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Combined directed *ortho* metalation–cross coupling strategies. Design for natural product synthesis

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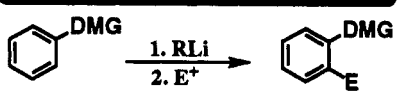
Abstract: Recent efforts in our laboratories have established connections between the Directed *ortho* Metalation (DoM) (**Scheme 1**) and transition metal catalyzed cross coupling (**Scheme 2**) strategies. The combination of these with the Remote Metalation (**Scheme 4**) tactic has led to the evolution of powerful new methods for aromatic synthesis. The application of these concepts, singularly or combined, for the construction of alkaloids (**Scheme 6**), fluorenone natural products (**Schemes 7, and 8**), naphthobenzopyranones (**Schemes 9** and **10**), and naturally-occurring phenanthrenes is given as illustration of the new synthetic aromatic chemistry.

INTRODUCTION

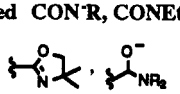
A specific ongoing thrust in our laboratories involves establishing general and practical synthetic links between directed *ortho* metalation (DoM) (**Scheme 1**) and transition metal catalyzed cross coupling reactions (1). In pursuit of these goals, cross coupling methodologies have been developed (2) based on the venerable Suzuki and Negishi processes (**Scheme 2**) which allow the regiospecific construction of diverse classes of condensed aromatic and heteroaromatic systems as well as polyaryls and heteropolyaryls. The recent discoveries that O-aryl carbamates, previously shown to serve as powerful DoM substrates, and S-aryl thiocarbamates also undergo Ni(0)-catalyzed cross coupling with Grignard reagents (**Scheme 3**) (3) has opened new doors in pursuit of these goals. The evolution of the remote metalation concept for biaryl amides **Scheme 4** (4) and biaryl carbamates (5) has led to useful synthetic consequences for fluorenones, dibenzopyranones, and related systems. This report will summarize the most recent results of the interaction of the troika of DoM, cross coupling, and remote DoM for the development of new synthetic methodology of value in aromatic chemistry and for the construction of natural products.

Scheme 1
Directed *ortho* Metalation (DoM)



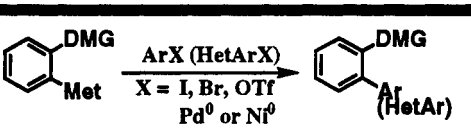
DMG = Directed metalating group

Useful DMGs: C-based CON^{-}R, $CONEt_2$,



Het Atom based N^{-}CO*t*-Bu, N^{-}CO_2*t*-Bu, $OCONEt_2$, $OCSNEt_2$, OMOM, $S(O)_nN^{-}R$ (n = 1,2), SO_2NR_2, $S(O)_n$*t*-Bu (n = 1,2)

Scheme 2
Aryl Boronic Acid - Aryl Halide and Triflate Cross Coupling



Met = $B(OR)_2$, ZnX
DMG = $CONR_2$, $OCONR_2$, OMOM
N*t*-Boc, SO_2*t*-Bu

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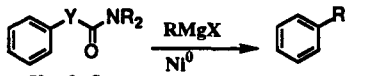
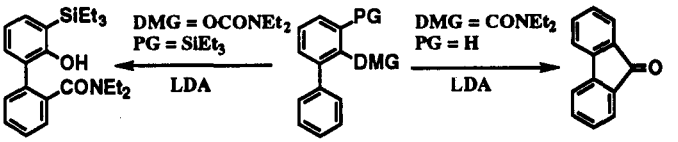
Scheme 3 O-Aryl Carbamate and S-Aryl Thiocarbamate - Grignard Cross Coupling



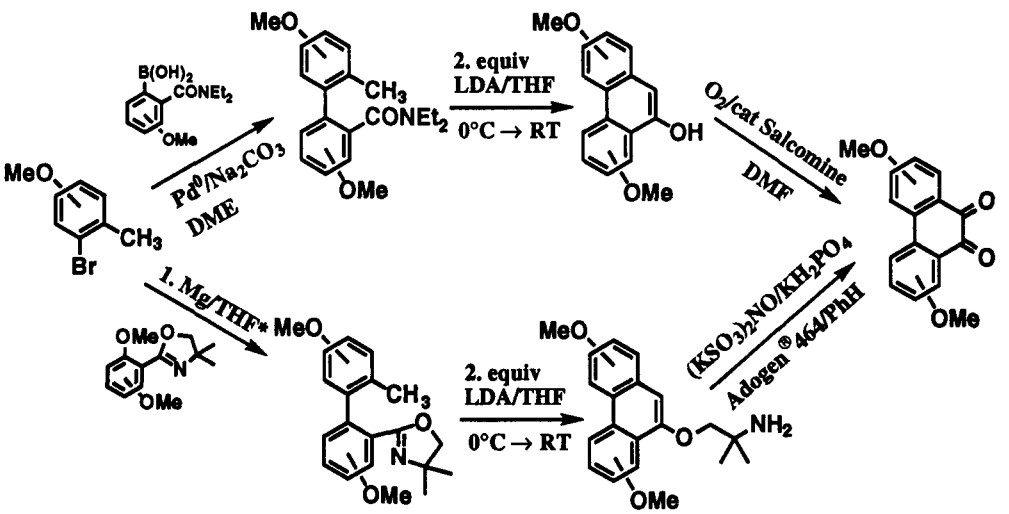
Scheme 4 Remote Metalation



New Construction Motif for 9,10-Phenanthraquinones. Synthesis of Oxoaporphine Alkaloids

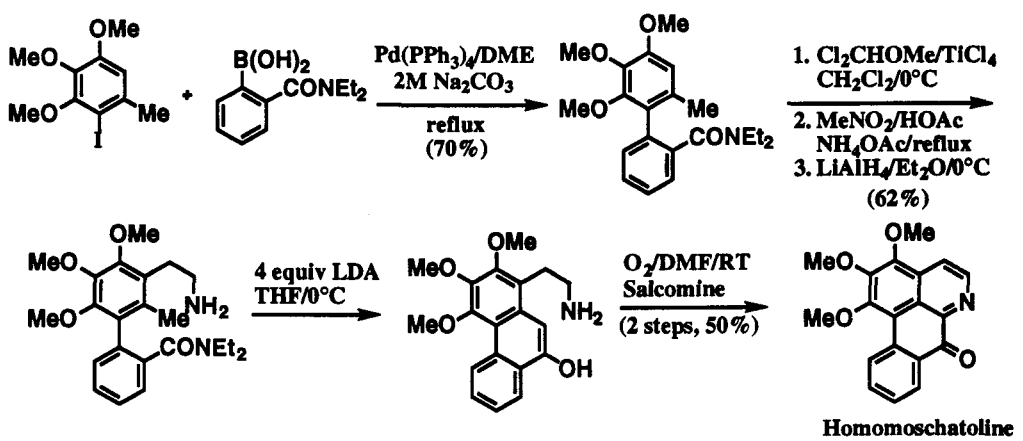
The combination of DoM, Suzuki cross coupling, and remote metalation proved valuable in the development of a general and regiospecific synthesis of 9,10-phenanthraquinones (**Scheme 5**) (6, 7). The application of this strategy to the construction of homomoschatoline, a representative of the large group of oxoaphorphine alkaloids, has been achieved (**Scheme 6**) (8).

Scheme 5 Cross Coupling - Remote "*ortho*-Toluyl" Metalation Route to 9,10-Phenathroline



• Review: Reuman, M.; Meyers, A.I. *Tetrahedron* 1985, *41*, 837.

Scheme 6 Total Synthesis of Oxoaporphine Alkaloid Homomoschatoline

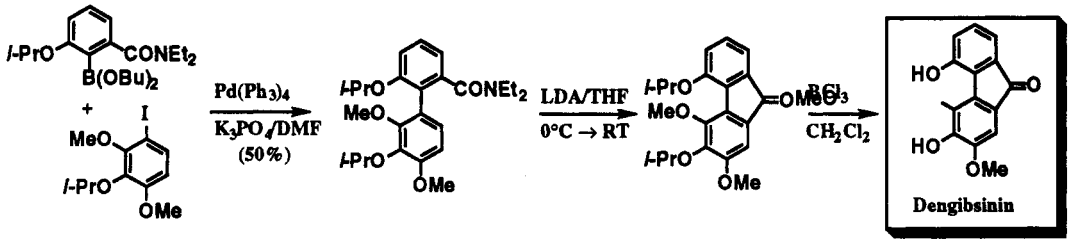


Homomoschatoline

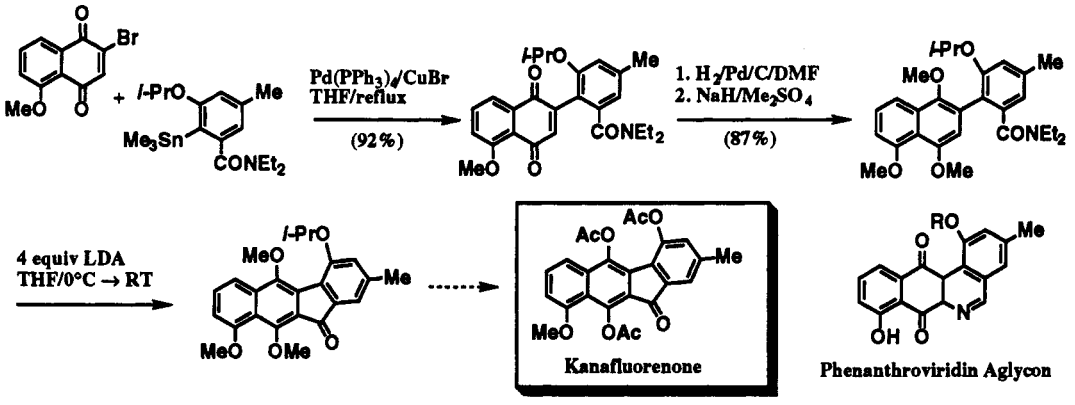
Biaryl Amide Remote Metalation. Synthesis of Naturally Occurring Fluorenones

The surprising discovery of fluorenones in Indian orchids by Talapatra (9) provided a timely application for the biaryl amide remote metalation concept (4). A short synthesis of dengibsinin (**Scheme 7**) (10) illustrates the advantages of the approach which constitutes an anionic Friedel-Crafts equivalent. A second illustration involves the construction of kanafluorenone (**Scheme 8**), a metabolite isolated very recently from *Steptomyces murayamaensis* (11). Minor modification of substitution in a requisite precursor for kanafluorenone also allowed the construction of WS 5995A (**Scheme 9**) (10), a metabolite from *S. auranticolor* which is part of the biosynthetic grid of the kinamycin group of antibiotics.

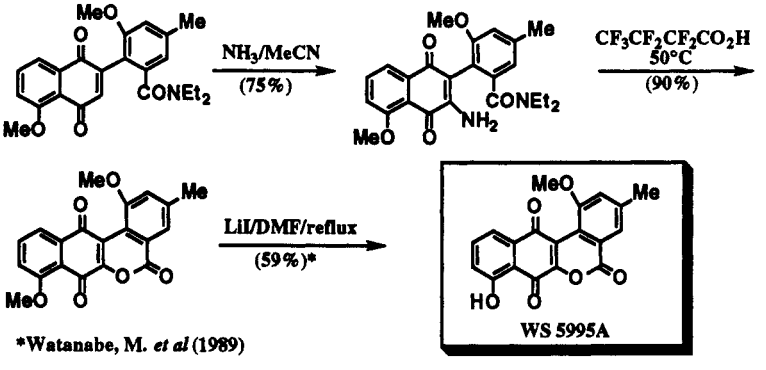
Scheme 7 Total Synthesis of Dengibsinin



Scheme 8 Biarylamide Remote Metalation: Synthesis of Fluorenone *ex Streptomyces murayamaensis*

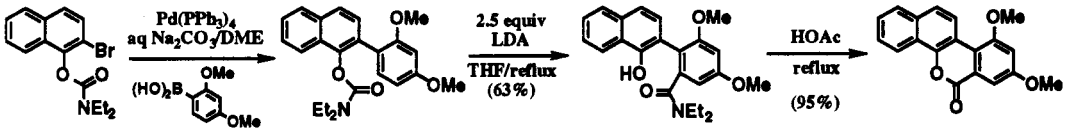


Scheme 9 Synthesis of WS 5995A *ex Streptomyces auranticolor*



*Watanabe, M. *et al* (1989)

Scheme 10 Biaryl O-Carbamate Remote Metalation. Ring to Ring Carbamoyl Transfer Route to a Gilvocarcin Model



Biaryl Carbamate Remote Metalation. Towards the Synthesis of Benzo[d]naphthopyran-6-one Antibiotics

The discovery of the biaryl carbamate remote metalation reaction (5) stimulated activity in the area of the intensely studied gilvocarcin, ravidomycin, and chrysomycin classes of antibiotics (12). Our current approach incorporates DoM, Suzuki cross coupling, and remote anionic Fries rearrangement (**Scheme 10**) (13).

Sequential Remote Metalation in Biaryl Amides and O-Carbamates. General Regiospecific Routes for Phenanthrols and Fluorenones Illustrated by the Total Synthesis of Gymnopusin and Dengibsin

The evolution of the biaryl amide and O-carbamate remote metalation concepts triggered ideas to couple them in total synthesis endeavours. Examples, which highlight advantages of integrated DoM, cross coupling, and remote metalation methodologies, concern the total synthesis of gymnopusin (14) and dengibsin (4).

CONCLUSION

The DoM strategy has rapidly evolved as a major synthetic method in synthetic aromatic chemistry. This fundamental process, when linked to transition metal catalyzed cross coupling reactions provides conceptually new routes to functionalized biaryls. The biaryl amide and O-carbamate remote metalation tactics, still in developmental stages, may be connected to DoM and cross coupling providing regiospecific routes, condensed aromatic and heteroaromatics. The present report attempted to place these methods, in their various combinations, into perspective for the chemist interested in aromatic natural product synthesis.

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REFERENCES

1. V. Snieckus, *Chem. Rev.*, **90**, 879-933 (1990), and refs cited therein.
2. X. Wang, V. Snieckus, *Synlett*, 313 (1990); M. Tsukazaki, V. Snieckus, *Heterocycles*, **33**, 533 (1992); C.A. Quesnelle, O.B. Familoni, V. Snieckus, *Synlett*, submitted (1994).
3. S. Sengupta, M. Leite, D.S. Raslan, C. Quesnelle, V. Snieckus, *J. Org. Chem.*, **57**, 4066-4068 (1992); F. Beaulieu, V. Snieckus, unpublished results.
4. J.-m. Fu, B.-p. Zhao, M.J. Sharp, V. Snieckus, *J. Org. Chem.*, **56**, 1683-1685 (1991).
5. W. Wang, V. Snieckus, *J. Org. Chem.* **57**, 424-427 (1992).
6. J.-m. Fu, M.J. Sharp, V. Snieckus, *Tetrahedron Lett*, **29**, 5459-5462, (1988).
7. J.-m. Fu, Ph.D. Thesis, University of Waterloo, (1990).
8. X. Wang, Ph.D. Thesis, University of Waterloo, (1992).
9. S.K. Talapatra, S. Bose, A.K. Mallik, B. Talapatra, *Tetrahedron*, **41**, 2765-2769 (1985).
10. B.-p. Zhao, Ph.D. Thesis, University of Waterloo, (1994).
11. For a leading reference with citations, see M.P. Gore, S.J. Gould, D.D. Weller, *J. Org. Chem.*, **57**, 2774-2783 (1992).
12. K.H. Parker, C.A. Coburn, *J. Am. Chem. Soc.*, **56**, 1666 (1991), and refs cited therein to earlier synthetic work.
13. C. James, V. Snieckus, unpublished results.
14. X. Wang, V. Snieckus, *Tetrahedron Lett.*, **32**, 4879-4882 (1991).