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Regiochemical Control in the Oxidative Coupling of Metal Phenolates: Highly Selective Synthesis of Symmetric, Hydroxylated Biaryls

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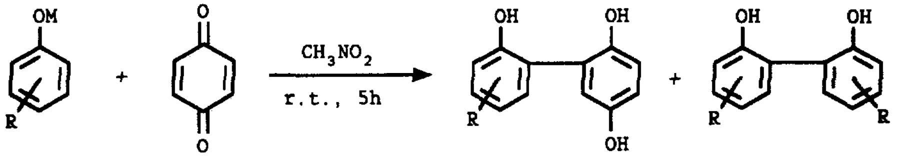
Abstract: Oxidative coupling of highly coordinating metal phenolates promoted by $FeCl_3$ afforded variously substituted symmetric 2,2'-dihydroxy biaryls in good yield and high regiochemical control.

As part of our continuing studies on the regioselective functionalization of phenols via metal-template catalysis,[1] we recently began to explore the arylation process with particular respect to the synthesis of polyhydroxylated and polymethoxylated biaryls, a class of compounds formally related to a large group of natural products[2] and showing interesting applications as useful synthons in the preparation of complex ligands such as podands and spherands.[3]

To this end, we studied the reactivity of highly coordinating metal phenolates with benzoquinone bis(dimethylketal), mono(dimethylketal) as well as unprotected benzoquinone. Our results suggest that titanium and aluminum phenolates react with benzoquinone bis(dimethylketal) and mono(dimethylketal) yielding ortho-hydroxyarylhydroquinone bis(methylethers)[4] and the corresponding mono(methylethers)[5] in 45-100% yield.

We found, however, that metal phenolates 1 react with benzoquinone 2 affording two products, 3 and 4, arising respectively from the electrophilic arylation of the quinone and from the oxidative coupling of the phenol promoted by the quinone itself.[6]



1 2 3 4

As our objective, we proposed achieving the optimum conditions to selectively direct the reaction towards the electrophilic attack product 3 or, alternatively, towards the oxidative coupling product 4. Herein we report our results on the regioselective, oxidative dimerization of metal phenolates.

It is well known that phenols are readily oxidized by many different reagents. Unfortunately the products are complicated mixtures of dimeric, polymeric and quinonoid compounds and the synthetic application requires very efficient methods for the separation of the complex reaction mixtures[7] or the use of specific substrates.[8]

We found that the reaction of oxygenophilic metal phenolates 1 with appropriate oxidant reagents represents a viable method for joining together two phenolate radicals producing the dimeric derivatives 4 in good yield and with high selectivity.

In the first stage, we analyzed the effect of the counter-ion M in order to obtain information on the role played by the Lewis acidity and the coordination power of the metal phenolate 1 on the reactivity and the selectivity of the phenol oxidative coupling process.

Table 1. Counter-ion effect in the reaction of different metal p-methoxyphenolates and benzoquinone. Selectivity in the phenol oxidative coupling versus quinone attack.(a)

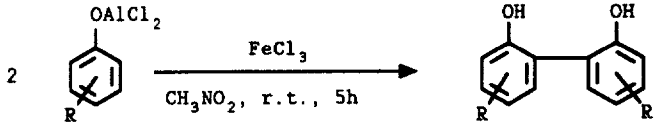
Entry	M	Recovered Phenol (%)	Product 3 (%)	Product 4 (%)
a	H	97	-	-
b	$AlCl_2$	20	14	64
c	BCl_2	60	-	39
d	$TiCl_3$	48	11	30
e	AlCl	65	3	24
f	MgBr	43	11	40
g	Al^{III}	95	-	-
h	Ti^{IV}	96	-	-
i	Zn^{II}	98	-	-
l	K	7	(b)	(b)
m	K/dibenzo--18-crown-6	5	(b)	(b)

(a) The p-methoxyphenol was employed as model substrate; all metal phenolates were prepared as reported in the literature[9] and all the reaction mixtures were homogeneous with the exception of the zinc and potassium phenolates; phenol/benzoquinone ratio was 2/1; reactions were carried out in dry nitromethane for 5 hours; (b) complex mixture of polymeric materials.

The best theory for the phenolic coupling mechanism is that the oxidant reagent converts the phenolate into a free phenoxy radical which rapidly couples to the dimeric product under kinetic control.[7a] Results from Table 1 indicate that the phenol itself does not react under the conditions employed in this study (Table 1, Entry a). Moreover the yield and the selectivity of this process depend on the Lewis acidity and on the coordination power of the counter-ion (Table 1, Entries b, c, d, e and f). Under these conditions, undesirable production of uncontrolled polycoupled compounds would be inhibited by the formation of a stable metal chelate of the dimeric product 4 with the oxygenophilic Lewis acid. Accordingly, the reaction of the poorly coordinating potassium phenolate or free phenolate anion results in the unselective production of polymeric materials (Table 1, Entries l and m).

The use of benzoquinone as oxidant reagent had the disadvantage of producing variable amounts of the addition compound 3. We overcame this problem by utilizing $FeCl_3$ as oxidant reagent under similar experimental conditions (Table 2, note a).[10] By reacting different dichloroaluminum phenolates with a stoichiometric amount of $FeCl_3$ in dry nitromethane,[11] we obtained the corresponding dimeric products in good yield and excellent selectivity. Representative examples are listed in Table 2 and demonstrate that the coupling occurs faster with aromatic substrates of higher electronic density, except when there is steric hindrance of approach.

Table 2. Reaction between different dichloroaluminum phenolates and $FeCl_3$ (a).



Entry	R	Recovered Phenol (%)	Dimeric Product (%)
a	4-CH_3	52	40
b	4-OCH_3	20	78
c	4-Cl	70	25
d	4-$C(CH_3)_3$	68	30
e	4-OH	45	50
f	4-[(4'-OH)-C_6H_4]	60	32
g	3,4-$(CH{=}CH)_2$-	20	77
h	3,4-(O-CH_2-O)-	12	80 (b)

(a) The selected phenol (0.01 mol) was added to a solution of $AlCl_3$ (1.33 g, 0.01 mol) in dry nitromethane (20 ml). After 1 hour, anhydrous $FeCl_3$ (1.62 g, 0.01 mol) in nitromethane (10 ml) was added dropwise. Treatment with aqueous 10% HCl after 5 hours, extraction with CH_2Cl_2 and drying with Na_2SO_4, followed by chromatography on SiO_2, eluant hexane-ethylacetate (30-50%), afforded the solid products; (b) AlCl was utilized as counter-ion and the reaction time was 1 hour.

The 8 examples reported above suggest that this method represents a general and extremely selective route to compounds 4 including tetraaryl derivatives (Table 2, Entry f). Thorough development of these results should make it possible to exploit the wealth of information on the detailed mechanism and to open a direct and selective route to polyphenols stepwise synthesis.

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10) By reacting p-methoxyphenol with a stoichiometric amount of $FeCl_3$ in nitromethane at room temperature for 5 hours, we obtained the dimeric product in 34% yield.

11) Similar results were obtained by carrying out the reaction in dry CH_2Cl_2.

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