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An Efficient Synthesis of Highly Functionalized Unsymmetrical Biphenyls Having Substituents on the *Ortho* Positions

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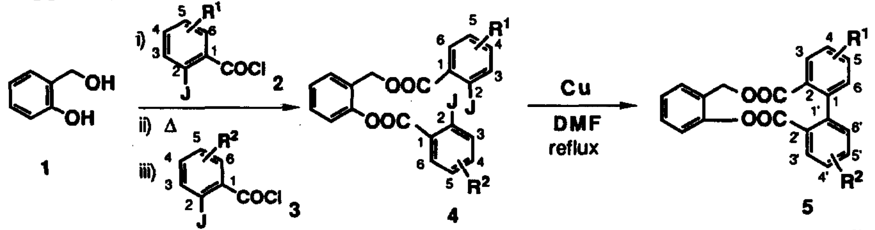
Abstract: The highly functionalized unsymmetrical biphenyls having electron-donating and/or electron-withdrawing substituents on the *ortho* positions were effectively synthesized based on the intramolecular Ullmann coupling reaction directed by salicyl alcohol as a template, followed by selective cleavage of the two ester bonds of 5.

Highly functionalized unsymmetrical biphenyls are of increasing interest recently, because of their intriguing biological activities.1) The transition-metal catalyzed cross-coupling reactions of an aryl metal with an aryl halide have served as a tool for the synthesis of functionalized biphenyls. In these reactions, however, the yields of the coupling products remarkably decrease in the case of highly functionalized biphenyls, especially having substituents on the *ortho* positions.2) Furthermore, difficulties are frequently encountered in the coupling reactions between two aromatics having the substituents which are incompatible with organometallic reagents.3)

We recently reported the basic features of a new aryl-aryl coupling reaction based on the intramolecular Ullmann couping reaction directed by salicyl alcohol as a template.4) We envisaged that the new method would overcome the problems involved in the known methods; the strain energy of the 11-membered ring to be

Scheme 1

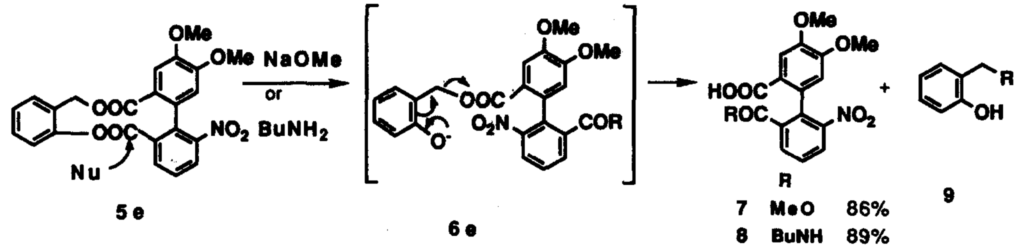


		Yield of 4[6]			Yield of 5[6]
a	R^1=3,4-OCH_2O- R^2=3,4,5-$(OMe)_3$	76%	a	R^1=5,6-OCH_2O- R^2=4',5',6'-$(OMe)_3$	86%
b	R^1=3-NO_2 R^2=3,5-Cl_2	72%	b	R^1=6-NO_2 R^2=4',6'-Cl_2	84%
c	R^1=3,5-Cl_2 R^2=3,4,5-$(OMe)_3$	75%	c	R^1=4,6-Cl_2 R^2=4',5',6'-$(OMe)_3$	89%
d	R^1=3,4,5-$(OMe)_3$ R^2=3-NO_2	77%	d	R^1=4,5,6-$(OMe)_3$ R^2=6'-NO_2	87%
e	R^1=4,5-$(OMe)_2$ R^2=3-NO_2	79%	e	R^1=4,5-$(OMe)_2$ R^2=6'-NO_2	90%

formed in the use of salicyl alcohol as a template is probably small enough to compensate the low reactivities of the two aromatics having substituents on the ortho positions.5)

Thus, we examined the intramolecular Ullmann coupling reactions of the diacylated salicyl alcohols (**4a~e**) which were prepared in 72~79% yields by selective acylations of salicyl alcohol *via* the intramolecular rearrangement of the acyl groups.6) The Ullmann coupling reactions of the diesters (**4a~d**) having substituents on all of the four *ortho* positions of the reaction sites nicely proceeded to afford the cyclized compounds (**5a~d**) in excellent yields. The result obtained in the reaction of **4a** having the five electron-donating substituents on the aromatics is in marked contrast to those in the transition-metal catalyzed cross-coupling reaction of an aryl metal with an aryl halide in which the yield is low without any exception.2a) The coupling reactions of the diesters (**4c~e**), in which the electronic characters of the two aromatics are quite different with each other, also took place efficiently to afford the biphenyls (**5c~e**) in good yields. The results obtained in the coupling reactions of **4b**, **4d** and **4e** indicate that the new method is applicable to the synthesis of the biphenyls having substituents such as nitro and ester groups with which the organometallic reagents used in the known methods are incompatible.3)

Scheme 2



We also succeeded in the conversion of the coupling products (**5a~e**) into the corresponding monoesters and monoamides by regioselective cleavage of the two ester bonds via **6**. For example, treatment of **5e** with NaOMe and $BuNH_2$ gave **7** and **8** in high yields, respectively, with concomitant formation of **9** (Scheme 2).7) This method should make it possible to convert the two ester groups into the other functional groups different with each other, thereby contributing to the expansion of the utility of this coupling reaction in the synthesis of the highly functionalized biphenyls.

As described above, this new method involving the intramolecular Ullmann coupling reaction followed by selective cleavage of the two ester groups should provide a new entry to the synthesis of highly functionalized unsymmetrical biphenyls having intriguing biological activities.

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2. (a) Widdowson, D. A.; Zhang, Y. -Z. *Tetrahedron* **1986**, *42*, 2111; (b) Semmelhach, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460.
3. Aryltin compounds, arylboronic acids and arylfluorosilanes have been reported to be compatible with carbonyl groups and amides. See, Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711, and references cited therein.
4. Takahashi, M.; Kuroda, T.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *Tetrahedron Lett.* **1991**, *32*, 6919.
5. The ring size in this type of coupling reaction is a crucial factor to make the Ullmann coupling reaction proceed efficiently. This coupling reaction leading to the 11-membered ring proceeds far more efficiently than those leading to the 10-membered ring and 12-membered ring using catechol and 1,2-benzenedimethanol, respectively, as a template. Salicyl alcohol plays an important role as a template to force the two reaction sites close to each other.
6. Isolated yield. All products were unequivocally identified by 200MHz ^{1}H-NMR, IR, and Mass spectra, and elemental analyses.
7. **9** was formed from **6e** probably *via* the *o*-quinone methide.

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