of catalyst **13** gave product **11** in 84% yield and 81% ee (Scheme 4).

In summary, a new broadly applicable oxidative coupling of 3-substituted catechols and pro-nucleophiles has been developed for the direct construction of arylated quaternary stereogenic centers. Pivoting on a base-catalyzed addition of a carbon-centered acid to an in situ generated *o*-benzoquinone, the method is general, atom economical, practically simple, and provides remarkably efficient access to one of the most challenging structural motifs. Further extensions and improvements to the work are ongoing and will be presented in due course.

Acknowledgment. We gratefully acknowledge the University of Manchester, the EPSRC, and GlaxoSmithKline for support (to K.M.B.).

Supporting Information Available: Experimental procedures and spectroscopic data for products **8a−p**, **11**, and catalyst **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] For examples of conjugate additions using cat. **12**, see: (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (b) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (c) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301. (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948. (e) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (f) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.