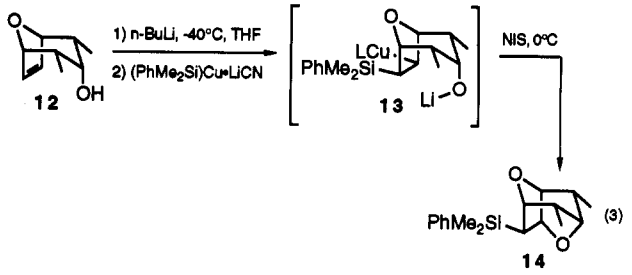

actions with organocuprates. Anti attack of an organocuprate, relative to the bridging oxygen, may be required for a successful ring opening in [3.2.1] systems.[13] In this mode of attack, as bond formation occurs, steric compression created by the incoming nucleophile may provide a driving force for the opening. The successful silacupration of **10** and **12** suggests that the reactivity arises from the release of strain in the olefin rather than any special features associated with the oxygen bridge or the ketone.[14]

(14) This supposition was proven correct by the successful silacupration of 2,4-dimethylbicyclo[3.2.1]oct-5-en-3-one with $(PhMe_2Si)$-Cu·LiCN or $(PhMe_2Si)_2CuCNLi_2$. The behavior of this compound was nearly identical to the oxabicyclic analogue. Similarly, treatment of a bicyclo[2.2.1] system with $(PhMe_2Si)$Cu·LiCN gave the product from silacupration in 87% yield. Thus the reaction appears to be general for strained olefins.

In conclusion, we note that in contrast to the displacement reactions of other electrophiles with alkyl- vs silylcuprates, significant differences exist between silylcuprates and organocuprates in addition reactions with oxabicyclo[3.2.1] compounds. The stereochemistry of attack is exo, with no more than 5% endo adduct observed in any case. While ring opening follows the addition for organocuprate nucleophiles, silylcuprates add to these substrates without subsequent ring opening. Substituted oxabicyclic compounds undergo silacupration and ring closure but at significantly slower rates. The decrease in rate of ring closure provides an opportunity to trap the intermediate with a variety of electrophiles so as to doubly functionalize the olefin. The use of silica gel to oxygenate the cuprate is a particularly novel process which is currently under investigation.

Acknowledgment. We thank the A. P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, Bio-Mega, the Merck Frosst Centre for Therapeutic Research, and the University of Toronto for financial support of our programs. We also thank Mr. Carlo DiFelice for preliminary experiments.

Supplementary Material Available: General and specific procedures and characterization for the compounds reported (5 pages). Ordering information is given on any current masthead page.

Remote Directed Metalation of Biaryl *o*-Carbamates. Ring to Ring Carbamoyl Transfer Route to Biaryls, Dibenzo[*b*,*d*]pyranones, and the Natural Fluorenone Dengibsin

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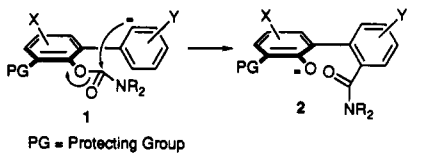
Received November 19, 1991

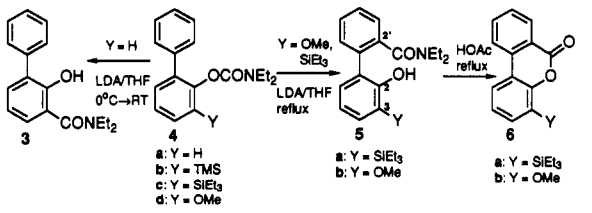
Summary: A new remote metalation, carbamoyl transfer process (Scheme I), is demonstrated and elaborated for the regiospecific synthesis of highly hindered biaryls, dibenzo[*b*,*d*]pyranones (Table I), and the naturally occurring fluorenone dengibsin (**15**).

We wish to report on a new carbanion-induced ring to ring carbamoyl transfer reaction **1** → **2** (Scheme I), formally a remote anionic Fries rearrangement,[1] which provides general regioselective entries into sterically encumbered biaryls and substituted and condensed dibenzo[*b*,*d*]pyranones and fluorenones, including the natural product dengibsin (**15**). The discovery of this reaction was based on the logic that, by prior protection of the normal site of metalation in **1**, alternate ring remote deprotonation is thermodynamically favored[2] by a complex induced proximity effect (CIPE),[3] a useful mechanistic concept[4] which posits that acid–base coordination may identify

Scheme I



Scheme II



weakly acidic remote C–H sites for potential deprotonation. Subsequent carbamoyl transfer, driven by departure of phenolate ion, a good leaving group, then leads to the 2,2′-substituted product **2**. Since this new carbanionic transformation may be closely linked to the versatile directed ortho metalation[5] and aryl boronic acid–aryl X (X = Br, OTf)[6] cross-coupling regimens, it has promising

(1) For the ortho equivalent, see: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. For a carbamoyl transfer from a benzylic alcohol induced by metal–halogen exchange, see: Lamas, C.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1990**, *31*, 6247.

(2) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Klumpp, G. W. *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(3) The synthetic advantage of this tenet has been previously provided in regiospecific routes to 9-phenanthrols and fluorenones: (a) Fu, J.-m.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459. (b) Fu, J.-m.; Zhao, B.-p.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.

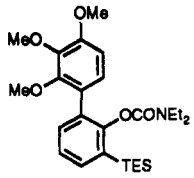
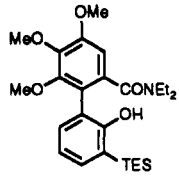
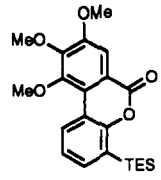
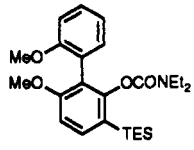
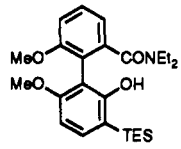
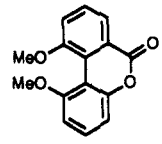
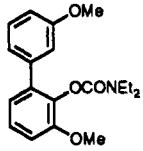
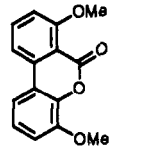
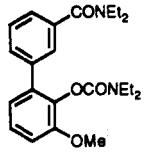
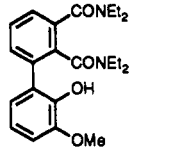
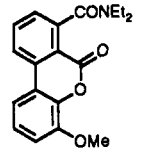
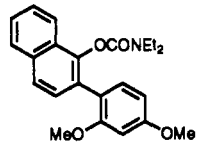
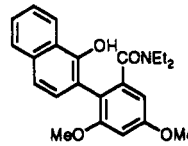
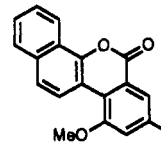
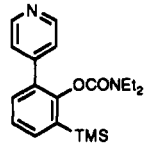
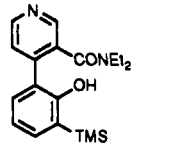
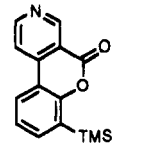
(4) For 2,2′-dideprotonation of biphenyl driven by double lithium bridging stabilization, see: Ashe, A. J., III; Kampf, J. W.; Salva, P. M. *J. Org. Chem.* **1990**, *55*, 5558 and references cited therein.

(5) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(6) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405 and references cited therein. Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665 and references cited therein.

0022-3263/92/1957-0424$03.00/0

Table I. Synthesis of Dibenzo[*b*,*d*]pyranones by Remote Aromatic Metalation

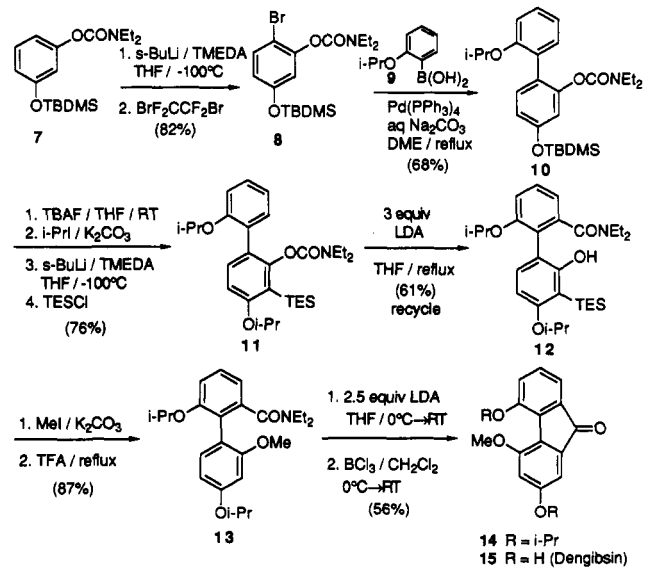
entry	carbamate	condns[a]	amide	yield,[b] %	dibenzopyranone	yield,[b] % (mp, °C)
1		A		80		93 (99–100) hexane/Et_2O
2		B		36 (75)[c]		84 (122–123.5) hexane/CH_2Cl_2
3		C				67[d] (183–185) hexane/CH_2Cl_2
4		C		96		94 (158–160) hexane/Et_2O
5		A		63		95 (210–211) CH_2Cl_2
6		C		76		90 (149–150) hexane/CH_2Cl_2

[a] Key: A, 2.5 equiv of LDA/THF/reflux; B, 5 equiv of LDA/THF/reflux; C, 2.5 equiv of LDA/THF/rt. [b] Represents yields of chromatographed and recrystallized material. [c] Based on recovered starting material. [d] Overall yield without isolation of the amide intermediate.

potential for diverse extension and application in synthetic aromatic and heteroaromatic chemistry.

Exposure of biphenyl 2-*O*-carbamate **4a** to LDA (2.5 equiv/THF/0 °C/rt) led, as expected,[5,7] to the anionic ortho-Fries rearrangement product **3** in quantitative yield (Scheme II). The desired latent protection[8] was achieved by preparation[9] of the relatively hindered 3-triethylsilyl (TES) derivative **4c** which did not suffer the same fate as **4b**[10] but underwent ring to ring carbamoyl transfer to give the biphenyl amide **5a** in high yield. Acid-catalyzed cyclization (HOAc/reflux) of **5a** led to the dibenzopyranone **6a** (94% yield).[11] With a permanent blocking substituent as in the 3-methoxy derivative **4d**, an analogous sequence

Scheme III



furnished the amide **5b** and hence the pyranone **6b** (68% overall yield).

Selective results indicating the scope of the remote metalation method for the preparation of highly substituted biaryl amides[11] and dibenzopyranones are collected in Table I. Sterically encumbered 2,2',6-substituted biaryl

(7) Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5097.

(8) For silicon latent protection of preferred ortho metalation sites, see: Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.

(9) The preparation of derivatives **4b** and **4c** follow standard conditions (*s*-BuLi/TMEDA)[1] except that lower temperatures (−100 °C) are required to avoid the rearrangement to **3**.

(10) Treatment of **4b** with LDA (2.5 equiv/THF/reflux) gave *N*,*N*-diethyl-α-[(2-hydroxy-3-phenyl)phenyl]dimethylsilyl acetamide (75% yield) confirmed by methylation (1. *n*-BuLi/THF/−78 °C; 2. MeI) and desilylation (TBAF/THF/RT) to give the known 2-methoxybiphenyl, mp 30–32 °C (lit. mp 30–33 °C, Aldrich Catalogue, 19,646-0). α-Methyl silyl deprotonations are relatively rare, see: MacDonald, J. E.; Poindexter, G. S. *Tetrahedron Lett.* **1987**, *28*, 1851.

(11) Some of these derivatives may exist as mixtures of atropisomers, and the carbamoyl transfer may be atrop-diastereoselective. These aspects are under study. For an insightful commentary and status report of this new field, see: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *92*, 977.

amides (entries 1,2), unavailable or formed in low yields by the direct cross-coupling route,[12] are obtained in good yields. Biaryl carbamates with the benefit of directed ortho metalation groups in the recipient aryl ring (entries 3,4) undergo the LDA-induced migration at room temperature. Extension to condensed biaryl (entry 5) and heterobiaryl (entries 6) synthesis is feasible. All biaryl amides are smoothly cyclized to the corresponding dibenzopyranones mainly without loss of TES substituent which may be removed (TBAF/THF/reflux or TFA/reflux) if desired. The benzo[*d*]naphtho[1,2-*b*]pyranone (entry 5) represents the ring system of ravidomycin and related classes of antitumor antibiotics of considerable current synthetic interest[13] while the azadibenzopyrone (entry 6) constitutes part skeleton of the chromone alkaloids.[14]

To demonstrate application, the synthesis of dengibsin (**15**), a fluorenone isolated from the Indian orchid *Dendrobium gibsonii*,[15] was undertaken. The 3-silyloxy carbamate **7**[16] was subjected to regiospecific metalation–bromination to give **8** which was smoothly cross coupled with boronic acid **9** under modified Suzuki conditions[3] to afford the biaryl **10**. A simple desilylation–isopropylation allowed the low-temperature ortho metalation–silylation sequence to give the key carbamate **11** which, upon exposure to LDA in refluxing THF, led to the carbamoyl migration product **12** in modest yield.[17,18] Methylation and C-desilylation proceeded unexceptionally to give the biary amide **13** which, upon treatment with LDA, underwent remote metalation–cyclization[3b] to provide the fluorenone **14**. Chemoselective deisopropylation[3b] furnished dengibsin **15**.[19] The conversion of other biary amides (Table I) to fluorenones by this general remote metalation protocol has been previously achieved in related systems.[3b]

In summary, a new general remote anionic Fries rearrangement has been uncovered and its broad utility for the regiospecific preparation of hindered biaryls and substituted dibenzo[*b*,*d*]pyranones[20] and fluorenones, including the natural product dengibsin, has been demonstrated. The retention of silyl substituents in the dibenzopyranones suggests exploration of potential regioselective ipso electrophilic and fluoride-mediated reactivity.[8] Consideration of the CIPE concept[2] coupled with advantages of synthetic connections to the adaptable directed ortho metalation[5] and cross-coupling[6] strategies promises future potential for effective and practical solutions in synthetic aromatic and heteroaromatic chemistry.[21,22]

(12) (a) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Josephy, P. D.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763. (b) For other studies showing negative effect of steric hindrance on cross couplings, see: ref 3b and Widdowson, D. A.; Zhang, Y.-Z. *Tetrahedron* **1986**, *42*, 2111. Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.

(13) For an extensive list of citations on structural and synthetic work, see ref 12a.

(14) Brossi, A. *The Alkaloids* **1987**, *31*, 57.

(15) (a) Talapatra, S. K.; Bose, S.; Mallik, A. K.; Talapatra, B. *Tetrahedron* **1985**, *41*, 2765. (b) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553. (c) Talapatra, S. K.; Chakraborty, S.; Talapatra, B. *Ind. J. Chem.* **1988**, *27B*, 250.

(16) Prepared in 90% yield from 3-methoxyphenyl dimethylcarbamate in two steps (BBr_3/CH_2Cl_2/−78 °C; TBDMSCl/imidazole).

(17) The 2′-deisopropylated product corresponding to **11** was also obtained (52%). The yield of **12** is based on the reconversion (*i*-PrI/K_2CO_3/Me_2CO, 98%) of this product into **11**.

(18) Attempts to use the Suzuki cross coupling for the direct preparation of derivatives related to **13** (without TES substituents) was uniformly unsuccessful, see: Fu, J.-m. Ph.D. Thesis, University of Waterloo, 1990 and ref 3b.

(19) Mp 234–235 °C (CH_2Cl_2) (lit.[15a] mp 227 °C), identical IR, MS, ^1H NMR with those reported.

(20) The recently announced[11] atrop-diastereoselective ring opening of dibenzopyranones related to entry 2 (Table I) by chiral nucleophiles anticipates considerable use of such systems for enantioselective biaryl synthesis.

(21) All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the assigned structures.

(22) We thank Dr. J.-m. Fu for initial experiments, NSERC Canada for sustaining financial support, and Professor B. Giese, Universität Basel, for the marvellous environment to complete this manuscript.

Pyruvate Aldolases as Reagents for Stereospecific Aldol Condensation

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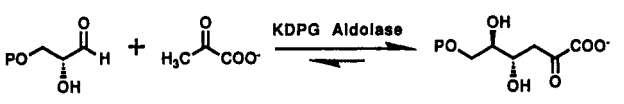
Summary: KDPG aldolase, a representative member of the largest but as of yet unexplored group of aldolases which utilize pyruvate as the nucleophilic component in aldol condensation, accepts a number of unnatural aldehydes as electrophiles in stereospecific aldol condensation, providing access to highly and differentially functionalized α-keto acid products.

The aldolases have emerged as useful catalysts for stereocontrolled C–C bond formation in organic synthesis.[1,2] These enzymes can be categorized into three broad groups according to nucleophile type. The dihydroxyacetone phosphate aldolases have been investigated extensively as synthetic catalysts,[1-8] while a report on deoxyribose aldolase (DERA, EC 4.1.2.4), the only known aldolase which utilizes an aldehyde as the nucleophile, appeared only recently.[9] The remaining and largest group of aldolases, those which utilize pyruvate or phosphoenolpyruvate as the nucleophile, have yet to be investi-

Scheme I. KDPG Aldolase. Throughout "P" Represents PO_3H^-



(1) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F.; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499.

(2) Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365.

(3) Bednarski, M. D.; Simon, E. S.; Bischofberger, N.; Fessner, W.-D.; Kim, M.-J.; Lees, W.; Saito, T.; Waldman, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 627.

(4) Durrwachter, J. R.; Drueckhammer, D. G.; Nozaki, K.; Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 7812.

(5) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F.; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924.

(6) Brockamp, H. P.; Kula, M. R. *Tetrahedron Lett.* **1990**, *31*, 7123.

(7) Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926.

(8) Ozaki, A.; Toone, E. J.; von der Osten, C.; Sinskey, A. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 4970.

(9) Barbas, C. F.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1990**, *112*, 2013.

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