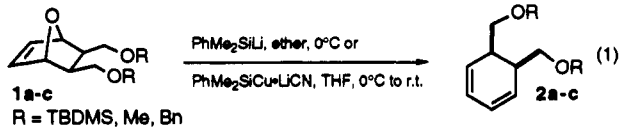
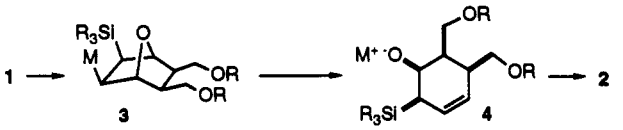


The proposed mechanism for conversion of the starting material to the diene invokes a silacupration or silalithiation of the highly strained olefin from the exo face to give **3** which undergoes subsequent ring opening to the alkoxysilane **4**, Scheme I.[10,11] Finally, Peterson elimination provides the diene **2**.[17] This mechanism is supported by the isolation of all of the proposed intermediates in the sequence.[18]

An examination of the scope of this reaction was undertaken. Table I lists the range of substrates studied. A comparison was made between $PhMe_2SiLi$ and $PhMe_2SiCu{\cdot}LiCN$ (conditions A and B in Table I). In contrast to **1**, oxabicyclic compounds **7–10** bearing substituents at the bridgehead position react smoothly with either the silyllithium or silylcopper reagent. Yields of the dienes ranged from 58–90%. Usually, 1.5–4 equiv of $PhMe_2SiCu{\cdot}LiCN$ is necessary to ensure complete consumption of the starting material, whereas 6–8 equiv of $PhMe_2SiLi$ are routinely required. When following the reaction progress by TLC, rapid formation of a more polar product (presumably either **5** or **6**) is observed.[18] Upon increasing the temperature, the diene is isolated. Efficiency, regioselectivity, and mildly basic conditions are characteristics of this methodology; no further isomerization of the olefins has been observed. The reaction is equally useful for small to medium scale and the yields improve with increasing scale. The rates of consumption of the oxabicyclic compounds are nearly identical regardless of the presence or absence of substituents at the bridgehead. However, the subsequent ring opening or Peterson elimination occur at different rates as a function of the substrate. Thus, while **1a** requires 50 min for conversion to the diene, **8** and **9** require 5–7 h.

Scheme I



In summary, we have shown that ring opening of [2.2.1]oxabicyclic compounds occurs with silyllithium or silylcopper reagents to form cyclohexadienes. Efforts to utilize this reaction sequence in the preparation of biologically active compounds are in progress and will be reported in due course.

Acknowledgment. This research was supported by the Alfred P. Sloan Foundation, the Natural Sciences and Engineering Research Council (NSERC) of Canada, BioMega Inc., and the Merck Frosst Centre for Therapeutic Research.

Supplementary Material Available: Experimental procedures and spectral data for all new compounds including ^1H and ^{13}C NMR spectra (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

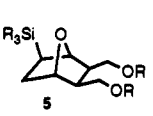
(14) Satisfactory ^1H and ^{13}C NMR, IR, and mass spectral data were obtained for all new compounds.

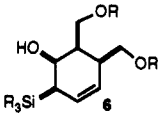
(15) A typical experimental procedure is as follows: Phenyldimethylsilyllithium is prepared by stirring phenyldimethylchlorosilane (1 mL) and lithium in tetrahydrofuran (14 mL) at 0 °C for 24 h to make an approximately 0.4 M solution. **General Conditions A.** A solution of phenyldimethylsilyllithium (4–8 equiv) was added to a flame-dried flask fitted with a vacuum adapter, and the THF was removed under vacuum. The resulting red-black concentrate was dissolved in diethyl ether at 0 °C (concentration was approximately 0.8 M). The oxabicyclic compound was dissolved in an equal volume of diethyl ether and transferred via cannula to the flask. After 8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. Flash chromatography gave the diene. **General Conditions B.** Copper cyanide was added to a flask and dried overnight in vacuo (0.1 mmHg). The flask was cooled in an ice bath, and a solution of phenyldimethylsilyllithium (1:1 ratio of Si–Cu, 2–4 equiv based on oxabicyclic compound) was added. After 30 min at 0 °C, the oxabicyclic compound was added as a solution in THF. After 30 min, the mixture was allowed to warm to room temperature and stirred for 4 h or until TLC indicated that all the starting material was consumed. Workup and purification were carried out as described above.

(16) When the substrate has a silyl protecting group, the dienes produced are contaminated with approximately 5% of a phenyldimethylsilyl-containing compound. Cleavage of the $PhMe_2Si$ group (5 equiv of Bu_4NF, THF, rt) gave the more polar diols which were readily purified.

(17) For a review of the Peterson elimination, see: Ager, D. J. *Org. React.* **1990**, *38*, 1.

(18) Reaction of **1** with $PhMe_2SiCu{\cdot}LiCN$ at −40 °C rather than 0 °C, followed by workup (NH_4Cl), leads to the isolation of **5** (89% yield). Treatment of **1a** with $(PhMe_2Si)_2CuCNLi_2$ in THF at 0 °C gave a 36% yield of **5** accompanied by 41% of the ring-opened product **6**. These results are in contrast to those obtained from reaction of oxabicyclo[3.2.1] substrates, see ref 11.





Ni(0)-Catalyzed Cross Coupling of Aryl *O*-Carbamates and Aryl Triflates with Grignard Reagents. Directed Ortho Metalation-Aligned Synthetic Methods for Polysubstituted Aromatics via a 1,2-Dipole Equivalent†

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Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, N2L 3G1 Canada, and Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

Received May 12, 1992

Summary: The first Ni(0)-catalyzed cross-coupling reactions of aryl *O*-carbamates and aryl triflates with Grignard reagents (Scheme I) to give diversely polysubstituted aromatics **2d** and **2e** (Table I) which feature regiospecificity based on directed ortho metalation (carbamate), minimal β-hydride elimination (triflate), and dependence on steric and electronic effects are described.

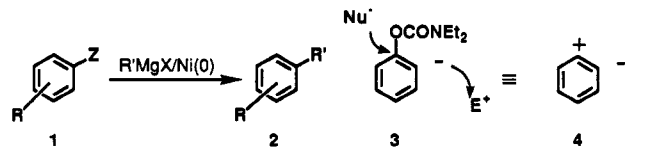
We report on the first Ni(0)-catalyzed aryl *O*-carbamate and aryl triflate cross-coupling reactions with Grignard

† Dedicated to Professor Virgil Boekelheide on the occasion of the first VB Reunion, University of Oregon, Aug 1991.

(1) (a) University of Waterloo. (b) Department of Chemistry, Jadavpur University, Calcutta, India. (c) Universidade Federal de Minas Gerais.

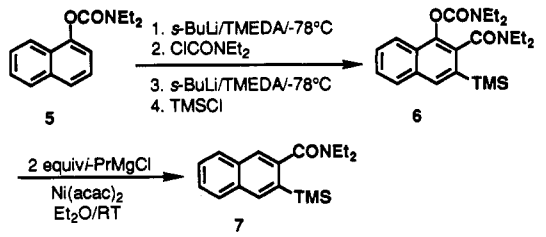
0022-3263/92/1957-4066$03.00/0

Scheme I



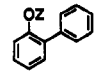
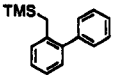
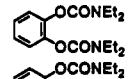
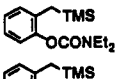
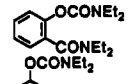
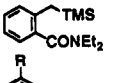
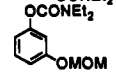
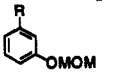
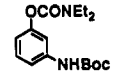
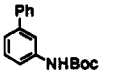
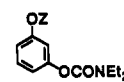
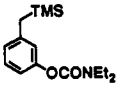
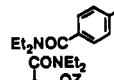
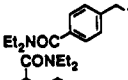
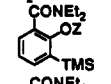
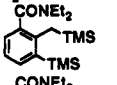
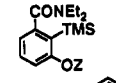
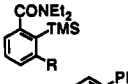
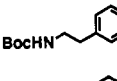
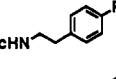
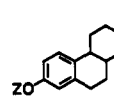
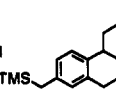
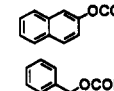
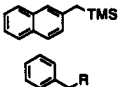
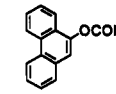
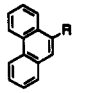
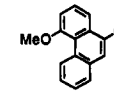
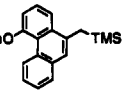
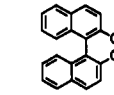
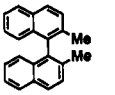
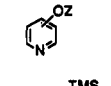
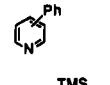
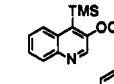
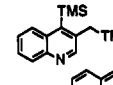
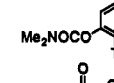
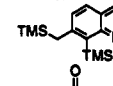
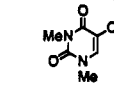
a: Z = OMe,[6e] b: OP(O)(OEt)$_2$,[6f] c:  ,[6g] d: OCONEt$_2$,[this work] e: OTf.[this work]

Scheme II



reagents (**1d,e→2d,e**, Scheme I). In the case of the carbamate, this discovery demonstrates a unique ortho functionalization via combined directed ortho metalation[2]–nucleophilic ipso substitution (**3**)[3,4] and introduces a new concept, that of an aromatic 1,2-dipole equivalent (**4**). Grignard reagents[5] occupy a prominent position[6] among organometallics[7] used in aromatic cross coupling reactions under Pd(0) and Ni(0) catalysis. Nevertheless, none of the phenol derivatives **1a–c**[6c–e] benefit from ortho metalation capability nor has their synthetic utility been adequately pursued. In view of the continuing evolution of the ortho metalation strategy in regioselective aromatic functionalization[2] and the revolutionary impact of cross-coupling regimens for C–C bond formation,[7–9] the methodologies reported herein anticipate broad scope and application in synthetic aromatic chemistry.[10]

Table I. Ni(0)-Catalyzed Cross Coupling of ArOCONEt$_2$ and ArOTf Derivatives with Grignard Reagents[a]

entry	ArOZ	RMgX	product	Z	R	yield,[b] %
1		TMSCH$_2$MgCl		CONEt$_2$		40 (92)[c]
2				CONMe$_2$		81
3				Tf		12
4		TMSCH$_2$MgCl				55[d]
5		TMSCH$_2$MgCl				60
6		RMgX			Ph	80
7					CH$_2$TMS	82
8		PhMgCl				73
9		TMSCH$_2$MgCl		CONEt$_2$		16[d]
10				Tf		70
11		TMSCH$_2$MgCl		CONEt$_2$		83
12				Tf		82
13		TMSCH$_2$MgCl		CONEt$_2$		44
14				Tf		73
15		RMgX		Tf	Ph	70[e]
16				Tf	*n*-Bu	65[e,f]
17				CONEt$_2$	H	28[g]
18		PhMgCl				30
19		TMSCH$_2$MgCl		CONEt$_2$		70
20				Tf		40
21		TMSCH$_2$MgCl				81
22		RMgBr			Me	93
23					CH=CH$_2$	55
24		TMSCH$_2$MgCl				82
25		MeMgBr				88[h]
26		PhMgCl		2-CONEt$_2$		30-80[i]
27				3-CONEt$_2$		72
28				4-CONEt$_2$		81
29				3-Tf		65
30		TMSCH$_2$MgCl				72
31		TMSCH$_2$MgCl				76
32		TMSCH$_2$MgCl		CONEt$_2$		61[j]
33				Tf		65[j]

[a] Unless otherwise stated, conditions are as follows: 5 mol % Ni(acac)$_2$/RMgX (1–2 equiv)/Et$_2$O/rt/2-24 h. [b] Based on purified (chromatographed/distilled) material. [c] Based on recovered SM. [d] SM (10–48%) and bis-CH$_2$TMS derivative (7–30%) were also isolated. [e] 5 mol % NiCl$_2$(dppp)/RMgX (1–2 equiv)/THF/rt/2–24 h. [f] Accompanied by reduced product (15%). [g] Yield of reduced product for RMgX = *n*-BuMgBr. [h] 5 mol % NiCl$_2$(dppp)/MeMgX (6 equiv)/Et$_2$O/rt. [i] Variable yield presumably due to possible Grignard-induced decarbamoylation. [j] THF solvent.

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A wide variety of aromatic (entries 1–20), condensed aromatic (entries 21–25), and heterocyclic (entries 26–33) derivatives participate in this reaction (Table I). The required solvent for carbamate coupling is Et_2O (THF fails, PhH has limited value) while triflate coupling proceeds in Et_2O or THF with similar facility. $Ni(acac)_2$ catalyst provided consistent results while the more expensive $NiCl_2(dppp)$ gave less clean reactions (especially with carbamates) and Pd(0) catalysts were totally ineffective. Methyl, $TMSCH_2$, and aryl Grignards are useful coupling partners while allyl and benzyl Grignards, as observed frequently in Ni-catalyzed reactions,[6b] fail or give complex mixtures. A major difference is observed with *n*-BuMgCl: whereas triflates (entry 16) undergo smooth coupling, the corresponding carbamates (entry 17) give reductive products, undoubtedly a result of β-hydrogen elimination.[6b] This difference, perhaps a reflection of the relatively faster rate of triflate over carbamate oxidative addition to Ni(0), is of considerable synthetic value as illustrated by a sequence leading to difficult to access 2,3-disubstituted naphthalenes (Scheme II). Thus, directed metalation-mediated consecutive introduction of carbamoyl and silyl electrophiles into carbamate **5** leads to **6** which, upon treatment with *i*-PrMgCl/$Ni(acac)_2$ gives **7**, demonstrating the latent DMG character of the $OCONEt_2$ group. Inspection of carbamate and triflate reactivity patterns indicates the operation of as yet poorly understood steric and electronic effects. Thus, an *o*-phenyl group retards reactivity for both the diethyl carbamate and triflate (entries 1 and 3), while the dimethyl carbamate (entry 2) gives an excellent yield of product, a result which, however, is compromised by its inadequate DMG character.[2] Comparison of more highly hindered cases suggests significant synthetic advantage of using triflates over carbamates (entries 14 vs 13).

In the carbamate series, *o*-oxygen (entry 4), *m*-oxygen (entries 6, 7), and *m*-nitrogen (entry 8) EDGs give good results except the *m*-carbamate (entry 9). *o*- and *p*-EWGs enhance rates considerably and lead to good yields of benzylsilane products (entries 5, 11, 12). Entry 10 documents the preferential triflate over carbamate coupling, a result of practical synthetic value.

Comparison of entries 7 vs 10 reveals that either acid (OMOM) or base ($OCONEt_2$) sensitive phenol protecting groups may be retained by choice. Functionalization of phenethylamines (entry 18), steroids (entries 19, 20), naphthyls (entry 21), phenanthryls (entries 22–24), binaphthyls (entry 25), pyridines (entries 26–29), quinolines (entries 30, 31), and uracils (entries 32, 33) is illustrative of additional scope for this chemistry.

In summary, we have described new Ni(0)-catalyzed aryl carbamate and aryl triflate–Grignard cross-coupling reactions which feature the following: (a) coupling partners that are easily derived from phenols and organic halides and carbamates and triflates which may be readily interconverted; (b) the use of carbamates singularly, and in conjunctive fashion, with directed ortho metalation (1,2-dipole equivalency (4)) providing rapid and regiospecific entries into complex polysubstituted aromatics; (c) the apparent superiority of carbamates and triflates over other phenol derivatives,[6e-g] most of which are incapable of ortho metalation; (d) new methodologies that offer competitive and complementary alternatives to the triflate–aryltin[7b] and triflate–arylboronic acid[7c] regimens. The triflate-based coupling overcomes β-hydride elimination, an oft-observed process of synthetic detriment. The ability to tune in the metal in coupling of aryl triflates with RMgX (Ni) or $RB(OH)_2$ (Pd) derivatives may be of distinctive synthetic value. Further refinement and exploration of these methods is in progress.[11,12]

Note Added in Proof. Since the submission of this paper, a Ni(0) catalyzed vinyl carbamate–Grignard reagent cross-coupling reaction has been brought to our attention: Kocienski, P.; Dixon, N. J. *Synlett* **1989**, *52*. We thank P. S. Bury for this information.

Supplementary Material Available: Experimental procedures and characterization data for new compounds (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) All new compounds show analytical and spectral (IR, NMR, MS) data in accord with the given structures.

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A New Channel-Forming Host Macroring. X-ray Crystal Structure of Its Inclusion Compound with DMF

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Summary: A macrocyclic host molecule composed of two conformationally inflexible 4,4′-dioxybenzophenone building blocks and two 2,6-methylene-substituted pyridine nuclei is shown to form a crystalline channel structure with included DMF molecules; the unsolvated host compound as a solid is capable of DMF vapor sorption.

Molecular arrangements that are representatives of a channel[1] are in great demand due to their potential behavior as chemical transporter systems[2] or as environments for topochemical reactions.[3] We report here a new mac-

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